

Department of Health and Human Services

Ophthalmic Devices Panel

Second Day

Tuesday October 21, 1997
Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

Proceedings By:

CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, VA 22030
(703) 352-0091

PARTICIPANTS LIST

R. Doyle Stulting, M.D., Ph.D., Chair

Voting Members:

Mark A. Bullimore, Ph.D.
Eve J. Higginbotham, M.D.
Marian S. Macsai, M.D.
James P. McCulley, M.D.
Richard S. Ruiz, M.D.

P. Sarita Soni, O.D.

Consultant, Deputized to Vote:

Joel Sugar, M.D.
Karen Bandeen-Roche, Ph.D.
Woodford W. Van Meter, M.D.
Mark J. Mannis, M.D.
Michael W. Belin, M.D.
Jose S. Pulido, M.D.
Walter J. Stark, M.D.

Non-voting Discussants:

Eleanor McClelland, Ph.D.
Judy F. Gordon, D.V.M.

P R O C E E D I N G S

[8:49 a.m.]

DR. STULTING: I would like to call to order this meeting of the Ophthalmic Devices Advisory Panel and turn the floor over to Sara Thornton for comments.

MS. THORNTON: Good morning and welcome to all attendees.

Before we proceed with today's agenda, I have a few short announcements. During the break this morning, there will be coffee, tea and pastries that you can purchase at the little restaurant down here on the end to your left.

I would like to request that messages and other things for panel members and participants, any information or special needs should be directed through Ms. Andrea Williams and Ms. Gloria Williams. They are either going to be outside, just outside the doors here at the table or they will be circulating in the room, but they will be available to help you.

I would like to remind those who are in attendance here that we do not permit cell phones to be used in the room. If you do have to make a call, receive a call, please go outside into the hallway so that we can keep the distractions down to a dull roar.

Please speak into the microphone so that the

transcribers and the reporter can capture your comments accurately and can identify who you are. They would appreciate it very much if you could speak your name before you make your comments. I realize that is difficult under heated discussion conditions.

I would like to extend a welcome to our panel and have them introduce themselves for the record this morning and that will begin with Dr. Gordon.

DR. GORDON: Good morning. Judy Gordon. I am with Chiron Vision and I am the industry representative to the panel.

DR. MC CLELLAND: Eleanor McClelland, University of Iowa College of Nursing, associate professor and consumer representative to the panel.

DR. MACRAE: Scott MacRae, Oregon Science University and I am a consultant to the panel.

DR. STARK: Walter Stark, professor of ophthalmology at Johns Hopkins University, consultant to the panel.

DR. MACSAI: Marian Macsai, professor of ophthalmology, West Virginia University, panel member.

DR. RUIZ: Richard Ruiz, professor and chairman of the Department of Ophthalmology at the University of Texas-

Houston, panel member.

DR. STULTING: Doyle Stulting, professor of ophthalmology, Emory University.

DR. SUGAR: Joel Sugar, University of Illinois, Chicago, consultant.

DR. BULLIMORE: Mark Bullimore, the Ohio State University, College of Optometry.

DR. SONI: Sarita Soni, professor of optometry and visual sciences, Indiana University, panel member.

DR. HIGGINBOTHAM: Eve Higginbotham, professor and chair, University of Maryland, Department of Ophthalmology, panel member.

DR. MC CULLEY: Jim McCulley, professor and chairman of the Department of Ophthalmology, University of Texas, Southwestern Medical School in Dallas, panel member.

DR. BELIN: Michael Belin, professor of ophthalmology, Albany Medical College, consultant to the panel.

DR. VAN METER: Woodford Van Meter, private practice in cornea and external disease in Lexington, Kentucky, consultant to the panel.

DR. FERRIS: Rick Ferris, director of the Division of Biometry and Epidemiology at the National Eye Institute.

And I don't have a clue what my status is.

MS. THORNTON: You are a consultant to the panel.

DR. ROSENTHAL: Ralph Rosenthal, division director of somewhere, FDA, OD.

MS. THORNTON: Ralph, I will chance it again and call on you because I know you have some remarks.

DR. ROSENTHAL: I have a few remarks. Dr. Ferris threw me off my train of thought.

Firstly, I should like to make some comments about the outgoing panel members. We are grateful for their deliberations and their work and the amount of effort they put in to assist us in making our decisions.

Dr. McClelland, who has been the consumer representative, has continued to bring to our attention the issues that relate to patients and assure that they are not forgotten and we are grateful for that effort.

Judy Gordon has been the industry representative and she has provided an impartial approach to the issues and has been an impartial industry advocate of the issues and has been enormous help in the discussions.

Drs. Soni and Ruiz, who have been panel members prior to my arrival last year, I have been grateful for their practical and insightful approach to the issues

brought before the panel and this has been of great assistance to the division in making its decisions.

Finally, to our esteemed chairman, Dr. Stulting, he has steered this panel through many uncharted waters and has always used the highest scientific principles in his deliberations of the issues. For these accomplishments, the division will be forever grateful.

So, I wish you all the very best and thank you again for the efforts that you have expended in our behalf.

I have one more comment, if I may, to start the day.

The Agency would appreciate -- this is to the panel, the consultants and the panel members and everybody at the table -- the Agency would appreciate your advice relating to the guidance for laser refractive surgery, which will be discussed today.

We should like you to draw on knowledge obtained from the literature and your clinical experience. The Federal Food, Drug and Cosmetic Act states that the summary of safety and effectiveness, i.e., the clinical data, and I may quote, "may not be used to establish the safety or effectiveness of another device for purposes of this Act by any person, other than the person who submitted the

information. Therefore, data from previous PMAs cannot be presented by this Agency for use in reclassification exercises, consideration of other PMAs or in the development and consideration of a guidance document."

Thank you very much for your assistance in this important matter. The Agency is sorry if there has been any inconvenience caused to any of the panel members or if there has been a misunderstanding created. Thank you.

DR. STULTING: Any questions?

[There was no response.]

Our task today is to provide recommendations regarding the guidance document for refractive lasers. Before we begin our deliberations, we would like to open the meeting for public comment. We invite any of you in the audience, who would like to make a statement before the panel to please come forward.

Seeing no one come forward, we will move on with our deliberations. You should have in front of you some documents entitled "Checklist of Information Usually Submitted at an Investigation" and one on proposed modifications as well.

Morris Waxler and Malvina Eydelman have put a lot of work into organizing this discussion for us today. The

assumption will be that all of us have looked at these documents and are familiar with them. We will be taking a look at individual parts as we go through the day. We have, at least, a proposed schedule to keep us on track so that we can finish the guidance document and we would like to try to move forward so we can comment on all of the issues that will be coming before us today.

So, I would like to ask your cooperation in keeping your comments to a minimum and when it is time to move on, we will need to do that. We will not be taking formal votes today at the request of the Agency.

I will try to summarize for the record what the consensus opinion appears to be or if there is dissenting opinion, I will try to summarize that.

Those are the ground rules. Now, I will turn the floor back over to Sara Thornton to read some information into the record.

MS. THORNTON: The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even an appearance of impropriety, to determine if any conflict exists to the Agency, review the submitted agenda and all financial interests reported by the panel participants.

The conflict of interest statute prohibits special government employees from participating in matters that could effect their or their employers' financial interests. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved is in the best interest of the government.

Waivers have been granted to Drs. R. Doyle Stulting, Michael Belin and Scott MacRae for their financial interest in firms at issue that could potentially be effected by the panel's deliberations. The waivers permit these individuals to participate in all general matters before the committee. Copies of these waivers may be obtained through the Agency's Freedom of Information Office, Room 12A15 of the Parklawn Building.

We would like to note for the record that the Agency took into consideration other matters regarding Drs. Mark Bullimore, Walter Stark and James McCulley. Dr. McCulley reported that he conducted a certification course for a firm at issue. Since this is not related to the issues before the panel, the Agency has determined that he may participate in the committee's deliberations.

He also reported refractive laser studies that are

not specifically related to the panel agenda. However, in the absence of any personal or financial interest, the Agency has determined that he may participate fully in the panel's deliberations.

Dr. Bullimore reported an NIH grant analyzing data from a research clinic for a firm at issue. Since this is not specifically related to the agenda items and he receives no remuneration, the Agency has determined that he may participate in today's discussions.

Dr. Stark reported his role in a refractive laser study that is not directly related to the issue for the panel. In the absence of any personal financial interest, the Agency has determined that he may participate fully in today's discussion.

In the event that the discussions involve any other products or firms not already on the agenda, for which the FDA participant has a financial interest, the participants should exclude themselves from such involvement and their exclusion will be noted for the record.

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

comment upon.

Thank you, Mr. Chairman.

DR. STULTING: Dr. Waxler, are you ready to begin?

DR. WAXLER: Well, ready or not, we are here.

Yes, we will have a little -- do it a little differently than we had planned because we don't have the slides.

I just want to say a brief comment at the beginning. This guidance document, I think, is extremely important. I think it has been very helpful to date and what we basically would like to do is expand the indications in this guidance document so that it will cover myopia in its entire range, with and without astigmatism and hyperopia, with and without astigmatism and there are a number of other suggestions that are made for changes.

These suggestions are not necessarily FDA suggestions. We have gone through an iterative process with the Eye Care Technology Forum Working Group, as well as received a number of letters related to a number of issues. We have tried to reflect that interim consensus and we want the panel and the individuals attending this meeting to discuss fully each of these issues so that we can understand where there is agreement and where there is not agreement. We feel that is extremely important in being able to take

action on additional PMAs as they come forward, as well as investigational device exemptions.

In addition, what we want to do is be able at some time in the near future use this kind of consensus in the eye care community and in industry and FDA as a basis for product development protocols. And the excitement there is that if we have a great deal of consensus about the product and the outcomes expected, we can essentially negotiate with the manufacturer up front what ought to be in that product development protocol, the Agency can do so, with concurrence of the panel and then we can have the company go away and do the study and come back with the data and go to market.

That will be a more hands off approach and we can build in whatever is necessary to build in in the product development protocol to make sure that bad things don't happen and if they do, that there are ways to deal with them.

I think we are a ways away from that, except, perhaps, for the low to moderate myopia, but I think it is an exciting possibility. The extent to which it will be used remains open, but I think it has another way to market and it has some potential for freeing up the panel's time in the long run perhaps, as well as freeing up the Agency's

time and allowing for a little more evolutionary development of these products.

To anticipate a question that came up yesterday, we have already built into the guidance document the engineering issues related to changes in the equipment. So, if the changes in the equipment are such that they don't change what happens at the treatment plane on the cornea, then we have made a number of comparability determinations and that rule, that principle, will still apply. I think there is general consensus within the center, as well as amongst many other folks that that is a very useful approach and presumably that would still be part of that matter.

I will be glad to have this process move ahead and I am excited to see us all here to deal with it. I am at your pleasure, Mr. Chair.

DR. STULTING: Let's begin. We are not going to have any projected materials?

PARTICIPANT: [Comment off microphone.]

DR. STULTING: Okay. Well, I think we can go ahead and follow that up here. It won't be quite as crisp and clear, but we can move forward.

The first topic for discussion are a group of proposed modifications to the low to moderate myopia

guidance document. You should have a full copy of the guidance document in your materials and then the discussion points that we will be addressing today are a separate document. So, we will be looking in the discussion points for the issues that we will be commenting on today.

Would you like to go ahead and introduce them?

DR. WAXLER: Yes. The first point is on contact lens wearers. Do you want me to read that or would that be redundant? Does everyone have a copy of what is currently in the current guidance and what the modification is?

DR. STULTING: Let's try to do it with -- maybe we should try to do it without reading them because it would be more efficient and then if people have questions, we can go back and read them. We are looking on page 1 of the discussion points. Anybody unclear about where we are looking on our documents?

It is a change from removal of hard contact lenses three weeks -- it is a change in the requirement to remove contact lenses basically.

So, the floor is open for discussion on that one.

Dr. Belin, you submitted a comment on this. Do you want to go ahead?

DR. BELIN: Michael Belin.

Though it is listed on the low to moderate, it also makes comments on high myopia and the way it reads now, a patient can remove contact lenses three days prior and this allows a 1 diopter change within three days and still be considered stable. And I don't think that represents refractive stability.

DR. STULTING: I think you may be misinterpreting what is required. They are required to leave them out, soft contact lenses, for example, three days before the initial exam and then there must be a second exam at least a week later that shows no significant change from the first one.

DR. BELIN: Right, but for high myopia it says 1 diopter of change. In other words, K readings, if on the day of scheduled surgery for the primary eye, central K readings and manifest refraction do not differ significantly from the initial exam, parentheses, and it goes "or by more than 1 diopter for high myopia." That seems like a large jump in a one week period to be indicative of refractive stability.

DR. STULTING: Any other comments?

Marian.

DR. MACSAI: I agree. I would be somewhat concerned with that patient of possible corneal warpage from

the gas permeable contact lens.

DR. STULTING: Any others?

Well, I will add a comment because I was involved in writing some of this and I went to the ECTF meeting. Before doing so, I did two things. One was to review the literature on contact lens warpage and changes. The paper that had been quoted and referred to in the ECTF before was one by Wilson and I looked at the changes and the rates at which they occurred. I also pulled some refractive data, particularly on high myopes to find out what the changes, at least in my practice, were with technicians measuring them.

What I found from the paper by Wilson is that eyes that had significant changes after contact lens wear demonstrated those changes most rapidly during the initial week or so after they were removed. So, although this is not meant to show -- to select a time at which there was stability, it was meant to select a time at which you could have a reasonable chance of determining that the eye was unstable, which is a different issue.

In other words, all the eyes that were unstable had significant changes early on. So, that is the reason this came out. And, surprisingly, to me at least, to address your comment, Marian, repeated refractions by

multiple observers for high myopes, that is, minus 10s or so, are not uncommonly off by as much as a diopter, at least in the data that I looked at.

So, I did look at some data and I agree that my first thought was that these were too high, but at least in my practice, I would have trouble getting good concordance for high myopes, closer than this in some cases.

DR. BELIN: The problem is going to be whether it occurs normally in the population or not is whether these patients can then be adequately analyzed for study purposes. If the initial starting point is plus or minus a diopter, which it will be on this, then it becomes very difficult for us to evaluate efficacy.

So, I think if we have a patient who has a 1 diopter scatter in the refraction over a one week period, that that person probably should not be entered into the study.

DR. MACSAI: Doyle, the question I have is you said a significant change. So, you are saying when it is more than a diopter of change, then it is significant, according to the Wilson paper, but 1 diopter of change is acceptable? That is where I am confused.

DR. STULTING: No. That was addressing Mike's

comment. Maybe I was commenting more on your written comment about this, which was questioning whether or not you got stability after contact lens removal at one week. Isn't that what your written comment said?

DR. BELIN: Actually, I pretty much read the written comment. I think I mentioned IGP wear, but it is really a concern of refractive stability and not as much corneal stability.

There are also patients, particularly high myopes, who have been over-minused and even with cycloplegia, you don't always get a full cycloplegic result. And, again, I have concerns about a 1 diopter shift, in essence, in a seven to ten day period. Again, I think it is going to confuse our data analysis if we enter patients, who are plus or minus a diopter. That becomes our minimal acceptable efficacy. We can't expect greater than that and then if the machine has variability, we end up with an end point that is so variable as to make the study very difficult to analyze.

DR. STULTING: Dr. Soni.

DR. SONI: We would be prudent to repeat that a week later and see if that is stable or not, just for repeatability and --

DR. STULTING: You mean a third exam.

DR. SONI: Yes, a third exam.

DR. STULTING: Well, presumably if you don't, that would be the remedy because if it is not within a diopter, you would have to cancel the procedure is my understanding of the document as it stands.

DR. SUGAR: You imply that all people who are unstable change by more than 1 diopter. Are there people who change by less than 1 diopter and then continue to change at the same rate for ensuing weeks? You were talking about your data from your practice.

DR. STULTING: I think that the ability to measure high myopes is not as accurate as I would have -- it is not as precise as I would have originally proposed or thought. Maybe somebody else should comment that actually has some data or has reviewed data.

DR. MACRAE: Doyle, I think just in looking at patients that I have seen and also just thinking of this practically, if a patient changes a half diopter from exam to exam, that is not very surprising for me, but if they change three-quarters of a diopter, it raises suspicion that something is going on. What I would suggest is that we use three-quarters of a diopter as a cutoff point since that -- it may not be significant, but you can check in a week or a

month or whatever. It is in the patient's best interest to do that, rather than going ahead and doing the procedure and then finding out a month or two later that you had contact lens-induced warpage.

One other point about this is that I am a little bit concerned about the rigid gas permeable lens group having this evaluation within ten days. My hunch is that most of the contact lens-induced corneal warpage that we see, ten days is really not an adequate time for a rigid gas permeable lens wearer. In my experience, the torique(?) soft lens wearers also -- actually you hide a lot of asymmetric astigmatism where you get superior flattening and inferior steepening with torique soft lenses.

Our fitters actually preferentially treat those types of individuals that have contact lens-induced warpage with torique soft lenses. So, there is both the rigid gas permeable lens wearers and the torique soft lens wearers. I don't think the ten day period is really adequate.

I would suggest that more than a half diopter of change would be something where you would delay the surgery.

DR. STULTING: So, you are speaking for removal of the gas permeable lenses long than soft contact lenses before the initial exam?

DR. MACRAE: My initial reaction is for three weeks, I would suggest, for rigid gas permeable lens wearers. I think it is for hard --

DR. MC CULLEY: It was two weeks for RGP lenses in the past. I just -- a simple question.

What is the stimulus for changing the current guideline?

DR. STULTING: The stimulus, I think, is that high myopes object to having their contact lenses out for long periods of time. The way it was originally written if you have them leave them out two or three weeks before their original visit and then another week or two before their second visit, then they have them out for more than a month and the concern was whether or not people would be able to do this and comply with study guidelines.

DR. MC CULLEY: I agree that it is a practical problem with them, but I am not certain that these kind of time frames are not going to create problems as Mike is suggesting with the outcomes, that we really want stability before we laser them. If we are going to be evaluating the laser for its effectiveness and we confound it by having unstable corneas, then that is going to work against us.

DR. MACRAE: I think one of the major driving

forces for wanting to change this is that there are lot of spherical soft lens wearers that are having to stay out of their lenses for two weeks and it is really unnecessary.

DR. MC CULLEY: I would agree with that.

DR. MACRAE: I would recommend a week period that they are out of their lenses and then if their topography and their refractive data is stable, that they could go ahead and have their procedure.

DR. MC CULLEY: I agree with that with soft lenses.

DR. MACRAE: With just a spherical soft lenses.

DR. STULTING: State your recommendation once again.

DR. MACRAE: I would recommend that soft lens wearers be out of their lenses for a week and then be evaluated or if their refraction is stable or if their refraction is stable and their topography looks normal, that they could have the procedure; stable being that it hasn't changed for more than a half diopter from previous values, whether it is a previous refraction or --

DR. STULTING: I am not clear about the recommendation once again. There is an interval from removal to first exam. There is another interval from first

exam to second exam and then there is a criteria for stability between the two exams. So, that is what we need to give the Agency.

DR. MACRAE: You could use your ten day cycle and just do it for soft lenses. That would be my recommendation.

DR. STULTING: Do soft lenses first.

DR. MACRAE: Right.

DR. STULTING: So, it is how many days between removal and first exam?

DR. MACRAE: I would say three days or one day. I don't see that it makes much difference.

DR. MACSAI: You mean spherical soft lenses, right?

DR. MACRAE: Spherical soft lenses.

DR. STULTING: So, that is three days since that is what the guidance document currently says.

DR. MACRAE: Let's keep it at three days and then they could be measured again in a week and if they are stable, they could have the procedure.

DR. STULTING: And what would stability be? What would the criteria for stability be?

DR. MACRAE: Within a half diopter.

DR. STULTING: For even high myopes?

DR. MACRAE: Yes. If they are changing, then I think it is in the patient's best interest just to wait and see what their final change ends up being.

DR. FERRIS: I know it is a problem and I like to see data, but has anyone --

MS. THORNTON: Dr. Ferris, could you speak loudly into the microphone.

DR. STULTING: The transcriptionist is having trouble identifying people up here and wants to have us say our names. Is that correct?

MS. THORNTON: Yes.

DR. STULTING: It is going to be real disruptive for people to say their name every time. We are just not used to doing that. Is there somewhere where you can sit and get names? We have never really had to identify --

REPORTER: I have got a name list now.

DR. STULTING: Okay. Go ahead.

DR. FERRIS: The question I have is can anybody show me replicate data on refraction for high myopia and what the distribution is, what the 95 percent confidence interval around the replicate data is? It seems to me that is relevant to this determination.

DR. BULLIMORE: This is Mark Bullimore.

I have looked at a fair amount of the literature and repeatability of refraction. The half diopter value seems to be reasonable for most refractive groups. I would suggest in the absence of any data to the contrary, we use that for high myopia as well. I would be happy to share references with the FDA staff if they want to pursue it further. We even have our own data set. Probably we can share in terms of repeatability of refractive measurements in high myopes, but I am not aware that the distinction has been made that rigorously in the literature.

DR. VAN METER: Mr. Chairman, Woody Van Meter.

Most of the problems that you are concerned about have to do with getting people from soft lenses and rigid gas permeable lenses suitable for surgery earlier. The statement that is proposed in the proposed change modification deletes sentence 2, which is to remove hard contact lenses and the proposed change mentions contact lens wearer should remove soft or gas permeable lenses but does not specify anything about hard lenses.

Will you at least mention hard lenses so that patients who might not be in soft or rigid gas permeable lenses are appropriately considered.

DR. STULTING: Okay. We can do that.

What I suggest we do is go ahead and complete the recommendations for soft and then go to rigid gas and then do the hard ones maybe, to keep the discussion organized.

So, there is a proposal on the floor for soft lenses to come out three days before the first exam; the second exam to be a minimum of three weeks and the criteria --

PARTICIPANTS: One week.

DR. STULTING: I am sorry -- one week between the two exams and the criteria for acceptance is within a half a diopter spherical equivalent.

Is there any other discussion or comments on that?

DR. MACSAI: Mr. Chairman, I think you want to specify spherical soft lenses as opposed to torique soft lenses. I think torique soft lenses and gas permeable lenses might fall into the same category.

DR. STULTING: Okay. Any other comments?

[There was no response.]

So, what was just stated then is the consensus for spherical soft lenses out for three days and exam; the second exam one week or more after that one and stability would be defined as a half a diopter.

DR. RUIZ: You also want to add, you know, clear and crisp topography.

DR. STULTING: And the topography is also included in the criteria there. We haven't talked about that but that would be part of the proposed change.

So, let's move on. The second issue now is rigid gas permeable lenses. As it is now, it is three days prior to baseline measurements and the proposal was that that be increased. I think I heard you say one week or two weeks -- two weeks.

DR. SONI: Two weeks.

DR. STULTING: The proposal is to increase that to two weeks and then continue the requirements as stated previously. Any discussion on that? Anybody disagree with that?

DR. MACRAE: So, they would be out for two weeks and then there would be a one week interval before they would be evaluated again. Is that the concept?

DR. STULTING: That is the proposal on the floor, yes.

DR. MACSAI: With a half diopter?

DR. STULTING: With the same criteria.

DR. RUIZ: So, the first exam is two weeks or

three days and then two weeks.

DR. STULTING: The lenses come out two week interval for the first exam and then a minimum one week interval for the second exam. So, the only difference is how long they have to have them out before the first exam.

PARTICIPANT: Is that what would be done in practice? It seems to me that it needs to be comparable to what is going to be done after the study is over.

DR. MACRAE: What would be done in practice generally would be the patient would be out of the contact lenses for two weeks. They would have their exam and they would probably have their surgery within a day or two after that because these patients don't want to -- once they have discontinued their contact lenses, they want to have their surgery as soon as possible.

DR. RUIZ: But what are you comparing to then? You don't have an initial comparison, just previous data or off the chart? Let's say that you hadn't seen this patient before. They come in and they are wearing gas permeable lenses. You tell them take it out and two weeks later you do the refraction and the K readings and so on and you go ahead and treat them on the basis of that. You have no previous comparison. You don't know whether it has changed

a half a diopter or two diopters or what it has done.

DR. MACRAE: Most of the time patients have a refraction from their previous exams that we encourage them to get.

DR. RUIZ: But if that is not your refraction, you accept that as the baseline? And so any deviation of a half of a diopter off of that refraction that they have furnished for you is what you use?

DR. MACRAE: That is generally what is being done out in the real world. So, I think one of the major determinants of whether somebody is thought to have contact lens-related corneal distortion is really a corneal topography, which -- so, if the topography is suspicious, then the patient probably should be deferred.

DR. RUIZ: I am not a corneal expert, but I do some contact lens fitting and there are cases that don't reach stability in two weeks.

DR. MACRAE: It is not uncommon, particularly with hard lens wearers for it to -- in Steve Wilson's paper, it took over 12 weeks for some patients, sometimes up to a half year.

DR. STULTING: That is the paper -- I reviewed that very carefully. The best I can determine essentially

all those people had obvious topographic changes and also virtually all of those patients were hard polymethyl(?) methacrylate contact lens wearers. I didn't find anybody in that paper who would have had normal topography and not have a measurable change during two exams taken early after the contact lens was removed.

In other words, they would have all been screened out by the criteria.

DR. STARK: Walter Stark.

Don't we have information from some previous PMAs? I know we can't use that to set guidelines, but in the Visex(?) and Summit studies, this was done and these eyes were looked at for a low to moderate myopia.

Shouldn't we be able to pull or look at that information and see the stability because --

DR. STULTING: That is what we can't do. However, you can speak from your experience and from your knowledge of publicly presented information in your review of the literature in your general area of expertise. So, if you would like to comment on that, you can.

DR. SONI: One of the ways to evaluate the effect of contact lenses on refraction or topography is to do topography in contact lenses immediately after you remove

contact lenses. So, if you are going to look for a change that has been created by contact lenses and then look for stability, it makes sense to take your topography and refractive data immediately after taking contact lenses and then do your three week or one week evaluation and then if you want to look at the rate of change, you need another data point.

So, I would suggest that we make a recommendation that refraction and topography is actually done immediately after taking contact lenses and then say for spherical soft contact lenses, three days afterwards and then a week later. That will give you a rate of change, which may be much better.

DR. MACSAI: Dr. Soni, I am not sure that is practical. I think what is actually happening -- whether or not it is correct, but what is actually happening are people contact and say what do I need to do be evaluated and then the patients are told you need to go without your lenses for two weeks. So, they set up an appointment two or three weeks hence, where they have had a period without lenses and then they are seen.

DR. BULLIMORE: I think it is interesting to have this sort of academic discussion about one week, two weeks,

you know, what is the appropriate waiting period, but I think we have to respect two parties here. One is the patients. We don't want to inconvenience them too much and also really at the end of it, it is the sponsor's responsibility to -- well, it is in the sponsor's interest to do their utmost to ensure refractive stability because, I think, Dr. Belin said earlier, we want -- if we don't ensure refractive stability beforehand, how are we going to sort of -- how are they going to hit the target in the post-op period?

DR. STULTING: Okay. We have used about 25 minutes addressing the first question and if we continue to do this, we are not going to do our job. So, we have got to move forward. We have already talked about spherical refractions. Let's make a recommendation for -- spherical soft contact lenses -- let's make a recommendation quickly for rigid gas permeables and non-spherical softs, to the best of our ability.

Dr. Belin.

DR. BELIN: I will try to move us along even more. I make a recommendation for lens removal one week prior to baseline for rigid gas permeables and non-spherical softs and three weeks for standard hard lenses. As long as they

are within plus or minus a half diopter, I will move to anyone. I just think we should group them altogether.

DR. STULTING: We are talking now about the interval for removal before the first exam for rigid gas permeable. Who likes one week? Stick up your hand, please.

Two weeks? Three weeks. The consensus is two weeks for rigid gas permeable prior to the first exam.

DR. MACSAI: Does that include torique soft lenses?

DR. STULTING: Who likes one week for torique softs? Two weeks? Three weeks? It is two weeks for torique softs. And if any PMMA(?) lenses still exist out there, who believes one week? Two weeks? Three weeks? The consensus is for three weeks for PMMA lenses.

DR. MACRAE: In keeping with Rick or Dr. Ferris's question, can the patient be evaluated, the time period between the first evaluation and the second evaluation, can that be one to three days, so that the patients aren't -- their contact lens free interval isn't extended beyond what would normally be -- what would normally be done?

DR. STULTING: Okay. The point that has been brought up is whether we should change the interval between the first and the second exam. It is currently one week.

That is the proposal for a recommendation. Who believes that one week is appropriate? Who believes that a shorter time would be appropriate? The consensus is one week.

Are there any other concerns about the proposed change? I hate to cut off debate, but we really do have some other important things that we need to get to quickly.

[There was no response.]

Okay. I see no other comment on the proposed change. So, it looks like our slides are ready. Can we move to the second point for consideration? This is an addition. It is Section 2.4 to add an additional requirement regarding gender, race and how they are to be dealt with in the studies. Does anyone have any comments on this addition?

PARTICIPANT: I have no idea what it means. I mean, I can read the words, but --

DR. FERRIS: If there are scientific reasons, then they must exist and if there aren't --

DR. MACSAI: I am not sure we are going to know -- I am not sure we are going to have scientific reasons for new technology to be different. So, we probably should just look at both of them anyway, both gender and race.

DR. STULTING: Any other comments?

Dr. Gordon.

DR. GORDON: Yes. I am just interested in what is the intent because then maybe then the language could be clarified because there was clearly some purpose here in calling this out?

DR. WAXLER: Well, the issue arose and it arose yesterday as well, as to how should and when should race and gender be considered in studies. It is partly a policy issue and partly a scientific issue. I really think that we need to wait and have some additional guidance from policy makers in the agency, but certainly in the meantime, if there are reasons to believe that there are good biological hypotheses for expecting a race or a gender issue with regard to refractive surgery lasers or corneal changes. And it would be helpful if people would let us know what those are so we would be able to surface those.

I mean, there may be some. There may not be some. But I think largely it is a policy issue. So, I don't know that we can really go very far with it today. It was an attempt to try to say that if there were good reasons to do it, then we ought to do it.

Obviously, you don't know necessarily until you do study it. But if it is -- the probability is extremely low

because you know the biology is such that is extremely unlikely, doing it for every device may not be warranted. But that is a kind of policy decision I can't make and we really can't deal with that today, I don't think.

So, I would appreciate any scientific comments you might want to send us about that.

DR. STULTING: Dr. Soni.

DR. SONI: Gender issue may be important for this particular device because if you are going to consider doing refractive surgery on pregnant women, it may be an issue that one needs to sort out and the other one that I was going to bring out later on as an exclusion criteria or inclusion criteria was women on oral contraceptives, whether that needs to be studied.

DR. WAXLER: And as I recall in the guidance, we already covered both of those topics. So, those are specifically covered elsewhere in the guidance. So, if there are other things that you wish to surface, please let me know and we will deal with those appropriately.

DR. STULTING: Dr. Ferris.

DR. FERRIS: My comment related to the fact that I view this as vague and if I was in a company, I wouldn't know whether I needed to do such analyses or I shouldn't.

