dispersion syndrome; that is, myopia young age in Caucasian race. Pigment dispersion syndrome is at least as common in women as in men.

One study quoted about a 2-1/2 percent incidence of pigment dispersion in Caucasians. Simply using this figure based on the number of Caucasians in the STAAR PMA, we'd expect six in this study to have pigment dispersion. The Sponsor reports zero, both before and after ICL implantation. Let's look to the literature.

A published study found pigment dispersion in the angle in 9 of 58 eyes, or 15-1/2 percent at 18 months. The authors postulated that the STAAR ICL pushes the iris anteriorly, and optic iris chafing leads to pigment dispersion syndrome in a subset of patients.

A 1998 study, using ultrasound after ICL implantation, found angle narrowing in all eyes, and peripheral anterior synechiae in 2 out of 9 eyes, or 22 percent. The ICL was in wide contact with the iris in all eyes.

For this study, I reviewed the submitted
PMA materials, and reviewed both the pre-op and post-op clinical study report forms. I didn’t find any gonioscopy data, which I was shocked to see that. I also didn’t find any ultrasound data presented to determine angle anatomy alterations following the ICL.

It’s my opinion that the lack of these data is a disservice to present and future patients with the STAAR ICL, and represents a major study design error.

Gonioscopy can assess angle pigment deposition, a sensitive and common finding in pigment dispersion syndrome. Perhaps no patient was diagnosed with pigment dispersion syndrome because no one looked at the angle post-op.

Moreover, gonioscopy can determine angle narrowing and synechiae. Further, if no gonioscopy examinations were performed, other relevant features could be missed, vascularization and other preoperative abnormalities.

The theoretical risk to the angle can be easily surmised given the design and intended use of this phakic IOL, and it’s my belief that the initial study design should have included gonioscopy, whether
or not it was mandated by the FDA.

Let's review issues related to pupil diameter and the lens optic diameter. It's well known that dim illumination mydriasis can be robust in the young. Dr. Vukich indicated that when this study was designed, that those parameters were not well known. Being an old guy, I beg to differ. Back in about 1993-94, I reviewed issues related to pupil diameter with small optical zone radial keratotomy. My literature review at that time revealed that the mydriasis being robust in the young was documented, well know, and in the literature at that time. I believe that predates the design of this particular study.

STAAR's study cohort ranged from 22 to 45 years of age, and we've heard that the lens optic diameter is 465 to 55. Given the young age of the cohort, as Dr. Bradley already noted, it's reasonable to expect that some patients will have dim illumination pupil diameters that exceed the lens optic diameter. We, therefore, have an expectation that some patients may experience halos and dim
illumination, or have nighttime visual aberrations.

Looking to the literature, Arne found a higher frequency of halos with small optic diameter ICLs. The rate of halos correlated to the difference between the scotopic pupil diameter and the optical zone size. Due to these halos, these authors recommended intentional under-correction for high myopia; that is, using a larger optic diameter lens followed by LASIK.

Hence, another study design error in this PMA is the absence of pupil size measurements. Relevant analysis should have included the rate of visual aberrations with increasing optic pupil mismatch. Regrettably, this was not performed for our review.

In the absence of this pupil size information, the best we can do is stratify the patient's symptoms by the lens optic diameter. I couldn't find this information in the materials given to me, but it should be required for later FDA review. Also, each symptom category should be reported separately; that is, separately none and mild, rather
than lumping the categories in the current tables. Of course, this information presumes that the small lens optic patients do not have skewed pupil sizes one way or the other. We'll simply never know.

Let's go on to endothelial cell loss. The threshold analyses that I presented in Appendix 1 of my written review show maximum rates of annual cell loss to reach various target levels at the time of death. Clearly, there's many assumptions that are made, including an annual instantaneous cell loss, and that it's linear, and it doesn't include information regarding stem cell repopulation. However, using these figures, if we desire a 1500 cell for millimeter square density at death, a .9 percent annual loss rate is the maximum, inclusive of all age ranges; that is, the 20 to 30 year old range. And if we desire an 800 cell per millimeter square density at death, a 1.9 percent annual loss is the maximum.

It's important to remind ourselves that 50 percent of patients will have endothelial cell densities that fall below the normal mean cut-off values; and, therefore, younger patients, that 20 to
30 age group, have a significantly higher risk of running out of endothelial cells during their lifetime if these rates are continuous. And now to the PMA itself.

Regarding the study population, the total eyes show with the blue bars indicate very good follow-up. I certainly recognize the difficulty of carrying out such a large study for an extended period of time, and commend the Sponsor for their efforts. The purple bars show endothelial data on approximately 200 eyes, with a large drop-off at the 48 month interval shown out here as 67 eyes.

I find it ironic, some studies we reveal at panel only have 6 and 12 month data, and we’re always wrestling with not enough data. And here a Sponsor has run a 3 and 4 year study, and we’re still wrestling with not enough data. I just found that amazing.

Unfortunately, the endothelial data in the written PMA have varying ends, and there’s no consistent cohort of eyes followed through each and every examination interval. The data we’ve seen today
with that 37 eye consistent cohort was not provided to me in the materials that I reviewed. That made the evaluation difficult.

Just one housekeeping item, and I believe Malvina already alluded to this. The inclusion criteria had a stable refraction within a half diopter over the prior year. The indications for use statement had a 1 diopter over the prior year, obviously, needs to be matched or reconciled.

Regarding the exclusion criteria, we know that phakic IOLs can alter the corneal endothelial. Dr. Macsai alluded to this. The corneal endothelial status was omitted from the exclusion criteria, and given the young age of these patients, I believe it would be a relevant material fact to be considered prior to implantation of this device.

Certainly, if a young patient had an abnormal endothelial layer, I would not recommend this device as a clinician. There is no question that I wanted pre-op specular endothelial analysis for this cosmetic elective procedure, where the alternative is glasses or contact lenses.
On to some safety issues. Let's discuss the learning curve associated with phakic IOL implantation. I believe we're all in agreement that the labeling should include relevant learning curve issues. Of the 13 upside down lens insertions, 11 occurred within the investigator's first 22 procedures, 6 out of 13 developed in AST in the early post-op period. Of the 14 eyes that developed anterior subcapsular cataracts, most occurred within each investigator's first 8 surgical cases. One investigator accounted for a disproportionate share of the ASCs, a 9.4 percent rate, and that same investigator accounted for both cataract extractions in the study. To lessen the impact of learning curve issues for the patient, I'd favor specialized course training or case supervision by an experienced surgeon for early cases.

On to change in best spectacle corrected visual acuity. As compared to the lower dioptic groups, there are larger post-op gains of best corrected visual acuity, 20/20 or better, in the high myopia group. For the less than 7 diopter group shown...
in the orange, there is an 8.3 percent gain pre-op among 36. For the 7 to 10 diopter group shown in the maroon, there's a 15.6 gain pre-op among 36, and for the greater than 10 diopter group shown down here in the blue, there's about a 20.4 percent gain pre-op among 36. These are findings strongly argued for an induced magnification effect as a result of the surgery.

In looking at greater than or equal to one line of best corrected visual acuity loss, high myopes have an increased rate of vision loss with time as compared to lower myopes. And we've already heard that for this particular group, a one line loss is the equivalent of a two line loss due to induced magnification as a result of the surgery.

The rate of greater than one line loss goes up to about 16 percent. I'm not sure why that would exactly be. I don't know if that has to do with lens optic pupil mismatch or other issues, but I'm not sure it's well delineated. It's certainly not clear in my mind as the ultimate etiology of that.

Another way to look at the same issue, the
mean improvement in lines of vision, high myopes with
time decline in improvement starting at 6 months, one
line improvement down to .4, two line improvement at
36 months. Certainly, appropriate labeling should
mention this trend.

On to interocular pressure, 20 of 526
eyes, or 3.8 percent had pressure spikes in the early
post-op period, 11 reached 40 to 50, 4 reached 55 to
58, and 1 reached a whopping 65 millimeters of
mercury. Most of the spikes occurred by day one or
two, 17 needed additional YAG, 3 required AC washout
for retained viscoelastic. Clearly, these pressure
elevations are not trivial. Myopic disks are perhaps
slightly more susceptible to damage from elevation of
IOP than ametropic or hyperopic disks.

Patient and physician labeling should
highlight the issue in order to appropriately plan
early post-op exams. As a clinician, I might consider
the use of Diamox on a case-by-case basis.

With regard to chronic pressure elevation,
the overall cohort shows an increasing trend for
patients to experience an increase in pressure greater
than 5, looking at the graph, at 6 months about a little under 3 percent, and at 36 months something over 6 percent, 6-1/2 percent had a change in baseline pressure.

Pre-op, looking at patients with a pressure greater than 21, about 3 percent had pressures greater than 21, and at 36 months about 6 percent had pressures greater than 21. Two patients were diagnosed with glaucoma and treated topically.

Given the potential for the STAAR lens to alter pressure regulation for the factors previously mentioned, I'm concerned about this finding. We must recognize these recipients are young, expected to live many future years. At a minimum, labeling should emphasize this particular issue. I again note that the STAAR study omitted gonioscopy for a device that affects the angle. Gonioscopy can assess pigment deposition, a sensitive and common progressive finding in pigment dispersion syndrome. Angle grade and synechiae formation are also relevant findings. Inexplicably, gonioscopy wasn't done. If I were a clinician, I would be doing gonioscopy.
The corneal endothelial data - in the materials provide there was no true consistent cohort data for each and every examination interval. There was fluctuating denominators at the various examination intervals, and this made our analysis difficult. We've seen data today on 37 eyes that had consistent cohort data, but the remainder of the application does not.

While this is not a consistent cohort of eyes, there appears to be progressive endothelial cell loss over time. The total at four years is insufficient to make conclusive statements, but the cell loss does not stabilize over the study period. These cell loss rates, if continuous, constitute a serious safety issue that may jeopardize approval of this device.

Looking at the 154 eye consistent cohort at year 3, pre-op to 36 months, 8.9 percent loss, that was higher than the table we just looked at with 8.4 percent. It took me a long time to figure out that there were two disparate groups that had an "N" of 57, and both reported 4 year loss rates, and both were
called the consistent cohort. Two groups, pre-op to 48 months, there was a 9-1/2 percent endothelial loss. Three year to four year there was a .041 percent endothelial gain, with the upper limit of the 90 percent confidence interval at 1.43 percent loss per year.

It’s this one isolated group, as we’ve heard, which the Sponsor is making the argument for stability in conjunction with the morphometric data that Dr. Edelhauser reviewed.

Let’s look closer at this 57 eye cohort. This is a histogram that was in the material somewhere, that outlines where these eyes fell in terms of cells gained or cells lost. The mean cell density increased by one cell. Overall, just looking on the number of eyes on either side as zero, 31 eyes lost cell density, and 26 eyes gained. More eyes lost zero to five here at 21, than gained zero to five. It’s about even on either side of 5 to 10, 8 versus 7. This is the group that had me wondering.

Here’s a group out here gaining 10 to 15 percent of cells, versus only one eye losing 10 to 15
percent. Of these 7 histogram analyses in the application, this is the only one that had more eyes gaining 10 to 15, than losing 10 to 15. Certainly, I'm willing to accept random measurement error that leads to an evenly matched set of gains and losses. That is a true bell curve due to precision errors measuring endothelial cell loss, but I can't come up with a physiologic reason that five eyes have truly gained a sizeable percentage of endothelial cells in 12 months. I'm wondering whether these big ticket outliers up here at 10 to 15 percent skewed the mean data and falsely elevated it, leading us to a conclusion of stability.

We've heard from Dr. Gray, and his comments were greatly appreciated by me. I place great emphasis on statistical analysis of the data. He noted that simple comparison of the two to three year loss versus the three to four year loss is not appropriate due to the likelihood of producing negatively correlated observations. And he mentioned that multiple ways by saying that the three year loss was lower than the other data points.
He also noted there was not strong statistical evidence that the cell loss levels off after year three. Additionally, of the 57 eye cohort with both three and four year data, 10 out of 57, or 17-1/2 percent had more than 5 percent cell loss over 12 months. Those are pretty big numbers if those are true for a young cohort.

Based upon these data, I remain scientifically unconvinced that this procedure provides a reasonable assurance of safety for the corneal endothelium in the long run. The preponderance of evidence that we were offered was weighted toward an unsafe level of endothelial cell loss, that if continuous, would jeopardize the safety of a future interocular procedure or cause corneal edema during the patient's lifetime, or both. I think we're all in agreement, we need a larger four year sample size. I would agree that ongoing endothelial surveillance to year five would be desirable, given the youth of the cohort.

I'll talk briefly about anterior chamber cell depth. We see that the endothelial loss in eyes
with shallow anterior chambers was 12.2 percent over three years, while the loss was 8.4 percent for eyes with anterior chambers greater than three. As Dr. Macsai noted, a 50 percent increase in shallow chambers. I would not necessarily disagree with an abundance of caution approach to limit the device to eyes with anterior chambers greater than 3.

It's worthwhile noting that only 5-1/2 percent of the total study cohort would be excluded by this limitation. And, therefore, I don't believe it's an onerous limitation that would exclude large numbers of patients. I think it's reasonable to do that.

Something interesting in this 57 eye cohort, in addition to looking at the histogram, if we look at the anterior chamber depths for 50 of these eyes in that cohort with three to four year data, 50 eyes had an anterior chamber depth greater than 3 millimeters. They gained .3 - excuse me - they lost .3 percent in endothelial cell loss from year three to four, and there were 7 eyes with an anterior chamber depth that was shallow, and they had a 2.9 percent gain in endothelial cells between years three to four.
From my vantage point, that didn't make sense. That was a counter-intuitive result that contradicts the generalized study results of a higher rate of loss in the shallow AC group. From my vantage point, something smells wrong with that 57 eye cohort. I would love for that four year cohort to be larger so that it would even it all, so that we'd have a better statistical sense of what's going on.

On to effectiveness, and at this point I'm going to stipulate to Dr. Slade's excellent presentation on effectiveness, and we're not going to go over all this data, so yadda-yadda-yadda, the procedure seems effective. That's enough of that.

In terms of willingness to have the ICL again, 5.6 percent less than 7 diopters were not willing to undergo it again. And in the greater than 15 diopter group, all patients were willing to undergo it again, despite poor effectiveness and high rate of complications. I interpret this finding just to mean that low myopes are less desperate for the surgery, as compared to high myopes who appreciate help of any kind, even though it may not be perfect.
And in conclusion, this does appear to be an effective device to reduce myopia. We must be reasonably sure that the endothelial cell loss does indeed stabilize following ICL implantation. It's critical to recognize that these devices are intended for a young population with 50 plus years to go. We can't afford an epidemic of bullous keratopathy for a cosmetic elective procedure.

I'm also concerned that while the morphometric data show that we don't have a change in pleomorphism or polymegathism, what I'm concerned about is that there's evidence to suggest that younger corneas may blunt our ability to see those changes. I'm just wondering whether we're not seeing much of a change for chronic stress simply due to the fact that the cohort is a bunch of young corneas.

Dr. Edelhauser, I believe, was in general agreement that younger corneas are robust, and may not show stress factors as readily as an older cornea, so I'm concerned that the data does not have statistical evidence to show that it tapers off for sure, and I'm concerned that the younger corneas may blunt our
ordinary morphometric data that would ordinarily tell us there's stress.

I certainly need convincing with a larger "N" for the four year endothelial data one way or another. I think that number needs to be bigger.

Thank you very much for your attention, and I apologize if it was redundant.

DR. WEISS: Thank you, Dr. Grimmett, for your usual detailed, insightful reviews.

We're going to now go on with panel discussion of this PMA. I'm going to ask the FDA if they'd be so kind to come to the podium. And I would also request that we go out of order of your questions. There's a method to my madness, so I'd like to start with question 3, which is a discussion of how to decide what size to put in the eye. And in terms of whether the currently recommended method measuring the white-to-white, which was recommended by the sponsor is an appropriate way to do it. And if not, what does the panel recommend.

I will remind you just in terms of what we've heard from our reviewers, Dr. Macsai was
recommending using the Orbscan or something similar, because the white-to-white is not very accurate. And Dr. Grimmett also agreed, the white-to-white was not very accurate. But I'd like us as a panel to determine whether we're going to recommend that the labeling include the way the panel -- the way the sponsor did the study, which is measuring white-to-white, or do we want something else. Dr. Sugar.

DR. SUGAR: I'd like to recommend that we recommend no changes from the Sponsor has recommended, given that we don't have anything better that I'm aware of. Certainly we don't -- while the white-to-white doesn't correlate with sulcus-to-sulcus dimensions, it is highly impractical to do ultrasound biomicroscopy as 20 or 50 megahertz. It's very unwieldy. At 50 megahertz you almost can't do it. You have to make a collage of the pictures in order to measure it, and I don't think we have anything better. If something better becomes available, it may be worth recommending in the future.

DR. WEISS: Dr. Macsai.

DR. MACSAI: I respectfully disagree with
Dr. Sugar, not about ultrasound biomicroscopy, just about the irreproducibility, if that’s a word, of the caliper method. And that since you need an anterior chamber depth measurement from the back of the cornea to the front of the lens, you’re getting two for one there with Orbscan. That’s been validated reproducible.

DR. SUGAR: I said measure white-to-white. You’re talking about measuring white-to-white in terms of what instrument? I didn’t say what instrument to use.

DR. MACSAI: Well, I did.

DR. SUGAR: That is, you’re saying -- I understand – that Orbscan is a better way to measure white-to-white. And again, I don’t -- I’m not aware of validation of that information apropos of this device.

DR. MACSAI: Well, then I guess we need to ask the Sponsor if they used that technique, because I thought the Sponsor used many techniques. I don’t know if I’m allowed to do that at this time, Madam Chairperson.
DR. WEISS: Not at this time. We can have them address it in the proper time point, but not at this point. Does anyone else have any opinions on that? We're going to get some musical accompaniment at the same time by Dr. Bradley which is quite kind. Anyone else have any opinions on this particular point? No, so I think that is -- does anyone have any concerns about measuring it with calipers, aside from those that have been expressed? So we will move on.