If the panel wants analyses by race and gender, then they should say they need analyses by race and gender. If they don't want them, they should say we don't want them. But this way a company could honestly believe there are no scientific reasons for expecting differences. They come with their data and the panel then says, well, gee we want to see this by sex or by race and if I was in the company, I would be confused.

So, it seems to me that actually I think it is reasonable that they ought to collect the race and sex data and present it. And I think they ought to give some guidance as to what racial division is appropriate and do the analyses. It isn't that hard to collect the data.

DR. STULTING: It has been proposed then that data be collected on race and gender and analyzed. Is that the consensus opinion of the panel or would there be further discussion or dissenting opinion?

Yes, Dr. Gordon.

DR. GORDON: I think it is very broad. Those pieces of information are collected already. I mean, race and gender is part of every case report form, but to say that it should be included in the analysis if you look at the multiple analyses that go into a PMA and to do each one

of those for race and gender -- it is a very broad statement that I would like to challenge.

DR. FERRIS: Well, I don't think it should be done for every analysis, but perhaps you could do it for -- there are some sort of primary outcome variables that it ought to be done for. If there are no differences in the primary outcome variable, then I don't see any reason to do it in every analysis that is done or it needs to be said that you don't have to do it, that there is not enough evidence currently existing, that there isn't any scientific reason for doing gender or race analyses, but to leave it this way, I think, puts the company in limbo as to whether they need to do it or they don't.

DR. STULTING: Are there other comments or new ideas?

[There was no response.]

Let's see if there is already a consensus. If you believe that there should be an analysis presented on the basis of gender, please raise your hand.

DR. HIGGINBOTHAM: For the primary outcome variable, which would be visual acuity, I would think.

DR. STULTING: For uncorrected visual acuity.

DR. HIGGINBOTHAM: Yes.

DR. MACSAI: Right. There was in --

DR. STULTING: Let me rephrase the question and see if there is a consensus. How many of you believe that gender should be analyzed with regard to uncorrected visual acuity and refractive outcome? Raise your hand if you do.

DR. MACRAE: There is no data -- I mean, there have been hundreds of studies done and there is no data to indicate that either race or sex has anything to do with outcome other than pregnancy and birth control pills. There is no data to indicate that. So, I am not sure why we are asking the companies to go out and get that information. It is like a fishing expedition.

DR. STULTING: Dr. Belin.

DR. BELIN: I agree with you except for one thing and that is that this document is going to be used for lasers with different wave lengths than our standard one, which all our data is currently -- so, there will be some additional wave lengths, maybe urberium(?) 210, et cetera, et cetera, and we don't know that that applies to different wave lengths.

DR. GORDON: But then I think that speaks to leaving the statement as is, meaning if there is scientific evidence or if there is -- which would imply if there is

something brand new, if it is -- then there may be questions, but I think the way that this group is trying to come to a consensus, it would imply that for every 193 nanometer X-More(?) laser, you would have to go and do that. And Scott makes a very good point and I would second that from our own data since I guess I can talk about -- can I talk about data that I am familiar with from studies we have done? I am free to do that?

Okay. We have no basis to see -- haven't seen any suggestion that there is any effect.

DR. BULLIMORE: As somebody who deals with large databases, this is a trivial thing to do, to basically -- for primary outcome measure, to -- I disagree, Judy. If you have got a database with your primary outcome measure, you want to cut it by age and gender and you have those as covariates in your database, it is not a difficult thing to do and we are asking people to maybe produce one or two extra tables here.

DR. GORDON: We are talking about race and gender and not age. I think that is a very different issue.

DR. BULLIMORE: Did I say age? Sorry. I meant race and gender. If you are collecting the data, it is --

DR. GORDON: Buy why do something else that

doesn't add value or provide new information unless there is a valid question?

DR. BULLIMORE: I agree with you, but --

DR. GORDON: Well, then, let's clarify that. Otherwise, it is just another exercise.

DR. MC CLELLAND: I agree with Judy. From my standpoint, I don't want to have to look at an extra one or two table if I don't have to. So, I don't want to do it just because it is easy to do, but we have not seen any indication of any of the data or anything I have seen that would suggest that gender, other than pregnancy or birth control pills, major hormonal status change in women make any difference.

So, I don't think we need to do that. I have yet to see myself, and maybe I have just missed it, any good race data and I think one of the real problems with this is that we are not seeing the minority data.

So, I don't know what to say about that. I think leaving it like this leaves that door open to where we can deal with it as we can best deal with it in the future. And I would suggest leaving the statement as it is.

[Multiple discussions.]

DR. STULTING: After all this discussion, how many

of you prefer to leave the statement as it is, the proposed change as it is? That is eight. Oh, no, we are not supposed to really vote.

How many do not like the proposed change? Okay. The consensus is that the proposed change is acceptable, although everyone is not happy with that. There is a moderate level of unhappiness in spite of that consensus.

DR. MC CULLEY: Minor level.

DR. STULTING: Minor level of unhappiness. We will talk about what numbers that translates into it later.

Okay. Let's do the next one.

The issue on the table is changing the recommendation for exclusion and exclusion criteria with regard to glaucoma. There you see the old and the new statement. The new statement is history of glaucoma or glaucoma suspect.

Comments on that one?

DR. RUIZ: What does the history of glaucoma mean? What does that mean?

DR. HIGGINBOTHAM: This is Dr. Higginbotham.

I couldn't comment on the contact lens issue, so please give me my time. I would suggest keeping it as it is because glaucoma suspect could be actually just physiologic

cupping with normal pressure. So, you don't want to exclude those patients certainly from the cohort necessarily. So, I would keep a number in the definition.

You might add on two occasions, on two readings, as another proviso, and I would like to hear from those of you that do refractive surgery to see if that would be feasible. But I certainly wouldn't just use one number.

DR. SUGAR: You would use or you wouldn't use one number?

DR. HIGGINBOTHAM: I wouldn't use -- I would not use just one number. I would add history of glaucoma or an intraocular pressure greater than 21 on at least two occasions.

DR. SUGAR: What does history of glaucoma mean? That they have glaucoma? What does history of glaucoma mean?

DR. HIGGINBOTHAM: I would interpret it as that they have glaucoma.

DR. SUGAR: So, why not just say it that way, glaucoma or glaucoma suspect?

DR. STULTING: I am not speaking necessarily for it, but I will explain the wording because I was around at least when the discussion occurred. The wording change was

recommended so that it would be broad enough that the physician could use discretion in determining who belonged in or out and it was noticed that a glaucoma suspect might have a pressure of less than 21 and the concern was not of including people with physiologically cupping, but of making people aware of the possibility that they had glaucoma and still had low pressures.

DR. BULLIMORE: I support Eve's suggestion because one could argue that an African American over the age of 60 is a glaucoma suspect.

DR. STULTING: Okay. Give us your proposal once again.

DR. HIGGINBOTHAM: My proposal is I am going to just say history of glaucoma or an intraocular pressure of greater than 21 on at least two occasions.

DR. RUIZ: But, Eve, you must see people all the time that have a history of glaucoma and being treated for glaucoma, who don't have glaucoma. So, what does "history of glaucoma" mean?

DR. HIGGINBOTHAM: Okay. Patients with true glaucoma, as defined by defects, visual field defects or optical nerve deterioration --

DR. RUIZ: Well, then let's say glaucoma, not

history of glaucoma.

DR. HIGGINBOTHAM: Well, I was in the middle of my statement, Dr. Ruiz.

DR. RUIZ: Sorry.

DR. HIGGINBOTHAM: Individuals who have been diagnosed with glaucoma, as defined by optic nerve deterioration or visual field defects or an intraocular pressure of greater than 21 on at least two occasions. I mean, it can be as long as you want, but --

DR. MACRAE: Eve, there is a fair -- as I understand it in talking to the glaucomatologists that are at our institution, there are about 10 percent of the population over the age of 40 has intraocular pressures of greater than 21. So, are we unnecessarily excluding a population of individuals that out in the normal population, that would eventually be exposed to this procedure?

In other words, I see patients that have pressures of greater than 21 and they may be persistently elevated, but they have no evidence of optic nerve damage. Should those patients be excluded from these studies?

DR. HIGGINBOTHAM: This is Dr. Higginbotham.

From my vantage point they could. I imagine whoever wrote this document put 21 there for some reason.

You know, as I thought about this, you could be actually underestimating the pressure since it has been shown that patients that are called ocular hypertensives could actually have thinner corneas. So, they might actually have higher pressure. So, perhaps, some of these people that are at 21 --

PARTICIPANT: Thicker corneas.

DR. HIGGINBOTHAM: Thicker corneas. Thanks. Some of these people that are at 21 could actually be at 23 or 24. So, I would just, at least, keep it on two occasions. I am not trying to make this more complicated. I am just trying to make it as definitive --

DR. STULTING: We really need to shorten the discussion. I hate to break in again, but -- wait a minute -- we are way behind time. We have to make some decisions about what to deal with.

From my view of this, this is a relatively small issue. We have got major issues to deal with. So, let's wrap it up as fast as we can.

DR. RUIZ: But I don't think it is a small issue. I think Scott is right. There are many, many people that run pressures of 20, 21, 22, you know, who never develop glaucoma. That is a large group to exclude if this is an

exclusion criteria. So, I think it is a big point.

DR. HIGGINBOTHAM: So move it up to 25 the. But I would keep it on at least two readings.

DR. STARK: What Eve says is important because with refractive surgery procedures, often the pressure is artificially low afterwards. So, I think for study purposes -- we are talking about for the study purposes -- people with glaucoma or you could say glaucoma suspect should be excluded from the study, from entering into these studies. That is really what you want.

DR. STULTING: So, you are speaking for glaucoma or glaucoma suspect. Is that correct?

DR. STARK: Correct. And a glaucoma suspect, you know, is the -- we know the definition of that and it can be a person with a pressure of 17, with the big optic nerve.

DR. MC CULLEY: I would rather leave it with glaucoma, glaucoma suspect. I would rather leave it to judgment than an artificial number.

DR. RUIZ: I agree with that.

DR. STULTING: Which is the reason it was written that way in the first place. So, we are back full circle on this one. We took "history of" to make it clear that we would not include people who have false diagnoses. So, the

consensus is that the evaluating physician takes a look at the patient and all of the material available to them and makes a decision in his best judgment as to whether the patient has glaucoma or is a glaucoma suspect and then excludes them if they are falling into one of those two categories. Is that the consensus?

PARTICIPANT: Yes.

DR. HIGGINBOTHAM: I hate to prolong this, but might I suggest that you might put in parentheses "as defined by elevation of intraocular pressure," just so people that have large cups can have refractive surgery.

DR. STULTING: Well, it is my impression that if you define them that way, you miss roughly half the people who actually have glaucoma.

DR. RUIZ: What about normal tension glaucoma?

DR. HIGGINBOTHAM: But you want to include people that have pressures less than 21, who might just have physiologic cupping. That is my understanding. By saying "glaucoma suspect," you exclude those people. So, I am trying to help you include more people.

DR. MC CULLEY: But if you leave it to our judgment, then if we see someone like that, we will judge them not to be glaucoma suspects by definition related to

the refractive surgery.

DR. STULTING: I think we have reached a consensus.

The next question is regarding haze in Section 3.2.1. The proposal is to delete haze beyond six months with loss of greater than two lines should occur in less than 1 percent of subjects.

DR. BULLIMORE: Morris, what is the motivation for this change?

DR. WAXLER: Malvina, what is the motivation for this change?

DR. EYDELMAN: At the Eye Care Forum, we went through again all the safety endpoints and if you will look at the section of the guidance, which lists all the safety endpoints, which this study must meet, this was felt to be not really additive. You would have to turn back to Section 3.2.1 for the full list and then please share with us your opinion on the subject.

DR. STULTING: Again, to try to transmit to you the gist of that conversation, looking at all of the safety endpoints, it was considered that this was not anything new or different or did not by itself add any additional information because there are already safety endpoints that

are captured otherwise.

DR. STARK: Doyle, I would like to speak to this issue a minute. I thought that was a little bit strict when you compare the table two pages on where it says that an adverse reaction is reported only if patients lose greater than two lines; 5 percent of the patients lose greater than two lines. That, though, if you throw this one out, that really doesn't capture some significant loss of visual acuity.

We have talked about this before but I talked with David Gatton(?) the other night. You know, I pushed for reporting of one line of loss of best corrected vision and one line of loss of best corrected vision is actually a 21 percent loss of resolving power of the eye.

A two line loss of best corrected visual acuity is a 37 percent loss of resolving power of the eye and a three line loss of best corrected visual acuity is a 50 percent loss of best corrected visual acuity. So, if you throw this out, you don't capture patients in any kind of adverse reaction reporting that have lost up to 37 percent of the resolving power of the eye.

So, I would like to -- taking this one along with what we are going to discuss in a few minutes go back to at

least having some place brought to our attention, if a patient is going to lose two lines and it might be from 20/17 to 20/25. That is still a 37 percent loss of resolving power of the eye. And I personally as a patient -- and my children are asking me about this refractive surgery -- I want to know what percent chance they have of losing two lines of best corrected vision.

This is even taken with the consideration that every diopter of myopia corrected gives you a 2 percent increase in resolving power of the eye when you correct from the spectacle to the corneal plane. So, if you take a 10 diopter myope, you should get a 20 percent improvement in magnification resolving power of the eye. So, you should theoretically gain one line of best corrected vision.

So, you should theoretically gain one line of best corrected vision. So, if you take that patient and they lose and they are not reported until they lose three lines. That is actually a four line loss of best corrected vision.

So, I think we have to have someplace in here, if not here, to be able to capture these two lines loss of best corrected vision. I have given up on the one line, but I think as a consumer, also, and my kids as consumers, we have got to have some numbers in there that you can tell patients

with these refractive surgery procedures when you are going to lose two lines or 37 percent of your resolving power.

DR. MC CULLEY: To move it along, I would like to see this left in myself.

DR. STULTING: Dr. Belin.

DR. BELIN: To move it along, I agree with what was just said, but maybe we should incorporate this when we get to the table on page 4 because you really can't separate this with the discussion on the table on page 4, which is the definitions of major safety endpoints.

DR. STULTING: Well, I think the issue is here is whether this should be a separate category from the information that is in the table. Notice that the table shows loss of visual acuity and we can expand that, knowing that we are going to talk about it to one line or two lines or whatever. This specifically subgroups people who have lost it as a result of haze.

DR. BELIN: I would agree with Dr. Stark. I would make a change, however, that rather than reading greater than two lines, to be two lines or more.

DR. STULTING: Okay. But the issue now is whether we should continue to have a category where the loss of visual acuity is attributable only to haze.

DR. BELIN: My suggestion would be "yes."

DR. STULTING: So, the consensus is to continue to have a category for haze.

DR. EYDELMAN: Just a point of clarification.

Since that somehow, if you look at Section 3.2.1C, Subpart of A, D1 Part A to be inclusive of these subjects, do we then change --

DR. STULTING: Does everybody understand the question?

PARTICIPANTS: No.

DR. STULTING: If you look in the guidance document on page 7, this is the original guidance document on page 7, there is a Category 3.2.1, definitions of major safety endpoints and target values and A under that is less than 5 percent of subjects lose two or more lines.

DR. EYDELMAN: More than two.

DR. STULTING: More than two lines. Sorry. So that a patient would be included in this one and if the loss was attributable to haze, he would also be included in C.

DR. MC CULLEY: Yes, I would want -- it would be included in A, yes, but it was also give us a separate category for haze, which I think we need. I would like to see this, quite honestly, I think, supporting Walter,

anyplace that says more than two lines, I would say two or more lines.

DR. FERRIS: This is Rick Ferris.

Is there a definition of more than two lines? I mean, are they required to use logarithmic charts and count letters?

DR. EYDELMAN: EDTRS(?), yes.

DR. FERRIS: So, then it is more than -- it is

DR. EYDELMAN: Ten letters.

DR. FERRIS: So, then it is either ten letters or it is more than ten letters.

DR. EYDELMAN: Correct.

DR. FERRIS: So, it ought to be specific.

DR. EYDELMAN: There is a definition in the guidance that it is greater than ten letters on the EDTRS.

DR. STULTING: Okay. It sounds like the consensus is that the proposed change should not be made.

DR. MACSAI: Well, also, should it be changed to two or more lines, as opposed to greater than two?

DR. STULTING: The consensus is that it should be changed to two or more lines, it appears. Is anybody unhappy with that?

DR. FERRIS: Am I right that you are now talking

about ten letters or 11 letters?

DR. RUIZ: Why not say it that way, Mr. Chairman, rather than two lines or more, two or more lines? If we are having to use the EDTRS chart, why not say it, like Rick says?

PARTICIPANT: Put it in parentheses.

DR. BELIN: One of the reasons is because occasionally -- not occasionally -- this always gets then transferred to patient information. How many patients lost and patients understand lines of vision versus telling them this is your chance of losing ten letters on the EDTRS chart.

DR. RUIZ: Then let's put it in parenthesis.

DR. STULTING: So, the proposal is that the EDTRS equivalent be included in parentheses. Does anyone not agree with that proposal?

DR. EYDELMAN: Just a clarification.

Was your consensus to change A also to two or greater?

DR. STULTING: I don't think we really dealt with that. I was going to defer that until we talked about that a little later, although I hear the consensus emerging.

The next issue is determining endothelial cell

loss and the current proposal is that it would not be necessary if the calculated distance of the surgery is 250 microns from the corneal endothelium and the proposal is that it be changed to 200 microns.

Is there any discussion on this?

DR. MC CULLEY: I have a basic question on this and I am not sure of the answer. Do we need to leave for corneal stability 200 or 250 microns behind or somewhere in between. Is there -- to me, it -- as best I can tell, this is still in flux; 250 we are all comfortable with. There is an increasing comfort, I think, down to 200. I am not sure whether that is seat of our pants or whether there is decent data. I have not seen it.

DR. STULTING: I actually reviewed this before I came in. There are a number of laboratory studies and there are two published papers and we have some data that is in press and all of those say 200. You are asking about the stability as well. There is very little data on that, except for the information on hyperopic ALK(?), where the data are very shaky but the number that is quoted there is 80 percent of corneal thickness is required to create ataxia(?) and that would be roughly a hundred microns remaining.

DR. MC CULLEY: I guess really I am kind of mixing things here in terms of endothelial safety relative to how close the laser comes to it, but in doing this, we also potentially create a problem with stating a standard for anatomical stability. And I guess that is really what I am more concerned about if we change from 250 down to 200.

Is your data that 200 is safe relative -- for the endothelium relative to how close the laser is being shot or is your 200 that there is stability of the cornea?

DR. STULTING: It is endothelial damage.

DR. MC CULLEY: Okay. And my concern is if we take this down to 200, that what we are implying and encouraging is going from 250 to 200 for stromal stability or corneal stability. And I am not sure of that. I don't know.

DR. STULTING: Well, the issue here is endothelial counts, whether or not they need endothelial counts.

DR. MC CULLEY: I don't think they need -- I think 200 is fine for endothelial counts. I just want to be sure that we take into consideration what we are implying with this 200 and to be sure that we are not going to be encouraging the development of ataxia and instability and problems.

DR. MACRAE: Just a quick comment on the 200. The 200 microns in terms of stability -- what you say about hyperopic ALK is true, but the 200 micron stability issue is that information is basically taken from Dr. Baracare's(?) 20 years of experience.

Granted it is not very well published in the literature, but it has been -- he has an extensive amount of experience and his statement is that if you go beyond 200 microns, the likelihood of ataxia in these patients long term is significant or is greater. So, that is just an observation that he has made and I think we should honor that until we know other information. With regard to endothelial cell counts, I think that this statement would be reasonable.

DR. MC CULLEY: And you are saying that 200 is the -- you would consider the accepted amount for stability and not 250?

DR. MACRAE: If you do more than -- or if you go to 190, you are starting to knock on the door of ataxia and, so, my personal feeling -- and I have talked to Morris about this quite a bit -- is 250 is a good number because it gives you some -- a margin of safety for the patient. The microkeratomas aren't accurate to within -- there is about a

40 micron variability. So, if you draw the line at, you know, 225, there is going to be some patients that actually get deeper than that. So, 250 gives you a margin of safety. That little extra 50 microns gives you more safety in terms of ataxia. That was the rationale behind that.

DR. MACSAI: But, Scott, ataxia and endothelial damage are different things. So, in light of what Dr. Belin said earlier, that we are talking about potentially new wavelengths, new procedures, I think, we need to still monitor for endothelial cell loss because we don't know.

But I think it is not necessarily true that ataxia equals endothelial cell damage. They are totally different.

DR. MACRAE: No, they are totally different. I agree.

DR. STULTING: Let's talk only about the issue at hand here so that people don't get confused. The question is whether endothelial cell counts need to be done.

Dr. Ruiz.

DR. RUIZ: Can we talk about the second part of the statement up here?

DR. STULTING: Sure.

DR. RUIZ: I don't hear anybody wondering about the endothelium. It is all turned over towards whether it

is too thin. So, I would like to talk about the second part there, which I am not sure I understand.

DR. STARK: Doyle, based on prior studies, it hasn't been shown endothelial cell damage to less than 250. We don't know between 200 and 250. So, I think it is reasonable to require that. We did show in the phototherapeutic cases that we did we would cut down about 180 microns and some of those eyes weren't successfully treated, so we did transplants. They had electron dense bodies in the endothelium and that has been shown in the laboratory animal also. Dr. Azar(?) published this, a pathologic case of transplanted eyes that had PTK, phototherapeutic keratectomy.

So, I think when you get less than 250, it is reasonable to require the endothelial cell microscope studies to assure us that there is no damage.

DR. STULTING: I could not find anywhere in the literature that demonstrated damage between 200 and 250. What are the papers that you are citing?

DR. STARK: I am not aware of the studies between 200 and 250. So, what you are --

DR. STULTING: Well, that is the issue. Is 250 the appropriate cutoff or is it 200?

DR. STARK: Well, do we have literature saying that between 200 and 250 is safe to the endothelium?

DR. STULTING: Yes, because all of the current laser studies if you calculate the depths or if you measure the depths go down to 200. That is why the number was changed.

Any other comments?

DR. BELIN: I think what Dr. MacRae said, however, we may have data suggesting that 200 microns is safe, but we don't have a microkeratoma that can assure us that our preoperative calculation that is going to leave 200 is 200 and isn't going to be 160. So, I think his point is, though it may be valid that you can leave 200 and be safe, we cannot assure the patient ahead of time that the planned 200 is going to be a 200 and 250 gives that patient a margin of safety.

My recommendation would be to leave it the way it is.

DR. STULTING: Other comments?

[There was no response.]

So, this essentially will mean that endothelial cell counts will be required for manufacturers for every single laser study.

PARTICIPANT: Will that be a hundred percent of the patients or a subset of the patients?

DR. BELIN: If you back the numbers and you start up with a 550 cornea, you take off the epithelium -- you are going to do a 160,

DR. STULTING: If you do that calculation, then there is 205 microns remaining if you assume 540 for the initial -- 160 for the plate and a quarter of a micron per pulse.

DR. BELIN: Okay. Which gives you the equivalent correction on a single zone. You have 200 microns to ablate. Correct?

DR. STULTING: Which is 700 pulses, which is the maximum ablation for approved lasers. In other words, what I am telling you is if you do the calculation to determine what the theoretical depth from the endothelium is for existing approved lasers, with lasic(?), with 160 micron plate, then it is 205 microns from the endothelium. That is what is being done today in practice.

DR. MC CULLEY: That is single zone you are talking about.

DR. STULTING: Yes.

DR. MC CULLEY: But most, when you are starting to

get into the higher ones -- that is single zone and when you start getting into the higher degrees of correction, the tendency is to use multi-zone, so that you take less tissue out.

DR. STULTING: That is correct or no more tissue. In other words, I don't want to influence the opinion unduly, but if you -- what is now in practice is performing lasic with a calculated and assumed depth of 205 microns from the endothelium.

DR. MC CULLEY: And we don't know that that is safe.

DR. STULTING: There are two published papers and one in press that say it is safe. And there are laboratory data that say that there is no damage unless you go closer than 200 microns.

DR. STARK: Could you do this then, rather than deliberate now -- this isn't written in stone -- circulate those two published papers and the one in press when it is available and if the panel agrees, then change it to 200.

DR. RUIZ: Mr. Chairman, how many thousands of cases have been done using those parameters?

DR. STULTING: Probably a reasonable number. I don't know.

DR. RUIZ: Nothing is showing up. I mean, if it ain't broke, don't fix it.

DR. STARK: You know, Dick, it is -- your statement is true if this were done under FDA guidance, but there are problems showing up that we hear about all the time from lasic, maybe done from inexperienced surgeons. I don't know.

DR. RUIZ: But are they endothelial problems?

DR. STARK: I don't know that -- well, it may be too early to determine, but I would like to see -- if Doyle has, you know, published and peer reviewed literature, good scientific data showing no endothelial cell changes, then I think it ought to be changed to 200.

DR. STULTING: I am unaware of any reported case of endothelial damage after PRK or lasic in someone who started out with normal endothelium by slit lamp. Is anybody aware of a single case of that?

DR. RUIZ: No, and if the damage was to occur from the laser, you would expect to see it relatively soon.

PARTICIPANT: Not necessarily.

DR. RUIZ: Well, not necessarily but most likely.

DR. STARK: You can send those articles out and by the next meeting, you can change it to 200.

I mean, I just think -- our peers always ask us and complain about the FDA being overly restricted and we are sitting here deliberating a test and no one is aware of a single case of this particular adverse reaction and we are aware of published cases where endothelial counts have been done and they are okay. And I just don't personally see why we should require something that doesn't appear to be a problem.

DR. MACSAI: Since this is a guidance document for the development of new technology and if we know that there are shapers out there that have an accuracy only to within 40 microns, plus or minus 40 microns, as Dr. MacRae said, then we do the math and we, you know, play it safe until we have peer reviewed data otherwise and leave it at 250.

DR. STARK: Well, apparently they have it. So, why don't you send it out and maybe it could be done by a vote by mail.

DR. MC CULLEY: Or just, you know, a few panel members could look at it and -- you know, I have not seen those manuscripts. So, my comfort level -- you know, I certainly trust your evaluation of it, but I like Walter's suggestion. Leave it at 250 as a semi-quasi homework assignment, circulate it to several panel members and get a

consensus back from them as to whether it really does look like it is, you know, safe at 200. And the problem here is that Doyle is the only one that is not ignorant relative to what is --

DR. STULTING: Well, I mean, these things went around. This was a homework assignment. Everybody got these things. The questions on the floor were sent out and se should have looked at them.

DR. MACRAE: I have seen Doyle's data and it is reassuring to me that doing 193 eximer(?) to the 200 micron level is not bad for the endothelium necessarily. As a matter of fact, his papers basically show that the polymegathism is reversed with time and the endothelium actually looks a little healthier after the procedure than when patients are wearing contact lenses.

My major concern is in a -- when individuals try to do intrastromal laser with a different type of system or -- I don't want this document to give them the impression that our target is now 200, the thinnest -- our target should be 200 microns. I still think the 250 microns is a good margin of safety. It protects the public.

DR. MACSAI: We don't know about erbium(?) or whoever that is coming up.

DR. STULTING: Morris, would you like to make a point?

DR. WAXLER: Just a point of clarification.

A number of times reference has been made to new wave lengths and other parameters. We should really consider this only with regard to 193, this guidance, because when there are changes in the laser, if there is an infrared laser that is going to be intrastromal ablation, we would not -- we will have a writing in this guidance that requires additional information to be submitted. We would not just automatically assume that what we know about 193 would apply to major changes in wave length or pulse width or major kind of issues.

DR. MACSAI: Okay.

DR. RUIZ: Why is the second part even on there?

DR. MACRAE: I agree that sometimes you are going to go down to 220 unknowingly, but if you do the math on this. If you are doing a hundred -- if you do the math on this, the corneal thickness, if you are treating with 150 micron treatment with laser, most of the corneas that are going to be treated are going to be much thicker than getting to that 250 micron lasic-free zone or treatment-free zone.

So, I don't think that this is a major issue. I think it does get to be a major issue when you get into higher myopia, but I still think we should try to encourage the companies to stay at the 250 micron lasic-free zone and I think that this recommendation may encourage them to try to go to 200 microns and I am not very excited about that possibility.

DR. STULTING: Okay. We need to move on. I hear the consensus being that the proposed change should not be made. Is that correct? Anybody dissent with that?

[There was no response.]

The next one is having to do with Section 3.6.1, 3.2.6.1. Sorry. That is why I couldn't find it.

DR. FERRIS: Doyle, can I just ask a question. You said did anybody dissent from that. I am a little confused. Did you say earlier that typically with lasic, everyone is doing what would get down to 205?

DR. STULTING: That is correct.

DR. FERRIS: I don't understand how you are --

DR. MACRAE: I disagree with that. If you do 160 micron pass and treat with 150 microns of laser treatment, that takes you to 310 microns.

DR. STULTING: Approved lasers go up to 175

microns of removal and if you add that to 160 and subtract it from 540, you come up with 205. That would be how I did the calculation. But I don't want to spend any extra time on this.

DR. FERRIS: I don't want to spend time. I just think it is a silly recommendation to say that companies need to study something that isn't being done. I don't want to be part of something that is silly.

DR. STULTING: Okay. We have a consensus and there is at least one person in the group that disagrees with that.

DR. RUIZ: Well, I disagreed, too, earlier.

DR. STULTING: Now we have two.

I am going to try one more time. Let's go back to the 250 and 200 slides. The slide on your left is the old way --

DR. ROSENTHAL: Mr. Chairman, could we just have the calculations. There seem to be two matters -- two differences of opinion. I think you might be able to make a decision based on calculations.

PARTICIPANT: It makes me nervous when the math comes out.

DR. STULTING: The currently approved lasers --

and I won't quote any specifics -- will ablate to 175 microns.

DR. MC CULLEY: That would be how many diopters?

DR. STULTING: That would be the maximum, 6, 7 diopters.

DR. MACRAE: That is hard to believe.

DR. STULTING: Okay. We have a --

DR. MACRAE: Judy, does that sound right to you? The laser that I work with has a 5.5 millimeter optical zoom with a 7 millimeter transition and the max that they allow on that is 150 microns and we can treat up to 12 or even up to 14 diopters.

DR. STULTING: Okay. But that is not the only laser in use. So, let's make two calculations, one for 150 -- is that what you would propose?

DR. MACRAE: I would say 150.

DR. STULTING: And 175 would be the one that I would bring to the table. So, if you add 160 and 175 -- 150 -- you come out with what?

PARTICIPANT: 310.

DR. STULTING: 310. And you subtract that from 540. What do you come out with?

PARTICIPANT: 230.

DR. STULTING: All right. And if you use the other estimate, which is 175, then what do you come out with?

PARTICIPANT: 205.

DR. MACSAI: And there are also known keratomas that slice at 180. So, you add on another 20 there. Now you are down to 185.

DR. MACRAE: Doyle, at the same time, why don't you send us the articles and let us look at them and if you are -- Doyle, why don't you send us the numbers and this will give us some time to think about this.

I think that the panel is recommending -- it sounds like most people are comfortable with 250 microns. They tend to get uncomfortable when we start going down to 200 microns and a recommendation could be made based on those numbers.

Doyle is upset because we are not familiar with his --

DR. STULTING: No, that is not it all. As I say there are two published papers in the literature. Everybody who performs -- and there is not a single reported case of endothelial damage that I am aware of anywhere in anyone's experience or the world's literature, in spite of the fact

that people are using currently existing lasers that go below 250 microns to perform lasic commonly.

DR. STARK: And let's make the change based on the scientific literature. Most of us or none of us have reviewed the two articles that you are -- we may have seen them but we can't remember them. So, if you could send them, we could probably change the recommendation.

DR. STULTING: We need to have a consensus on this. Once again -- and we will revisit it because I heard two dissenting thoughts. Those of you who are in favor of the old criteria and 250 microns, raise your hand or kind of nod or something.

Those who are in favor of the new criteria, 200 microns, signify somehow. Okay. There is a slight preponderance toward the new recommendation. This time we have taken a straw poll.

But there is a moderate number of people who are unhappy with that.

DR. WAXLER: Could I add a point of clarification? We don't have to come to unanimity on any of these issues.

DR. STULTING: I understand.

DR. WAXLER: You can provide and I hope you will

provide us your individual comments so that we can look at the variety of points and try to figure out how to resolve them. There will be some issues like this that we will not get to agreement.

DR. STULTING: Great. I think it is pretty clear that it is controversial and the record will probably reflect opinions on both sides, including that things are --

DR. BELIN: A real quick question because I think this will probably come up later. The depth per diopter and single zone is the Munlin(?) formula and I think we are all confusing it and I am forgetting it, but I know there has got to be someone in the audience who can quickly tell us what the depth per diopter of a 6 millimeter optical zone is. That will assist us --

AUDIENCE: 11.

DR. BELIN: It is roughly 12 microns per diopter at a 6 millimeter optical zone. Since that is what is currently approved and that is how you can compute what Doyle is saying at the 1-7. It is 12 times 7 diopters roughly.

DR. BULLIMORE: I will go on the record as dissenting. That doesn't sound right.

[Multiple discussions.]

For a 6 millimeter optic?

[Multiple discussions.]

DR. STULTING: Okay. There is not unanimity on this and I think this probably ought to be reconsidered at some other time. There is considerable dissent.

Okay. We are looking at adverse events now, Section 3.2.6 -- before we do this, let me -- it is 10:20 and we are fairly far behind. We have the option of taking a break. Would everybody like to have a short break at this point? Let's take a short break and be back in five minutes.

[Brief recess.]

DR. STULTING: Please take your places so we can move on. It is about 10:35. We will plan a lunch break at noon and that will give everyone a chance to check out of the hotel and go have some lunch.

During the break it was pointed out to me that there are a number of conversations that are going on among panel members and other individuals in the audience and FDA staff. I was asked to remind you that this is a public proceeding that is being recorded. It is inappropriate for conversations to be going on that are not on the record. So, if you have something to say, please come to a

microphone and be recognized and say what you have to say so that everyone can hear it.

The next issue for discussion is shown on the two slides. It has to do with modifications to the adverse event reporting section and the floor is open for comments.

Dr. Higginbotham.

DR. HIGGINBOTHAM: Mr. Chairman, I would suggest adding to the last line any reading -- any two readings above 25 millimeters of mercury, just so you can capture the more persistent elevations and intraocular pressure as opposed to just transient diurnal variation(?).

DR. STULTING: Okay. Any other comments?

DR. STARK: Doyle, I don't know if it has been discussed previously, but epithelium and the interface is a potential problem and with or without loss of best corrected vision during the 12 months of the follow-up or if we shorten the follow-up to six months, I think that that number should be known because I think those are potential problems later on. They are going to require -- they may require second surgery. They may have loss of visual acuity later on and we have seen some people that had what seemed to be an innocuous epithelial inclusion in that flap go on to have problems later on.

DR. MACSAI: Dr. Stark, you mean they don't have any problems for a year and then later they have problems from their epithelium in the interface?

DR. STARK: Correct.

DR. SUGAR: You are asking that it be reported and it would still be reported under complications, just not as an adverse event. In 3.2.6.2C, you still report epithelium in the interface.

DR. EYDELMAN: That is exactly the point I was trying to make, Mr. Chairman. This is a list of adverse events, each requiring a report to FDA within ten days. However, the list of complications is all that the sponsor is responsible for tracking and reporting in annual reports and any PMA proposal.

DR. STARK: Okay. Well, then I misunderstood. So, I would say that should not reported within ten days, but it will be reported.

DR. MACRAE: Doyle, under F, miscreated flap, I would like to add which results in a loss of two line best corrected visual acuity loss. There are a lot of patients that have a flap that an incomplete flap or whatever. The recommendation is that you simply put the flap back down and not do any further surgery, not do any lasic. Most of those

patients do not lose best corrected visual acuity.

Also, patients that have free caps, often have excellent visual acuity results. So, I don't think they should be included under adverse reaction. They could be included under a complication, but I don't think it qualifies as an adverse reaction.

DR. BELIN: Just on that last comment, I probably would leave it to be reported only to catch -- there will be some other keratomas and if 20 patients are done in a two week period and 10 of them have thin or incomplete caps, that probably needs to be noted very quickly in the study by the FDA and that study may have to be revised.

If you have to wait to determine if those patients have a loss of best corrected vision, that may be too late. So, I think we do want to know if there is a major problem in creating the flaps.

DR. MACRAE: Do you want it to be reported or do you want it to be -- just reported or reported as an adverse reaction? I think that is an important distinction because companies then have to --

DR. BELIN: What are the reporting requirements for anything other than adverse reaction? It doesn't have to be reported --

DR. STULTING: I believe I am correct in saying those go in on annual reports.

DR. BELIN: Right. So, in other words you may have -- you are not guaranteeing or you are not protecting patients -- I think the FDA needs to know if 50 percent of the patients undergoing this one study are having problems with flaps.

DR. MACRAE: Morris, is there a way that -- let's say that there -- is there a way just to report to the Agency that you had a free cap or an incomplete flap outside of the adverse reaction reporting system.

DR. EYDELMAN: The only other ways annual reports or -- but not in any specific time frame.

DR. GORDON: Judy Gordon.

One would assume that any keratoma used in an IDE application would have been a cleared keratome or is being studied under the IDE, but typically would be cleared as a 510(k), a substantial equivalent and so there would have had to have been some demonstration of the ability of the keratome to cut. That is the same as a predicate device, as other keratomes. So, I am -- I guess what I am saying is unless this was the first use of a keratome, so there was no experience with it, it would be an established product

already in and of itself.

DR. BELIN: But the approval of a microkeratome as a 510(k) is very different than the approval of a laser and you are not submitting patient's, say, safety data.

DR. GORDON: Right, but you would have to show that the keratome cuts as intended.

DR. BELIN: I will defer --

DR. EYDELMAN: I just wanted to clarify that as per FDA definition, lasic device encompasses keratome and the laser utilized. Therefore, we look at it as a one complete unit. So, regardless of whether it was cleared under 510(k), regardless of which purpose it was cleared for, what was the indication for 510(k), we still look at it as one unit.

DR. STULTING: Let me attempt to summarize what has gone on so that we can try to get back on track here. There is agreement with E. There is general agreement with F, with the exception of concern that a microkeratome, which has a high incidence of miscreated flaps should be reported early. There is a suggestion that H be modified so that it reads any two readings above 25 millimeters of mercury and I didn't hear any other dissent on that one.

DR. EYDELMAN: I just wanted a clarification, if

Dr. Higginbotham was aware that this is an adverse event form. So, therefore, two readings of 25 are not necessarily consist with an adverse event, i.e., after 25, the physician usually treats it and we will never have adverse event for the high IOP.

DR. HIGGINBOTHAM: Well, you want -- I would think you really want true elevation intraocular pressure and not a transient increase in intraocular pressure. Because it is only the true increase that you would actually treat and would be considered a true adverse event. I mean, you wouldn't be interested in a pressure of 25 once.

DR. STARK: So, then add on to it requiring treatment, would that be? I think the 25 may not be worth a report within two weeks. I would say over 30 might be, repeatable over 30, but 25, you may have a spike in pressure after manipulation.

DR. MACRAE: In a study that was designed to use corticosteroids, 10 percent of the population is going to have an increase in intraocular pressure and those patients are going to probably -- you know in the -- in one of the studies, let's say, that has previously been done, 10 percent of the population that was treated did have an increase in intraocular pressure and they were treated with

anti-glaucoma medication successfully. I don't think that is an adverse reaction. I don't consider that an adverse reaction. But if it was sustained, I agree with what Dr. Higginbotham said. If it is sustained even with treatment, then I think it should be considered an adverse reaction. It is uncontrolled glaucoma.

DR. RUIZ: Mr. Chairman, the word -- the whole phraseology up there bothers me, uncontrolled intraocular pressure, with increase greater than 10 millimeters of mercury. Well, you know, if they started at 12 and it went up to 22, that is greater than 10 millimeters of mercury. Is that uncontrolled intraocular pressure?

I mean, I would rephrase that whole statement. I agree with Scott and Walter. I mean, I don't think a pressure of 25 is a major consideration, especially if it is only one time. I agree with Eve on that.

DR. STULTING: Other comments?

DR. EYDELMAN: Dr. Higginbotham, would you further clarify is two consecutive or any two measurements above 25?

DR. HIGGINBOTHAM: I would suggest two consecutive measurements and I certainly would also suggest that one might consider a higher level of intraocular pressure as a threshold for an adverse event.

DR. RUIZ: Like 30.

DR. HIGGINBOTHAM: Such as 30.

DR. STARK: And would you take out the 10 because, you know, you may get a pressure of 12 going to 22 and that wouldn't be worth filing an immediate adverse reaction, I wouldn't think.

DR. HIGGINBOTHAM: I would think you really want to capture that. I mean, for that patient that has a pressure of 12, that is going to be very, very few patients. So, I would actually consider keeping the 10 above baseline on two consecutive readings. That is going to eliminate a lot of people if you do two consecutive readings.

DR. STARK: But they have to front fill an adverse reaction report and that is a big event for a pressure of 10.

DR. STULTING: It is IRB notification and FDA notification.

DR. STARK: And a lot of letters for a pressure of 10. I just don't think -- a pressure of 10 that is greater than -- and greater than 30 maybe, but -- I mean, an increase in 10 and greater than 30 or greater than 25.

DR. HIGGINBOTHAM: Fine.

DR. STULTING: Would somebody else like to state

the consensus?

DR. HIGGINBOTHAM: I would say in an intraocular pressure with an increase of greater than 10 millimeters of mercury above baseline and an increase in intraocular pressure greater than 30 millimeters of mercury on two consecutive occasions.

DR. STULTING: Okay. So, the -- well, she stated it just fine. Is there anybody who disagrees with that? I am not going to try to do it again.

DR. STARK: Doyle, is ocular penetration included in F and if so, maybe we ought to just put it at -- I know that they toyed with the idea of saying lost or misplaced flaps if vision drops, but ocular penetration should be something we should capture, especially with new tree finds because if you are seeing that happen, maybe you pull back a little and -- I reckon that would be an adverse event. It is not on there.

Without prolonged discussion, I think we could probably say that would be something we would recommend being included as an adverse event.

DR. MC CULLEY: Doyle, I had three quick comments. One, we have miscreated flaps, but there is nothing in here -- maybe it doesn't belong, but if the flap displaces a day

after the procedure, there is nothing about delayed flap problems, either in adverse events or in complications.

DR. STULTING: My thought would be that in belongs in complications and we can --

DR. MC CULLEY: It is not there.

DR. STULTING: The next slide will bring that up. You don't know that, but it will.

DR. MC CULLEY: Okay.

DR. MC CULLEY: What are the requirements for reporting complications?

DR. STULTING: Those get put in the annual reports to the FDA. Then this is the issue -- it is actually a recommended change in Section 3.2.6.2, to change the existing wording to misaligned flap, but I think we ought to open up the discussion to describe all flap complications, including whatever is left over from adverse events and postoperative misalignments and things.

DR. MC CULLEY: Okay. I just wanted to be sure it was somewhere and I see that it is.

There were two other things in the 3.2.6.1 that weren't addressed as changes. This just says late onset of haze beyond six months that decreases vision by two lines. What about persistent haze beyond six months? You would

have to go -- it is not on here. You would have to go back to the guidance document.

DR. STULTING: No, I see it.

DR. MC CULLEY: Page 15.

DR. STULTING: Okay. Be sure everybody is on the same page. It is 15 of the guidance document, 3.2.6.1, Section I. It says, "Late onset of haze beyond six months with loss of two lines or more. Best spectacle corrected acuity."

DR. MC CULLEY: So, completely left out is persistent haze past six months. The onset before six persists past six. This is just late onset. So, it is a wording issue, but I think it needs to be -- I think that should be there.

DR. STULTING: We just decided to include haze beyond six months with loss of greater -- two or more lines of spectacle corrected acuity for -- okay. So, that is an outcome. So, your recommendation is that leave out late onset of and say haze beyond six months with loss of two lines?

DR. MC CULLEY: Yes.

DR. STULTING: Is that a consensus?

PARTICIPANTS: Yes.

DR. STULTING: I believe it is.

DR. MC CULLEY: And then J would be -- this just relates to two lines of best corrected loss, not related to irregular astigmatism and, therefore, leaves out two lines of loss related to irregular astigmatism. So, where is irregular astigmatism dealt with?

DR. STARK: So, why don't you just put down loss of two or more lines on two consecutive visits because they may actually lose one line temporarily -- I mean, two lines temporarily.

DR. MC CULLEY: I mean, this gets back to a discussion that I think you pushed before on irregular astigmatism and determining that it is irregular during a hard lens refraction, that I think we want in there to determine how much is or isn't irregular, but we want to -- we don't want to exclude irregular astigmatism with two lines of loss from the adverse event category.

The way this is written, it does that. I don't think that would be the intent. As I read this, that is what has happened.

DR. STULTING: Malvina, do you want to comment on that? It is my understanding here that we need to separate adverse events from outcome measures. Adverse events are

handled by filling out an adverse event report. It is required by law to be reported to the FDA immediately after its occurrence. It also has to go to the IRB and so we would need to be real sure that everything that we --

DR. MC CULLEY: I think the creation of irregular astigmatism by a laser would be an adverse event.

DR. STULTING: That means that every time you see a patient who has two or more lines of visual acuity loss at an exam after laser, then you have to complete an adverse event report form.

DR. MACRAE: In some of the other studies that we looked at, there were as many as 5 to 7 percent of patients who had lost two lines of best corrected vision, even in the untreated eye because the technicians were not accurately recording the data, my assumption would be.

Rick, I think, discussed this a long time ago.

DR. MC CULLEY: This says at six months or later.

DR. MACRAE: Right, but once that form gets filled out and there is a two line loss, then that would be considered an adverse reaction.

DR. MC CULLEY: I think your irregular astigmatism leading to two lines or more of loss of irregular -- loss of vision, secondary to irregular astigmatism, six months or

later would be an adverse event.

DR. STULTING: Dr. Ferris.

DR. FERRIS: Is it potentially reasonable to say that an adverse event would be, as Walter said, two consecutive visits of two lines loss and the reasons for those -- reason or reasons for that event needs to be filled out on the form.

DR. STULTING: Any other comments?

DR. MACRAE: One of the problems is that if you have a patient that starts out 20/15 preoperatively and drops to 20/25, and they don't get a -- let's say they don't get a good endpoint or something at six months, that is an adverse reaction. Well, is that really an adverse reaction -- from my vantage point, is that really an adverse reaction? You know, we have listened to people that have worked in the field and they -- that are respected scientists and they say that that is not uncommon and, yet, these patients are not severely disabled as a result of that.

My experience is that that is -- I agree with that. So, I don't know that that type of patient -- reporting that type of patient is from my vantage point a true adverse reaction. I am more concerned about the

patients that lose 15 letters of EDTRS or three lines of vision in 20/40 vision. That is the patient that I think is an adverse reaction.

DR. RUIZ: Malvina is going to say something first. Maybe I won't ask the question.

DR. EYDELMAN: We just have to be a little bit careful when the wording "consecutive exams in adverse events" because if you just look at the protocol, if it is at three months and the next exam is not called upon until six months, if you truly believe it needs to be reported to FDA, we might not get the reports until 3 1/2 months later.

DR. RUIZ: That is exactly what I was going to say.

DR. MC CULLEY: I would like to just point out again that if you read J, decrease in best corrected visual acuity of greater than 10 letters, not due to irregular astigmatism, as shown by hard contact lens refraction at six months or later, and I am just saying that I think whether it is irregular or not irregular, we need to determine it but it should be all inclusive.

DR. STARK: The point about consecutive, if a patient has two lines of loss of best corrected visual acuity at six months, it seems like you may want to see the

patient back a little shorter than six months anyway. I am worried about two lines of loss because that is 37 percent loss in the resolving power of the eye.

So, I agree with Jim. Let's capture it at six months.

DR. EYDELMAN: Do I understand correctly then the recommendation is to change J, adverse events, just as a decrease in spectacle corrected visual acuity of greater than ten letters period?

PARTICIPANTS: Yes.

DR. MC CULLEY: But we do want the point that Walter made very well before. We want with the hard contact lens refraction to determine whether that is irregular stigmatism or not. So, I think something along those lines needs to stay in there.

DR. EYDELMAN: That is stated in the safety outcomes. There is a note to that effect in the guidance.

DR. GORDON: This would be at six months or later.

DR. EYDELMAN: Just one more point of clarification. At six months or later for any study because as we are moving along the lasic era, some studies claim to be able to show stability at three months and want to reach the panel open session before six months. So, is everybody

comfortable with six months? I just want to verify that.

DR. STARK: Doyle, are they stable at three? Are they stable enough to put those criteria at three months? It would make it harder on the manufacturers because at three months there may be a higher percent.

DR. STULTING: The onus is on the study sponsor to demonstrate stability and if they want to demonstrate it at six months, then the exams have to be there prior to that time presumably to demonstrate it.

DR. EYDELMAN: How about if we change it to at anticipated stability or later without putting the exact months? Because as we have different devices, each one anticipates a specific stability.

DR. STARK: I think that is a good way to state it, but no later than six months.

PARTICIPANT: And no earlier than three.

DR. STULTING: So, it would be anticipated stability or six months, whichever comes first.

DR. BELIN: I am confused. This is best corrected visual acuity. What does that have to do with stability?

DR. STULTING: It has nothing to do with it, but from a procedural point of view, the goal is -- the proposed goal is to get the information before the study is over.

DR. BELIN: That part I understand. It was the part about stability and two line loss that -- I can understand uncorrected visual acuity. It is best corrected that I am confused about.

DR. EYDELMAN: Well, I heard that people weren't happy with just leaving it without a time frame, that there was a consensus from this side of the table at six months or later.

DR. STARK: So, we take out the term "stability" because it really doesn't -- I see what Rick is saying. So, you can't use the term "stability" there. We are talking about visual acuity.

DR. STULTING: The purpose of adverse event reporting is so that there can be a heads up to the agency to identify major problems with the system, that they were unaware of beforehand and stop enrollment or modify the system or whatever. It seems to me that if you have a -- you know, if you have a short term study, you are going to get the same information at the same time if you say six months. I have trouble understanding why you want it sooner in a short term study because you are concerned about enrollment of future patients, right?

DR. EYDELMAN: If you, indeed, deem decrease in

best spectacle of greater than two lines as an adverse event, we have later on in the safety endpoint, that none of the adverse events can exceed 1 percent. The definition of all other adverse events necessitates reporting to FDA within ten working days, which translates into FDA knowing about the occurrence of each of these adverse events as a study is going on. If you are now putting now the artificial time point on the specific adverse events, that stops us from the possibility of monitoring this particular adverse event while the study is under IDE purview and it can be not until the PMA submission potentially that we will find out about the total additivity of these adverse events. That is where my concern is.

DR. STULTING: I understand that.

DR. STARK: Would it be appropriate then just to change the wording to loss of two or more lines of best corrected visual acuity at three or more months after surgery? In your wording, you said greater than two. I think it was the consensus that we are going to talk about two, two or more lines.

DR. GORDON: I have a comment on that because I think we have confused a couple of issues here. The intent was to capture as an adverse event, okay, which triggers a

whole series of activities when it is serious and when it is not something that you might anticipate. Okay? So, I think it means that when that happens after you would have expected the outcome to be stabilized and that that was Malvina's intent in saying, you know, after stability has been established and her concern is that there are going to be sponsors, who are coming in with three month follow-up and saying, okay, we have established stability at three months. She wants to be sure to capture the information, but if you have, you know, a typical study that is six or twelve months, you probably don't want to be reporting this at three months if you don't see your results stabilized until, say, six months.

So, having it always reported when it occurs at three months or later, I think, is just going to increase needlessly the number of reports that aren't truly adverse events.

DR. BELIN: I agree with Judy and I think what happens then is you put sponsors who are doing longer studies at a disadvantage and perhaps we should word it six months or later or -- and this would be bad wording, but basically if you are doing a study of less than a year, you need to report it at six months or later or the last two

scheduled exams.

You need to capture that information.

DR. GORDON: I guess I appreciated Malvina's language in saying when stability has been established because the sponsor who is claiming that from three months forward nothing is going to change and has a patient like this at three months, then at three months, it should be reported as an adverse event.

DR. BELIN: It would be if you used the last two exams. So, what we are doing basically is trying to --

DR. GORDON: Then you would have to report it at one month and three months?

DR. BELIN: Well, I assume if someone is going to claim stability at three months, they had better have a lot more exams than one day, one month and three months.

DR. GORDON: I don't know that you can assume that.

DR. MC CULLEY: I think our intent is clear. It is a matter of the FDA working out wording and I don't think we are -- we are spinning our wheels here and I think our intent -- what we want is clear. You guys work it out.

DR. STULTING: You want to state the consensus opinion?

DR. MC CULLEY: Well, that it is decrease in visual acuity, ten letters not due to regular or irregular astigmatism with the differential being determined by a hard contact lens refraction at six months or later or for shorter studies blank, and FDA fill it in.

DR. STULTING: That would be two lines or more.

DR. FERRIS: Do I understand this to now have no adverse effects that are related to visual acuity that have to be reported at the time or is 20/40 the adverse effect that has to be reported? If it is 20/40 or worse, they have to report it, but if it is a two line loss they don't have to report it?

I would like to know if you are going to use adverse effects as monitoring patients and the only adverse effect that the patient really cares about, I think, is their lost vision. There ought to be some way early on to determine that more than some reasonable number of patients are losing vision from this procedure, so you can stop it. If you wait until enough people have six months visits, you are going to have, at least I would think, a potential for a disaster or a problem. There needs to be some acuity monitoring.

DR. STULTING: What is your proposal?

DR. BELIN: Well, one proposal -- I think Scott's proposal would be anybody who has best corrected visual acuity at 20/40 or worse has to be reported whenever they have it, with the reason for decreased vision.

Another proposal would be anybody with two lines lost. Now, there may be some time period after the procedure and I don't know what that is, where you wouldn't want to say a two line loss because it is an expected decrease, but is there some point at three months or whatever, after which you wouldn't expect a decrease in best corrected visual acuity.

DR. STULTING: I think we are going to have to get away from the 20/40 at this point because later on on page 6 we allow patients who are worse than 20/40 into the study. So, maybe we should delay that.

DR. BELIN: I was about to comment on that.

DR. STULTING: That is for high myopia. Now, 20/40 is -- that is something to be discussed. 20/40 is low to moderate and something we will discuss. It is in here, but we probably should get away from that 20/40 right now.

DR. STARK: Doyle, what is your experience with stability? It puts more responsibility on the manufacturer and probably more reporting. If we insist at three months,

a two or more line reduction in best corrected visual acuity be reported, but you certainly wouldn't want to miss a -- you wouldn't want to miss a three or four line at that point.

When does it stabilize, Doyle?

DR. STULTING: You are asking two separate questions. One is loss of best spectacle corrected acuity and the second is stability. But, let's see, how should I phrase this? Based on data that are generally available and past experience, I would say that if we leave the criteria to be reporting of patients who lose two or more lines of best spectacle corrected acuity at three months or beyond, then we are probably going to see adverse event reports on somewhere between, oh, 5 and 10 percent of patients. And I think that is a high number given what we already know about these procedures that we are generating a guidance document for.

DR. BELIN: Now, Doyle, as a safety monitoring device, what about doubling individual angle? If you go to a three line loss, what percent would have that, who are eventually fine?

DR. STULTING: That number would probably be fairly small, down in the 1 or 2 percent range or less.

DR. BELIN: Because maybe from monitoring, you would use a doubling of the visual angle and for final acceptance, you would use something like a 10 letter loss.

DR. STULTING: My personal opinion would be that there is a big difference between two or more lines and more than two lines. If I were designing the study and looking for bad things, I would be wanting to see more than two lines loss.

I understand your point, Walter, and you are correct about the amount of loss that is associated with two lines, but the other side of that argument is that there is a certain amount of variation in best spectacle corrected acuity numbers that are obtained. And if you look at most of these studies that are published, what you find is that the number of eyes that gain two or more lines is more than the eyes that have lost two or more lines.

What that says is that there is a fair amount of measurement error, particularly in these postoperative corneas that have multi-focal surfaces and what not. I would be in favor of setting the gait at more than two lines of visual loss and reporting it at some reasonable intervals, say, three or more months after surgery.

I think if you do it at that level, then you can

bring the interval down to three months and get reasonable --

DR. STARK: Why don't we do then three lines at three months, but two lines at six months? I mean, at six months you want better visual acuity. So, that seems like an easy solution. If they have lost three or more lines of best corrected vision at three months or two or more lines of best corrected vision at six months.

DR. STULTING: You are still going to get 5 to 10 percent of eyes.

DR. STARK: Well, we want to know that, don't we?

[Multiple discussions.]

DR. STULTING: We already know that.

DR. GORDON: And the question is does FDA need to know that in a 10 day time frame for each patient when that occurs? That is really the issue because you don't -- I think you do get meaningful monitoring by FDA out of the annual reports, but having that volume of adverse event reports, I don't know if that is particularly useful.

DR. FERRIS: Well, what is the volume of the three line loss? I mean, I understood from Doyle that three line loss would be less than 1 percent.

PARTICIPANT: It is about 1 percent.

DR. FERRIS: Okay. So, if it is 1 percent, that, to me, doesn't strike me as a huge volume and if the issue here is safety and you have to wait until six months and you have some machine out there that is unsafe and is creating 5 or 10 percent such events at three months, three line loss, I -- maybe we can come to an agreement as to whether we are going to say it is a three line loss or a four line loss, but there must be some visual acuity criteria as far as I am concerned at which time and promptly find out about 10 percent three line loss at six months -- six months -- you know, by that time, maybe hundreds of people have been subjected to this, that there ought to be -- that the purpose of the adverse event is an early warning.

So, there needs to be some mechanism for an early warning. As far as I am concerned, the FDA can decide how many letters that is. I think we have had enough discussion about that, but there needs to be some visual acuity criteria of loss that is reported promptly.

DR. STULTING: Okay. It has been proposed more than two lines at three months.

DR. FERRIS: I would say three or more lines, 15 or more --

DR. STULTING: Three or more lines at three or

more months.

DR. BULLIMORE: You are defining an adverse event.

DR. STULTING: As a definition for an adverse event. That is correct.

PARTICIPANT: But two at six months.

DR. STULTING: Well, I will point out again that already in the literature there are published reports of PRK, which are existing machines, approved machines that show between 5 and 10 percent loss of two or more lines at six months or more.

DR. MACRAE: One of the studies was 6.9 to 9 percent, two or more line loss and when they went back and looked at their non-treated control population, they had a 5 percent two line loss in the non-treated control eye because of variability of probably examination.

DR. STULTING: I think that the published data are real clear that if you -- that we are going to get adverse reports on up to 10 percent of the population and I think that is too high for the definition of adverse events.

DR. FERRIS: I would think that the definition of adverse event is something that would not be expected by random chance. So, a three line loss, it seems to me, is not expected by random chance. That should be reported. We

understand that there may be 1 percent of those that are just variation in measurement, but for the adverse event reporting, the three line loss out to be used, in my opinion. For reporting of efficacy of the instrument, I think the two line loss is appropriate.

DR. STULTING: So, it is three or more lines at three months.

DR. MC CLELLAND: Just a general question in regard to the discussion. I guess I need assurance that there is adequate communication of the potential for adverse events to the patient subjects that are going to be included in these studies.

I know when I have raised this question before, I believe the answer has been that this is covered in the IRB consent form and so on, but given that the nature of this discussion and the potential for even 1 percent of the subjects continuing with this amount of visual acuity change loss, i.e., vision loss, is there, in fact -- can I be reassured again that this is adequately communicated to those participating?

DR. STULTING: The approval of the consent form is the purview of the IRB or the HIC, as it is now called. Those things that are known about the procedure are required

to be presented to them in the informed consent document.
So, this information should be in there.

Ours is an HIC. What is yours?

DR. MC CULLEY: I am still an IRB, southern trend.

DR. ROSENTHAL: What does it mean, Mr. Chairman?

DR. STULTING: Human investigational committee.

DR. ROSENTHAL: That is what it used to be called.

DR. STULTING: Okay. Let's move on to the next one and try to get it done. The issue on the table here is how to treat flap problems under complications. The existing one is flap is not of the size and the shape as initially intended or microkeratome stopped in mid cut.

I will make a recommendation and see if everybody goes along with it, just as a trial of something different to move things on here. It seems to me that we ought to retain flaps that are not the size and shape or initially intended under one category and then add a category that says misaligned flaps, which would be a postoperative complication. So that everything that goes along with the flaps gets retained or reported.

DR. EYDELMAN: As it stands right now is adverse event F on the previous slide, miscreated flap, which included lost, incomplete or too thin; therefore, a flap,

which is not the size or the shape as intended now becomes an adverse event.

DR. STULTING: We are down in 3.2.6.2, under "Complications" now.

DR. EYDELMAN: Correct, but the reason it was moved, because it was a new language of the adverse event.

DR. STULTING: I understand. Okay.

DR. RUIZ: Mr. Chairman, would the word "imperfect" or "misaligned flap" cover it?

DR. STULTING: My assumption is that the verbiage in H has to do with things that happen while you are making the flap and the verbiage in the replacement over there has to do with things that happen when you put it back or fail to get it back correctly.

DR. RUIZ: Or it gets back and then displaces, but wouldn't "imperfect" refer to the formation of the flap rather than "create" and "misalign" refer to either right after surgery, at surgery or after surgery.

DR. STULTING: So, your suggestion is rewording so that "miscreate" or -- instead of those other words.

DR. RUIZ: I think "imperfect" or "misaligned flap" covers everything.

DR. STULTING: I personally would like to see them

segregated out into the two things because one of them has to do with microkeratome abnormalities and the other one has to do with probably other events.

DR. HIGGINBOTHAM: I like your suggestion, Mr. Chair. Nothing in medicine that we do is absolutely perfect. So, I am concerned about perfection as part of the document.

DR. STULTING: Okay.

DR. FERRIS: I would like to know the definition of "perfect" and who decides.

DR. STULTING: Does anybody else have any comments?

DR. MACSAI: I think we should accept this proposed modification.

DR. MC CULLEY: I think we need to keep both H's. Keep them both.

DR. MACSAI: We do. It is. One is just moved to an adverse event and another is a complication. It is just --

DR. STULTING: Remember, we decided that the adverse event, I believe, was a serious miscreated flap that caused loss of vision or some sort of reporting mechanism that would catch a very large number of miscreated flaps and

create adverse events out of them. So, we don't really collect miscreated flaps that occur occasionally and don't cause visual loss unless we put it down here in a complication.