I guess for the FDA, I think what's been expressed is if the Sponsor has shown that Orbscan is any more accurate than calipers, we would go with that, but I doubt that's what they've shown, because if they did, that would have been clearly presented. Malvina.

DR. EYDELMAN: The nature of the question wasn't to try to determine the instrumentation that's best to perform the measurement with. The question -- during the study, the white-to-white was only measured with calipers. The Orbscan was used for ACD. What this question intends to get at is whether the white-to-white measurement is appropriate for sizing of the ICL.
DR. WEISS: Well, I think the panel would probably agree that it may not be great, but we don't have another option. And nothing else was done in the study, so we don't have a choice. Would anyone disagree with me, any of the primary reviewers disagree with that spin? So the answer is, we think it's just great, since we have nothing else. We will go to question 4.

DR. EYDELMAN: Did you want me to read it, or do you want me to just project the question part?

DR. WEISS: Why don't we -- can you read the question part of the question?

DR. EYDELMAN: Question 4(a), "Does the safety and efficacy data for eyes with preoperative myopia of greater than 15 to 20 diopters support this range?"

DR. WEISS: From what I understood from all of the primary reviewers, everyone seemed to be in agreement that it supported this refractive range if the labeling was changed to reduction of myopia, as opposed to correction. Dr. Macsai.

DR. MACSAI: Maybe I misled you. I didn't
mean that. I think that this is something the Agency has to provide a guidance document on. I think when the Agency tells us what are acceptable outcomes in the minus 15 to minus 20 range, then we can approve it. But right now, we’re throwing the dice. It’s arbitrary.

DR. WEISS: Dr. McCulley.

DR. MCCULLEY: I have to ask a question of what the Agency expects of us. If they bring something to us for an opinion, and they have a guidance document, then we would apply our opinion, or use that in our decision making. If they bring something to us and ask us an opinion where there’s not a guidance, then I think my impression would be the FDA would be asking us to provide our best opinion based on what’s provided to us.

DR. WEISS: You’re entirely correct. And also guidance documents are just that, you don’t have to adhere to guidance documents. They’re just meant as guidance. So with that in mind, Dr. Macsai, what is your opinion sans guidance document?

DR. MACSAI: My opinion from history is
once approved, guidance or no, it’s set as a standard for those that follow. And I urge the panel to proceed with caution. I think it’s arbitrary. I think the numbers are limited, and I have trouble with it in this range of myopia because once this is approved, every other device will be measured compared to this. Whether appropriate or not, the comparison will be made.

DR. WEISS: I see Dr. Rosenthal shaking his head, and I think really what we have to do - this is not a guidance. This is, we have to decide on the efficacy and safety of this particular device. And you can have the labeling reflect. So, for example, as has been suggested by Dr. Sugar, you could say that this does not -- this is not for correction of entire myopia in above minus 15, but it’s for reduction of myopia in this group. Dr. Rosenthal.

DR. ROSENTHAL: May I just clarify, Dr. Macsai, that in fact, each Class 3 PMA must stand on its own, and a decision should be made without comparison to data from any other PMA. And I think that’s the way -- we’ve been pretty consistent about
that over the past 7 or 8 years. So hopefully, what
decision you make on this will not bear on another
decision made on another device.

DR. WEISS: Dr. McCulley.

DR. McCULLEY: My impression is that often
despite guidance to industry, they will try to use
prior PMAs and compare, despite the fact that they're
advised not to do that. We don't have any control
over that. But it really should not set anything that
can be legitimately used in the future in a PMA
application or presentation.

DR. WEISS: And also, we've just been, you
know, guided by Dr. Rosenthal, is that we should not
be -- that should not reflect what your opinion is at
this particular point. Your opinion should stand
alone for the devices being brought forward to you.
So with that in mind, without thinking of the future
or the past, just the moment, is this efficacious for
reducing myopia in patients who have more than a minus
15? Dr. Schein, then Dr. McMahon.

DR. SCHEIN: Jayne, I hope I don't throw
too much of a wrench in the works, but it seems to me
there's one overriding question that needs to be addressed before getting into the sub-levels. So assuming that there's some consensus that there is efficacy, which I think I've heard some consensus, there also seems to be some consensus of concern about certain adverse events.

DR. WEISS: Which we will get into, so this is --

DR. SCHEIN: Which you cannot separate this tension between having an appearance of safety during a short time period, and uncertainty in a long time period. You can analyze this all day long, and that uncertainty will still be there. So my entire focus on these questions has to do with the level of rigor and detail that one can request in a post market setting. Everything else depends upon that.

DR. WEISS: Because these are going to be very -- this is going to be, obviously, a much longer discussion and much more detailed, I'm trying to get some of the housekeeping out of the way. I understand this is not scientific, but on the other hand, I think it'll work, so I'd ask you to bear with me.
DR. SCHEIN: Okay.

DR. WEISS: We may not get to the bottom line on all these questions, but certainly, once we start getting involved in the question of what are the endothelial cell specular microscopy data mean, are we talking about post-market studies, this is going to be a more lengthy discussion, and I want to delay that lengthy discussion.

DR. SCHEIN: Okay. So to answer, I'd say efficacy, yes - safety, unknown.

DR. WEISS: Fine. That's good enough.

Dr. Matoba.

DR. MATOBA: Then maybe we should do the first of those questions first, and then come back to this.

DR. WEISS: Well, I'm actually mostly interested in efficacy, so I think if the answer is it shows efficacy for reduction, then we have an answer. And then I think for the question of safety, that's going to be going across the refractive ranges. Is there any other discussion on this particular question? We may need to come back to it.
SPEAKER: Can you get a sense of the panel for us?

DR. WEISS: I'm just going to have a hand show, a brief vote. What -- if the members of the panel could raise their hand if they believe that this device is efficacious for reduction of myopia in patients with refractive errors greater than minus 15. Those of you who believe it's efficacious, we're not discussing safety at this moment, can you please raise your hand.

(Vote taken.)

DR. WEISS: So I think that's --

SPEAKER: Is this a reduction, Jayne?

DR. WEISS: Reduction, yes. I think that's consensus, so that would answer for efficacy. I'm going to skip then to Question 6 on IOP rise, if we could.

DR. EYDELMAN: There was a 4(b), but I was instructed to skip it.

DR. WEISS: What was 4(b)? I'm sorry.

DR. SUGAR: Corrections to treatment.

DR. WEISS: Well, we did say reduction.
We said reduction of myopia. Question 6 relates to IOP increase. Would you be able to read that?

DR. EYDELMAN: Certainly. "Do you believe that specific recommendations regarding early post-operative follow-up are needed in the labeling?"

DR. WEISS: So Dr. Macsai has suggested in relationship to the IOP rise that it be suggested that the pressure be checked 4 to 6 hours later. Dr. Sugar suggested that there should be -- the Sponsor should indicate a better way to assess the size of the iridotomies when they're too small. Could I have some discussion on these particular recommendations? Dr. Macsai.

DR. MACSAI: I would also ask maybe Dr. Coleman to help us with the question of timing of the iridotomies, if 7 days in advance is the appropriate amount of time to ensure patency. And then the second part is, which I forgot to mention in my verbal review, I did in my written review, is whether or not irrigation and aspiration of the viscoelastic would be recommended by the Sponsor, because that's what was used when the pressure rise was thought to be due to
retained viscoelastic in those problematic cases.

DR. WEISS: Dr. Coleman.

DR. COLEMAN: This is Dr. Coleman. In terms of the timing, it's really hard to tell from their data whether or not the problems that they had with the iridotomies closing in the post-op period was because the iridotomies were done within 7 days of the surgery. They were still on steroids when you look at the PMA at the time of surgery, so it would be recommended that they actually had done the iridotomies at least two to three weeks prior to surgery, confirmed the patency of the iridotomies prior to placing the implant. And then also having the patients off of steroids, because that would reduce their steroid responders, because they also had problems in the PMA of individuals that they identified as having interocular pressure elevations due to steroid response.

And in their labeling, they do have that irrigating with a 27- gauge cannula to the wound is sufficient to flush viscoelastic from the eye. I would say that's not true. Their own data shows that...
it's not sufficient, and so you would -- they would need to change that wording, and also to show in the labeling that if you don't flush the viscoelastic from the eye, you can have some major problems with interocular pressure spikes. So as Dr. Grimmett had mentioned, IV Diamox may be beneficial in preventing these.

In terms of checking the interocular pressure afterwards, that would need to be within like 4 to 6 hours of a procedure, and then the following day they would also need to check it within 24 hours, and also 48 hours, because they had spikes up to two days. And it's well known that viscoelastic can remain in the anterior chamber from 48 to 72 hours, if it's not flushed out.

DR. WEISS: Let me just clarify. You would then suggest in labeling that it be indicated to check pressure 4 to 6 hours, and 48 hours. And what are your time points?

DR. MACSAI: I would say 4 to 6, 24, and 48 hours.

DR. WEISS: Is that not onerous? We don't
do that with cataract extractions. Dr. McCulley.

DR. McCULLEY: The issue is -- I mean, if you're going to irrigate, as I understand it, the way the viscoelastic was removed, it's a cohesive viscoelastic. You tried to irrigate it out with a 27-gauge cannula. Why not use something like a Simcoe needle for I&A? I mean, I think that's the point. Then there would be less concern. I still would go with the 4 to 6 hours, and the 24 hours, but I would think that would be a better approach.

DR. COLEMAN: Because one of the problems is you get -- this is Dr. Coleman. You get viscoelastic in the trabecular meshwork, and even sometimes even irrigating it out, you don't get all the viscoelastic out in certain eyes. And some of these eyes are going to be predisposed to having interocular pressure spikes. Because of the study design, they were already on steroids, and so that's predisposing them, in addition to their being myopic.

DR. WEISS: How many procedures do we do that we require patients to come back 4 to 6 hours later to check if we still have viscoelastic in them?
I mean, I think that’s not -- that’s fairly burdensome in my book.

DR. COLEMAN: Well, there may -- I think one of the issues is that if you take eyes that run and spike pressures up to 55 or 65, and these eyes are, you know, very painful and stuff, it’s an issue in terms of in the orange study when Dr. Grimmett had pointed out, where they looked at those 50 eyes. They actually gave people IV Diamox on the table, and the 4 hours later post-operatively, and they didn’t report any of those acute IOP pressure spikes.

DR. WEISS: But if we’re talking about such a small percentage of eyes that are -- in which that’s happening, wouldn’t it --

DR. COLEMAN: You don’t know the long-term ramifications of elevated interocular pressure spikes to 65 for 24, 48, 72 hours, even in a young person.

DR. WEISS: Dr. Mathers, and then Dr. McCulley.

DR. MATHERS: In common sense terms, I don’t see that this is terribly difficult from filling an eye with viscoelastic when you do cataract surgery,
measure pressure the next day, and if there's a problem, you continue to measure it. It sounds to me like this would work if you did that, but I certainly think it's necessary to measure it the next day. And if you treat promptly, you perhaps will tolerate, like cataract surgery patients do, a brief pressure rise.

DR. COLEMAN: This is Dr. Coleman. It's debatable how brief is 24 hours with a pressure up to 65. And even if you potentially irrigate it, they can re-spike again. I mean, it's -- we see it in terms of the management of individuals with cataract surgery, where we have to go for 48 hours, sometimes managing pressure spikes. Now these are eyes with compromised angles, but you don't know how many of these individuals do have already potentially compromised angles because we don't really have the gonioscopy on it. And so it's some -- unfortunately, the issue is muddled with the viscoelastic, the closed iridotomies, and then potential problems with the angle due to the placement of the phakic lens.

DR. WEISS: You know, I think on this particular issue, since it's -- we can agree to
disagree on this particular one, so that has -- the
idea of perhaps suggesting an IOP check in 4 to 6
hours, and 24 hours, and also putting in labeling that
the IOP rise may occur if viscoelastic is not rinsed.
Those have both been suggested. Can you elaborate,
Dr. Sugar, about the labeling advice you would want as
far as the iridotomies go?

DR. SUGAR: I will -- well, I need to back
up a little bit. I think that there were only 2 or 3
patients that required re-irrigation of viscoelastic out of 20 that had pressure elevations that were substantial. I don’t think that’s sufficient to mandate a change in the way you get rid of the viscoelastic.

There’s a cost issue if you’re going to have to have a machine to do I&A, and having tubing and stuff, or even a Simcoe. I don’t think there’s sufficient evidence to suggest that the techniques suggested by the Sponsor should be altered. Your question was?

DR. WEISS: You had mentioned having a better way to assess the size of the iridotomy when
it's too small.

DR. SUGAR: I just wonder if the Sponsors had from those 17 patients that needed their iridotomies enlarged, if there was -- you know, if the distance between them was insufficient and, therefore, they were covered, or if there was something about them that would suggest a different approach to doing the iridotomies to make that less likely to happen. I certainly think that Anne’s suggestion that you do it longer in advance, and you look and see that they’re patent makes perfect sense.

DR. WEISS: So basically, if the Sponsor could provide information of what they’ve learned for those iridotomies that had to be enlarged, what was done incorrectly the first time around?

DR. SUGAR: If they have such information.

DR. WEISS: I think unless anyone has more comments on this question, we’ll go to Question number 1.


DR. WEISS: I know. Intentionally.
DR. McCULLEY: Okay.

DR. WEISS: Because I was afraid that Dr. Schein was going to be getting out another wrench.

DR. McCULLEY: You pretty much rusted his wrench.

DR. WEISS: I have a feeling it was going to be headed in my direction, so we'll go to 1. One is the question which has been sort of the most emphasized point during the discussion, is about the significance of the specular microscopy data. And I'm going to hit a couple of things concerning this question that maybe we can reach consensus on before we get to the more contentious issue.

Dr. Grimmett and Dr. Macsaí both suggested that a minimal number of cells, specular microscopy be performed pre-op, and that patients have a minimal number of endothelial cells before consideration is made for having this procedure. I'd like to have some discussion on that by the panel. Is that something that people agree with or not? Dr. McCulley.

DR. McCULLEY: Oh, I was just nodding to myself.
DR. WEISS: That's dangerous around here.

DR. McCULLEY: I see. I think that's reasonable. I think that to screen patients to be certain that they have normal endothelium for age prior to the procedure is wise and prudent.

DR. WEISS: Dr. Mathers, and then Dr. Grimmett.

DR. MATHERS: Some of the subjects had very little endothelial counts to begin with, and that's going to be part of this population if you do any sizeable number. I think it would be very unwise to not have some lower cut-off for endothelium. And I think it's appropriate to look at endothelial cell counts.

DR. WEISS: Dr. Grimmett.

DR. GRIMMETT: I agree with Dr. McCulley, but I would ask Dr. McCulley, would you set your lower threshold at like one standard deviation, or two standard deviations lower than a normal mean value for that given age range, or how would you set your threshold?

DR. McCULLEY: I suppose I'd need -- you,
again, have more confidence in these counting things than I do. I guess I'd want to look at the data for normal, and for age, and one and two standard deviations before I would answer that. I would just leave it loose and for right now that it be normal for age. And I would think that would add additional comfort to all of us, and those who are really concerned about the accuracy and reproducibility of the density. But I think that would be a reasonable thing to add, that should give us all more comfort with this whole issue.

DR. GRIMMETT: Dr. Grimmett again. I agree with Dr. McCulley. I had suggested a year ago to use age stratified normal means, plus or minus one standard deviation. But I think that's debatable exactly where you draw the line. Normal for 20 to 30, for example, is about 2950 plus or minus 150 or so, something like that.

DR. WEISS: Dr. Macsai had also suggested in line with this that post-op endothelial cell counts be done, and consideration of explantation be made if the cell count is dropping. Is that -- what does the
panel -- Dr. McCulley. You're shaking your head again.

DR. McCULLEY: Again, we don’t know -- we’re missing so much information. We need to know what the remodeling process of the endothelial is over time based on degree of initial injury, surgical injury, and age of the patient that has incurred the injury. So I’m not sure that I would know what to say in terms of when to do it, when not to. I think it ends up being surgeon judgment to make those decisions. I don’t think we can dictate anything because we just simply don’t know.

DR. WEISS: Dr. Sugar, then Dr. Schein.

DR. SUGAR: I agree that we don’t know, and that we have no data, you know -- having no reason to postulate a source of progressive endothelial cell loss, and having no data on what that second intervention would do to progressive endothelial cell loss, I would think that that would be actually the opposite of the recommendation that I would want to make.

DR. WEISS: Dr. Schein.
DR. SCHEIN: We can make a distinction between recommending doing a monitoring test and the timing of an intervention. So by analogy, one might recommend in a glaucoma setting, visual fields at a certain frequency without recommending when a trabeculectomy be done. And I think that there is a concern about long-term endothelial attrition, it makes sense to recommend that the only test that we have be performed on some schedule.

DR. SUGAR: But we don’t know what intervention.

DR. SCHEIN: Well, no, but we have an opportunity to, one, learn the natural history. And the other is to describe to a patient that over the last five years, you’ve had a 25 percent loss of density.

DR. WEISS: Dr. Sugar.

DR. SUGAR: There’s a difference between recommending that the Sponsor get post-marketing data on that, and recommending that the practitioner do that, because we don’t get that data. And presumably, the Sponsor doesn’t get that data.
DR. WEISS: Dr. Sugar's point is very important, and we're going to be getting into whether there should be any post-market studies, is data that is interesting shouldn't be put in labeling. That's up to any of us here or outside to do a study. But data that would be important, we feel, for patient care, should be put in the labeling. So is the specular microscopy post-operatively important for patient care? And Dr. Sugar would disagree. Dr. Mathers.

DR. MATHERS: I would agree that it is important to patient care. There are some patients here that had very substantial loss in cell count, and you would want to pick those up. And it would be important for that patient's well-being that you do so at some not short interval after surgery, perhaps a year or something like that.

DR. WEISS: So if you're going to give guidance as far as when repeat specular microscopy would be done, what would you suggest?