DR. EYDELMAN: So, therefore, under adverse event F, you propose miscreated flap with a resultant decrease in visual acuity -- with resultant loss of 10 letters or more and --

DR. STULTING: I think we already did that. We said we were concerned about and we were also concerned about a very high incidence of them and left it to the Agency to figure out how to capture that.

DR. EYDELMAN: Correct. And --

DR. STULTING: That is an adverse event.

DR. EYDELMAN: Correct. And what I was trying to finish and there is a complication that keeps the same statement without visual loss.

DR. STULTING: That is what I would propose.

DR. EYDELMAN: That is what I was trying to clarify.

DR. MACRAE: If you had a number of free caps, they would not be reported as adverse reactions unless they cause vision loss, but they would be reported as

complications, which I think is reasonable. It would be helpful in the study to know as a panel reviewer what the incidence of free caps are and misaligned caps that are then aborted cases, just so that could be part of the -- just, if nothing else, for the labeling.

DR. BELIN: I am going to give a disagreeing opinion on this. Again, it was said earlier that when we are looking at lasic, we consider the microkeratome in the laser as one unit. If we had a laser -- that is what someone said, right? -- if we have a laser that 50 percent of the time stopped in the middle of treatment, okay, no loss of best corrected visual acuity, would we not consider that an adverse event? And would we want that reported more than in an annual report, if we are truly treating this as a unit and the unit fails to function in mid-treatment, that should be reported early enough not in an annual report.

DR. MACSAI: But you just said that there is no problem with its failure to -- with its midway stopping. What difference does it make?

DR. BELIN: Well, you are not -- patients are not obtaining the treatment -- I would say if the machine fails 50 percent of the time to accomplish its intended treatment or complete treatment, that needs to be brought to the

attention earlier than in an annual report.

DR. STULTING: We already made that decision. We already made that recommendation, was my understanding. That has already been done.

DR. MC CULLEY: What we are talking about here is keeping the old age and adding an age prime.

DR. STULTING: Yes. Good. Is there consensus with that?

PARTICIPANTS: Yes.

DR. STULTING: So, we are recommending to retain the old age and add the new age.

Next slide, please. It has to do with endpoints and target values and the rationale behind this change here is to make it clear that the agency considers the device and the procedure to be initial treatment, plus enhancements, if the sponsor considers enhancements to be part of the planned use of the device; in other words, that a sponsor would be given a choice. If they want to define a device that is to be used one time, then the end result is whatever you get after one time use. If they want to define it as a device where you have to use it twice to get the intended result, then the outcomes are to be judged after the second use.

Is that clear? Is there any discussion or

recommendations contrary to this or dissent?

DR. SUGAR: Will there still be reporting of the frequency of enhancements?

DR. STULTING: Yes. This has to do only with endpoints and targets values. Later we are going to talk about percentage of eyes within a half a diopter and 20/20 vision and all that. So, this makes it clear when those target values are to be applied.

DR. MACSAI: Right. Well, what is not clear to me -- maybe it was clear in the statement, though, is if a device is going to be used twice or three times and the endpoints reported after it has been used twice or three times, will we know what was the result after one use versus two uses versus three?

PARTICIPANT: Yes.

DR. MACSAI: And the other question I have is about the word "planned." What exactly does that mean?

DR. EYDELMAN: Under the IDE stage, each manufacturer or each sponsor has to outline their plan. And together with safety endpoints and efficacy endpoints, which they intend to meet. So, it is a protocol basically.

DR. MACSAI: Okay.

DR. STULTING: So, if they say the device is one

treatment plus one enhancement, then they are required to give the data as of no more than one enhancement and a patient requires two, then they are a failure under those rules and definitions of the device. And they are at liberty to define it as two enhancements.

DR. MACSAI: Or four.

DR. STULTING: Or four. Whatever.

It sounds like there is agreement with this one. Okay.

Next slides, please. Hopefully, the astigmatism discussion will be quicker than we had planned for.

This series of questions and issue has to do with astigmatism, how it is defined, how it is analyzed and how it is reported. The first one is is vector analysis needed for all eyes treated or for only eyes with best spectacle corrected visual acuity loss or complications.

Comments, please.

DR. BULLIMORE: I suggest that it should be required for all eyes.

DR. BELIN: I would agree with that; otherwise, you really can't make a distinction between a unit that treats on axis and one that treats and induces a new axis if the magnitude of the cylinder is the same and the patient

satisfaction will not be the same.

DR. STULTING: We spent about, what would you say, an hour and a half at this at the Eye Care Technology Forum, discussing just about every conceivable permutation. In the end, we went back to this recommendation, that it be done for all eyes.

I think once you develop the formula and once you set it up, you might as well just do it for all of them. I think that was the endpoint.

Dr. Ferris.

DR. FERRIS: I would think that as a reviewer I would like to see it for all eyes and I would like to see it for those who had visual acuity loss separately because that small component that had visual acuity loss are going to be loss in the overall analysis.

DR. STULTING: I think that is implied.

Okay. So, the answer for this is all eyes.

No. 2, for eyes treated for astigmatism, what effectiveness criteria are needed in addition to those recommended for other indications? Let me make sure I am understanding this and it is clear for everybody.

The question here is should we add effectiveness criteria, other than best spectacle corrected visual acuity

outcomes and the other things that we are going to be looking at that are already in the existing document?

DR. MACSAI: Correct.

DR. STULTING: Do we care what the astigmatism is if the patient sees sort of?

DR. MACRAE: I think that we should -- that the effectiveness criteria should include the reduction in absolute magnitude of the cylinder, as well as the percentage of eyes with axis shifts and that table that you had, I thought, was a good suggestion. In addition to that, just a percentage reduction in absolute astigmatism would also be helpful. If I was a practitioner, I would want to know what percentage of reduction of astigmatism is occurring, so I could explain that to my patients.

DR. STULTING: The table that Dr. MacRae is referencing is now shown on the slide on your right and it is part of the suggested format for presentation of astigmatic data. I think maybe this would work better if we went back and went ahead through the questions and then saved the definitions and the filling in of those numbers for a little bit later, if that is okay with you.

But let's, for now, just say that our consensus is "yes," we need to have criteria for correction of

astigmatism and we will generate those in a minute.

Question No. 3, for eyes treated for astigmatism, what safety criteria are needed in addition to those recommended for other indications? We are talking about safety criteria. Realizing that we have adverse event information here and we have other safety outcomes like we had in the other -- in the original document, are there any additional safety criteria that need to be applied?

PARTICIPANTS: No.

DR. STULTING: The consensus is "no."

Question No. 4, should effectiveness criteria include both vector analysis and absolute magnitude with axis shift?

PARTICIPANTS: Yes.

DR. STULTING: The answer is "yes."

PARTICIPANT: Is there a formula that is decided? There are several formulas out there for vector analysis.

DR. MACRAE: The answer is "no." There is no set formula for doing vector analysis.

DR. STULTING: There was a lengthy discussion of this as well in the Eye Care Technology Forum. This is a trigonometric solution and when I ask the question of where the alternative formulas came from, the answer was there are

some published formulas that essentially discount residual astigmatism of a half a diopter and what that and it seems to me that the real formula figures out the trigonometric solution. It doesn't discount anything. It doesn't round anything off. It doesn't eliminate anything. And there is only one answer to the problem.

There is only one solution to a vector problem.

DR. BULLIMORE: You are correct, Mr. Chairman, and there are, however, since you are dealing in three dimensional trigonometric space a lot of the time, there are different conventions as to where you define your axes. All valid methods should give the same answer as you suggest and which particular method, whether it is the Tybos(?) method, the Katon(?) method, the Holiday(?) method, the Harris method, should give the same answer. I am happy to provide the FDA with an adequate number of citations.

DR. STULTING: So, that would be up to the FDA to validate the method that is submitted with the IDE.

No. 5, how should these data best be presented? Is the following example of optimal categorization of clinically -- is the following example an optimal categorization of clinically relevant data and the table that you are being shown on the right is one that has been

proposed and suggested to the FDA as a method of tabulating the results of vector analysis for inclusion in PMAs. So, the issue before us is whether this is a reasonable way to look at data or not or whether we should look at it in another way and if we accept this or some other way, what are the criteria that we should give as target values?

DR. BULLIMORE: I would say it is unreasonable, given the fact that you can't have a shift in access for residual cylinder of zero. That is in essence a nonsense. I would propose that the first category just get abolished completely and you change the second category to .521 and ignore cases where there is zero residual cylinder and 025. So, that would be my first proposed modification to the table.

DR. STULTING: So, your proposal is for the first category to be zero to --

DR. BULLIMORE: The first category should be abolished. Just red line it.

DR. EYDELMAN: If I can just respond to that.

DR. STULTING: You have to have a place to put all the eyes so that you total up to all the eyes. So, you are saying -- you need to categorize all eyes with data.

DR. BULLIMORE: Just say for zero to -- or less

than .5 residual cylinder and gaining axis, who cares.

DR. EYDELMAN: The only point is since some devices indications require us an evaluation of .5 diopters as part of the indication is correction of astigmatism of .5 diopters.

DR. BULLIMORE: So, if you started with .5 and conducted less than .5, I would say that is an effective device.

DR. STULTING: If you take a patient who has plus a half at 90 and winds up plus a half at 180, then he is going to wind up in the category that we would consider efficacious.

DR. BULLIMORE: No. My additional modification was to make the first category less than .5 and the second category, .5 to 1.

DR. STULTING: Okay.

DR. BULLIMORE: This is when it is nice to have overhead projectors rather than the modern technology, so you can actually update this on line.

DR. STULTING: Does everybody understand what is being recommended.

PARTICIPANT: 0 to .49 and then --

DR. STULTING: The first category is 0 to .49

and --

[Multiple discussions.]

DR. FERRIS: All of these, it seems to me, need to be presented in 0 to less .5, if that is what it is and then .5 to less than 1.0, if that is what it is. The same with the shift in axis, this plus or minus. I don't know what that means, but you can say that it has to be between 15 and 30, greater than 15 and less than 30 or less or equal to 30, all inclusive and -- I mean, that it is the way it is right now. The left side is all inclusive, except it is sort of meaningless because nobody refracts to .51.

DR. STULTING: I am sorry. I think you are recommending that we have a .5 to less than 1.

DR. FERRIS: If it is going to be 0 to less than 0.5, that is category 1. Then the next category is .5 or greater but less than --

DR. STULTING: .99.

DR. FERRIS: Less than 1. Then it is greater than 1 but less than 2, greater than 2, but less than 3, greater than 3. It is all right the way it is. It is just sort of not the way people refract.

DR. STULTING: Dr. Belin.

DR. BELIN: This table is not going to be

reporting every patient. Is that correct? This is just reporting those patients that deviate from that axis shift.

DR. STULTING: I think the purpose is to categorize everybody and that there will be a category provided, which is the top one, that would include patients that were basically corrected.

DR. BELIN: Let me look at the last line. Greater than 3 diopters of residual cylinder shift in axis, greater than a plus or minus 5. So, that means if you have a residual -- I am just trying to understand the table. If you have a residual cylinder --

DR. STULTING: Correct me if I am wrong, Malvina. I think that the recommendation was that you would include the person in the category if they exceeded either one of those criteria.

PARTICIPANT: So, that won't include everybody.

DR. STULTING: Is that right, Malvina? I had trouble with this when I did it the first time.

DR. MACRAE: The table needs to be separated. Is that correct?

DR. MACSAI: Are these two separate tables or is this -- I don't understand --

DR. MACRAE: It can't be two separate tables if

you have -- let's look at this first and second line --

DR. EYDELMAN: This table is a table on evolution. It was originally suggested for catching poor results and then it was presented as something to start working from for all data. So, it is not an optimal form or shape as it currently stands for all data.

So, the first the question comes back as to do we want all clinical data reported in subgroups or just those with not best results, i.e., there was basically some concern to a clinician that analysis might not mean a lot and that is how the proposal for this table originated to help the clinician to make some clinical sense of the analysis.

So, there are two separate issues, Dr. Stulting. One is does all data need to be categorized in some subgroup and, second, how should it be categorized. This is not --

DR. BELIN: I am glad to hear it is an evolution but as it stands now, it really does not make any clinical sense because you have a patient who has three diopters of residual cylinder or more than three and as long as they are on axis, that is considered all right and not listed on the table.

DR. STULTING: No, they would be in the table

because they have more than 3 diopters of residual astigmatism. So, they would appear in that last line.

DR. FERRIS: You need two rows for each line. You need 0 to less than 5 cylinder with greater than 30 degree shift and less than 30 degree shift.

DR. DRUM: If I could just clarify a bit --

PARTICIPANT: Can you state your name into the record?

DR. DRUM: -- original table, this was intended to be acceptable amounts of axis shift for these different ranges of cylinder magnitude. That was the original purpose of the table. So, if you had half a diopter or less, why, it didn't matter much what the axis shift was. If you had over 3 diopters, why, you want virtually no axis shift.

DR. BULLIMORE: So, this isn't residual. It is really preoperative cylinder.

DR. DRUM: No, this is the result -- this was axis shift product, preop versus postop.

DR. BULLIMORE: Could we backtrack a minute and go through wherever we are going?

DR. DRUM: Sure.

DR. BULLIMORE: Absolute -- primary outcome measure for an astigmatism correction, can we start off with

a presentation of data in terms of absolute cylinder in terms of starting and proportional percentage corrected. Have we already agreed on that?

DR. DRUM: That is already done.

DR. BULLIMORE: So, that is a given. So, now, the intent of this table is really to what, to capture the change incident or axis?

DR. DRUM: Its purpose is to provide a standardized forum for reporting vector changes because, you know, you have -- you have magnitude of direction and the question is how are you going to format that report.

DR. BULLIMORE: So, this is solely for the purposes of translating vector analysis to the masses. Okay.

DR. STULTING: Or even to the individuals. How are you going to -- you know, you do 500 patients and you have got two values for each patient. What are you going to report and how are you going to report that in some way that it is assimilatable even by people who understand vectors?

DR. MACRAE: When I read this -- and I have seen the data reported this way -- I split the table. So, the first set of data would be residual cylinder and then the

second set of data would be shift in axis, just -- I split it and then if you want to combine it, you know, to get more meaningful information as well, then that is fine, but I just naturally split that table and it seemed to work.

DR. FERRIS: Well, it could also be two separate rows. There could be a small shift in axis row and large shift in axis row -- I am sorry -- column. So that the total for each row is the number of people with 0 to .5 or less than .5 residual cylinder. Then there is the percent of that total that had a small shift in axis and the percent of that total that had a large shift in axis and then the same thing for the next.

DR. MACRAE: I would like to see it separated.

DR. FERRIS: Well, it is all separated there.

DR. MACRAE: And then combine it --

DR. FERRIS: Well, it is separated in that format. All of the data is there and it is also --

DR. STULTING: So, what you are recommending is a two dimensional table that has residual cylinder on one axis and shift in axis on the other, so you get values for each. Is that correct?

DR. FERRIS: Or just another row in that table. If you just imagine that table -- I am sorry -- another

column. If you imagine that table that says residual cylinder on the left hand margin and then no large shift in axis is the first column, let's say, and the second column is large shift in axis or whatever you want to define it as and then a total column. So, the total column gives you the number of people who had that much residual cylinder and then each of the other columns tells you how many had -- what proportion of those that had small change in cylinder had a big shift in axis and what proportion had a little shift in axis. All of the data is there, so you can sort it out however you want.

DR. STULTING: How are you going to define "small," "none" and "big"?

[Multiple discussions.]

It is a two dimensional table that has these categories. Is that right? That is what I understand you to be saying.

DR. ROSENTHAL: You could say that those were acceptable shifts in axis and then there was the unacceptable shift in axis, which was greater than 5, 10, 15, 30 and --

DR. FERRIS: I assume from that that greater than 30 degree shift in axis for those who had a .5 to 1.0 is

unacceptable or is thought as extreme.

DR. STULTING: WE haven't talked about target criteria yet. We are right now trying to figure out how to report it.

DR. MACRAE: Why don't we just report it? Just take this, make a column, move this over here, another column, this over here, another column. Then we would have all the information reported.

DR. FERRIS: That would be fine if you put for residual cylinder, you had those that had more than 30 degrees, those that had 30 to 15 and those that had 15 to 10, those that had 5. Now, you have got a table with five rows. Now, you really have pretty much --

DR. SUGAR: You present it as a 5 by 5 grid with the axis shift on the top and the magnitude of the cylinder on the left and then we haven't -- this is just presenting the data. We don't know what is good and what is bad from this.

DR. FERRIS: Then you can add up if you like -- you know, we may have different ideas as to what is acceptable and then anybody can add up their acceptable proportion.

DR. STULTING: Okay. I think the consensus has

been reached on how to present it. Do we want at this point to put target values in those boxes or would we like not to put target values in or would we like to think about this overnight?

DR. EYDELMAN: Or you can try to put target values on the sum of some boxes. Did that just confuse you?

DR. BULLIMORE: No, I am fine with that. As someone who spends some of their time in vector space, I am willing to stick my neck out and say that those values, those criterias, ignoring the top one, that the other ones, 30, 15, 10, 5, they smell reasonable.

DR. ROSENTHAL: And the top one doesn't matter. Is that what you are saying?

DR. BULLIMORE: You can put whatever you want in there. Who gives a whatever.

DR. DRUM: I believe that is what the intent of that intent of that greater than 30 degrees meant.

DR. MACRAE: So, you can have that reported as well, just for the guidance of the clinicians, so they -- you know, a lot of clinicians don't understand what is a significant change and what is a not insignificant change. It would be helpful for the practitioner to know, well, this is what the FDA recommends as something that is significant.

DR. BELIN: I think this is going to take a lot of thought, which we don't have time for, rather than don't have thought, but the last line, plus or minus 5 degrees, is probably equal to or beyond our ability to mark the cornea and align the patient currently.

DR. STULTING: Now, correct if I am wrong, but I believe that if this is the way that we report our astigmatic results, then it is not necessary to use vector formulas because this is residual cylinder and you can report that straight off the postoperative refraction. And it is shift in axis and you can report that by subtracting the postoperative axis -- the preoperative axis from the postoperative axis. So, no vector computations are required for this table. So, unless we recommend some other form of reporting, then we now really have reversed what we said in answer to question No. 1.

DR. EYDELMAN: No, my understanding was that this is an addition to the vector analysis.

DR. STULTING: Okay. How are we going to present the vector data? Because we are going to have a magnitude and a direction for every single patient that is in the study.

DR. DRUM: My understanding was that the vector

analysis would be presented as the difference between postop and preop. In other words, the change in astigmatism would be presented as a vector quantity.

DR. BULLIMORE: To put it another way, what the vector analysis gives you is the induced or the effective change in astigmatism, which you can then compare with the attempted. The problem with an astigmatic correction, as Dr. Belin already alluded to, is that there is a number of components that affect the effectiveness of the technology. Those include in the repeatability of your initial and final refraction, your ability to align the instrument or device appropriately and finally, you know, whether the device under optimal circumstances can correct astigmatism.

So, you are trying to deal with a multitude of sins, if you like. And the vector analysis ignores your ability to align the instrument and just says can it correct astigmatism, yes or no, to what degree. So, I, in essence, think we should retain it.

DR. MACRAE: I understand that but how are we going to report it?

DR. BULLIMORE: In terms of induced astigmatic correction.

DR. MACRAE: For every patient?

DR. BULLIMORE: Well, you tabulate them, but --

DR. MACRAE: So, you would have a preoperative astigmatism, a target-induced astigmatism and a surgically-induced astigmatism.

DR. BULLIMORE: I think I followed that and I think I agree.

DR. BELIN: The other reason to do the vector analysis if you just utilize this table and you had a machine that for some reason -- let's take away everyone who was over two, just had a residual cylinder of two and less and for some reason the machine always gave you 15 degrees additional plus cylinder, you would never notice that unless you had vector analysis. You would just have a table that was completed and everyone would say it looks good. But it is probably important to know that the machine is inducing 15 degrees in every patient.

DR. STULTING: I understand what you are saying. Maybe I am the only one that sees it this way, but when you say "vector analysis," you are talking about computing a value for every patient. But so far we haven't talked about any way that those can be tabulated and assimilated as a group.

DR. BULLIMORE: Yes, we have. You get your -- in

essence, with vector analysis, all you want to do is the -- what was your term you used, Scott? Surgically -- target-induced astigmatism and then surgically-induced astigmatism and you can tabulate that as a function of attempted.

DR. STULTING: Yes, but that table up there, which we have said is the way we are going to see this, will not --

DR. BULLIMORE: No, no, no. This is a different table.

DR. STULTING: Okay. Then we need to create the other table. That is my point.

DR. BULLIMORE: I assume, given on past PMAs, those tables have been --

DR. STULTING: We have never seen such a table that reports and tabulates --

DR. MACRAE: I think it could be -- I think you could leave that up to the manufacturer somewhat as long as we recommend that we want to see preoperative astigmatism, target-induced astigmatism, surgically-induced astigmatism and if they -- in the statistical analysis of that and whatever else they want to provide, you know, with Alpen's(?) method, there is, you know, a number of other sort of things that they can add as well, but those are the

basic components of it.

DR. STULTING: So, what we are asking for mean attempted astigmatic magnitude and achieved magnitude and mean attempted direction and achieved direction and some measure of the spread?

DR. MACRAE: Yes.

DR. STULTING: Then that is what we need to specify for the document.

DR. BULLIMORE: I think the people on the FDA staff have a much better handle on this than the panel. We have said we would like vectors. We have said we like some sort of summary table for clinicians and -- are you happy with what we have said?

PARTICIPANTS: Yes.

DR. BULLIMORE: Okay. I propose we move along.

DR. STULTING: Any other comments on astigmatism and how it is calculated, reported?

Dr. Ferris.

DR. FERRIS: I think this is an interesting academic exercise. Just for the record, I would like to note that yesterday on the radio I heard someone advertising for patients who had astigmatism and I think the term is one I hate, "laser vision correction" was going to be used. So,

this is very interesting, but it may be that it doesn't matter too much what we do with regard to what is done.

DR. STULTING: Any other comments?

[There was no response.]

Do you have any other issues that we need to address that we may have passed over?

DR. EYDELMAN: I wasn't sure what your resolution was on Dr. MacRae's earlier comment proposing effectiveness criteria. Did we decide not to pursue it?

DR. MACRAE: You are asking me?

DR. EYDELMAN: Would you like to repeat what you earlier proposed?

DR. MACRAE: Oh, you mean in terms of effectiveness criteria, that comment? Oh. I just said that we should essentially use this table the way that we had described -- that we had split it out and --

DR. EYDELMAN: And assign some numbers to what is acceptable --

DR. STULTING: In other words, what we decided was a format for presentation. What Malvina is requesting is whether we want to have targets for effectiveness. You know, we are getting ready to say we would like to see a target of 95 percent plus or -- 20/20 uncorrected. Do we

want to have a target of some percent that are within a half a diopter and 30 degrees of intended or something like that? Or do we not want to have any targets at all and just consider them to be analyzed under some other criteria?

DR. MACRAE: It is a gray area. It is a very gray area. I think that, you know, if you had the general guidance that you wanted to see the astigmatism reduced by 50 percent -- that is what we are seeing in the literature -- that would be reasonable effectiveness criteria.

PARTICIPANT: What about shift in axis?

DR. MACRAE: If you say an absolute astigmatism reduction rate of 50 percent, that that would be acceptable. That is a very complex question.

DR. MC CULLEY: That doesn't sound right to me. Only 50 percent reduction?

DR. STULTING: That is what we approved a couple of months ago.

DR. EYDELMAN: It depends on the dioptic range.

[Multiple discussions.]

Well, from the literature, the percentage correction that is achievable is highly dependent on the original dioptic range of astigmatism, which we are trying to correct.

DR. MC CULLEY: So, it sounds like you would have to different criteria based on the initial --

DR. STULTING: One approach to this would be --

DR. MC CULLEY: -- uncorrected visual acuities, rather than setting targets for this. What would the response to that be? I wouldn't be comfortable yet with my degree of information, knowledge from whatever source, appropriate or inappropriate to be setting targets yet.

DR. MACRAE: Yes. There is very little information in the literature that actually stratifies data like this and gives us astigmatism reduction data. Most of the studies just say, well, when we looked at vector analysis, there was a reduction on vector analysis and the absolute magnitude of astigmatism was reduced by 60 percent and that is how the reports are.

They are just not that sophisticated yet.

DR. STULTING: Let me try this. The consensus is that we have recommended the format for presentation but we believe that there are not enough available data to come up with reasonable target values. Is there any dissention?

DR. FERRIS: I would like to suggest a different format and that is in order to able to assess what happened after surgery, this table needs some sort of preop cylinder,

too. It needs another -- it needs a third dimension. Of those who started with 1 or less, how many wound up this way? Of those that started between 1 and 3 or I don't know -- the FDA can decide that -- how many wound up -- how did they wind up and then of those that started with more than 3, how did they wind up? Then at least you could see -- you could get some sense as to --

DR. STULTING: Are you recommending then that this table then be presented for different amounts of preoperative cylinder?

DR. FERRIS: Yes. They can do it overall and then subdivide it by different preop and then you can get a better sense as to what the percent correction was.

DR. MC CULLEY: Stratified based on preop.

DR. STULTING: Stratified based on preoperative cylinder, still with no target values. I think that would be our consensus.

Any other issues relating to astigmatism or the other categories we discussed this morning? It sounds like "no." Okay.

We are just a few minutes before our target for lunch.

MS. THORNTON: Just a moment of your time.

For those people who are here today and were not here yesterday, I wanted to give you the dates of the 1998 panel meetings: February 11th, 12th, 13th; April 23rd and 24th; July 23rd and 24th, October 22nd and 23rd. Those dates are on our Web site at WWWFDA.GOV. Changes and cancellations will also be posted on the Web site.

For those on the panel who need taxi service, there is a sign-up sheet in the lobby.

Thank you. Have a nice lunch. We will see you back in how long, Mr. Chairman?

DR. STULTING: 1 o'clock.

[Whereupon, at 12:00 noon, the meeting was recessed, to reconvene at 1:00 p.m., the same day, Tuesday, October 21, 1997.]

A F T E R N O O N S E S S I O N [1:12 p.m.]

DR. STULTING: I would like to call the meeting to order and we will proceed with our discussion of the refractive laser guidance document.

The issue at hand is inclusion and exclusion criteria. These are ones for all indications that would include low myopia, high myopia, hyperopia and astigmatic protocols.

"LM" would be low myopia?

DR. EYDELMAN: Correct.

DR. STULTING: "HM" would be hyperopia -- high myopia, I mean, and "HP" would be hyperopia, for those of you who are wondering what those mean. And the proposed inclusion criteria are shown on the charts.

Are there any comments?

DR. RUIZ: What does "CL Wearer" mean? Contact lens wearer. That means that they have to have worn contact lenses?

DR. STULTING: That means that it is okay for them to be in the protocol.

DR. EYDELMAN: The full language you can find in the actual FR guide. This is just abbreviation. We discussed already the contact lens wearers inclusion when we

started this morning.

DR. BULLIMORE: Do any of these represent changes?

DR. EYDELMAN: The only changes are now presented on the right slide, i.e., new criteria for high myopia and hyperopia.

PARTICIPANT: I have a comment on one of them.

DR. STULTING: Go ahead.

PARTICIPANT: The amount at which manifest refractions should progress or can -- I guess it should be can progress -- during the year prior to the baseline up to 20 percent of spherical inclusion for high myopia. That means that a 12 diopter myope can have a 2.4 diopter change within the last year.

PARTICIPANT: That would be correct.

PARTICIPANT: Okay. I think that is a lot.

DR. STULTING: I would agree. Do you have a proposed alternative?

DR. BULLIMORE: I will try a half diopter there just to have it shot down.

DR. BELIN: This kind of leads into something I am eventually going to bring up, which is using percentages, rather than absolute numbers. You started doing it in some of this with the 20 percent. I would say 10 percent is

probably an appropriate amount.

DR. STULTING: Ten percent has been offered as an alternative.

DR. RUIZ: Ditto.

DR. STULTING: So, this means -- let me just make sure that we are clear about what we are talking about. If someone comes requesting inclusion of protocol and they bring a prescription that was provided to them a year ago and you refract them and they are off and they are a 5 diopter myope and you find that they are 5.7 diopters or 3.25 diopters, then they are excluded from the study. Is that correct?

DR. BELIN: That would not be my intention to utilize outside data. I am interpreting this, I guess, a little differently than you are. I am interpreting this as stability in my own patient population. I don't trust -- and there is not a good way, other than what we discussed before, doing the exam and following it over x period of time. But, no, I do not utilize someone else's refraction to determine stability.

DR. STULTING: What would be the proposal for people that don't have a refraction from the provider that is going to be doing the surgery?

DR. BELIN: I think we need to set up a baseline and a time to treat when you redo the refraction. So, two successive refractions over a period of time.

PARTICIPANT: Or old glasses could be -- but, you know, getting back to that 10 percent, if you are taking an 18 year old, myopia doesn't stop progressing until you get to be about 21 or 22 and -- I mean, that was my case and I see that all the time.

You know, the 10 percent wouldn't be a bad rule if people just thought of it as a guideline. It certainly would help in standardizing the study if you picked a myope that wasn't progressing. You know, if they are progressing when they are 30 years of age, probably because they are getting a nuclear cataract, these high myopes.

DR. BULLIMORE: That is not what the recent literature suggests. Two points for information. One is myopia does progress in a significant proportion of the adult population. By "adults," I mean people in their twenties and even in their thirties.

Data from the PERC(?) study, unoperated eyes in the PERC study progress by over a half a diopter over the ten year period. Now, that was with 30 year olds entering the study. And if you look at people in their twenties, you

see even greater progression.

This is an artificial classification because what we already discussed about the vagaries of repeatability of refraction, if we make it anything less than, say, half a diopter, you know, we are all going to say, well, we can't repeatably account for the same answer. So, it is meaningless.

I think we just need to have some ground rules that we can all live with and then move on to the next issue.

DR. MACRAE: How about for high myopia, 10 percent; so, that would be 7/10ths of a diopter for a 7 diopter myope.

DR. BULLIMORE: I could live with that.

DR. MACRAE: And then for low myopia it would be greater than a half diopter change.

DR. BELIN: I would stay with 10 percent, realizing that the lower limit can't be more than plus or minus a half diopter because that is the limit of our refraction basically.

DR. BULLIMORE: Half a diopter or 10 percent, whichever is the appropriate one.

DR. STULTING: What are we going to use the

baseline or comparison value if there is not a refraction available in the treating physician's office?

PARTICIPANT: Why don't you put down "known progression" greater than 10 percent or half a diopter, whichever is greater?

DR. STULTING: I guess the issue that I am raising is one that I frequently encounter and that is a patient that comes into the office, who does not have an available refraction or has a real old one or has an old pair of glasses or has one that is written down, but you are not sure it is correct.

DR. BELIN: There is not going to be an answer to that. I mean, there is no way we can do that. But what you want to exclude is the patients who you know are progressing who -- the way this is written now, you can have someone who three years ago was 3, four years ago was 4, a year ago was 5, today is 6, and according to that, that meets criteria.

DR. STULTING: So that the wording would be such that it would be clear that we are talking about someone who has some reliable indication that there has been progression.

DR. EYDELMAN: How would you define "reliable"?

DR. STULTING: Well, it sounds to me like people

are saying that there is no good way to define that in the guidance document.

DR. BULLIMORE: I think it is an impossible thing to do, given the repeatability of our measures and the target population. I mean, half a diopter per year in a low myope, that is equivalent to 5 diopters over a decade. That is a lot. I think, once again, the responsibility is on the sponsor to be prudent about this and buyer beware, if they start recruiting people with raging progressive myopia because that is obviously going to hurt them down the road in terms of their outcome measures.

I think just set some guidelines, encourage them to be prudent and move along.

DR. STARK: If you just put "known," then let the sponsor -- or we can determine what "known" means, is by best evaluation of past refractions.

DR. RUIZ: I am not totally comfortable with 18 years of age. How does the rest of the panel feel about that?

DR. STULTING: Discussion or comments?

DR. MC CULLEY: For simple myopia, it was 21 -- it was 18, I guess, and for myopic astigmatism, it was 21, because of the data that was available. So, we already have

different numbers.

DR. RUIZ: My concern is, number one, they are minors and, number two, they -- Walt said it, a lot of them, most of them are probably not stabilized yet.

DR. MC CULLEY: At 17 and over, they are responsible for themselves.

DR. RUIZ: They can sign their own consent form, don't need parental --

DR. MC CULLEY: At 17, a person becomes responsible for themselves.

DR. RUIZ: At 17?

PARTICIPANT: Isn't that a state regulated issue?

DR. RUIZ: I think it is.

DR. MC CULLEY: Well, I mean, there are ages of consent and all sorts of things that vary by state, but I think that by -- my impression is that from a legal standpoint, that at 17 that they are responsible adults.

DR. BULLIMORE: I don't think Dr. Ruiz is raising it from a legal standpoint. I think he is raising it from a myopia progression standpoint, which I think 21 sounds more reasonable than 18 in that regard. The problem is, of course, when it comes to the labeling, if the manufacturer wants it down to 18, they have got to recruit patients

presumably in that range.

DR. GORDON: My comment to that is if you are establishing a definition or a limit on progression of myopia, then you are going to address patients between 18 and 21, who would not be eligible and on the other side, I think, just from a sponsor's perspective -- and I am now only speaking as one sponsor -- we don't want to enroll patients with progressive myopia. It really has a dreadful impact on your outcomes. So, I don't think it is a big issue. But I think the critical issue is to exclude the progressive myopia irrespective of the age.

DR. RUIZ: How does the sponsor feel about the market at 18 versus the market at 21?

DR. GORDON: The mean age of patients having refractive surgery is close to 40. It is like 39.5 years or something. That has been across many, many, many studies and including our own data. So, I think it is not a big issue.

DR. BELIN: Can we technically exclude a population, a portion of the population, who otherwise meets all criteria, strictly because of age? I mean, it is like restricting -- excuse me?

DR. GORDON: What for, if you have addressed it --

DR. BELIN: No, I am asking kind of a rhetorical -- it is like restricting it by gender, race, et cetera. If they are adults and they meet all other criteria, which many of them will not, because they are not stable at 18, but if they meet it, I would leave them.

DR. STULTING: Any other comments? I detect a sentiment to leave it as is, at 18.

DR. MACRAE: Is that for PRK and PARK or --

PARTICIPANT: Well, it depends on data.

DR. STULTING: That would be for everything that the document affects.

DR. MC CULLEY: The 18 and 21 was a product labeling issue because there wasn't data.

DR. STULTING: Okay. And I believe that the consensus for the definition of "progression" would be 10 percent of the preoperative spherical equivalent or a half a diopter, whichever is greater, using as a baseline, reliable measurements, if available.

DR. EYDELMAN: Can I ask the panel to address the hyperopia issue, as well, please?

DR. STULTING: Hyperopia. Okay. The floor is open for discussion of hyperopia.

DR. EYDELMAN: The reason that there was a strong

opposition to it being the same, that was expressed at the Eye Care Forum, is due to the latent hyperopia and whether the previous refraction was cycloplegic manifest at 18 years of age, how much latent hyperopia was there and if you are - - it comes back to known refraction. If you are taking a patient who first walks into your office, unless you wait the year before you operate on them, what are the chances that at age 18, they are going to have a documented cycloplegic refraction?

DR. STULTING: Dr. Belin.

DR. BELIN: I agree with you, hyperopia becomes much more difficult to define because of that, but you are not going to find a whole lot of hyperopes in that age period that don't have the accommodated reserve. They are going to come in and require surgery. But I agree, that becomes a very difficult point to address.

I think the way we worded it, leaving it somewhat nebulous, asking us to define it historically stable is probably all right, but I think anyone who is doing a hyperopia study has to realize that if you have someone below the age of 25 or even in the late twenties coming in with hyperopia, you have to be real careful in making sure that you have gotten full correction and that they tolerate

the full correction.

DR. EYDELMAN: So, is then the panel's recommendation to compare cycloplegic within 10 percent of the previous cycloplegic or refraction for hyperopia or within 10 percent of previous manifest refraction?

DR. BULLIMORE: Dr. Eydelman, what literature does exist and, unfortunately, most of the people that study refractive error in myopes and the hyperopes and, therefore, hyperopes get ignored -- what literature there is suggests that hyperopia is relatively stable and progressive hyperopia in the under 45s is not an issue.

DR. EYDELMAN: That is why the not application recommendation was made.

DR. BULLIMORE: So, I would be happy in terms of stability of refraction to leave as is and address any concerns you have through the manifest versus cycloplegic --

DR. EYDELMAN: I agree with you and that is why the recommendation, but I heard that not everybody on the panel was in consensus, was not applicable being appropriate.

DR. BELIN: I still think you want something there. I think it is applicable. You don't want to have progression because there may be other reasons for the

refractive to be changing. So, you do want to make sure you have a stable refractive base.

DR. STARK: And I think another issue -- I mean, the hyperopes aren't going to come in until they are 45, 40 to 45, but the other issue is if you are treating older hyperopes, which in the 50, 55 range, the stability of refraction is important because they get nuclear cataracts and they begin to get less hyperopic with time. So, those are issues that need to be considered for doing PRK on a 55 or 60 year old hyperope.

DR. RUIZ: Also, the cycloplegia that is used, you know, if you are 50 years old or 45 years old, a dry cell is fine, but if you are 18 or 20 years old, you are not going to get a full cycloplegic refraction with that drug.

DR. BULLIMORE: I will repeat what I said, but also I want to counter Dr. Stark's assertion that myopia increases over the age of 45. That may be true in a cataract population, but recent cross sectional and longitudinal data suggests that refraction actually moves in the hyperopic direction over the age of 45 years of age. That is data from Baltimore and Beaver Dam.

DR. FERRIS: But that is cohort effect. That is not necessarily progression.

DR. BULLIMORE: Yes, but we have longitudinal data from our sample, which suggests that it is actually longitudinal effect rather than the cohort effect.

DR. STULTING: Any other comments?

Let's see. Those that think there should be a stability limit for hyperopia, please raise your hands. Those that believe there should not be, please raise your hands.

PARTICIPANT: What was the question again?

DR. STULTING: Those that believe there should be a stability limit of some sort for hyperopia please raise your hand. That is five.

Those that do not believe there should be a stability limit, please raise your hand. That is three. So, the sentiment is slightly toward a stability limit. Those that believe there should be a stability limit, what do you think that should be? Do you think it should be the same for both? That is easy.

Does anybody think it should be anything other than what we have already recommended for high myopia and low myopia? Okay. Sounds like the sentiment is for the same limit but only by a small margin.

The next slides. We are going forward with

inclusion criteria. The first is normal video kerotography. Are there any objections to that?

[There was no response.]

The next one is the minimum best spectacle corrected visual acuity; 20/40 for low myopia; 20/60 for high and 20/40 for hyperopia. These are inclusion criteria.

Dr. Belin.

DR. BELIN: I am not comfortable with that.

DR. STULTING: Okay. What is your alternative?

DR. BELIN: 20/25, 20/30 or I can go 20/40 and 20/25. I just have problems with taking someone who is 20/40 OU and has a minus 3 and we have criteria that allows that person to lose two lines and still consider it a success and that, to me, is -- we are taking someone whose has legal driving and putting them below legal driving vision bilaterally and saying it is a success.

PARTICIPANT: Ditto.

DR. FERRIS: What is wrong with it? Why does this low myope have 20/40 vision best corrected? There is something else going on.

DR. STULTING: Well, they could be, for example, people that have got macular disease, people who have had previous retinal detachments.

DR. FERRIS: Right. That is fine if you want to do them as patients, but if you want to do them in a study where visual acuity is an outcome variable, it would seem inappropriate to put someone who has some other reason for decreased vision in a study where visual acuity is an outcome variable, at least inappropriate to me.

So, I would have thought that you would make these criteria the lowest or the highest -- the worst vision that would be consistent with the myopia. I assume the reason the high myopes are higher is because with high myopia, particularly given the minimization issue, that they don't read 20/20, even though they otherwise have a pretty normal looking function.

DR. STULTING: Or because they have myopic retinal degeneration.

DR. FERRIS: Well, that is the issue where -- you know, I wonder whether you want to put somebody -- that is not do you want to do this for them after it has been approved, but in a study where you are using visual function as the outcome, it seems to me you want to take people who have normal visual function to start with, so that you can assess it.

DR. STULTING: Dr. Eydelman.

DR. EYDELMAN: I just want to point out this addresses OU. So, we are simultaneously talking about the operated eye and the other eye, i.e., even if they are operated.

DR. MACSAI: But still you are taking --

DR. EYDELMAN: Right, but they are two separate issues. Perhaps you want them to specify minimum acuity for the operated eye and the minimum acuity for the non-operated eye, i.e., if you have somebody 20/20 and their other eye is 20/40, according to -- if this is left the way it is and it is changed to 20/20, that subject is no longer -- can receive treatment because his other eye does not meet the 20/20 criteria, regardless of your plans for future surgery for that eye.

DR. FERRIS: Well, I would think it would just be the study eye that has some sort of visual acuity criteria for it. I don't care what the other eye is.

DR. RUIZ: Well, visual acuity OU is meaningless, anyway.

DR. FERRIS: They could be blind in the other eye and presumably --

DR. EYDELMAN: No.

DR. FERRIS: Oh, I see. The idea of this is that

if they have some decreased vision in the other eye, you don't want to put the good eye at risk.

DR. EYDELMAN: Correct.

DR. FERRIS: So, this is not talking about the study eye. This is talking about the --

PARTICIPANT: It is talking about both.

DR. EYDELMAN: It is talking about both. That is what I am trying to point out.

DR. FERRIS: I think it ought to be separated then. I think it ought to be talked about -- the study eye has to be something and the --

DR. BELIN: But there is an argument for having both eyes with good vision and we have heard, at least, three times today when we were talking about endpoint variability that, well, it is variable because we even looked at the other eye. We all know that as we lose our acuity, our ability to define refractive endpoints are not as sharp. And we repeatedly, at least on three occasions, utilized the other eye as showing the variability of the endpoints.

If we have someone who is 20/20 and a number of other eyes that are 20/40, 20/60, those endpoints are not going to be as sharply defined. And it is a study and we

need to get good data. The only way you can get good data is to get good entrance criteria.

DR. MACRAE: Just to move this along, I would go along with what Mike suggested, 20/25 in the study eye and no worse than 20/40 in the non-study eye. That way you would -- that way, if the patient did lose, let's say, two lines of vision in the study eye, it would go down to 20/40 and in the non-study eye if they -- inevitably the non-study eye, the patient is going to want treatment.

DR. FERRIS: I was going to say, are you doing treatment in one eye only in this study?

DR. MACRAE: No. In both eyes.

DR. FERRIS: So, why not -- then why aren't they both study eyes?

DR. MACSAI: So, why not just have 20/20, 20/25 OU?

PARTICIPANT: Yes, that is what I would do.

DR. MACSAI: I don't understand it. You can do anything you want after the device is approved, but let's get, you know, normal people in the study.

DR. GORDON: Just two comments. First of all, I am surprised to see this going in the direction of tightening what has been a criteria that has been in use for

a number of years, without getting into any specific PMAs, but, again, I guess I am free to speak about our own data, but this -- I am not aware of any problems that have resulted from enrolling these patients. And, granted, I agree, and I think a sponsor can certainly in wishing to assure good outcomes be more selective in enrollment, to have a better outcome.

But I worry about going in the other direction and comparability of data over time and generalizability because, in fact, patients are going to be treated and does limiting enrollment then have an impact on labeling in terms of what patients can be treated after approval? And Malvina is nodding her head "yes" and given that that is the case, is there some basis for tightening this criteria from what it has been for -- I guess we must going on almost a decade of experience in treating these patients.

DR. STULTING: I think it is also a fallacy to say that if you have known published data where the percentage of eyes that lost two or more lines, say, is 5 percent, then you can assume that 5 percent of people who begin at 20/40 or 20/60 are also going to lose two lines because the usual reason for that loss is mild or regular astigmatism. It is only going to be detectible in people who have visual

acutities of 20/20 or better frequently. In fact, most of the two lines of visual loss in the published data that I am aware of is, in fact, attributable to those people who have excellent vision before the study began.

For what it is worth, I would like to throw that comment out.

Any other comments?

DR. GORDON: One last comment. Although, obviously, the intent of the protocol and of this discussion is to -- you know, to limit so that this panel does the right thing and protects patients, et cetera, I think it should be given consideration, in light of the fact that there haven't been issues with enrolling these patients until now, that it becomes more and more difficult over time as there are commercially available products to enroll patients in studies. So, tightening criteria where there is no basis for doing so -- I think where there are concerns, it is appropriate. It benefits patients and sponsors, but tightening criteria in the absence of any reason to do so in an era of increasingly difficult enrollment, when patients can go anywhere they want and not participate in a study and have the same treatment, I think should be given some consideration. It is a practical issue.

DR. BELIN: I think it is a very practical issue. I think the entrance criteria is supposed to exclude eyes with ocular pathology. There should be no reason anyone who is otherwise healthy and is 6 diopters or less myopiate, doesn't have normally corrected vision. And if we enroll someone who has a best corrected of 20/40, there is some reason that person is 20/40 or not.

We have enough trouble interpreting good data from our past experience. We will have a hell of a worse time trying to interpret poor data. And if everyone's entrance point is at a different level, it becomes even more difficult to determine valid endpoints.

DR. FERRIS: For example, the safety issues, which were alluded to earlier, if you start enrolling people who are 20/40 at the start, it is pretty hard to use that as a cut point for some sort of safety issue.

So, I wouldn't argue that when a device is approved that there would be some reason to say that you can't use this on people that are 20/40, but I would argue that when you are evaluating a device and you are going to use visual function as an outcome, that you ought to be dealing with patients where you can use visual acuity as an outcome.

If you take people who are 20/40 ambliopes, I don't think you can assess what has happened to their visual acuity after this procedure. I think the data is virtually useless unless they have a -- it is probably even hard for them to have a big --

DR. GORDON: Just another comment.

There is an exclusion criteria that is in the current standard and that I don't believe is being proposed for any change that speaks to any residual, recurrent or active ocular disease or corneal abnormality. And the intent of that is to exclude any ocular pathology and I think that is a statement that could be tightened. But maybe FDA can comment, but it is my understanding from Malvina's head nodding just a moment ago, that limiting the inclusion of patients does have an impact on labeling and commercial use afterwards.

DR. FERRIS: It may have -- we have talked about labeling and use and those are clearly different things. I suspect that it doesn't matter what the label is in terms of whether people would use it. But --

DR. GORDON: But I think sponsors would prefer to have the product studied how it is going to be used and be able to discuss that as opposed to have, you know, off-label

use. And we are trying to get away from that.

DR. FERRIS: Well, the fact is that I am sure in previous studies and in any new study, given the down side of enrolling such patients, that you would not have the capability of analyzing as a subgroup those patients who started with decreased vision. And I suspect that has not been done. I know I haven't seen such analyses. The sample size would inevitably be so small that you would be so limited in terms of what you could say that what you said would be virtually meaningless.

I just think the whole thing is a non-issue here.

DR. BULLIMORE: I agree that we should tighten up the criterion for ocular disease and I think having a visual acuity for what is normal and abnormal is a step in that direction. I think we ought to adopt a tighter visual acuity criterion for all of these categories.

DR. MACSAI: Malvina, what does the current guidance document say regarding inclusion criteria?

DR. EYDELMAN: 20/40 is not a change. The changes are for high myopia and hyperopia. But 20/40 is the current.

DR. GORDON: That is why I was questioning why the tendency now after there is a basis of experience with the

device to tighten from where it has been.

DR. MACSAI: Because we didn't write that.

DR. BELIN: I have been involved in a few studies and though it may be 20/40 in the guidance document, I can't enroll patients at 20/40 nor can I enroll patients at 20/60. And I think there is a realization on the sponsors that if you do 20/40 and 20/60 patients, you don't get -- you may not get reliable interpretation of the data. So, I think we are -- just because it is an existing -- we are changing existing guidelines and I think this is one that we can improve on not for necessarily making it more difficult, for making it easier for us to interpret the results.

DR. MACRAE: Even though you may lose a few patients, 20/25 or better, I think it is reasonable and in both eyes -- there just aren't that many patients that you are going to exclude as a result of this. So, I don't think it is going to have a significant impact on recruiting and if it does, it is probably -- there is probably a good reason from what Dr. Ferris has been saying. So, I would go with 20/25 in both eyes.

DR. SUGAR: You really mean in each eye.

DR. MACRAE: In each eye, right. 20/25 or better.

DR. STULTING: Is that for low myopia or high

myopia or --

DR. MACRAE: Low myopia. High myopia is a whole different animal.

DR. STULTING: Would you like to make some proposals for that?

DR. MACRAE: I can tell you what the information I have is about from Zaldivar's(?) study. He had about 37 percent of patients in his moderate -- or about a minus 10 group that were 20/40 -- only 20/40 or better best corrected. So, it is a different group altogether.

DR. BULLIMORE: I could live 20/30 or even 20/40 for the high myopes, acknowledging that there is issues of retinal image size, but I don't want to go to 20/60 for the reasons we have discussed for the low myopes. It is difficult to pick up on issues of safety if you are starting off with a group with relatively dodgy(?) acuity.

DR. STULTING: What do you believe would be the change in visual acuity that would be accounted for solely by a myope that is between, say, 10 and 15 diopters? How many lines, what percent change or whatever you want to express it?

DR. BULLIMORE: Dr. Stark has the figures at his fingertips, at least he did --

DR. STULTING: Let's say a 15 diopter myope, how many lines would he lose or what percentage change in his visual acuity would you calculate --

DR. STARK: If you went from the spectacle to the corneal plane, it is 1 diopter equals 2 percent. So, there would be a 30 percent increase in magnification of the image size. So, that should theoretically be 1 1/2 lines of improved visual acuity.

DR. BELIN: Which makes sense if we are doing 20/25 for one and 20/40, which basically covers that line and a half. So, I would propose 20/25, 20/40 and 20/25.

DR. MACRAE: Could you say that again, Mike?

DR. BELIN: 20/25, 20/40 and 20/25 for the hyperopes.

DR. STARK: In Zaldivar's study, 37 percent of patients preoperatively were 20/40 or better. In his study, best corrected vision, in his study 75 percent of patients postoperatively were 20/40 or better actually uncorrected, which is amazing, but --

PARTICIPANT: Was he using EDTRS charts?

DR. STARK: I doubt it.

PARTICIPANT: There is a significant optical effect going on.

DR. STARK: Maybe the thing to do is to encourage the sponsors to do a contact lens refraction.

DR. EYDELMAN: If I can just point out, as is, it currently reads best spectacle corrected visual acuity. If you start changing numbers implying a different definition, then we must change the definition of what we mean.

DR. MC CULLEY: Can we agree on Mike's suggestion, 20/25, 20/40, 20/25 reading left to right and go on?

PARTICIPANT: For each eye.

DR. MC CULLEY: For each eye.

DR. STULTING: 20/25, 20/40 and 20/25. Is that the consensus?

DR. MACRAE: So, let me just clarify. So, with high myopia, you are going to exclude a large number of high myopes from these studies.

DR. STULTING: I think we are making --

DR. MACRAE: Over 50 percent.

DR. STULTING: I think we are making a big mistake and I would go on record as supporting the existing criteria.

We actually have been requested to take some comments from industry and I see an industry standing. Would you please identify yourself and you are recognized?

MR. OVERICH: Hello. Mark Overich, Visex(?).

Historically, we started awhile ago with 20/40 and the reason was because patients came in, would have one eye to 20/40 and the other eye at 20/20. We did not want to dictate which eye was treated first. So, if you have some small degree of amblyopia or, hopefully, no other pathology but small amount of amblyopia, the patient might decide which eye to be treated first. And it is a very practical consideration.

Most patients do not want to have their better eye treated on an investigational device. So, this would limit us pragmatically. So, we strongly suggest that you reconsider. The minimum of 20/40 was designed so that we could get and recognize that most patients want both eyes treated at the end of the study, but you don't want to have to turn to certain patients and say, well, gee, terribly sorry; yes, you are right. You did fit 20/20 in one eye, but you have to wait and not be treated.

I understand it is a study, but we are still looking at, hopefully, only amblyopic eyes and they can certainly be segregated and have been. So, I would strongly suggest you rethink this. I think 20/40, if you wish to put it straight across is reasonable. Please recognize that

hyperopes do have a significant amount of amblyopia if there is any amount of anisometropia(?), even 2 diopters, we found out.

So, you might want to loosen up a little bit with the hyperopes. The high myopes, 20/40, I think we can live with but if you start talking about 20/25 in high myopes, we will be here a very long time before we get enough numbers to really discuss. So, please do rethink that.

DR. STARK: Another issue that you sort of peripherally mentioned was that we may find that high myopes who began with 20/40 or 20/50 best corrected wind up with better best corrected after the study than we originally anticipate, theoretical considerations aside. And if we don't enroll those people, then we will never know that. It will not fog the eye as much as in a normal eye. So, those patients may not report a decrease in visual acuity with haze. So, you may actually -- if you do too many ambliopes, you could get a significant haze that may not be picked up associated with the reduced visual acuity.

So, I am like Rick, I would try and limit the numbers to a minimum or exclude them if you could on patients with amblyopia. It just adds too much of a variable.

DR. STULTING: The proposal, I think, on the table is 20/25, 20/40 and 20/25. Is that correct? Is there a consensus? Does anybody disagree with that?

DR. BELIN: Since I made the proposal, I would just like to make a -- change it in light of -- and I agree since I am involved in the hyperopia; 20/25, 20/40, 20/30.

DR. MACSAI: Can I just make the comment that you may want to consider for the high myopes because we all know that when we move them from glasses to spectacles there is improved -- excuse me -- from glasses to contact lenses, there is improved vision, you may want to have a contact lens refraction on enrollment. I mean, it may solve the whole problem of the 20/60 patients, who end up 20/30 because you have treated 15 diopters of myopia.

So, you may want to consider that at the agency?

DR. EYDELMAN: So, your proposal is to change this to a minimum contact lens corrected vision in each eye being -- would you like to fill in the rest of the sentence?

DR. MACSAI: 20/40 in high myopes for the middle category.

DR. EYDELMAN: How about the other categories, would you keep it as a spectacle corrected or would you propose contact lens for those as well?

DR. STARK: Well, in a hyperope when you use a contact lens, you are going to minify the -- so, with this treatment -- that is why I was -- Mike, I don't know if I would reduce it to 20/30 because you may actually knock some people down to 20/40 if you correcting 7, 8 diopters of hyperopia.

At one time I thought, well, we ought to compare preop vision for contact lens vision, but that would make the studies actually look worse. If you started putting contact lenses on these minus 10 myopes and they were getting a line better and then -- another reason it is not fair is because with the contacts, you would be neutralizing any irregular astigmatism. So, It is not really a fair comparison, which you couldn't do with the laser.

So, I would leave it at spectacle and let's stick with that.

DR. FERRIS: One other comment. With regard to these eligibility criteria, I can't say for sure that it happens, but it wouldn't surprise me if you had loose eligibility criteria, that the refraction that was done at baseline may be somewhat less aggressive than the refraction that was done after follow-up if the patients could get in. It seems to me that by making sure that the patient had

20/25 vision -- I don't know about these high myopes that don't get to 20/25. Most of the high myopes I see get to 20/25 if you refract them. I suppose of them don't. 20/40 is okay for me for the high myopes, but for the others, it seems to me that if we are going to be comparing visual acuity over time, we need a good refraction at baseline, too. And this doesn't guarantee it, but it makes it more likely.

DR. STULTING: Okay. We have to move on from this topic. Let me express what I think the consensus is and we will take a vote on people who agree and those who don't.

20/25, 20/40 and 20/25 spectacle corrected acuity. Who agrees with that? And those who don't, please raise your hand. Okay. There is agreement with that one.

We will consider the next criteria, cycloplegic correction.

DR. FERRIS: Doyle, can I ask one question and it relates to the one abstention and I am not sure -- or the one dissention and their previous vote --

DR. STULTING: Let's not go back. Really, we need to move on forward. The Agency has a lot of discussion and if it is okay with you, let's move forward. We really have to stop debate at some point.

DR. FERRIS: It is not debate. It is a question and the question is whether --

DR. STULTING: Please. Can we just -- really, can we just move forward. Is that okay?

DR. FERRIS: No, actually, I really would like to ask the question and that is for those high myopes who are less than 20/40, who the examining ophthalmologist wants to enroll, if the contact lens visual acuity is 20/40 or better, I would hate to have a rule that we make here, in fact, exclude half of the potentially eligible patients. I think that is a mistake.

All I want to do is go on record as saying that that is potentially a mistake and if it is true that we are going to exclude half, I would not want to vote that way and I don't know whether it would exclude half or not because I don't know what the distribution is.

DR. STULTING: Okay. The next issue, which I read before, is open for discussion. We are on the right slide, the top inclusion criteria.

DR. STARK: Does this correspond with page 6 of this --

[Multiple discussions.]

Doyle, we skipped --

MS. THORNTON: Top of page 7, Dr. Stark.

DR. STARK: But we skipped -- after we do this, could we go back to page 4 because we need to just clarify that two lines. I don't think we ever resolved -- we kind of bounced around more than two lines or two lines. But there is one important point on the top of page 4 that -- on the revised tables for all indications.

PARTICIPANT: We haven't done page 4 or 5.

DR. STARK: I thought they said we are on page 7.

PARTICIPANT: Hopefully, they are jumping and not skipping.

DR. STULTING: They will be coming up later. The order is a little bit different from what you have them in here.

DR. RUIZ: Mr. Chairman, why does a contact lens trial have to be used here? Subjects with latent hyperopia should undergo a contact lens trial with full cycloplegic correction. Why can't you just do it with spectacles?

DR. STULTING: That is a good question.

Dr. Eydelman, do you want to speak to that?

DR. EYDELMAN: There was an issue raised at the Eye Care Forum where there was an opinion from practice expressed, which is not really in the published literature,

that if you take a patient with a significant latent hyperopia and you treat them for the full cycloplegic refraction rather than their biggest push plus manifest, that they still seem to accept at post-treatment. And there was a large debate that comment provoked since nothing to that effect has really appeared in the published literature yet.

This was our attempt in trying to somehow mediate between the two.

DR. RUIZ: Yes, but what does a contact lens have to do with that?

DR. EYDELMAN: Well, if you truly state that a young subject is going to be able to tolerate full cycloplegic correction, even if when you are trying to do push plus and you cannot push them all the way to their cycloplegic correction, then theoretically if they have a trial with contact lens, that should really tell you if they are truly capable of tolerating that post procedure.

DR. RUIZ: Versus glasses? What is the advantage of contact lens over the spectacle?

DR. EYDELMAN: Well, it reduces all the optical aberrations and it --

DR. RUIZ: I don't think that is a very practical

kind --

DR. BULLIMORE: My impression is you are trying to explain somebody else's clinical anecdote and I think --

PARTICIPANT: Which has no basis really.

DR. BULLIMORE: Yes, which has a questionable basis. I mean, I could offer an explanation, but I think if the refraction is done in the spectacle plane, then spectacles should be an equally acceptable --

DR. EYDELMAN: So, the bigger question is if you take somebody with a significant latent hyperopia, do you then treat them for the most push plus manifest or do you treat them at that point in their life for their cycloplegic refraction?

DR. BELIN: You can bring them back -- if you are over three-quarters of a diopter, you bring them back for a post-cycloplegic and let them see over a period of hour whether they can adapt to the spectacle.

There is nothing to gain by putting contact lens on. If anything, contact lenses can confuse it because if the lens doesn't fit and then you adjust power, you adjust base curve and size, you are going to change the power of the lens and you are not going to ever be sure that you -- unless you cycloplege them again after they have the contact

lens on whether you truly --

DR. EYDELMAN: That was the intent.

DR. BELIN: That is a huge job to do.

DR. RUIZ: And very expensive. We know from experience with accommodative esotropia that they will accept the plus, if they put it on and wear it. I think that is a clinical judgment thing.

DR. STULTING: Is there anyone who is in favor of adding this inclusion criteria?

DR. BULLIMORE: I guess the bigger question is intent to treat. Are we intending to treat latent hyperopia? Are we going to correct to the manifest, to the cycloplegic or are we going to leave that to the judgment of the investigating doctor?

DR. STULTING: I don't think that the document addresses that at the current time.

DR. EYDELMAN: Well, this was an attempt to address that issue given that the cycloplegic is the intended treatment.

DR. MACRAE: I would suggest that I would let the sponsor determine what they want to evaluate. If they want to treat latent hyperopia, they can have a strategy to do that. If they want to do regular hyperopia, they can have a

strategy to that. I don't -- I am not interested in instigating treatment policy. I think we should let the sponsors do that.

DR. BULLIMORE: This is really analogous to the case with the treatment for myopia, where the sponsor might choose to be conservative in their myopic correction and then do enhancements. They can come up with any strategy, knowing full well that their outcomes are going to be uncorrected visual acuity and refraction and if they want to aim for the manifest rather than the cycloplegic, then that is their call.

DR. EYDELMAN: So, from what I understand then, this statement can merely -- the first part of it can be deleted and the second one would be sufficient, as far as subject protection and subject information?

DR. RUIZ: I think that is correct. You know, there are so many variables here. There might be 30 years old with 3 diopters of latent hyperopia, you know. There might be --

DR. STULTING: So, in summary, there is sentiment for the second sentence but against the first.

Can we go to the next slide? These are exclusion criteria.

DR. EYDELMAN: And there are no changes since the current guidance. So, if there are no questions, we can proceed.

DR. MACRAE: I have got one under "Systemic Medications." There has been some confusion whether systemic steroid inhalants or steroid inhalants are a problem and I have talked to several allergists and they all agree that steroid inhalants don't get into the systemic circulation enough to really have any effect on wound healing. So, I would not exclude that group.

DR. RUIZ: I don't know if we know that, Scott. We certainly know it will raise the intraocular pressure significantly.

DR. STARK: And there is a recent article in The New England Journal of Medicine that shows an association with posterior subcapsular and even some nuclear cataracts. Now, they didn't really divide it out. They didn't show as good of a correlation on those that had not been on systemic storage, but that may be something worth considering because those people are liable to get a cataract earlier.