DR. MATHERS: As early as three months, possibly six, and at latest, one year.
DR. WEISS: Somewhere between six months and a year. Dr. Macsai.

DR. MACSAI: That's not what I intended by my comment.

DR. WEISS: What did you intend?

DR. MACSAI: My intention was that in my hands and my practice, if I was to implant this device, which appears to be an efficacious device, we don't have an answer about the long-term endothelial damage. And I, as alluded to by both Dr. Sugar, Schein and Mathers, would want to know if my patient was getting into trouble. And if they go from 28 to 2000, there's trouble right here in River City, and it's time to decide if that thing is safer in or out. And I don't want to wait until there's microcystic edema and we're transplanting that cornea in a 4 year old.

DR. WEISS: What do you recommend for labeling though? This is what you do when --

DR. MACSAI: I want to suggest --

DR. WEISS: You suggest, okay.

DR. MACSAI: -- that the practitioner
follow their patients with endothelial cell counts, because that’s all we have.

SPEAKER: For what time?

DR. MACSAI: Well, my personal opinion, I would say five years. And when we got all this long-term data that comes in, and it shows that I’m off the wall, I’ll be the first to stand up and say thank you. I’m wrong, and then we can change the labeling on the device, and that will be a wonderful thing.

DR. WEISS: Well, actually, you know, we don’t even have to --

DR. MACSAI: Annually for five years.

SPEAKER: Oh, annually.

DR. MACSAI: Is that what you want?

DR. WEISS: And actually, we don’t even have to -- and I’ll defer to Dr. Rosenthal. We could just say if this was what we’re trying to -- everything is a suggestion here. Even our vote is a suggestion. We could say that --

DR. ROSENTHAL: If you suggest that you put it in labeling as a suggestion, you put doctors in
liability risk if they don’t do it. So if it’s in the
labeling, and it’s not done, even as a suggestion, I
think it holds greater water than a suggestion.

DR. WEISS: So you might be suggesting to
the malpractice attorney to take that case.

DR. ROSENTHAL: Did I make myself clear?

DR. WEISS: Malvina.

SPEAKER: You put people at medical legal
risk.

DR. WEISS: Yeah. Did you want to
comment? No. Dr. Sugar and Dr. McMahon.

DR. ROSENTHAL: Excuse me. So therefore,
I think what you put in as a suggestion will be done.

SPEAKER: That will just be a suggestion,
maybe wrong.

DR. WEISS: Dr. Sugar and then --

DR. SUGAR: To use Mike Grimmett’s term
arguendo, to play devil’s advocate, we don’t know what
to do with that information. I think that it is
appropriate in the labeling to suggest that
practitioners monitor corneal health subsequent to the
procedure, period, and to deal with however you see
fit. We do not have any information that I am aware of that suggests that knowing that the cell count is now 1200, and it was 2000 eight months ago, that any intervention that we're going to do is going to alter that state. So how could we make a recommendation that you gather that information so that you can alter that state, when you don't know how to do it? That's -- my point is that if you go in and take the IOL out, my suspicion is you're going to lose more endothelial cells. You're not going to help the situation.

DR. WEISS: Well, you could say that physicians should monitor the corneal health with such means as A, B, C, or D, and include this as the possibilities.

DR. SUGAR: I think that as Ralph suggested, the more specific we get, the more we constrain the practitioner.

DR. WEISS: Dr. Ho.

DR. HO: Furthermore, just as a retinal surgeon, give me a sense for what percentage of anterior segment surgeons have or do specular microscopy. Is this something that is routine?
SPEAKER: Yes. Routine.

SPEAKER: yeah.

DR. HO: Routine for all cataract surgeons? Okay.

DR. SUGAR: No, it is not. No, he's talking about the average doctor --

DR. WEISS: Dr. Macsai.

DR. MACSAI: When it was reimbursable --

DR. WEISS: Dr. Macsai.

DR. MACSAI: I'm going to tell you when it was reimbursable it was routine, so that the access to it, I think, remains.

DR. HO: Furthermore --

DR. WEISS: How about let's tell you who -- Dr. Ho. Yes.

DR. HO: But I suspect that this procedure, were it to be approved, would be something that would be done by comprehensive ophthalmologists, as well.

DR. WEISS: Dr. McCulley.

DR. McCULLEY: From a practical standpoint, there are a couple of issues here. One,
we've already said we thought that a person should have pre-op specular microscopy. Number two, most people who are active in these areas are going to have a specular microscope then to do it post-op. And if not, it's available in the community, so I don't think we'll be limiting the market scope or the number of people doing this if we require specular microscopy. On the other hand we did, we required high frequency ultrasonography, we might. But with specular microscopy, I don't think it's going to have a negative impact or be unfair to have it pre-op. But whether we do make a specific suggestion about it post-op or not, I feel less strongly about. I kind of lean toward Joel, that we need to -- if I interpreted Joel correctly, we need to leave that to the judgment of the physician. And then if we want a post-market study, then rather than suggesting that every ophthalmologist do it, that we request a post-market surveillance study on endothelial cell count.

DR. WEISS: So I'd just like a poll at this point in terms of how the panel views this question. Those who would be in favor of suggesting
or mandating, or indicating in the labeling that endothelial cell counts not only be performed preoperatively, but also be performed post-operatively, and we don’t even have to indicate at what time point. Those of you who would like them performed post-operatively in the labeling, could you please raise your hand.

(Vote taken.)

DR. WEISS: So we’re almost split down the middle on that, so that issue is not decided at this moment. Yes, Dr. McMahon.

DR. McMAHON: We’re getting into a circular argument here. And we don’t have the data to know what’s happening with the endothelium, so making suggestions to the Sponsors and practitioners is not -- it’s more emotional than logical. And my suggestion is, is that we get the information from the sponsor so that you can then address the labeling question, which goes to a post-market study, which goes to Dr. Grimmett’s seeing year four and year five data. And actually, directing to this question, the answer is have we showed stability? The answer, I
think, is no, they haven't shown anything yet. The second part of the question is, is how many eyes and for how long? And I think we should decide.

DR. WEISS: We will in a moment. I want to get to the more difficult stuff, and just get the simpler things out of the way. The anterior chamber depth cut-off of 3, should this -- would you be able to read that portion of the question?

DR. EYDELMAN: "Do the outcomes of the endothelial cell density analysis provide reasonable assurance of safety for this device for eyes with 1 ACD of 2.8 to 3, and 2 ACD of greater than 3 millimeters."

DR. WEISS: And all the primary reviewers, Dr. Sugar, Dr. Macsai, Dr. Grimmett, all suggested that this not be implanted in ACDs less than 3. Is there any discussion on that from the panel? Dr. Bradley.

DR. BRADLEY: Dr. Gray, in his statistical presentation, showed no evidence that there was a dichotomizing of the data. You did a linear model to fit all of the data, and I queried Dr. Gray on how
much of the variance is explained by this linear model. It looked to me like not much of it. And, therefore, I wonder about making judgments about a certain threshold level of anterior chamber depth based upon that study. It didn’t seem to me that that was warranted. I wondered why one of the proponents of this dichotomy would argue this case, and maybe Dr. Gray could comment on it.

DR. WEISS: Any proponents want to argue this case? Dr. Sugar.

DR. SUGAR: Your point is, you know, the data, I think, does show that there is a linear, an apparent linear relationship between anterior chamber depth and endothelial cell loss. And the only question is, is there a point where we should cut it off because there is no obvious dichotomy, an obvious point to cut it off. Is that correct?

DR. BRADLEY: Two points, yeah. One is that there is no dichotomy in the data themselves. And the other point is that this is a mean linear regression, and the data were highly variable around that point. And it looked like some other factor was
the -- or factors were the primary determiner of cell
death, or cell loss, not the anterior chamber depth.

DR. WEISS: Dr. Eydelman, I think, has a
comment.

DR. EYDELMAN: We actually -- well, the
Sponsor has actually ran several analyses, and there
were no apparent other factors associated other than
anterior chamber depth. And if I may comment on your
earlier statement; yes, you're correct, from Dr.
Gray's model, it is a linear association.

One must keep in mind, however, that as we
progress up that line, the percentage of the overall
population was that ACD depth is going to increase,
i.e., we know that below 3 there's only 5.5 percent of
the overall cohort. And when we get up to 3.5, we're
close to 50 percent of the cohort. So while it's
possible that this line could be drawn somewhere
higher, just keep in mind that then you would be
excluding a higher percentage of patients from having
the surgery.

DR. WEISS: Dr. Bradley.

DR. BRADLEY: Just an interpretational
point. What you said is correct. It’s important though to realize that with such an exclusionary criterion, you would be excluding candidates from the procedure who would have a much smaller level of cell loss. And you would be including patients who would have a much larger level of cell loss, simply because of the variability in that population. And that was the question I was asking Dr. Gray about, because it seemed there was so much variability in that regression analysis. He’s nodding his head there, so perhaps he could --

DR. WEISS: Dr. Gray, did you want to address this?

DR. GRAY: Well, the question you asked me was how much of the variability was explainable by ACD. And unfortunately, I don’t have that with me. But you are correct, the relationship appeared to be linear without an obvious break, and there is a fair amount of spread around the line. But the decision about where, if at all, to put a cut point on the ACD is purely a judgment call at this point, I’d say.

DR. WEISS: Dr. Grimmett.
DR. GRIMMETT: I was in agreement with making the cut-off 2.8 to 3 for three reasons. One, the data on that arbitrary break point showed 50 percent higher loss with a shallow depth. Number two, the cut-off would not be overly onerous, only 5-1/2 percent of the cohort would be taken out. Number three, my review of the literature back last year at our guidance discussion showed that the closer that phakic IOLs are -- the closer they are to the endothelium, the greater risk to the endothelium with angle supported having a higher risk than high risk clip versus posterior chamber. So I was using all three in combination just to make that determination.

DR. WEISS: Aside from Dr. Bradley, does anyone else have any concerns about limiting it? Dr. Bandeen-Roche and then Dr. McCulley.

DR. BANDEEN-ROCHE: Yes. I have two comments. First, I agree with Dr. McMahon that the primary point, as far as I'm concerned, is whether stability has, in fact, been achieved. And, you know, I am not at all convinced that it has been, so at that point, the distinction between 2.8 to 3, versus 3 and
above, I think is totally arbitrary.

The second point just goes back to a point that Dr. Bradley was making about what else might have explained the variance. And I wanted to ask Dr. Gray were you able to reproduce, or did you even try to reproduce the sponsor's analysis of what were the factors related to cell loss, and finding only ACD being the only thing that was related?

DR. GRAY: Well, that's a hard question to answer.

DR. RANDIEN-ROCHE: Sorry.

DR. GRAY: There's a -- we had a fairly complicated situation in terms of the data because we had multiple measurements per person over time. We have baselines, and there's a lot of missing data. It's difficult to know how to actually model it. The Sponsor went through a particular procedure where they cut up -- they binned the data into categories, and they checked quite a number of potential co-variates, and the only one that ended up to be significant was the anterior chamber depth.

If you do some alternative analyses using
things like the percent of hexagonal cells at baseline, or the endothelial cell density at baseline, sometimes those show up to be significant predictors. It’s not obvious how to, for an individual patient though, say whether they are at high or low risk of having a high rate of endothelial cell loss. That’s a very difficult procedure which we didn’t go through, and that would take some amount of effort on everyone’s part to do that.

DR. BANDEEN-ROCHE: Thank you.

DR. WEISS: Dr. McCulley.

DR. McCULLEY: My comment was with Mike. I don’t think it’s so much the distance, necessarily, as how you’re fixating it. So you’re taking AC versus, you know, a posterior chamber. I think it’s apt to be more influenced by the way you’re fixating than the distance, except for possibly surgical trauma. If you’ve got a bigger space to work in, less problems - smaller space to work in, more damage. But I’m not convinced that just the distance -- if you start throwing in, and try to extrapolate that, the AC to iris to PC, that that holds up. It’s apples and
oranges, and grapefruits.

DR. GRIMMETT: Mike Grimmett. Certainly with the angle supported lens data, there were some minimum distances that had some very unacceptable rates of endothelial cell loss for the angle supported data in and of itself. And grant it, some patients are eye-rubbers, which would deform the cornea, touch the edge of the IOL. So certainly for the anterior chamber at the angle supported phakic IOLs, I think there's a very strong argument that the closer that the optic is to the endothelium, the higher the rate of endothelial cell loss.

Now, obviously, trying to translate that to all three groups with some meta-analysis, obviously, you get fairly sticky in that. But at least in that one group, I think the data is fairly strong.

DR. WEISS: Dr. McCulley.

DR. McCULLEY: You'd have to keep it within the category of lens type, fixation type.

DR. GRIMMETT: Anyway, enough.

DR. WEISS: Just a -- I think we're at the
point that panel members are calling for time out. That definitely means we’ve belabored that one. But I’m not sure we have a consensus on that, but I guess we will go to --

DR. ROSENTHAL: Vote.

DR. WEISS: It doesn’t actually really matter if we have a consensus on it or not.

DR. ROSENTHAL: It helps the FDA. It helps us a lot.

DR. WEISS: At this point?

DR. ROSENTHAL: It depends what you ultimately say, but we need --

DR. WEISS: Well, do you want the consensus right now?

DR. ROSENTHAL: Yeah.

DR. WEISS: Fine. Let’s have -- okay. For those of you who want to limit it, please vote that you’d like to limit it to 3 and above anterior chamber depth.

DR. EYDELMAN: It’s actually above 3.

DR. WEISS: Above 3.

(Vote taken.)
DR. WEISS: Okay. So I guess we do have a fairly good consensus. We're going to -- if you could read Question 1(a).

DR. EYDELMAN: I guess I'll read the whole thing. "The main change between 3 and 4 years in 57 eyes was a gain of .1. A decrease in co-efficient variation and increasing percentage of hexagonality were observed. Is there sufficient data to support the Sponsor's conclusion that the losses in the first three years are reflective of the surgical trauma was a prolonged remodeling culminating in stabilization of cell loss after three years."

DR. WEISS: And I'm going to just cut the question off there. We spent quite a bit of time having the data presented to us in different formats, showing us the impressions of this, so I don't know that we have to discuss this. But I would like to get an impression of the panel's opinion on this particular one by vote. And for those of you who agree there's sufficient data to support the Sponsor's conclusion that there is stabilization of cell loss after three years, for those of you who agree with
that statement, can you raise your hand.

(Vote taken.)

DR. WEISS: So what I can see is that no
one on the panel believes that there is a
stabilization of cell loss -- that the data support
that there is necessarily -- well, why don't you
phrase it, Dr. McCulley.

DR. McCULLEY: Well, I mean, your question
was -- we don't know. The question was, do we agree
the Sponsor has presented data that assures us that
there's stabilization after three years. We don't
have that data.

DR. WEISS: Fine.

DR. McCULLEY: We have an opinion, but
it's opinion based on things, not based on data. I
like to base it on data.

DR. WEISS: That's fine.

DR. McCULLEY: We don't have data to
support that.

DR. WEISS: So we do not have any data --

DR. McCULLEY: Up to three years, and then
we can argue the three to four years.
DR. WEISS: Okay. We do not have data showing that there is stabilization at that period of time.

DR. EYDELMAN: So what is the minimum number of eyes, and the minimum length of follow-up that you recommend for this assessment?

DR. WEISS: And what this is getting to, I think is, in order to get this information, are we talking about any --

DR. BRADLEY: Let Karen answer that.

DR. WEISS: Well, are we talking about any further studies, longer studies? Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: Yeah. I mean, I would consider it entirely a question of a minimum number. I mean, if you're looking for a number to establish a power, I mean, I would hope that you would at least try to establish power to ensure a rate of decline less than something, or a precision to establish what the post three year rate of decline is.

I would also encourage you not to only focus on the mean, as Dr. Grimmett has raised; that it's also important to think about what are the
proportion who are declining at an unacceptable rate. And so one could do power calculations or precision calculations to establish a number sufficient for that quantity. But it does also go to representativeness of the cohort, you know. And so that's certainly unlaying my question about how many providers was it. You know, I would be totally less convinced about the quality of the data if it was the one or two best surgeons who had provided the 67 eyes. It sounds like it was not, that that was not the case. But I don’t have any feel for how representative the 67 eyes that we have are. And, moreover, if I look at Dr. Gray’s data, one thing that I have been worried about was regression to the mean. And so, for instance, if the eyes that are contributing to that 3 to 4 year, the 57 eyes, I guess, 3 to 4 year interval were those who had declined, you know, particularly far from 2 to 3, or were particularly low. Then one could expect somewhat of an improvement just due to regression to the mean, let alone things like contact lenses and issues like that. And so, indeed, according to Dr. Gray’s table, all visits, the cohort of 37 has a mean cell count,
100 cells less than all of the other eyes at three years. So that is in the direction of that concern.

And I guess a final point that I would make would be everyone has been commenting that we’re in a gray zone, that the physicians who participated in this study were the best of the best. And so I would not at all just settle for a 95 percent confidence found, you know, just barely squeaking in there at a level of a 95 percent confidence found. I think that I would recommend a bit more assurance than that, taking into account the fact that this is a precedent, that these are the best physicians who participated in this study.

DR. WEISS: I think we have to be careful about this best physicians talking about lack of data. I’m sure these were good docs and good surgeons, but creating this extra god-like category, I think we should take out of the discussion.

DR. BANDEEN-ROCHE: That’s a point well-taken. That’s a point well-taken. Nonetheless, I mean, we hardly expect better performance in the field than we do in a clinical trial.
DR. McCULLEY: You don’t have data to support that statement, do you? Do you have data to support that statement? You do. Okay.

DR. ROSENTHAL: With all kinds of devices.

DR. McCULLEY: All right.

DR. WEISS: What I would then like to lead to is since there’s agreement --

DR. ROSENTHAL: Wait.

DR. WEISS: Yes.

DR. ROSENTHAL: I want to make sure I said the right thing. Once they go out in the field, they tend to have more problems than they do within the clinical trial.