DR. RUIZ: I think this term "ocular disease" is too broad. I am not sure I know what that -- whether every ocular disease ought to be an exclusion criteria.

DR. STULTING: Let's refer to page 10 of the existing document, where these things are --

MS. THORNTON: Page 10 or page 7 of the --

DR. EYDELMAN: Or page 8 of the proposed changes.

MS. THORNTON: Page 8? 8 is the examination schedule.

DR. EYDELMAN: I am sorry. I have a different printout.

DR. STULTING: Yes, 7, 7 of the proposed changes and 10 of the existing document give them in a little bit better detail.

DR. GORDON: Mr. Chair, I would like to make a comment. I was going to suggest that we totally delete "glaucoma suspect" and in place of -- in reference to Dr. Ruiz's earlier comments, visual field defect or optic nerve pathology, indicative of glaucoma and just leave it at that and just totally avoid this whole arena of glaucoma suspect. I think given the fact that we are now in the blue and yellow visual field arena, we are going to be seeing more and more glaucoma suspects that aren't necessarily glaucoma.

DR. STULTING: As I understand it, the proposal is to change the exclusion criteria for glaucoma, which now says history of glaucoma or an intraocular pressure of

greater than 21 millimeters in the old document to visual field defect or optic nerve abnormality indicative of glaucoma.

Is that correct?

DR. GORDON: Yes. I said optic nerve pathology but either is fine.

DR. STULTING: Optic nerve pathology.

DR. FERRIS: For ocular disease, could we say any ocular disease which might confound the assessment of visual acuity or visual function, to try to get at what Dr. Ruiz was saying. I think that is the intent of the ocular disease.

DR. SUGAR: It is not necessarily the intent. The intent is also that some diseases, like lephritis(?) and surface disease make a difference.

DR. STULTING: Confound the outcome or might increase risk. Is that fair?

PARTICIPANT: Yes.

DR. STULTING: So, the recommendation is to change the disease to those that have those characteristics we just mentioned.

Any other comments on the diseases?

DR. RUIZ: What are subjects at risk for

developing strabismus post-treatment? What does that refer to?

DR. STULTING: I suppose those are hyperopes that are going to be strabismic if you fix their -- I don't know.

DR. EYDELMAN: That was the idea, yes, if there was some kind of --

DR. RUIZ: That is what it refers to? Accommodative or what do you call it, divergence excess, accommodative insufficiency or -- I don't think that is very appropriate.

PARTICIPANT: People who have prisms in their glasses.

DR. STULTING: Or people who accommodate to maintain alignment.

PARTICIPANT: Hyperopes who are exotropic.

DR. STULTING: Who accommodate to maintain alignment.

PARTICIPANT: Why not say subjects with strabismus?

DR. STULTING: Well, they don't have it. They have latent strabismus. They have --

DR. MACSAI: But this is fine. They are at risk for developing strabismus if you treat them. They won't

need to accommodate. They will --

PARTICIPANT: Leave it the way it is.

DR. HIGGINBOTHAM: Mr. Chair, I would suggest regarding Item 4 that we state previous intraocular or corneal surgery or previous intraocular excluding laser surgery or corneal surgery because certainly a person, for instance, that has had laser trabeculectomy(?) could have this procedure. So, I would exclude laser.

PARTICIPANT: But they would be excluded by their glaucoma.

DR. HIGGINBOTHAM: Not necessarily. You have some of your colleagues out here treating patients with elevated pressure with no visual field change or optic nerve change.

PARTICIPANT: [Comment off microphone.]

DR. HIGGINBOTHAM: No, not in the study, but I am just suggesting that these are individuals that could be included in the study.

DR. MACRAE: What about a patient that has had a retinal hole or something? Those patients could be included.

DR. MACSAI: -- with a hole at the edge that is walled off.

DR. HIGGINBOTHAM: That is why I am suggesting

excluding laser. I mean, all of this is subject to the judgment of the practitioner, but I didn't want to have anyone's hands tied by stating all intraocular surgery. I think there are certain laser procedures that would allow some individuals to be included.

DR. EYDELMAN: If I can just comment, as it reads currently it says any residual, recurrent or active ocular disease.

DR. STULTING: I think we are down on No. 4 now.

PARTICIPANT: No. E on the list.

DR. EYDELMAN: No, I am referring back to Dr. Macsai's comment.

PARTICIPANT: I would go back to what Rick Ferris said, that -- with the intent, we would exclude patients where they have an ocular problem either from previous surgery or a disease that would affect -- that would have an impact on the outcome.

DR. BULLIMORE: Yes. Confound the safety and efficacy endpoints, was the verbiage I was --

DR. MACRAE: I think that is very helpful in terms of getting around a lot of these detailed issues.

DR. STULTING: Does everybody agree with that kind of wording?

PARTICIPANTS: Yes.

DR. STULTING: I understood what you said, Dr. Higginbotham.

DR. HIGGINBOTHAM: Well, thank you.

DR. STULTING: The point that she was making was directed at Item No. 4 down here. So, I think that the recommendation I am hearing is that the verbiage we recommended for disease, that is, those that would be reasonably considered to affect the safety of the procedure or the outcomes of the procedure should also be applied to previous surgery.

Any other comments?

DR. STARK: For medication, you might want to include the Amiotorone(?) products that come into the cornea, any of those cardiac medications that --

PARTICIPANT: Why?

DR. STULTING: Maybe we should add drugs to that list of things that have those same qualifications.

DR. MACRAE: That would fall into what Rick is talking about also.

DR. MACSAI: But Amiotorone doesn't affect vision. It causes a vortex keratopathy(?) that -- why exclude it?

MR. OVERICH: Mark Overich, Visex.

We have two patients in Canada with severe loss of best corrected acuity on Amiotorone.

DR. MACSAI: From Amiotorone?

MR. OVERICH: Yes, specifically. The border seal pattern does decrease best corrected acuity. We believe strongly it should be a contraindication.

DR. MACSAI: Okay.

DR. STULTING: How would it be if we added drugs to the list of diseases and surgery and included them in that same verbiage that could reasonably expected, et cetera, et cetera?

PARTICIPANT: Good.

PARTICIPANT: Perfect.

DR. STULTING: And we take note of the Amiotorone as one of those drugs in case people are unaware of that.

Any other comments? If no one has any other comments about these, then we will go to the next slide.

DR. SONI: Doyle, I have a question.

I am not sure whether I have missed it, but this exclusion criteria somewhere address the issue of monocular patients, patients who may not have good enough vision in one eye and yet have 20/20 in the other eye?

DR. STULTING: It is my understanding that this

particular document is directed toward bilateral people who don't have previous disease and the Agency would accept proposals for protocols that deal with monocular patients and those that have disease and other things separately. Is that correct?

DR. EYDELMAN: That is correct.

DR. STULTING: Maybe I should say that for clarification. This document does not preclude the submission of protocols that would deal with the treatment of patients with previous corneal surgery, retinal diseases, visual acuities less than 20/20 and other abnormalities that would exclude them from these protocols.

We are getting nods of agreement from our FDA personnel.

Okay. Next slide, please. Let's look at these and see if there are any questions or comments about these exclusion criteria.

DR. MACRAE: In terms of participation in other trials, if a patient is participating in one eye, let's say, as a minus 4 and the other eye is a minus 7 and the physician believes that lasic is a better alternative for that patient, would that exclude them from participating?

DR. STULTING: Is that an eye specific exclusion,

I guess, is the question, maybe in one trial for one eye and another trial for the other.

DR. MACRAE: Well, basically because we do have patients that are -- you know, I have patients that are in two separate trials, one in lasic and one in -- some patients are in PARK(?) and some patients are in PRK trials. I don't those should be an exclusion.

DR. EYDELMAN: I think this was meant as an eye specific. We can clarify it if you prefer.

DR. STULTING: Are you talking about eliminating people that are, for example, in a drug trial for some unrelated reason?

DR. EYDELMAN: Yes. Correct.

DR. STULTING: How about angle closure, is everybody happy with that?

DR. MACSAI: In the hyperopes?

DR. STULTING: I had a question of why it would be an exclusion criterion for one protocol and not for another. I didn't understand exactly why that might be.

DR. HIGGINBOTHAM: It is more common in hyperopia.

DR. STULTING: I know that but if it is an exclusion criterion --

DR. MACRAE: Why wouldn't you want to know what

effect it has on the population? I don't know that there is any direct effect.

PARTICIPANT: What difference does it make?

DR. MACRAE: Why would you exclude it?

PARTICIPANT: If they actually had angle closure glaucoma, I think you would want to exclude that eye.

DR. SUGAR: If they had previous, but hyperopes are at risk for angle closure glaucoma. Do you want to exclude hyperopes from a study of hyperopia?

DR. HIGGINBOTHAM: I would delete it. I mean, it is going to be covered -- I mean, you are going to do a general exam, a comprehensive eye exam. I would just delete this.

DR. STULTING: Dr. Eydelman, do you want to make a comment about that?

DR. EYDELMAN: I guess where the concern came from is since it is likely that they are going to be receiving several cycloplegic refractions, it is just an assurance of making sure -- an assurance of somebody assessing the angle prior to enrolling them in the study.

DR. FERRIS: You don't care about the myopes. You care about the hyperopes. If that is the case, it must be for everybody.

DR. EYDELMAN: I mean, you can certainly make it across. It is just that chances of that occurring are much, much smaller.

DR. STULTING: Do you have a comment?

DR. HIGGINBOTHAM: Well, I guess my comment is -- I mean, a lot of this we have to leave to the judgment of the practitioner. I mean, they are going to be having comprehensive eye exams and they would have had a dilated eye exam before and they would have had gonioscopy before. So, I think -- I would just delete it. That would be my suggestion.

DR. STULTING: If we delete it here, it still falls under the exclusion criterion that we discussed before because it is an ocular disease that may have bearing on the outcomes, et cetera.

DR. FERRIS: Absolutely. So, narrow angles don't exclude you. It is only if you have the disease. If you dilate them and they get angle closure glaucoma, then maybe you don't want to put them in the study. But if they don't, I don't see any reason not to dilate them again.

DR. STULTING: So, we are going to exclude that one and -- it seems to me that post-treatment strabismus is not something that you can determine before treatment,

except with regard to that exclusion criterion. We already mentioned subjects at risk for developing post-treatment, right? So, this we have already dealt with.

Next slides. Now, we are going back now, I believe, two pages back, to page 5 on the -- I beg your pardon -- page 4 and 5 on the discussion document to try to set reasonable safety target values and reasonable efficacy target values.

At the Agency's request, I want to make one more statement to clarify what has been said about the use of previous data. We cannot use PMA data that have been supplied to us as panel members or have been discussed in presentations before us. However, we can use data that we have access to from other publicly available information and we can use that in concert with our expertise that has been obtained from clinical activities and from available literature and from any other sources that we wish to use.

So, we are not going to reference, perhaps, the sources of that information but it is okay for us to say 5 percent, we believe, would be a reasonable number for this particular end point or something to that effect.

Does anybody have any questions about the ground rules for this?

[There was no response.]

Okay. Let's proceed.

DR. STARK: This is the slide that I was waiting for. I thought we had passed it.

[Laughter.]

You knew I had a meeting in Baltimore, but I wasn't about to leave.

Two lines is a 37 percent loss of best corrected vision. So, I would be comfortable with that if it said loss then two or more lines of best corrected vision, 5 percent.

DR. STULTING: Other comments?

DR. BULLIMORE: I agree.

DR. STULTING: I have a -- I think it is difficult to evaluate this because essentially what -- nobody argues with the 37 percent. We all accept that. The issue is determining what percent of those eyes that fall under that category represent random variation and what percent of eyes represent true loss of visual acuity to the procedure.

So, when I look at safety data like this for evaluation, there are other things that I try to use to sort that out. One of the things is the percent of eyes that gain two lines or more, taking into account, of course, the

magnification change. But if you have an application where it appears that the distribution of eyes gained and lost is symmetrical or even that there are more eyes that gain vision than lose vision, taking into account a magnification, then it makes me think that this is a random variation.

Given that, setting criteria like this alone becomes more difficult and has to take into account the variation that we ordinarily see in these studies.

Other comments?

DR. BULLIMORE: Doyle, if you look at the literature, I would suggest that using the ten letter criterion is entirely reasonable in this population. We have people who have certainly in the low myopia group good acuities. There is no a priori reason why they should be particularly variable, plus they have the magnification acting in their favor.

We should expect an improvement in their visual acuity based on the increase in retinal image size from transferring the correction from the spectacle plane to the corneal plane.

I think referring to the symmetry and both sides of the distribution merely sort of promotes the collection

of sloppy data. We should be promoting good practices in the measurement of visual acuity as in all of our measurements here. I certainly think 5 percent is a reasonable guideline figure.

DR. STULTING: Other comments?

DR. MC CULLEY: I would question -- well, just to raise the question that I raised to myself when I read this, the 5 percent, if it is at the endpoint, is too high for two lines loss. I would be more in favor of 2 percent.

DR. STULTING: Any other comments?

DR. STARK: That is music to my ears. I mean, that is what -- I agree with you, but I thought we -- Rick finally agreed with me after it has been -- we have been talking about this issue for a year. I used to want one line. So, two lines at 2 percent would be fine.

DR. MC CULLEY: What is the percentage for one line?

DR. STARK: 1 percent.

DR. MC CULLEY: 21 percent.

DR. STARK: No -- yes, about 20 percent lose one line.

DR. MC CULLEY: But 37 percent for two lines.

DR. STARK: Oh, sorry. It is a 20 percent loss of

resolving power for one line; 37 percent for two lines; 50 percent for three lines. That is loss of resolving power of the eye.

DR. SUGAR: Can we ask for clinical experience of people on the panel?

DR. STULTING: Yes. That is an excellent question.

DR. BELIN: I think the 5 percent is reasonable. I think, in addition, since we have tightened up the entrance criteria and in addition to it, it is not a single criteria. We are also saying only 1 percent or less, 20/40 or worse, that that is a reasonable endpoint. In my refractive practice, you do -- it is not that uncommon. I think it is at a higher level than 2 percent to see a loss of two lines and I think this is probably reasonable the way it is.

I have no problem with changing it for ten letters with just two or more though.

DR. STULTING: Dr. Ferris.

DR. FERRIS: Yes, I agree that we ought to put in parentheses whatever the number of letters is, whether it is ten or nine or eleven. The other thing is that perhaps the 5 percent does -- is a good compromise because it probably

includes the 2 or 3 percent that are related to the procedure and the two or three percent that are related to the error of measurement.

One final comment is that if you wanted to decrease the error of measurement, you could probably do replicate exams and that should decrease the error of the patient having a bad day, but that I would think would be up to the individual study.

PARTICIPANT: I will withdraw my concern.

DR. STULTING: Other comments from over here?

DR. MACRAE: I am in agreement with the direction of where things are going. So, I just agree with what Rick said and not change things dramatically.

DR. STARK: Would it also be agreeable on the second line to add best corrected spectacle visual acuity less than 20/40 or a drop of three or more lines, 1 percent? Because if you have -- that is outside the range. So, if you have more than 1 percent of people losing three or more lines, that is 50 percent lost.

PARTICIPANT: That is reasonable.

DR. STULTING: Say that -- I am sorry, I missed that. Repeat what you --

DR. STARK: The second line would be best

corrected -- best spectacle corrected vision of less than 20/40 or a drop of three or more lines or 30 letters or more and that would be 1 percent -- 15 letters. Sorry.

DR. FERRIS: Now, Walter, is this for people whose visual acuity was worse than 20/20 at baseline or this --

PARTICIPANT: You could say 20/20 or better.

DR. FERRIS: Because for those that are better, at least I took Scott's comment and other comments that if they -- you know, you could have a doubling of the visual angle and be 20/20 at the end of the day.

PARTICIPANT: But if you lost three lines --

DR. FERRIS: That is three lines, 20/10, 20/12 and you are 20/25ths at the end. That is three lines. That may be different than what the intent of this less than 20/40 is. It is a debatable issue, but, for sure, I think, it ought to include for those patients who come in at worse than 20/20, 20/25ths, for example, those that have a doubling of the visual angle ought to be part of that 1 percent.

DR. BULLIMORE: They are with the 20/40, aren't they?

DR. FERRIS: No -- oh, well, I don't know what -- what if you have 1 percent that come in at 20/40. The

person that comes in at 20/40 shouldn't be counted as an event here unless they -- at least I would think the implication is that they have a bad outcome, which is a doubling of the visual angle. So, they would have to go to 20/80, I would think.

DR. MACRAE: Practically speaking in that low myopic group, we are not dealing with that.

DR. BELIN: Actually, the chart does have high myopia also, which obviously needs to be changed since you can't have a safety factor that equals your inclusion factor.

DR. FERRIS: Right. That is what I was talking about. For the high myopes that can come in at 20/40, they can't be counted as a bad outcome.

DR. STULTING: Let's try to deal -- could we try to deal with one issue at a time? I understand the proposal to combine some. Can we start at least with the first line, loss of two lines or maybe it is more than two lines and a target figure for that.

DR. STARK: I think you can just change that to loss of two or more lines. Then that is correct.

PARTICIPANT: Ten or more letters.

DR. STARK: I am sorry. Two or more lines of best

corrected visual acuity.

PARTICIPANT: Parentheses, ten letters.

DR. MACRAE: That is for low myopia?

PARTICIPANT: That is everybody because the high myopes get the advantage of more magnification.

DR. BELIN: On the second line, I am going to suggest the way it is written in our handout, which is percent of eyes that have BSCVA, worse than 20/40 with 20/20 or better preoperatively or a loss of greater than three or more lines of vision. Then the numbers can stay where they are, less than 1 percent across the board.

DR. STULTING: Since that is going to be an "are/or," I would suggest that we add another line there that has the three or more lines, so we can at least figure out who is who in that group.

PARTICIPANT: Fine.

DR. STULTING: Is there any other sentiment for that one?

PARTICIPANT: Say that again, Doyle.

DR. STULTING: The recommendation was to have a criterion, the best spectacle corrected acuity of less than 20/40 or three or more lines. I was just recommending that we have two separate categories so we can at least figure

out who is who in that group.

Now, you realize, having said that, if we say three or more lines, that is --

PARTICIPANT: 15 or more letters.

DR. STULTING: Right. So, that is going to be 15 or more letters.

DR. STARK: That is going from 20/20 to -- the reason to combine them would be to -- if you said "or," it would take care of the high myopia because they may go from 20/30 to 20/50.

DR. STULTING: If you say "or," there is no advantage to combining them because you get the same -- if you say "and," then you get a different number if you combine them. Do you understand what I am saying?

DR. STARK: Well, you can say "and."

PARTICIPANT: He wants "or" so you can see it separately or add them together.

DR. STULTING: So, really what you are suggesting is another criterion. We have got loss of two or more lines and then we are going to have another one that says loss of three or more lines.

DR. BELIN: I am talking about the second line, which is BSCVA, less than 20/40, less than 1 percent. We

have already said you really can't have that if you have an entrance criteria of 20/40 for high myopia. What I am saying is the way that is written in our handout says that only applies to 20/20 or better preoperatively and what I am saying is to capture the other patients, we include, in addition, three lines loss of vision. That will allow us to incorporate those patients that are 20/25, 20/30 and 20/40 into this safety factor.

DR. FERRIS: It would seem to me you have to do that if -- let's say half of the patients are 20/20 or better. Is it half a percent then or is it 1 percent? And I think the idea is 1 percent of the total, have a doubling of the visual angle --

PARTICIPANT: So, you have to be able to include your total population.

DR. STULTING: Okay. So, we are now recommending three different line items on the chart, the two that stand here with the addition of line two to be specified for those who are 20/20 or better preoperatively and the addition of a third line that says --

PARTICIPANT: It is joined as one.

DR. STULTING: You want to join those and say "or"?

DR. BELIN: In essence, what you are doing is I think you are saying is we are trying to be able to look at every patient in the study who has had a doubling of the visual angle. Actually, we are being a little bit more lenient than that because we are saying if you come in at 20/ --

PARTICIPANT: 12 or 20/15, we are going to give you --

DR. BELIN: We are going to give it to you, but this is a major safety factor and we are saying that this now enables us to look at the entire patient population.

DR. STARK: Is that fair to do, though? I remember checking one of the quarterbacks for the Baltimore Colts and that guy was 20/10 every time I checked his eyes. Is that fair to say that if he dropped to 20/20, that was not a doubling of the visual angle? I mean, it really is and he may not have been happy with that.

DR. FERRIS: Well, I can tell you I am not happy with 20/20 when I --

DR. STARK: Okay. So then why should we -- going from 20/10 to 20/20 should be --

DR. FERRIS: But I might be perfectly happy if I was a myope wearing glasses.

DR. STARK: Exactly, but all we need -- but what we want to be able to do is tell the patient that there is a 5 or 10 percent chance that that is going to happen to you. So, let's just capture that information.

DR. EYDELMAN: That information would still be captured. It is a matter of whether that needs to be a safety endpoint.

DR. STARK: I see. Okay. Good point. So, I agree with Rick on that.

DR. STULTING: Is everybody clear with what is going on here? We are trying to set safety targets. I am still having trouble sensing what the recommendation here was to -- it modified the second one to include best spectacle corrected acuity less than 20/40 or greater than -- I am sorry -- three lines or more lost.

DR. BELIN: Let me reword it and I think that is what we are trying to say.

For patients preoperatively with 20/20 -- for patients with 20/20 or better preoperatively, the percentage of eyes that have BSCVA worse than 20/40 or for those patients that are worse than 20/20, a three or more line loss of vision.

DR. MACRAE: They are two separate groups

essentially. For the patients that are 20/20 or better, the regular criteria that you have and then for patients that are less than 20/20, those individuals --

DR. BELIN: Well, I will tell you what. Let me throw something out. Is this an easy way of doing it? Three line or more loss of vision and worse than 20/40. That covers everybody then and I think it makes more sense.

DR. STULTING: Okay. So, that is loss of more than two lines --

DR. BELIN: Loss of three lines or more --

[Multiple discussions.]

PARTICIPANT: It is not more than two because it is being converted to an EDTRS number.

PARTICIPANT: More than two was 10 or more letters. More than three was 15 or more letters.

DR. STULTING: More than two is 11 or more letters. Correct?

DR. EYDELMAN: We understand the previous recommendation and we will work on the language if that is acceptable.

PARTICIPANT: Thank you.

DR. STULTING: And the target numbers we are putting in there is 1 percent still. Is that correct?

PARTICIPANT: Less than 1 percent.

DR. STULTING: Less than 1 percent.

Okay. Induced cylinder of over 2 diopters.

PARTICIPANT: 5 percent seems high from what little of the literature I know.

DR. STULTING: Other comments?

DR. BULLIMORE: I assume we are dealing with spherical corrections here or is this meant to cover --

PARTICIPANT: This is cylinder.

DR. BULLIMORE: No, but this is induced cylinder and an attempted spherical correction.

PARTICIPANT: It is both with and without astigmatism.

DR. STULTING: It is not specified. So, I assume that this applies to --

PARTICIPANT: It is at the top of the table.

DR. BULLIMORE: And we need to be careful how we define induced astigmatism in the case of an astigmatic procedure because it is very possible that a relatively safe and effective procedure might quite possibly induce 5 percent of astigmatism over two diopters depending on how you define it.

DR. EYDELMAN: As it currently reads, it states,

"Induced manifest refractive astigmatism of greater than 2 diopters of absolute cylinder power."

DR. BULLIMORE: So, if I start at 1 1/2 and postoperatively on 2 diopters that means I --

DR. EYDELMAN: You induced half.

DR. BULLIMORE: I have induced -- so, it is relative to where you start. But what if there is a concurrent shift in axis. So, if I start a diopter with the rule and finish a diopter against the rule, is that -- that counts as 2 diopters?

DR. EYDELMAN: No, this only addresses absolute cylinder power.

DR. MACSAI: 5 percent to induce 2 diopters?

PARTICIPANT: Too high.

DR. MACSAI: It seems very high if you are talking about 2 diopters of absolute cylinder power.

PARTICIPANT: Can you induce that much cylinder power and --

DR. MACSAI: That is a lot.

DR. MACRAE: In terms of a safety target, I am not sure that this is a relevant issue. I mean, if -- the example of this, I mean, practically speaking, you would have to put the wrong cylinder into the laser to get that

kind of a result and I know that, hopefully, most studies are -- you are going to get less than 5 percent.

So, I don't think we should spend a huge amount of time -- I don't think this is a significant safety issue. If the patient does get the wrong cylinder, it is not a safety issue. It is an efficacy issue, I would argue. I would be concerned about it, but they can be corrected with glasses or contact lenses.

DR. EYDELMAN: Then the question is do you feel that any specific amount of induced cylinder is a safety target if you are attempting spherical correction because we have seen some under our numerous reports, some significant induced cylinder in an attempted spherical correction. How much is safe?

DR. MACSAI: If you start out spherical and end up with 2 diopters of cylinder, you are going to be unhappy, yes.

PARTICIPANT: It is a decentration(?) problem.

DR. BULLIMORE: Decentration is a very easy way to induce astigmatism in a spherical procedure. I have seen that in patients.

DR. MACSAI: One percent might be okay.

DR. STULTING: Is this to capture abnormalities

that crop up when you are treating spherical patients to start with?

DR. EYDELMAN: That is how it started out, but then it was suggested that it is really applicable across.

DR. MACSAI: Well, if you are attempting spherical and you end up with 2 diopters of cylinder, that is an adverse event, it would seem to me, and I would think you would only want 1 percent or less than 1 percent.

DR. MACRAE: If you look at the definition of adverse event, it is not a sight-threatening event.

DR. MACSAI: Maybe not. It is a complication for sure.

DR. MACRAE: It is a complication.

PARTICIPANT: How about greater than -- induced cylinder greater than a diopter?

DR. BELIN: I think you will see a lot of patients -- I think less than a diopter or a diopter or less, you will see a large number -- it is not unusual to see patients who are in the high degrees of myopia, even moderate, who do not take the cylinder because they have such a greater spherical component and when you correct their myopia, you actually get some residual cylinder expressed.

I don't have a problem with the way it is now,

which is greater than 2 as a safety at 5 percent. Again, this is a safety value. Well, it is a safety and this is not associated with the loss of best spectacle corrected vision.

DR. MACSAI: This is pretty -- kind of vague or loose maybe, this terminology here and maybe it should be tightened up somewhat or if it is going to be left this loose, then the percentage should be decreased.

DR. EYDELMAN: We are open to suggestions.

DR. MACSAI: 1 percent if you are going to leave the wording as such. 2 diopters is a lot.

PARTICIPANT: My gut feeling is that we don't have the information to be able to really create these criteria. So, I would rather defer --

DR. BELIN: Is there anyone on the panel or in the audience that has information on the amount of patients in the study that have had a diopter of induced cylinder?

DR. MACSAI: I didn't hear you, Michael.

DR. BELIN: There are probably a lot of people here who have been on different studies and there are people in the audience. Does anyone have information --

PARTICIPANT: You know, in PTK we can induce it. We do this blend and reduce the hyperopia and others and I

think as we start expanding these indications, hyperopia and others, we just have to watch out for a cylinder. I don't care where we put it. Mark, could you -- this is Mark Overich.

MR. OVERICH: Mark Overich, Visex. Correct that spherical treatment induction because you are saying at the top of it with or without astigmatism. So, obviously if you have a skew towards a high astigmatic group, you are going to want to have more than 5 percent, hopefully, correct that. So, I think there is a typo there that is probably unintended. That is first of all. Second of all, the issue if spherical treatment is inducing one diopter and two diopters of cylinder it does occur, it is about 10 percent that I recall from our 1-diopter group. Two diopters was zero of unintended induction. That is in the low myopia, and I freely give that to the panel.

So, that is what we are looking at today. The issue regarding safety or efficacy I think we are always uncomfortable with it when we run a study because is it sight threatening? Well, no, you can give them their cylinder, but binocularity is disturbed by this, and so there is a little subtlety there that is never captured on case report forms. Where you have a patient who now has 2

diopters and do cylinder and by God you can get them to 20/20, but they are not walking around with that. So, I think we have here something that does bridge both efficacy and safety and really make take a lot of time to weed out.

DR. BELIN: You gave us numbers at 10 percent at 1 diopter and you had none in two.

DR. OVERICH: Right.

DR. BELIN: Between the 1 and 2 what was it?

DR. OVERICH: I don't remember it that well. That was low myopia. I just don't know. The trend towards the decline is what you mean. It is what was the break-off, was it one and one-half or --

DR. BELIN: You could have had 8 percent at 1.8 diopters.

DR. OVERICH: I don't remember. I don't think we looked at it that closely that I recall.

DR. STARK: Would a fair number be then greater than two and less than 1 percent?

DR. BELIN: Yes. I would suggest again having higher limits for high myopia, again, because as you do greater corrections whatever you are doing will have a greater effect.

Do you have a proposal for a statement? If you

are going to make low myopia 1 percent at 2, I would make high myopia 2 percent. I mean if you are doing twice the correction, you are going to get twice the scatter.

DR. MACSAI: Is there any data to base that on?

DR. BELIN: Logic. I mean this is really going into the next thing, but it is a normal function. The machine has certain capability. If you ask it to do twice as much there is an inherent scatter. You haven't increased your scatter, but you have increased your target. So, your variability increases. It is like shooting a rifle. If you go twice as far the rifle is just as accurate, but your bullets will be scattered twice as, you know, actually four times the area.

DR. STULTING: So, the proposal to fill in those blanks would be 1 percent, 2 percent, 1 percent as I understand it.

PARTICIPANT: I am a little concerned. He is quoting us PRK data, and we are going to be reviewing Parke(?) data, and so, that data may be different in terms of that.

DR. STULTING: Along those lines I think we need to clarify whether we are talking about what happens to spherical patients who are receiving a spherical ablation or

whether we are talking about the difference between intended astigmatic correction and actual astigmatic correction which would induce cylinder. It is not exactly induce cylinder but you have to figure out some way of dealing with people who start out with astigmatism and get treated for that.

DR. MC CULLEY: If you put unintended as was suggested by Dr. Overich, that will work, percent of eyes with unintended induced manifest, would that not cover it?

DR. STULTING: Yes, except I am not sure whether you would describe induced astigmatism as something that was worse than what they started with or whether it was just not fully corrected. In other words, if a person started out with 3 diopters at 90 and wound up with 2 diopters at 45, then would he have had a diopter of unintended induced astigmatism or would he have just had an incomplete correction?

DR. BELIN: You have got to look at the vector.

DR. STULTING: In other words which vector do we look at, do we look at the end vector or do we look at the deviation from intended vector.

DR. BELIN: You look at the surgical effect vector from the surgical intended vector and determine what the difference is.

DR. STULTING: Okay, so that is a deviation of actual from intended, and then we are saying that that should be fitting those criteria. Those are pretty loose criteria for that one I would guess.

DR. GORDON: I think that is because now what you are talking about is an efficacy criteria. How effective was the laser in functioning as intended and that is what Dr. Overich was saying as well, why you need the separation between the sphere only treatment where any cylinder at the end is induced cylinder versus what is your outcome, and have you induced more cylinder than you attempted to treat and has the axis shifted so that the patient has a bad visual outcome?

DR. STULTING: So, you are recommending that this criterion be applied to spherical corrections for spherical patients.