DR. McCULLEY: But you don’t have data to support that the people who do the trials are the best of the best.

DR. ROSENTHAL: No.

DR. McCULLEY: I think that is opinion --

DR. MACSAI: That’s my opinion.

DR. McCULLEY: That is Marian’s opinion, and it should not be in our discussions.

DR. WEISS: So we’re going to take out the
"god" factor out of the discussion.

(Laughter.)

DR. WEISS: But what I would like to introduce into the discussion is the fact that since there is consensus that there's no data demonstrating stabilization of cell loss between 3 and 4 years, what would please the panel to do perhaps to demonstrate that the issue of endothelial cell damage is not present here? Dr. McCulley.

DR. McCULLEY: Yeah. My impression that we -- I could not argue the point and present data to absolutely support that we have stabilization. My impression of everything presented is I would lean toward we probably do. At least -- or that we probably will. At least to the point where I would be comfortable not voting on this, that if the panel recommended approvable, that I would be comfortable with that, with some form of continued surveillance or gathering of data about the stability or lack thereof of the endothelium.

DR. WEISS: Okay. So if we're talking about post-market study, would we be talking about a
post-market study following the initial cohort, or
would we be talking about -- and would we require
those patients who have had preoperative endothelial
cell counts, or would we be talking about getting a
new cohort with specified time points at which they’ve
had endothelial cell counts? Dr. Schein, and then Dr.
Sugar, then Dr. Mathers.

DR. SCHEIN: I would argue that one needs
both, but for different reasons. So on the specific
question of the data related to the endothelial cell
count, the existing cohort will tell us a lot more
about the natural history. I mean, if there’s a three
year lead time on any new cases that come along.

On the other hand, when I use the word
"post-market surveillance", it doesn’t at all mean a
continuation of a pre-market cohort, because the
question from a public health perspective is very
different. And what you’re worried about is a
situation, which I think we have here, where you’ve
got reasonable short-term safety, and some -- an
inclination - if I could speak generally, you know, to
approve based on that, but concern about longer-term
issues which cannot be addressed from this particular pre-market cohort.

It's an analogous situation with the extended wear contact lenses, which is currently undergoing a 5,000 person study looking just for ulcerative keratitis. So the concerns here are not just adequate length of follow-up for endothelial cell count, but the representativeness. We don't have to get into the glorified surgical skill, but there are means of examples where you go from an efficacy study pre-market, to an effectiveness evaluation, which is how the product is actually used once it's approved. And it never performs as well. So one needs some kind of way to sample cases from a post-market setting, from surgeons and different kinds of patients, to look at big outcomes; corneal failure, new treatment for glaucoma, retinal detachment, and cataract, because there has been some concern in my mind about some of these other complications, which have all been reported on a per-eye basis; whereas, obviously, retinal detachment is a per-patient issue.

DR. WEISS: Can you tell me the study --
the number of patients, numbers of years that you
would suggest if we’re just actually going to make it
crime? What would you like?

DR. McCULLEY: For which purpose?

DR. WEISS: For both.

DR. McCULLEY: No, I’d have to do some
sample size calculations.

DR. WEISS: So you would like --

DR. McCULLEY: But even this is, you know,
done in a few hours.

DR. WEISS: But you would like, basically,
both types of studies getting a new cohort of patients
with specular microscopy prior to the procedure, and
then following them through, as well as following
these patients?

DR. McCULLEY: No. No. So for the
specular microscopy, I would go with the existing
group, because in a post-market surveillance study
that I’m more concerned about, I want to know about
corneal graft. I want to know about retinal
detachment, because the absence of a control group
here is a major deficiency. And, you know, using
control groups based on other case series is inadequate, so I would like to know on a much larger sample, with less defined testing, less onerous testing, about major outcomes; cataract surgery, new treatment for glaucoma, retinal detachment.

DR. WEISS: And how long out would you follow those patients?

DR. McCULLEY: Probably -- initially about probably 3 to 5 years.

DR. WEISS: Do you think for -- I mean, say those posterior keratotomy took 20 years for them to get corneal edema, so will that --

DR. McCULLEY: Well, each one of these things is different, so ones that occurred in my lifetime, professional lifetime. One example would be extended wear contact lenses, approved for 30 days in 1981. They were reduced in 1989, so about 8 years later, with a very, very inefficient way of making that determination. Anterior chamber lenses was even more inefficient. There was no surveillance mechanism. There was a lot of controversy about what we're seeing. The literature is a very inefficient
way to do post-market surveillance. There are many, many patients who have rigid anterior chamber lenses with no clinical inclination that one could see as one followed them.

DR. WEISS: Well, we're going to make this efficient.

DR. MCCULLEY: Right.

DR. WEISS: So for this particular efficient way of doing it, how long of a follow-up would you recommend? Would you still say 3 to 5 years?

DR. McCULLEY: Yes.

DR. WEISS: Okay. Dr. Mathers.

DR. MATHERS: In terms of modeling, addressing what Karen Bandeen-Roche said, I think we could reasonably have an objective as we model this, that we would like to stay above. And I think from our various analyses here, that it is reasonable to propose that at the end of the expected use of the device, that we end up with an endothelial cell count of 1500 or greater, because this is still far less than the normal cell loss.
Normal cell loss is quoted here as being .6, but if you do the numbers on the data from Dr. Grimmett, the normal is really like .4 percent per year. And if we have a loss rate that you're calculating of 1, 1.1, we are still like three times greater than the normal. So if we do our projections and model this to keep above 1500 by the end of the device use, I think we will be serving the public reasonably well. And it's still a relatively conservative approach.

DR. WEISS: So are you saying take the original cohort and if the cell count kept on dropping off, at what point, how many years they would take --

DR. MATHERS: As this gets modeled and we have more data, the model is going to get better. The projections are going to get better, and the width of -- or the data is going to get more accurate. And as we can determine this, when we know how accurate it is, if we set the parameter to keep the end point at greater than 1500, which we will be able to do as you continue to model it.

DR. WEISS: So you're basically saying to
the FDA that statistically they should try to predict into the future, and that will tell them how long that they would be able to do the study. And if that's -- if I'm correct, I'm being told at the same time that that can't be done.

DR. MATHERS: Well, as we get more data, we don't know how good the data is going to be when it comes in, and it may be possible in a year or two to determine what the rate of this loss is.

DR. WEISS: I think we probably have to tell them up front what we want, as opposed to let this go on for as long as we see fit. Dr. Macsai.

DR. MACSAI: I'm a little lost here in this conversation, and I just want to -- reel me back in here. I'm listening to what Dr. Schein is saying, and I'm in no way disagreeing with you, that it would be interesting to know this information from a public health perspective. I'm not sure it's the Sponsor's responsibility to get that data. It would require a National Registry akin to the Australian Graft Registry, and I don't know that we have that set up in the United States.
I think it's a wonderful concept if we could do it. We have to register every patient that has this device, and follow them forever, and I'd love to know. And I just don't know that it's reasonable to know. So to the second thing, though --

DR. WEISS: Actually, he was saying 3 to 5 years.

DR. MACSAI: Well, we'd look at them for 3 to 5 years.

DR. WEISS: Okay. So you would prefer not to have a new cohort --

DR. MACSAI: I know about the cataracts, and I know about the retinal detachments. Okay. But I thought we were supposed to be talking about the endothelium here. And I thought the question was how many patients do we have to follow and for how long to establish stability of the endothelial cell change, because we're all setting around not raising our hands, because we don't know if the endothelial cells are decreasing to a stable level, so the question is how many.

My answer to you in my review was, I am...
not a biostatistician. Dr. Gray is a biostatistician. Dr. Edelhauser is an expert in endothelium, you know. Put those two in a room, figure it out, tell us the answer, we’re done.

DR. WEISS: Dr. Edelhauser is about to tell us the answer. Sometimes you get what you want.

DR. EYDELMAN: If you’re not ready to give us the exact number, maybe you can give us the parameters on which to base the calculation, so we can certainly perform the calculations. But if you tell us the rate that you’d like to ascertain, and with which predictability, or with which -- what statistical parameters you want us to include, we can certainly perform the calculations.

DR. WEISS: Well, let me just get one thing from the panel, just in terms of following the initial cohort. Whether it’s those 200 -- one question for the panel. For this cohort that would be looked at with specular microscopy, does the panel want these patients to have had pre-operative specular microscopy done? Those of you who would like to have at least pre-operative specular microscopy, could you
raise your hand.

(Vote taken.)

DR. WEISS: So I think there's -- Dr. McMahon. There's a majority that would like pre-operative specular microscopy. So from what I recall from the FDA's presentation, there were 206 patients who had pre-operative specular microscopy, and at least two time points afterwards. Correct me if I'm wrong. So of those 206 patients, perhaps we're starting out that with -- that's the maximum number. And then we could -- we'll probably go down from that.

Does the panel think that 206 would, starting out, be too low? Would it be feasible to tap into that population? Anyone have an opinion on that? Dr. Macsai.

DR. MACSAI: I think that's the only population we have. I think we expect a 10 percent loss to follow-up. You know, unfortunately those 206 weren't told you've got to come back every year for five years. So the Sponsor, I'm sure, will do their best to track them down and reel them in, and look at their endothelium. And whether or not it's
statistically significant, Dr. Gray will tell us.