DR. GORDON: I think it is straightforward for the sphere only patient where any cylinder is induced, unintended induced.

DR. BELIN: One last quick question. I have no idea on this one. We came up with a number for hyperopia. Does anyone have clinical experience? Do you get similar induced cylinder with hyperopia; do you not get it; do you

get more? I have no idea. So, we are setting a number based on low myopia. I don't know if that is applicable or not. So, does anyone have experience?

DR. GORDON: I would pose that it is premature given the absence of --

DR. STULTING: That is my concern.

DR. GORDON: -- published or presented data.

DR. STULTING: Put an asterisk next to it.

Remember these are target values. They are not binding and what we are being asked to do is to pretend that we were presented with a PMA today with numbers on it; what would our thoughts be about something we would be comfortable with? Am I correctly representing that?

DR. ROSENTHAL: It, also, reasonable to say even though you haven't seen it, would you accept it; would you accept a hyperope to go from plus 3 sphere to plus 2 and I think you probably would not accept that anymore than you would accept a minus 2 going to --

DR. STULTING: I think it is a fair question even though we don't really have data to base it on.

Okay, we are now down to adverse events and that would be percent of eyes with adverse events per type of event.

DR. BELIN: Could we change it to persistent going back to yesterday's discussion of this cumulative versus persistent versus --

DR. EYDELMAN: We don't have those definite equivalent definitions in this guidance. We count adverse events as they come in. We can if you are proposing that, then you have to propose what would be your definition of cumulative versus --

DR. STULTING: We are setting target values, and we have defined adverse events. So, what we would like to do is then say how many of those it is okay to have.

DR. MACSAI: I think this less than 1 percent is fine.

DR. STULTING: Does anybody have any other thoughts about that?

DR. MC CULLEY: The only thing that is footnoted, it says, "The frequency of miscreated flaps makes 1 percent." Do we not want to put a percent on the miscreated flaps that is acceptable?

DR. STULTING: I was going to bring that up if nobody else did. Remember when we were talking about adverse events we had an adverse event originally defined as a flap complication that led to loss of two or more lines of

best spectacle-corrected acuity and then concern was raised about what if there are lots and lots of those, and so, I believe technically we were recommending that a lot of those be defined as adverse events, too, which essentially puts all flap complications in the adverse event column. Am I correct about that?

DR. EYDELMAN: I understood your recommendation for adverse events to be those flap complications resulting in loss of visual acuity. That was my understanding from this morning's discussion.

DR. STULTING: Okay, so, if we define them like that, then this footnote disappears so that now we are talking about adverse events, and those are the things that we defined already today, and flap complications for clarity would be only those that resulted in two or more lines of lost acuity.

DR. BELIN: Two quick questions. Is loss of two or more lines of vision an adverse event?

DR. STULTING: I thought that was going to be a real quick question. You could have waited just a few minutes. I have two quick questions. I thought they would be very quick. The first question is is loss of two or more lines of best spectacle corrected visual acuity an adverse

event? If it is you cannot have line one be greater than line four. You cannot have an acceptable rate of one adverse event to be higher than the fact that there can be no adverse events that -- so, you are right because we redefined loss of two or more lines as an adverse event. Right. So, the bottom line has to be 5 percent at least or you cannot do it that way.

DR. EYDELMAN: No, the top line includes all causes of loss of best spectacle. The bottom line specifies now that those that are due to miscreated flaps should be less than 1 percent, and one becomes a subset of the other.

DR. BELIN: No, the bottom line is percent of eyes with adverse events per type of event, period.

DR. MC CULLEY: With the exception that loss of two lines is fine.

DR. BELIN: Okay, the other quick question, and I said it was quick, I will leave that, where we talk about the frequency of miscreated flaps may exceed 1 percent, we have deleted it. Should we have something that is the inverse, that the frequency should be no greater than? That is a safety factor. I mean we should be able to say that it does not exceed a certain number.

DR. STULTING: Discussion on that?

DR. MACSAI: I just want to ask a question. I thought that microkeratomes weren't a device that we were looking at and miscreated flaps are usually due to those microkeratomes. So, can we put that number down?

DR. STULTING: I think we had clarification from the agency that device includes the laser, the microkeratome and any retreatments that are planned as part of the procedure. That is the device.

DR. MACSAI: So, then, Michael, what are you recommending, 5 percent, 1 percent, what?

DR. BELIN: I will let someone with more lasic(?) experience talk about the number. I do think as a safety end point we should have a number that flap complications should not exceed.

DR. MC CULLEY: For miscreated flaps, what something in the, if we take, are we going to, also, include misaligned flaps that occur subsequently; are we going to lump it all together?

DR. EYDELMAN: I just want a point of clarification. Are you proposing, Dr. Belin that complications rather than adverse event become a safety end point because prior to this the way it treats currently it is the adverse event as related to the flap creation which

is a safety end point?

DR. BELIN: The answer really is yet and that is that if every patient undergoing this one microkeratome, one laser procedure has to have two flaps done because the first flap didn't work, nowhere is that reported as a safety -- so, the answer is yes. I think flap complications should be less than a certain number.

DR. GORDON: I think that leads you then to four other types of complications as well, starting to try to define thresholds. Why for a flap complication only particularly if you want to be broad enough in your definition in capturing flap complications so you can tell the patient right in labeling that this is the incidence and it is really all inclusive?

DR. BELIN: The reason is because it usually results in terminating the procedure. So, it is somewhat different.

DR. GORDON: Not necessarily.

DR. BELIN: Then maybe we should word it those that result in termination of the procedure. As I said, I am throwing it out, open to discussion. I just think it should be incorporated somehow.

DR. GORDON: I think Malvina made a very good

point in that the safety targets are kind of a pass/fail threshold for the device, and so having that based on what is an adverse event and what the consensus has defined as an adverse event makes sense even though it is important to inform patients on incidence of complications. I think it is very different in terms of a safety target which is used in this way.

DR. BELIN: We are being harder on the laser than we are on the microkeratome. Let us look at induced cylinder greater than 2 diopters. That results in no loss of best spectacle-corrected visual acuity but we are incorporating it as a safety factor. To me a flap complication that doesn't result in a loss of best spectacle corrected visual acuity should be treated the same, and if it occurs at a significantly high level and it adversely affects whether your procedure is completed or not that should be somehow a major safety factor.

Otherwise induced cylinder is not a safety factor no matter if it occurs at 100 percent because best spectacle corrected visual acuity is not affected. So, we have already made that distinction, and we have acknowledged that we can have an adverse event that doesn't require a loss of BSCVA, and I think major flap complications even if

they don't --

DR. MACRAE: Michael, I don't think that, unless I misheard the conversation, if you have a patient that doesn't lose best spectacle corrected visual acuity I don't think that that is an adverse reaction.

DR. BELIN: No. 3 is induced cylinder greater than 2 diopters, and as a matter of fact not only have we done that, but we have tightened it up, and we have said that it is 1 percent.

DR. MACRAE: I will go down on the record to say that that is a mislabeling. I don't think that that is a -- it doesn't qualify from what FDA defines as an adverse reaction and really is not an adverse reaction. It is not a significant sight-threatening complication.

DR. BELIN: We are talking now of safety target values. I am talking safety target values. We have set up at least one safety target value that is not associated with a loss of BSCVA. If I was a patient, and I had to look at two, quote, lasic units, lasers, microkeratomes, etc., and they had the same efficacy, the same loss of BSCVA but one of them had a 30 percent rate of flap complications and one had a 5 percent rate of flap complications, I would want to know that.

DR. MACRAE: But you are not going to know that in the study. I mean as the study goes on you are not going to know that as an investigator anyway. Unless your sponsor is a lot more informative than most sponsors, the investigator is not going to know what the flap loss rate is during the study.

DR. MC CULLEY: Again, it is safety target values, and nothing precludes us from setting guidelines on things other than adverse events, and we have already done it as Mike pointed out, and that is what is being proposed to do for flaps. We are mixing in here adverse events and safety target values, and a safety target value does not have to be an adverse event by FDA standards.

So, we are just saying that we should consider putting a percentage on flap miscreation, misalignment. We can lump it all together. We can split it out.

DR. MACSAI: Does anybody have any experience, personal experience, published experience that they might share with us regarding the incidence of miscreated flaps?

DR. STULTING: The figures that I am aware of would be roughly 3 percent. So, why don't we set it at 10? That would be intraoperative.

DR. MACSAI: That is sort of what I was thinking

actually. So, 5 percent might be a fair number.

DR. STULTING: My flap complication rate is about 3 percent.

DR. MC CULLEY: At the time of creation?

DR. STULTING: Yes. So, that seems to be common experience. That doesn't necessarily mean that that would be the criterion we set, but that will at least give us a basis for making that determination independently.

DR. MC CULLEY: So, we could put a limit of 5 percent on miscreation and then put another whatever percent on subsequent misalignment.

DR. STULTING: Yes, I think 5 percent would be generous.

PARTICIPANT: If necessary it can be revised.

DR. BELIN: But one of the problems is that you are dealing with a learning curve in these studies, and so if you have 20 investigator, and they are all starting out doing lasics, they may have a much higher flap complication rate.

DR. STULTING: So, I hear a consensus that we capture intraoperative flap complications, and those would be defined to include any abnormalities of the flap whether or not surgery was performed. So, that would include

irregular flaps, buttonhole flaps and it would include free flaps and other flap abnormalities that we do not believe interfere with best spectacle corrected acuity, and that would allow lasering of the patient. Am I correct in describing that? That would be the definition that I would have used when I quoted the number that I quoted and I assumed that was the same for both of you.

DR. EYDELMAN: Can I just ask for one point of clarification? Does the panel intend for this to be less than 5 percent at the end of the study referring back to the earlier comment about the learning curve because you will exceed that early on in many, many studies?

DR. STULTING: You shouldn't exceed 5 percent early on, should you? The denominator it seems to me for a complication that relates to creation of the flaps should be the number of flaps that are created. So, that would exclude enhancements from that denominator, but it would include eyes that had a flap but not laser.

DR. BELIN: I, also, think whether it is early or not is somewhat going to be in the FDA's purview because the data won't come to us until the end, and that is when we will be looking at it.

DR. STULTING: That is what these are. These are

targets for what we think would be an okay PMA.

Can I ask for a point of clarification? I am actually confused about it myself. Did we decide that a decrease in best spectacle corrected acuity of more than 10 letters or more than two lines was to be considered an adverse event earlier today or not?

DR. EYDELMAN: My understanding was after 3 months.

DR. STULTING: After 3 months? Okay, so that is an adverse event, and then we need to go back to Dr. Belin's point that No. 4 up there has to be at least as much as No. 1 to make sense.

DR. MC CULLEY: No, you could still have no adverse events except loss of best spectacle corrected visual acuity.

DR. STULTING: So, we have excluded that.

DR. MC CULLEY: We have set it out as a separate category and put it at 5 percent and everything else is 1 percent.

DR. STULTING: Okay, I just wanted to make sure.

DR. MACSAI: Just on the previous one since we now have flap intraoperative complications less than 5 percent, does the miscreated flap with a loss of visual acuity still

become less than 1 percent?

DR. STULTING: Yes, it is still an adverse event.

DR. MC CULLEY: Could I just try to move miscreation of the flap, and we have then subsequent flap misalignment or misalignment of the flap, postop flap complications and that the miscreation of the flap be 5 percent and postoperative flap abnormalities include misalignment, epithelium and so forth. For the sake of argument I will say 5 percent as well.

DR. STULTING: So, you are proposing 5 percent for postoperative flap complications, for postoperative misalignment, correct?

DR. MC CULLEY: Well, any postop flap abnormalities that would include misalignment. It would mean melting, too.

DR. STULTING: Would it include epithelial ingrowth?

DR. MC CULLEY: If it melted and affected vision, then it would be 1 percent.

DR. SUGAR: Melting is already listed as an adverse event and that is already stated as per type of event less than 1 percent, and I think that is appropriate.

DR. MC CULLEY: I would agree. Okay, so that would

then fall out of this because we catch it somewhere else.

DR. SUGAR: And epithelial downgrowth with loss of vision, also, is less than 1 percent.

DR. MC CULLEY: Then I will try again, misalignment of the flap. So, miscreation of the flap 5 percent, misalignment of the flap 3, 5, 2?

DR. STULTING: I think a good number for that would be 3 or 5 percent.

DR. MACSAI: I would have thought about 3 percent.

DR. STULTING: Anybody else have any numbers?

DR. MACRAE: I tend to keep it high because we just don't have --

DR. STULTING: So, 5 for each. Five percent would be generous for a postoperative alignment abnormality of the flap. That is slipped flaps, dislocated flaps, etc.

DR. EYDELMAN: Can we just say postoperative flap complications?

DR. STULTING: Not otherwise covered.

DR. EYDELMAN: Okay.

DR. STULTING: Now, do we want to capture epithelial ingrowth that does not lose visual acuity and have a safety target for that or not?

DR. EYDELMAN: Yes.

DR. STULTING: We are going to capture the information. We already decided that, but do we want a safety target for that or not?

DR. STARK: I think because you are going to be seeing new trephines. It could be 5 percent or 10 percent but if they are getting more than 5 percent epithelial ingrowth that is going to be problems down the line. It may not show up in the first year, but that study has to be looked at and the trephine modified I would think.

DR. SUGAR: Is that true that it is a problem down the line if they have just marginal epithelial ingrowth, a year later it is going to progress? I thought that didn't happen.

DR. STULTING: The data of which I am aware says that they do not progress or if they do it is a rare, rare event, the ones that are just within a couple of millimeters of the edge.

Dr. Macrae, would you like to comment or Dr. Macsai?

DR. MACSAI: To my knowledge some practitioners outside the United States say that it can progress after a year.

DR. STARK: I think until we know, I certainly

would be real disappointed if I had it in my patients or in my eye, an epithelial ingrowth in that interface. So, until we know we have to capture it and look at it.

DR. STULTING: We already captured it. That is not the issue. The issue is whether we are going to set a safety target.

DR. EYDELMAN: The previous proposed safety target would be postoperative flap complications. That would be included in it.

DR. STULTING: I think that our safety target was just with misalignment. At least that was what the numbers that were proposed were relative to. I think we made that real clear.

DR. MC CULLEY: What I said was postop complications of flap not otherwise covered under adverse events, 5 percent.

DR. EYDELMAN: So, that would really cover the epithelial ingrowth not causing visual acuity loss.

DR. MACRAE: I think that that would be okay. I don't have any numerical basis for that but 5 percent sounds like a reasonable number at this point.

DR. MACSAI: Is that 5 percent to include both any epithelial ingrowth and misalignment?

DR. MACRAE: Yes unless it is covered under an adverse event.

DR. MACSAI: That may be a little bit high.

DR. MACRAE: Doyle, can you give us any idea of what just in experience what epithelial ingrowth --

DR. STULTING: If you count every identifiable epithelial ingrowth then it is about 12 percent, 10 percent.

DR. MACRAE: In more recent studies?

DR. STULTING: I think it is probably less than that in more recent studies, but you have to plan on initial experience with surgical procedures and that would be what I would predict that we would see.

DR. STARK: That is what I thought when I saw George present some of this material, and that seems high. That would worry me.

DR. MACRAE: It seems high from my perspective, also and from the different types of epithelial ingrowth and obviously there is a malignant form and then there is a relatively benign form and then there is a relatively benign form. From what I have seen in the literature I think that Jim's suggestion is a reasonable starting point. We just need to watch the literature and try to adapt based on that.

DR. STULTING: Assuming and knowing that we are

going to capture all cases of epithelial ingrowth perhaps a better safety parameter that we would like to look at is epithelial ingrowth that is sufficiently severe to require surgical intervention, and that number I suspect would be in the 1 or 2 percent category.

DR. STARK: And I would like to keep that there, but I think you ought to, also, I mean if you are getting, I mean you could raise it to 7 percent but with modern keratomes and modern techniques we have got to set a line for epithelial ingrowth because we don't know what is going to happen 5 years out, and boy, it would be a shame to have somebody look back and say, "You guys didn't even care about it. Now, 5 years out this is a major problem." Until we can get good data from some of the people who are doing these, then --

DR. STULTING: The tendency in data with which I am familiar and have personal experience with is that small amounts of epithelial ingrowth near the edge disappear with time. They don't progress, and that is not to say that that never happens, but the typical course is that they disappear.

DR. GORDON: I am familiar with data that would concur with that, and I would, also, comment that there is

tremendous surgeon-to-surgeon variability and so I worry about setting targets that reflect the experience of the surgeon as opposed to the safety of the device consisting of the keratome and the laser because you are going to end up with studies by only surgeons who have vast experience. It doesn't reflect what is really going to happen and I think there are disadvantages to that in terms of labeling and what patient expectations can be.

DR. BULLIMORE: I am having difficulty as someone who doesn't cut up corneas for a living for whatever reason with defining epithelial ingrowth that requires intervention. Would someone be happy about putting a millimeter value? Is half a millimeter okay? Is 1 millimeter ingrowth okay or am I --

DR. MC CULLEY: We can adjust this. We are on something that we need a starting point with and I would go back, and we can adjust it. We all know what we are doing, and we don't have to be too rigid about it, but we need a starting point, and I think a reasonable starting point is miscreation of flaps 5 percent and postop complications of flap not otherwise covered under adverse events 5 percent, and let us see what happens. We can always change.

DR. STARK: And you could bring it back to the

panel and say, "We have got a group that has 10 percent," and by that time it is known that a year further or 2 years further down the road we have more comfort in that peripheral epithelial ingrowth, but right now --

DR. STULTING: Postop target for flap complications not otherwise specified has been recommended to be 5 percent.

Any disagreement?

Let me see, we need to be a little more brisk here. We are falling behind slightly.

DR. MACSAI: Go to Page 5. I have a question about the definition of effectiveness, end points and target values.

DR. STULTING: We are about to get into that. Would you like to wait for just a minute? They are on the screen behind you. That is the next issue for us to talk about and the table of proposed effectiveness end points is shown in the slide on your left. So, ask your question wherever it is relevant.

DR. MACSAI: Okay, in all of the definitions here you talk about percentage of eyes that achieve predictability, parenthesis, attempted versus achieved of the manifest refraction spherical equivalent either 1, 2 or

1/2 diopters but what about in studies that might intentionally undercorrect the mild? Then it is the target refraction. It is not necessarily the attempted.

DR. EYDELMAN: It is attempted.

DR. MACSAI: Of the manifest.

DR. EYDELMAN: Attempted versus achieved covers that specific point.

DR. MACSAI: Even if they are not attempting the manifest refraction?

DR. EYDELMAN: Even if you are doing monovision this covers this.

DR. MACSAI: I am not sure that is exactly clear because the word "manifest" refraction is in there.

DR. STULTING: Attempted manifest versus achieved manifest, is that what you are recommending?

DR. MACSAI: Right or else just attempted versus achieved because it is not --

DR. STULTING: It was clear to me when I read it.

DR. MACSAI: Okay, so that it is separated out.

DR. BELIN: I am just going to bring up a point, and everyone may not like it but historically I have not liked the artificial breakdowns into low myopia, high myopia, etc., and having different efficacy variables, and I

have been a proponent of using a percentage of correction obtained so that whether the machine is 80 percent, you know, it obtains 80 percent correction or 2 diopters 80 percent or 4 diopters 80 percent at 6 diopters, what we have here really is a breakdown. We are using 7 diopters. That means we expect a 7 diopter to have different efficacy variables than a 7.25 diopter. It, also, means that the study that incorporates 1 to 7 diopters on one company that may have an average correction of 3 diopters will behave differently than a study whose average correction is 4 diopters. If we use a percentage of correction we don't have these artificial breakdowns, and we can compare different studies even though the average correction attempted was different, again, going back to the rifle. You know, what we are doing is we are shooting a rifle at 101 feet, and if you move the target in 1 foot we are changing how accurate the rifle has to be.

DR. MACSAI: I think that we are getting at the same problem because the second point I wanted to bring up is that looking at the data just by less than 7, 7 until infinity in hyperopic it is easier to advise patients if the data is stratified by diopter.

DR. STULTING: Other comments?

DR. MC CULLEY: I think in an idea world that those points are correct, but given where we are and what we have and again trying to have a starting point and our approach has been to take this, I agree with Mike that there is logic to his approach, but this is what we have been working with. So, what I would like to do is try to fine tune this.

DR. MACSAI: But you could fine tune this to be closer to what Mike wants if you stratify it.

DR. BELIN: I am going to read what was written by me 2-1/2 years ago. So, I don't mean it to be -- but this is the concept I had back then which was a reduction of 75 percent or more of pre-existing myopia, hyperopia no greater than this is induced 15 percent of preoperative spherical equivalent, unplanned and do cylinder no greater than 15 percent of preoperative spherical equivalent, those are the type of things that cross any bounds. I mean you don't have to -- you basically are saying that this is what the machine does. The machine has a certain amount of scatter, and as you increase the expected correction the scatter stays the same but you are trying to do twice the correction, and I think it allows companies not to have these artificial breakdowns. They can come in with data and say, "We have

data from 1 to 9," rather than saying that we have low myopia and high myopia, if they have patients in their study that go up to 9, they can present it because it is the same criteria from any correction. The only distinction would be you have to set a lower limit because there is some known error in just biological testing, and you cannot get better than plus or minus half a diopter probably. That will be the end of my selling point.

DR. STULTING: People are beginning to leave. We ought to be able to get a lot done now.

DR. BULLIMORE: I tend to agree with Mike and Jim, but I thought that I guess Jim's more pragmatic approach in thinking about greater or less than 7 is probably where we should stay, but I would encourage the FDA to consider Dr. Belin's approach.

One question I want to raise, comparing the first and the third row for low myopia, low to moderate myopia we have uncorrected visual acuity. We are setting it at 85 percent within plus or minus 1 diopter we are setting it at 75 percent.

In view of what we have seen and heard about in terms of conservative approaches and planned undercorrection are these numbers encouraging or discouraging people in a

conservative approach? For example, the fact that the 85 percent is higher than the 75 percent, does that, for example, encourage people to, or inadvertently encourage people to overcorrect and push people into small amounts or in some cases large amounts of hyperopia?

Does anyone know what I am talking about?

DR. MACRAE: It may, but I don't think it is an issue. I think that most of the 1 to 7 diopter trials have been able to achieve 90 percent 20/40 or better. So, I don't think it is an issue. I do think that your point is well taken though that we need to look real seriously at the hyperopic overcorrection rate, and I do think that that is an efficacy criteria that we should set, and I think that a hyperopic overcorrection of more than a diopter in more than 10 percent of cases is a concern.

DR. BULLIMORE: I have never liked the uncorrected visual acuity criterion. As clinicians we measure in diopters. We are dialing in diopters to the instrument. That is ultimately what should be our primary outcome measure and visual acuity is almost a surrogate. Obviously in terms of safety it has added benefits and in terms of what the patient can digest easily it is attractive.

DR. FERRIS: I don't think the patient could care

less what number of diopters you have dialed in. The only thing they care about is how do they see.

DR. MACSAI: How do they see, and are they legal to drive? That is what they want to know.

DR. MC CULLEY: A specific question, I would wonder about the low myopia and the percent of eyes with uncorrected 20/40. We were 20/20 before, and the aim was emmetropia for postop. Should that not be a higher percentage than 85 for the low myopia?

DR. STULTING: Other comments on that? Does anybody want to throw out some numbers?

DR. BULLIMORE: It is too low. I agree with Jim. I heard Scott mention 90 percent. I could be encouraged to up it to 90.

This is spherical, again, correct?

DR. MACSAI: No, it is with or without astigmatism.

DR. BELIN: That becomes confusing. If we are talking about a 7 diopter spherical equivalent someone who has 6 diopters of cylinder falls into this range, depending on what they are. I mean they can be a minus 3, minus 6 and their spherical equivalent is minus 6. I think expecting a 90 percent uncorrected vision of 20/40 in that group is

probably not realistic.

DR. MC CULLEY: That is going to be such a small percentage, and we can take that into account.

DR. MACSAI: Jim, are you moving to increase it to 90 percent?

DR. MC CULLEY: At least 90 percent, yes, for the low.

DR. MACRAE: If you include the Parkes a number of at least a number of the literature reports would have failed that criteria.

DR. BULLIMORE: I just want to reiterate my latent dissatisfaction with using uncorrected visual acuity to sort of set target end points. In terms of patients, it is great, I agree with everybody who said that. In terms of efficacy, in terms of this panel and the FDA evaluating new procedures I think we could and should concentrate our efforts on the numbers related to diopters. I think it is useful to debate the visual acuity, but in terms of efficacy and clinician talking to clinician, I think the diopters are much more useful.

DR. MC CULLEY: But we have to have both because we have to talk to our patients, too, and I would not object to 90 for PRK or whatever for spherical and 85 percent for

spherical plus cylindric, and we cannot do a PRK in part because this is going to cover lasic as well. So, it would be --

DR. MACRAE: These are recommended end points. They have nothing to do with what happens in the field. So, I don't know that getting too concrete in terms of this is going to change things dramatically. Judy has gone, but what does this do to the industry?

Marc, do you want to speak to that?

DR. OVERICH: I would like to just address Dr. Belin for a second because Dr. Belin came up with a recommendation, and it has been around for a while, a percentage reduction. The problem with uncorrected acuity as you see up here is that many patients will have both eyes treated, and those eyes may or may not be counted as part, and this does not allow comfortably for the type of targeting that we may see in the future specifically monovision.

You could wind up having 50 percent of your patients worse than 20/40, have an entirely happy population and really not give a number. So, I agree. I think uncorrected acuity is an interesting number. It has to be brought out. It should be in every labeling, and you could

have the asterisk to appropriately inform the public that half of the patients were targeted for undercorrection, however you want to do this, but this uncorrected acuity should at all levels I think take a back seat. I think the real important issue is you are taking your laser. You are aiming at getting 4 diopters and what percentage did you get? You are aiming at getting 10 diopters. My question to the panel as part of this is what is our definition of high myopia. It has been made inelastic, and it is going to change, and I think we really have to start looking at percentage reductions where you are comfortable. I mean just arbitrarily you want to have 70 percent reduction for 5 diopters correction or less, 60 percent. I mean you can make the numbers up, but I think we have to stop this low myopia high myopia because as was alluded to I can make almost every patient a low myopia patient by adjusting my criteria.

For instance if I take 1.5 diopters as my break off for spherical treatment as an inclusion criteria I may fail this abysmally, this uncorrected acuity. However, if I decide to use only .75 for a spherical treatment my low myopia numbers will then reflect if it is a spherical treatment a higher rate of uncorrected acuity.

Now, that may not go out to the public. They may

have no sense of that. So, it doesn't really have a labeling issue. You can bend that as an industry person. What you really want to know is for the doctors what did you do; what did you reduce and from the patient's perspective what you want to know is for those patients who were aimed at emmetropia what was their final uncorrected acuity in a mean sense? Those are the two pieces of information, and I think that it makes an awful lot of sense to start aiming now that we are through the first wave of percent reduction. You aimed at something. What was the percent reduction? I think that industry would support that.

DR. EYDELMAN: I would just encourage the panel if the consensus is to go with the percent reduction to go the next step and try to recommend to FDA the percent that would be acceptable to this panel.

DR. BELIN: I would be willing to work on that with other people. I really don't think it is something we can do because we can do it easily with spherical but it is a more complicated thing with astigmatism, and you, also, want to incorporate overcorrections, etc. I would have no problem working on that. I think it has always been something I have pushed for about 2-1/2 years, and since someone else brought it up I really think it is the way to

go. I would have no problem working on it because I don't think you can do it in the remaining time that we have.

DR. STULTING: Could you have it finished next week?

DR. BELIN: I can do it within 2 weeks after the academy.

DR. STULTING: I think it is worthwhile looking at these numbers in more detail because it is certainly not the first time they have been suggested, but there are a couple of things that need to be done to flesh them out a little bit. First of all in your proposal I don't see any way of dealing with greater than 100 percent change in spherical equivalent.

DR. BELIN: As I said in the letter I wrote you, these are the things that were actually proposed, I think well before. This was July 1995. So, there is a lot that has to be done. I am just throwing out the concept of getting away with these arbitrary groups and going with a percentage, reduction percentage, overcorrection, etc. These were not meant to be -- that is why I said that these were not meant to be what I am proposing. It is just the concept is going to a percentage reduction and getting away from these breakdowns so you don't have this step going from

7 diopters to 7-1/4 diopters.

DR. STULTING: I understand that. I am about to make some recommendations on how to modify them so they might be more accurate and acceptable. One is to figure out a way of dealing with overcorrections which is not really dealt with in here.

DR. BELIN: Actually No. 2 I wrote you is hyperopia no greater than 15 percent of preoperative spherical equivalent. I don't mean the 15 percent to be, but that is the type of, the way I would approach it.

DR. BULLIMORE: I would like to hear just within a few minutes a little bit more about how these might be worded. Are you talking about 90 percent of patients achieved within plus or minus 10 percent of their intended correction? Is that kind of where you are leading? We are going to have sentences with two percentage numbers in them invariably.

DR. STULTING: That is what I was getting to, but I haven't been able to complete my statements here. The second thing is to consider astigmatism which is not in here and perhaps as well if you are going to take on the task of doing this which is what I heard you volunteer to do, I believe.

DR. BELIN: With help.

DR. STULTING: With help. Is to maybe look at some existing published data so that we can get some feel of what current procedures are offering patients and get some feel for what we should require here, but Morris with your approval maybe we should table this and consider it to be something that we would return to at another day.

DR. WAXLER: I think that is a good idea. In addition I would suggest at your pleasure, Mr. Chair that you perhaps could appoint Dr. Belinto head a small group that could work on this actively in the next few weeks and report back to the entire panel by letter and try to work out some consensus by that actual process if that is okay with you.

DR. STULTING: Does anybody object to that?

DR. MACRAE: I would be glad to help out, Mike. I have got a lot of that data already. I have even got a table on some of it.

DR. STULTING: Would anybody else like to volunteer to do that?

How about Dr. Stark, Dr. Ruiz, Dr. Sugar and Dr. Higginbotham and Dr. Van Meter, none of whom are here at the present time?

DR. BELIN: Dr. Macrae and I can cover it.

DR. STULTING: All right. Shall we move on to effectiveness?

DR. BULLIMORE: I have one more question about the table. It is a question of stability. Have we defined stability?

DR. STULTING: I believe that is the next --

DR. BULLIMORE: Sorry, I thought we had finished.

DR. STULTING: The proposal up there is the definition of refractive stability, a change less than or equal to 1 diopter of manifest spherical equivalent refraction between two refractions performed at least 3 months apart. We are being given that definition. At this point we are being asked to say what we think the appropriate numbers are that would be targets for that.

Discussion is open on that issue.

Dr. Soni?

DR. SONI: I believe we decided one-half diopter this morning

DR. STULTING: That was for preoperative.

DR. SONI: So, why would it be different?

DR. STULTING: Because people who have refractive surgery have multifocal corneas, and their refractions are

not as repeatable as people who have preoperative corneas.

DR. BULLIMORE: Is that addressed in the label of any existing devices?

DR. STULTING: The effect of a multifocal cornea is loss of best spectacle corrected acuity, and I think that is reflected in the labeling or it is reflected in what people normally tell patients who are undergoing refractive surgery or about to do so. I have actually tried to find these numbers in the literature so that I could get some feeling for what actually exists out there, and I cannot find them. Does anyone have any knowledge of these numbers and what they might be under any kind of clinical conditions, RK, PRK, lasic or anything else that they can provide for us?

DR. MACRAE: I think if you look at the curves of the entire population you can get some information, but I have never seen data following individual patients with standard error bars, but you can, you know, you can evaluate the steepness of the --

DR. STULTING: That is not what we are talking about. There are plenty of data on mean spherical equivalent postoperatively, but this is a different issue.

Would anyone from industry in the audience like to

comment on this? Does anybody have any of this data at their fingertips?

DR. BULLIMORE: I will make a comment, Mr. Chairman, and that is that we should acknowledge that there is a paucity of published data on the topic and that as you said, postoperative refractions may be more variable than preoperative refractions. I would be hesitant to use the same criteria of 050. Plus or minus one seems a little bit too much, but I would like to see some data.

DR. STULTING: Based on my clinical experience I think that the number of eyes that deviate is going to be greater than the numbers that have been brought to the discussion and mentioned here.

Dr. Overich?

DR. OVERICH: I don't think we have really looked at the data this way. What we did was what you said, Doyle. All the data have been accumulated where we have shown these curves for mean rather than looking at individual patients, but having been in the PRKA and the PRK pile and a couple of other piles with my hands I think that this certainly would capture a majority of patients I would feel comfortable were captured by this, but the one caveat here is this means if we can get it up there that if you have 3 months apart, that

means these people could march out and cite 1 diopter for a year which would be 4 diopters in a year, and I want to warn people that that is not the intent of this. You cannot then expand this to say, "Well, then if I can show 2 diopters within a year, I am within my stability parameters."

I think that this is a good outside number. In other words, if you can demonstrate this at 3 and 6, for instance you will be okay. If you can demonstrate this at 1 and 4, you are probably going to be okay, but to sit there and then extrapolate from industry, I think we need to be sure everybody understands the ground rules here. You are not going to sit here and start to play games with these numbers and say, "Okay, well, I had 3 diopters in a year; therefore, I am stable." According to this there is nothing that precludes me from doing that.

So, I just want to make sure that people understand that that is not really written out here.

DR. BELIN: Are we confusing or should we I guess maybe separate patient variability and study variability? Don't sit down yet. You have looked at study variability and know that over a 3-month period there is a point where you reach stability and that --

DR. OVERICH: You can do a linear regression and

go backwards to figure out where your change is no longer significant.

DR. BELIN: I would want to make this real clear that this is not study stability. I would be very hesitant to approve a study that is claiming stability when the entire population mean changes by a diopter over a 3-month period.

DR. STULTING: No, no, make it real clear. What we are talking about is a study where the main spherical equivalent is stable, plus or minus --

DR. BELIN: I think we need to put it in there.

DR. STULTING: Something like that. Now, we are talking about individual variation from time point to time point.

DR. MACRAE: You are talking about something very similar to what they did in PERK(?) where they looked at the number of patients that had, the percentage of patients that had more than a diopter of let us say hyperopic shift or myopic shift. That is the kind of thing that you are --

DR. BELIN: Right, but what I want to make real clear is that a sponsor doesn't come up and show us a graph to indicate study stability and what they are going to show is study visits, the number of patients that varied by 1

diopter or more between, and they will come out and say, "One-half percent, 1/2 percent, 1/2 percent," even though the mean population hasn't changed by 3/4 diopter over 3 months, and unless we clarify how we are wording that we are leading, we are kind of letting someone present data that way.

DR. EYDELMAN: We will make a note and change it to reflect of individual subject manifest spherical equivalent.

DR. MC CULLEY: Right and is it not that 95 percent of the patients should be stable within a diopter between the two time points and the two time points are stated as 3 months apart?

DR. EYDELMAN: The proposal is for the individual subject for 95 percent of the individual subjects.

DR. MC CULLEY: To be within 1 diopter between two time points that are specified as being 3 months apart in order for one to claim stability.

DR. EYDELMAN: Correct.

DR. MC CULLEY: That seems like a reasonable point still to stay on.

DR. STULTING: Based on personal experience I think that those are numbers that are not going to be

achievable by procedures that are generally accepted to be safe and effective and are available today.

DR. BELIN: But if we looked at a whole study population you would be more comfortable with the --

DR. STULTING: No, I am basing that statement having looked at outcomes of procedures that are generally considered to be safe and effective over a period of time.

DR. BELIN: I agree with you that individual variability post PRK or post lasic is large and I will agree that your postoperative refractions change. When you look at the whole population study though are you finding the mean to change by a diopter between study visits? I would say, "No."

DR. STULTING: Maybe we are confusing what this is talking about. There is one measure of stability which is the population mean, and that would be the mean manifest refraction with error bars that the change with time. That is not what we are talking about here. I believe that what we are talking about here is the number of individuals whose refraction changes by these numbers from one exam to another.

So, in order to get the number that we are talking about targeting here for an efficacy variable you would take

every individual who reached the 6-month visit and subtract the refraction obtained at the 3-month visit, and that would be their change from that interval.

DR. MC CULLEY: And 95 percent would have to be less than a diopter to claim stability.

DR. BELIN: So, then we aren't saying that if you take a minus 3 diopter and correct them and at 6 months they are minus 1 and at 7 months all of them are minus 2. They are stable.

DR. MC CULLEY: No.

DR. BELIN: Three months apart. At 6 months they are minus 1 and at 9 months they are all minus 2.

DR. STULTING: But, see you have to understand that is not going to occur given the fact that the whole population is stable. You are going to have a balance of pluses and minuses. Otherwise you won't have the stability.

DR. BELIN: Okay, that is what I am saying. I just want to make sure that these two are interrelated. You already know that the changes in a positive direction are going to equal the changes in a negative direction. Otherwise the population won't have stability.

DR. EYDELMAN: Just like your example with the gun, they are going to fly all over.

DR. MACRAE: This has already been done in the PERK study and I think the methodology is pretty clear.

DR. ROSENTHAL: Mr. Chairman, you were concerned about the 95 percent level, is that correct?

DR. STULTING: I think it is a good idea that we collect this information because it gives us information about stability that we have never collected before, but we are now moving toward proposing targets for this, and I think that the targets that are being proposed in my opinion are not -- I would be comfortable with procedures that do not meet the proposed target. That is what I am trying to say.

Maybe the thing for us to do is to try to generate data and not propose a target at this point because there are no data available.

DR. EYDELMAN: Mr. Chairman, without specifying any sponsors or any PMAs I was told I can say that this information has been collected in the past. That is all I can say.

DR. MC CULLEY: I think, Doyle, again, just as with some of the other things to have a starting point and for us to look at what our guidelines are and what data comes in thoughtfully and intelligently that doesn't keep us

from putting something down as a target.

DR. STULTING: Okay, well, with regard to what you said without talking about sponsors and PMA I think some of those numbers exist, too, and I think the 95 percent level is too high. That is what I was trying to say.

DR. BULLIMORE: Mr. Chairman, with respect I think you should perhaps declare a conflict of interest.

DR. STULTING: Exactly why?

DR. BULLIMORE: We are in a catch 22 here. We cannot discuss a PMA by name, but we have been presented at a previous meeting with data in this form, and now, members of the panel are being asked to sort of draw a line in the sand even though there is a potential at least for someone to have an interest in those data.

DR. ROSENTHAL: We have an understanding, Mr. Chairman, of what the issue is. I think the fact that you have agreed that refractive stability can be defined this way is a great leap forward. I think, also, we cannot base any data on the previous PMA data, but we can certainly take the sense of the panel or the members of the panel away when we set target figures, and of course, target figures are just as they are. They can change at any time. So, I think we have a sense of what is being discussed here with regard

to refractive stability, and maybe it would be better not to set an absolute number at this point in time.

DR. STULTING: Any other discussion?

Okay, next slide, please?

DR. EYDELMAN: If I can just clarify, these two slides just summarize the actual table, but the following set of slides will go through each proposed change. So, these two slides are not meant for people to dwell on for a very long time since it is hard to read.

DR. STULTING: Do you want to highlight the examination schedule changes? It is on Page 8 of the document that you have.

DR. EYDELMAN: They are up on the screen now.

DR. MACSAI: I assume this definition is different for lasic than hyperopia and high myopia, saying that they are new indications and that they need to be followed for 24 months but lasic doesn't. I mean I am confused here.

DR. EYDELMAN: No, lasic in the whole document we tried to define the same end point for surface and lasic ablations. What this tries to elucidate is that we perhaps have more experience now with myopia and with amount of regression we can anticipate as opposed to new indications like hyperopia and perhaps until we are comfortable with the

minimum amount of follow-up we are proposing initially under the IDE that sponsors propose a longer follow-up and then when they can demonstrate scientifically that they are indeed stable, then they can send in the proposal to FDA requesting shortening the follow-up.

DR. MACSAI: But by lumping those, I don't want to belabor this point or play devil's advocate too much, but by lumping together the PRK and lasic, we are assuming that the lasic is the same as PRK, and we have recently reviewed the first application that showed that it wasn't stable at 3 months. So, why wouldn't that, also, be a new indication? That is what I am confused about.

DR. EYDELMAN: I guess from the literature the overall impression is that there is no significant question of big swings in myopia, low to moderate myopia regardless of the technique with which it was achieved. The claims usually in the literature are made for earlier rather than any problems with the later as opposed to hyperopia where there are quite a few articles indicating late onset of refractive change. So, this was merely to reflect that.

DR. BELIN: There is a fair amount of literature to support that patients below eight and maybe even below 10 behave very similar to those in the five to six to seven

range. So, again, I kind of agree with Dr. Macsai. I think we are separating it artificially or else we just should have something that if you can support that the eye behaves similarly in the available literature than avoid it, but you know, 7, 8 diopters, there is a lot of literature to suggest they behave very, very similarly.

DR. EYDELMAN: That is true and the sponsor under the statement always has the option of sending in that proposal.

DR. STULTING: Any further discussion?

Shall we move on?

Cycloplegic refraction is recommended at preop visit and at months 6, 12 and 24. So, this eliminates cycloplegic -- I am sorry, the alternative is at the preop exam and the final exam.

DR. MACSAI: Again, I have a question for this one. What do we do with those lost-to-follow-up patients who don't get their final exam?

DR. EYDELMAN: I don't really know what to do about people you cannot see.

DR. STULTING: I think wasn't there, also, a recommendation that it be done before any enhancements?

DR. MACSAI: Yes, that is a good point.

DR. EYDELMAN: That is a typo. That should be corrected. You are correct.

DR. STULTING: It is preop, final exam and the last exam before any enhancements, if planned and performed.

Discussion on it?

The intent was to eliminate unnecessary cycloplegic refractions, hopefully to get more patients to come for follow-up. I don't hear any objections to that one.

Next slide?

Near uncorrected visual acuity. The change to recommended at preop visit and final exam and in addition for hyperopia studies to be measured at month 3.

PARTICIPANT: That sounds fine.

DR. STULTING: Any comments?

No objections.

Next slide?

DR. EYDELMAN: We have an objection.

DR. STULTING: I apologize, go ahead.

DR. OVERICH: Just to go back for a second and just make everyone aware, we will supply the data that you asked for regarding stability. It is about 2-1/2 percent, and we went back and looked at that from 3 to 6 months, a fall

outside of 1 diopter change, 2-1/2 percent.

DR. STULTING: You mean 1.25 diopters?

DR. OVERICH: One or more inclusive of one, 2.5 percent.

DR. STULTING: And that is for low myopia.

DR. OVERICH: That is for low myopia just to give everybody a reference point.

DR. STULTING: So, 95 percent is a reasonable thing for low myopia but no data on high myopia.

DR. OVERICH: No, we do have data on high myopia. I just haven't gotten it yet.

DR. STULTING: Can we have that at some point?

DR. OVERICH: Sure.

DR. STULTING: Meanwhile let us take a look. Near best spectacle corrected acuity not required. In other words, we are not taking that anymore except at the preoperative and the final exam. Pardon me, I am confusing two things. Not required at all.

Any objection to that?

DR. MACSAI: If you are doing monovision, wouldn't you want to know it?

DR. STULTING: That is uncorrected near vision.

DR. MACSAI: Okay, sorry.

DR. STULTING: Next slide?

Current exam does not include recommendations for hyperopia and the proposed examination schedule would be for a manifest refraction using a standard procedure that pushes plus. I think this was a compromise as opposed to cycloplegic refractions that nobody knew what to do with for sure and hyperopes anyway.

Any discussion? Has anybody thought about this one?

DR. MACRAE: It seems reasonable.

DR. STULTING: No objections.

Next issue?

Currently the pupil size is assessed whenever we measure visual acuity and the change is as you see.

Preoperatively and at one of the following after discontinuation of steroids stability or final exam.

DR. MACRAE: Doyle, what is the significance of at the time of discontinuation of steroids?

DR. STULTING: Steroids cause mydriasis.

DR. MACRAE: Why are you doing it at all? I understand checking pupil size, if you do have a group of patients that do have problems with let us say a group of high myopes that have relatively small optical zones. I

want to know is there a risk factor, and I think pupil size is probably an important one as to why those patients may have symptoms. So, in that population I want to know preoperatively, and I don't think it is going to change during the study but postoperatively if you wanted to measure it on the last visit that is fine.

DR. EYDELMAN: If you read the statement again it says at the preop and one of the following, i.e., it gives you an option of one of those three times.

DR. STULTING: The other reason for measuring it is that there are at least anecdotal reports that PRK and other procedures can cause mydriasis.

DR. EYDELMAN: Does that clarify? It is at any time basically following discontinuation of steroids.

DR. MACRAE: I would recommend you evaluate it at the end of the study and just leave it at that. If their pupil dilates a little bit while they are on steroids and then it comes back down to normal it is really not a major problem. I don't think it is an issue.

DR. MC CULLEY: I would be consistent and agree with that to do it at the final exam. Why have the other two? Then you have data that is from three different potential time points.

DR. EYDELMAN: It was given for the sponsors who are potentially coming in with smaller optical zones who will then be asked at some time perhaps prior to the end of the exam to correlate potential of glare and halos as a correlation of their optical zone and pupil size. So, if that is the substudy that they would want to undertake before they finish --

DR. MC CULLEY: Then they should take it at multiple times, determine it at multiple times.

DR. BULLIMORE: Are there any a priori reasons why other than due to medication the pupil size is going to change over the course of the study?

DR. STULTING: Yes, the laser can induce miosis, mydriasis, I am sorry.

DR. BULLIMORE: How?

DR. STULTING: I don't know how. I just said that they were anecdotal reports, and it is reasonable to collect the data. I don't think we need to collect it at every visit, but at the initial time of examination and at the final exam I think would be appropriate.

DR. SONI: In that case why not do it immediately after discontinuation of steroids which is relatively early, initially and then after steroids?

PARTICIPANT: Not every patient is going to be on steroids. Final exam.

DR. STULTING: I think the consensus is for the final exam.

Next slide?

The current guidance is axial link should be assessed on all eyes preoperatively and the proposal is to drop this requirement.

No objection to that one.

Next slide?

Topography should be performed at the preop exam and at months 1, 3, 6, 12 and 24, and the proposed modification at the preop and at the time of anticipated stability.

DR. BELIN: I would put back at least 1 month. If you do anticipated stability and really all you are looking at is the eye after it has regressed and/or healed and you really will never get a picture of what the laser itself has done, and you will get changes in centration, and it is best to look at it at about 1 month out after epithelialization has healed but before you get significant regression or remodeling.

DR. FERRIS: And for the same reason as I said it

before I think you have a data mess if you have patients with this measurement at all different times. If you want it at 1 month, it ought to be done on everybody. If you want it at the end of the study it ought to be on everybody, but to have it done on some people at month 3 and some people at month 6 and some people at month 12, I don't know how you make sense of that.

DR. MACSAI: It would be a mess to interpret and you know, anticipated stability or proven stability. So, they anticipate it is stable at 3, but then it turns out it is not and then we do again. Just do it at the end. Do it at 1 month and the end.

DR. BELIN: I agree, right, preop, 1 month, termination, end of study.

DR. MACRAE: I am not quite sure why we are doing 1 month other than let us say to document central islands.

DR. BELIN: Centrations.

DR. EYDELMAN: Just to clarify, according to the definition we were provided for final exam that definition is an evolving definition, i.e., the first 50 or 100 subjects might have a final exam at 24 months and the subsequent subjects if you leave it at that will have that

performed at perhaps 6 months.

DR. MACSAI: Well, so then better we have 50 subjects that are at 24 months and 150 subjects that are at 6 months than 200 subjects that are all over map. No play on words intended.

DR. OVERICH: This is in answer to the question regarding high myopia defined as between 6 and 12 spherical equivalent. The percentage of patients that did not have a change of more than 1 diopter between 6 and 12 is 86 percent. So, it is a significant difference between the low myopia and the high myopia.

DR. STULTING: So, 14 percent had a change of more than 1 diopter between two subsequent exams.

DR. OVERICH: Correct, and that was 6 and 12.

DR. MC CULLEY: We are looking at 3 months. You don't have 9 months?

DR. OVERICH: We don't have 9-month data, no, but the 6 and 12 if you look at the mean this demonstrates I think Dr. Belin's point and your point. If you look at the mean there was no statistically significant difference in the mean, of course. So, we might want to modify the high myopia group, and that goes along with their spherical equivalent refractive capability and why we argued earlier

for a little more leniency, whether it is 10 percent or 20 percent noise.

DR. FERRIS: This data screams for some reproducibility data on the reproducibility of refraction.

PARTICIPANT: That is what we really need.

DR. OVERICH: Zadnich in 1992 published the reproducibility of refraction but that was specifically not in high myopes. So, I think this is where this stands now. If you look at our standard deviation early on and use that as a distorted control that is about as close as you are going to get for these high myopes. I mean I don't know of any literature where you have a collection of greater than 200 eyes that are highly myopic. So, unfortunately, there just isn't a lot of data out there. You are right.

DR. BULLIMORE: Isn't the issue a repeatability study on the --

DR. OVERICH: You are not going to make us do this twice are you?

DR. BULLIMORE: No, I am not suggesting you do it. That is why we have master's students. Isn't the issue though the stability or the repeatability of the postoperative refraction? I mean really that is what Doyle was suggesting that because of the optics that you end up

with it is not a stability problem per se, it is a repeatability issue.

DR. OVERICH: The reproducibility at the visit, and that may be an issue. Hyperopia I will share with you is the same as low myopia.

DR. STULTING: Thank you.

Dr. Ferris' point is well taken that what we really need is for people to do repeated measures. Instead of making them 3 months apart, we need to make them a day or a week or whatever apart so that we can separate at least short-term variation and observer variation from long-term variation.

Where were we?

I will just interject a comment here. We have requested topography on all of these refractive surgical studies and laser studies that have come in, and I haven't really seen them used for much, and I think we eventually need to come to a point where we either have to use them for something or figure out what they mean or else stop requiring them.

DR. BULLIMORE: I was trying to find them in the adverse events, complications, safety or efficacy measures, and it may have been my poor scholarship, but I couldn't

find them. So, that supports Dr. Stulton's suggestion that we might excuse them. Obviously it is good clinical practice, standard of care, but I didn't find it helpful in past PMA reviews to have those data available.

DR. MC CULLEY: The thing that I can remember that maybe was leaning toward helpful is that when there have been problems in a patient population we have asked the sponsor if there were explanations from the topography, at least with our expectation that if it was from the topographical change the topography would have shown us something and the response typically has been back, "No."

So, I wouldn't be quite ready to throw them out, but I agree with Doyle that at some point we need to make them more meaningful or possibly delete them.

DR. BELIN: They are useful in patients that have problems. If you don't have problems, they are of no use, but the problem is that you really need to always look at difference maps. So, you have to do preops on every patient in order to make them useful, and if you never have to use them that is all the better, but if you have a central island or decentration the only way to look at it is to do a preop, postop, and they are going to be useful in analyzing otherwise unexplained decrease in vision, and that is how we

determine the central island problem. So, I think it is important to continue it, as well as its being used for screening.

DR. STULTING: I used to be very much in agreement with that, because you can take patients who have poor best spectacle corrected acuity and good contact lens acuity and look at their topography and see flat spots or peninsulas or whatever, but the other side of that issue that I have more recently become familiar with as we try to sort out some of these problems is that the exact same difficulties exist in patients who have 20/12 and 20/16 uncorrected acuities and topographies that are indistinguishable from those we attribute poor visual outcomes to. So, I think the story is really more complex than we would at first imagine, and we just don't have very much data.

Okay, so I think the consensus here is for preoperative for sure and final exam on everybody, and I don't know whether we reached a consensus on the middle ones or not.

DR. BELIN: I would propose that you should do 1 month.

DR. STULTING: At 1 month. Okay, any other thought on that?

The next one, please?

Questionnaire should be administered at the preop exam, at 1 week and at subsequent visit to be changed to the questionnaire should be administered at preop and the time of anticipated stability and the final exam.

Is that correct, they are going to be given at three times now proposed?

DR. EYDELMAN: Yes.

DR. STULTING: Okay, I don't remember that time of anticipated stability one. What was the rationale for that?

DR. EYDELMAN: Again, this had to do with there was some concern as to patients' quote, unquote, happiness factor whatever that is at the time of stability as opposed to at the final exam, and there was some discussion to that effect after you left I think.

DR. FERRIS: Is the idea that an individual study would say that given our procedure we think everybody ought to be stable at 6 months? So, it is not an individual decision?

DR. EYDELMAN: That is correct, anticipated stability for the device.

DR. FERRIS: One of the thoughts that goes through my mind if there are going to be these studies that are

going to have variable follow-up and everybody is going to have one length of follow-up, whatever that minimum length is, 6 months or something that you might want to get the questionnaire done at the time when everybody was going to answer it, and if you wanted a subgroup that went on for 2 years you would get that, too, but the time that you should have it is a time when you have the data on everybody at the same time. So, if 6 months was the minimum follow-up, that would be the second one, and then if you wanted long-term data you would get it on the cohort that made it out to 2 years.

DR. EYDELMAN: When we tried to come up with definition for final exam they tried to get away from the minimum follow-up for all devices because we cannot really perceive at this point what is acceptable minimal follow-up for all the devices to come, and even the devices that we are seeing currently the minimum follow-up would be different depending on the device.

DR. FERRIS: But within the study you could get it. I mean if the minimum follow-up within that study is 6 months, then everybody gets a 6-month exam and then they have a long-term follow-up whatever that is. With a big enough cohort you have got to figure out, do the

appropriate sample size.

DR. EYDELMAN: I guess I am not clear. I think what this says, what this is attempting to say is what you are verbalizing. So, I am not clear what the discussion is.

DR. FERRIS: I guess it is because it is hard to know exactly what that -- anticipated stability is hard to know what that means and final exam it is hard to know is that the final exam for the patient or final exam for the study.

DR. EYDELMAN: We just had a slide a few slides up where the final exam was defined and the same for anticipated stability. The reason we are using the term "anticipated stability" is to help sponsors design protocols under the IDE as opposed to waiting to the study to go -- because we have seen problems that are generated from that.

DR. SONI: Dr. Eydelman, talking about the time of anticipated stability in other words what you are suggesting is that a sponsor would come in at the time that the study is being planned and suggest a time, say, 3 months or 6 months of what they anticipate as stability?

DR. EYDELMAN: That is correct, and if the early data doesn't support that, they would have to move that.

DR. SONI: So, in that case to answer Dr. Ferris'

question you could then say that the questionnaire is going to be administered at 3 months because that is what their anticipated stability is.

DR. EYDELMAN: That is correct.

DR. STULTING: Consensus?

PARTICIPANT: It is fine.

DR. STULTING: Fine like it is. All right, are there any other issues that the agency would like for us to consider?

DR. BELIN: Could I bring one last question up?

DR. STULTING: Yes, sir.

DR. BELIN: Yesterday during the IOL statement that no more than 25 percent of subjects should be entered in at any one study site, we don't have a similar concern for any of the refractive procedures. I think we should. I would urge that similarly we have those guidelines and I wrote a minimum of five separate sites, but I think similarly worded to the IOL that no more than 25 percent of patients should be supplied at any one center site. I have bit concerns over single-site studies.

DR. EYDELMAN: Something similar is usually recommended, but it should be added. You are correct.

DR. BELIN: How would that apply to unique lasers

and their applications?

DR. WAXLER: I think it is fairly obvious that regardless of whether it is a unique laser of whatever vintage and parentage it is only one. If it is one laser it obviously can only be studied at the one site. There is nothing legally that prevents it being studied at that one site. So, we have to build in other kinds of controls, other kinds of, build more scrutiny in several more ways in the pipeline.

DR. MC CULLEY: I would like to refer you to Page 8 of the guidance document, and it says, "Single site studies may suffice if adequate data are provided to demonstrate the device can be used safely and effectively by other practitioners." So, that is in there, and then I guess what you really -- what are you going to require?

There is something in there. It is under 323 study design.

DR. WAXLER: Right. That is what I was referring to. We ask the sponsors to have other investigators, and we ask them to stratify their data according to those investigators just to make sure that there is nothing untoward. I mean we do what we can do with the limited situation that you have with a single site. Clearly we

would prefer to have multisites, no question about it, and I would assume although we haven't yet approved any single site of PMAs I would assume there would be some sort of restrictions on labeling that would apply to that single site that would be commensurate with that data.

DR. MC CULLEY: But what you are saying here is that single site will work, but it cannot be single site, single investigator.

DR. WAXLER: Right.

DR. MC CULLEY: Doyle, I had one thing. Should we not have under complications events that result in greater than 2 diopters of intended overcorrection?

DR. STULTING: Of unintended overcorrection?

DR. MC CULLEY: Unintended overcorrection, greater than 2 diopters. We don't have that under complications on Page 15. It wouldn't be an adverse event because you could refract it by the definition of adverse event that we are using, but should we not have as a complication greater than 2 diopters, a complication if the procedure results in greater than 2 diopters of intended overcorrection?

DR. STULTING: Any other comment on that?

DR. BELIN: Overcorrection beyond intended?

DR. STULTING: Intended minus --

PARTICIPANT: That would definitely be a complication.

DR. BELIN: I would, also, think that should be one of the safety variables. It has been in the past.

DR. EYDELMAN: I am sorry, could you repeat it?

DR. MC CULLEY: Okay, should we not have listed under complications 3262 overcorrections by greater than 2 diopters of intended correction?

DR. EYDELMAN: Any refractive data is collected, and reported and this --

DR. MC CULLEY: I know, but I am saying that if it is more than 2 diopters of intended, if you make someone a plus 2 instead of a plain 0, that to me is bad. That is a complication. It is not just a let us fill that number in and say, "So what?"

DR. EYDELMAN: Right. I am not arguing with that. My question is do you propose then to put the percentage of acceptable number to that because if it is merely for the purpose of collecting the data --

DR. MC CULLEY: Less than 1 percent.

DR. EYDELMAN: Okay, then we are going back to putting that to the safety end points because the list of complications was merely to collect this data.

DR. MC CULLEY: Okay. I think it should be listed as a complication, and I think it should be under the safety with a number.

DR. STULTING: Would you care to propose a number?

DR. MC CULLEY: I said, "Less than 1 percent."

DR. STULTING: Less than 1 percent. It is becoming easier to gain a consensus.

Is there any dissension?

DR. EYDELMAN: Could the Chair repeat the exact proposal?

DR. STULTING: The proposal as I understand it is to include among the list of complications unintended overcorrections of greater than 2 diopters. An overcorrection would be defined as a manifest spherical equivalent of the achieved minus the intended correction and to place as a safety target less than 1 percent, and we have a comment.

Go ahead.

DR. OVERICH: I think you should put a time frame on it because there will be in some lasers a hyperopic overshoot for a small period of time. So I think you want to put at final visit.

DR. MC CULLEY: That is one of the reasons I

picked 2 diopters.

DR. OVERICH: It is conceivable that there could be. I am not speaking generically.

DR. EYDELMAN: How about at 6 months at stability?

DR. MC CULLEY: It could be at stability, but I will tell you though if you have a laser that is reproducibly overcorrecting greater than 2 diopters and you let it go through doing that to too many patients then we have done harm.

DR. BULLIMORE: Then you need to have it as an adverse event for the FDA to --

DR. MC CULLEY: By definition it cannot be an adverse event because it doesn't result in decreased visual acuity.

DR. OVERICH: We did have this I think in the original document and it was taken out, and I think we are proposing now putting it back in. Just to remind everybody of the discussion it was that we were concerned that it was an efficacy variable cloaked as a safety variable, and then we decided it was really a safety variable. So, we have been full circle on this.

DR. MC CULLEY: I wouldn't want to propose taking it out because we don't know where to put it. I would let

the FDA figure it out.

DR. OVERICH: We already removed it once. It has already been removed once.

DR. MC CULLEY: I am saying, "Put it back in." But I don't know where to put it.

DR. OVERICH: It may be better as an efficacy rather than --

DR. MACSAI: As you stated it, that would be safety.

DR. MC CULLEY: I am happy with that.

DR. MACSAI: Because if you are looking at best spectacle correction you will never see it.

DR. STULTING: Any other comments?

DR. EYDELMAN: So, there was a clarifier on time?

DR. STULTING: Pardon?

DR. EYDELMAN: There was a time frame in that comment at point stability or --

DR. STULTING: No, 3 months.

I don't hear any objections to 3 months.

Any other comments?

Dr. Waxler, it looks like you are about to say something?

DR. WAXLER: I wanted to thank you , first of

all, Dr. Belin, for volunteering to chair this small group to come up with the information on the whatever that was, efficacy end points.

The other issue that I think was left unresolved which would be very helpful if there was another subgroup that wished to work on it and that is the astigmatism values, efficacy end points for astigmatism. If someone, Marc, who would like to look at that, it would be really helpful to do that so that we don't -- I guess I feel very strongly that the sooner we can get the guidance in the shape that there is reasonable consensus on it, the better it will be for all of us in terms of not having to beat up on the next applicant that comes through and as we are trying to decide what is approvable or not. You don't mind, I realize, but -- so, that would be helpful.

DR. STULTING: Dr. Bullimore, did you agree to --

DR. BULLIMORE: I think with one arm behind my back, yes.

DR. STULTING: So, you are going to formulate some idea about how astigmatism should be incorporated in terms of safety and efficacy?

DR. BULLIMORE: Just to put some parameters, who am I allowed to talk to? Other panel members, FDA staff,

industry, my mother?

DR. STULTING: Anywhere you want.

Any other items of business?

DR. EYDELMAN: And if we can put a proposed time frame?

DR. STULTING: A couple of weeks, maybe 3 weeks?

DR. BULLIMORE: In terms of circulating materials, the FDA staff will be available to help with that?

DR. STULTING: Sure.

DR. BULLIMORE: Okay.

DR. STULTING: Any other items of business?

I think we are about done. This is my last meeting, and I would like to express my thanks to Dr. Rosenthal for his kind comments this morning and to FDA staff for their diligence and their cooperation over the years. They are a hard working group, and I think they are under appreciated by the ophthalmic community. I would like, also, to thank the panel members for their support and cooperation over the years and I would like to express my appreciation for being given the opportunity to chair this fine group.

Thank you.

We are adjourned.

(Thereupon, at 4:19 p.m., the meeting was adjourned.)