DR. WEISS: So then I would propose that that 206 could be at least the cohort that we're looking at for a post-market study. Then the second question that the FDA has asked us and I will ask the panel, is there guidance for number of years that you would like these people followed? Dr. McCulley.

DR. MCCULLEY: I think five is reasonable.

DR. WEISS: An additional five years?

DR. MCCULLEY: No.

DR. WEISS: Total of five years.

DR. MCCULLEY: Total of five years.

DR. WEISS: So that you want one more time line at one year down the line.

DR. MCCULLEY: No. What I want -- what I would ideally like to see, again, I have a sense that all we've done is shift the things to the right or left, however you're looking at it. But I would like to see yearly up to five years for as many years as possible. We've already missed some years for that cohort of 206.

DR. WEISS: Okay. Well, those -- okay.
Dr. Sugar.

DR. SUGAR: I was going to say the same thing. The last patient -- the first patient should reach the five year time window next month. And the last patient would reach that time in December of 2007, so I think as many patients as possible should get -- of those 306, not 206. There are 306 that had baseline specular microscopy. As many of those as possible should get annual data for as long as -- up to as many --

DR. WEISS: Dr. Eydelman, would that answer 1(a)?

DR. EYDELMAN: So you want all eyes in the PMA cohort that had pre-operative endothelial cell counts to be followed for five years. Is that correct?

DR. SUGAR: With specular microscopy.

DR. WEISS: Dr. Sugar, is that correct?

DR. SUGAR: That's what I'm suggesting.

Yes.

DR. WEISS: That's correct. Dr. McCulley, you concur?
DR. McCULLEY: I think that's reasonable, annually for five years.

DR. WEISS: Is that -- Dr. Rosenthal, is that burdensome?

DR. ROSENTHAL: No, but we need to know whether you want it done in the pre-market arena, or in the post-market arena.

DR. McCULLEY: Post.

DR. WEISS: Post-market arena is what Dr. McCulley.

DR. McCULLEY: It depends on whether you approve it now or not.

DR. WEISS: Dr. Sugar, post-market arena?

DR. SUGAR: Yes. I mean --

DR. WEISS: Post-market.

DR. SUGAR: That's assuming that we're going to approve the product now, which I presume, and that we shouldn't --

DR. ROSENTHAL: No. We can't presume what we're going to do, because we haven't voted it for it yet.

DR. SUGAR: No, but I can tell you what I...
presume. And my presumption is that we will approve it, and that we should not hold up approval of the product based on acquisition of this data.

DR. WEISS: Dr. McCulley, and then Dr. Macsai.

DR. MCCULLEY: I would agree with Joel, but to put it back more broadly for Ralph, I mean, if it's not approved, then we would request that -- or recommended for approvable, that they be followed annually. If we do recommend approvable, which I too would - not being a voting - not going to get to vote, but I would. And I would be comfortable with that, and I would say then, I would prefer this -- as I said, I'd be comfortable with a recommendation for approvable with a post-market surveillance annually of that initial cohort. You had pre-ops for a total of five years.

DR. WEISS: Dr. Mathers.

DR. MATHERS: When you say "approval" there, you're talking about three different groups here, and they are very different. You have myopes for minus 3, myopes for 15 to 20.
DR. WEISS: We're going to get to that in a moment.

DR. MATHERS: Okay. But that's -- I mean --

DR. WEISS: We're just talking about the specular microscopy portion, and then in terms of the different categories, we will be getting to that. Have no fear.

DR. MATHERS: Okay.

DR. WEISS: Dr. Macsai. And I'd sort of like to wrap-up this. Dr. Macsai, then Bandeen-Roche, and then I'd like to wrap-up this particular issue. Yes.

DR. MACSAI: I agree with Joel about post-market surveillance. I would add two comments. One, if approvable, it's got to be labeled that this stability has not been documented, and it's got to be an education for patients and physicians. And if data comes out later that shows there's massive problems, the FDA has an obligation to take an action.

Number two, if perhaps we're all wrong, and we don't have to wait until 2007, and at 2006 the
biostatisticians, or 2005, the biostatisticians say hey, this was much ado about nothing, then the labeling be changed at that point, and we accept the statistician's interpretation that it is, in fact, stable.

DR. WEISS: With that in mind, if you want to put in labeling that stability of endothelial cell loss has not been documented, would you want to put a warning in there that there could be risk of corneal edema or no? Dr. McCulley.

DR. MCCULLEY: I don't remember well enough. There are different implications to these words, and I don't --

DR. WEISS: Dr. Rosenthal. Would it be fair, if we're going to be putting in labeling that there is no documentation of a stabilization point as far as endothelial cell loss by specular microscopy, would it be fair to put in labeling there could be the risk, or the risk of corneal edema is undefined. Or because it's undefined, we shouldn't say it?

DR. ROSENTHAL: That's the panel's decision.
DR. WEISS: Dr. Macsai.

DR. MACSAI: I don't -- we don’t have corneal edema. We don’t have one patient yet with corneal edema. What we have is --

DR. WEISS: Well, that’s what we’re talking about, isn’t it?

DR. MACSAI: Right. But no --

DR. WEISS: That’s what we’re afraid of.

DR. MACSAI: No, what we’re talking about is long-term endothelial cell loss. So what we say is that the data and the outcomes and long-term effects on the endothelium are unknown.

DR. WEISS: But for patient labeling, I think you’d have to put that in terms that it means something to someone, because endothelial cell loss doesn’t have any significance to a patient. And I would maybe defer this one to Glenda Such.

MS. SUCH: Yes. I was just going to say, I don’t know if this belongs in the labeling section of our discussion or not, but I was going to say there should be something at least at the bottom of the precautions that says something about the fact that no
information is known about this beyond four years. Whether or not it’s regarding this issue or any of the issues.

DR. WEISS: So maybe we’ll get back to that when we get back to labeling. When we’re talking about -- so we’ve talked about, and I think hopefully to your satisfaction, we’ve talked about a post-market study, and following the cohort. Does anyone want what’s suggested, taking another fresh cohort of patients who are having this done after, if it gets approved, after approval, and following these patients. Does anyone want that?

DR. SCHEIN: May I make another comment?

DR. WEISS: Dr. Schein.

DR. SCHEIN: What is the logic of having a post-market surveillance study for an extended wear contact lens where not a single ulcer is seen in a pre-market trial? The logic is that there’s a concern about the particular end-point, which requires a different kind of study. And I think the situation is exactly analogous. We have a new kind of device. We don’t have any historical data to rely on. The
situations is analogous to the way the rigid anterior chamber lenses were when ophthalmologists were putting them in their mothers, which is just after the pre-market approval. There was a lot of excitement, so I think to not set up some mechanism that’s an early warning is completely irresponsible on our part. And I do believe it’s the industry’s responsibility, if they want to introduce these kinds of products.

The idea is not to stifle innovation. As you’ll see, I’m going to be voting for approval. But the idea is to set up a mechanism that we can trust to either restrict labeling in the future, pull back the product, or to provide very sound information about its safety.

DR. WEISS: Well, in that case I think what we’ll do is we’ll confine that one to labeling. If anyone else wants to comment on specifically a labeling issue. Dr. Matoba.

DR. MATOBA: In the case of the contact lens issue, that we had an indication from your study that there was a certain risk for microbial keratitis, and here we don’t have any information that there is
that type of calamitous outcome that could occur, so here you’d be fishing.

DR. SCHEIN: The rate of retinal detachment is higher in this study is higher than ulcerative keratitis was in any of the other studies. The rate of cataract is higher, so it’s not just corneal edema.

DR. WEISS: Dr. Bandeen-Roche, then Dr. McCulley, then Dr. Mathers, then Dr. Sugar. Not Dr. Sugar.

DR. BANDEEN-ROCHE: If you want to defer this to the safety discussion, that’s fine. But I have to at least raise it now, which is that we saw no hint of stabilization through three years. I mean, it was just, you know, all of the year-to-year changes were pretty even. So suppose the data come in, and my overly pessimistic tendencies for once, you know, bear out, and we see exactly the same continuing rate of decline, once all of the data are in. Would you then declare the product safe and go ahead?

DR. WEISS: Dr. McCulley.

DR. McCULLEY: Yeah. Could we ask maybe
the FDA to respond to that? And could we also ask the
FDA to respond to Oliver's suggestion for -- I don't
ever recall a discussion at a panel, at least that
I've been at, where that kind of study post-market
surveillance, or whatever the term would be for that
particular one, would come up. I'd like to hear what
the FDA says about both of those issues in terms of
authority and practicality.

DR. ROSENTHAL: We have a member of the
staff from the Office of Science and Biometrics who's
ready to address this issue for you. Dr. Roselie
Bright.

DR. BRIGHT: One minute.

DR. ROSENTHAL: I still -- while Dr.
Bright is getting ready, you still have to decide
whether you want this fourth and five year data on the
existing cohort before it goes to market, so you have
assurance of -- a reasonable assurance of safety and
efficacy. Or do you have that reasonable assurance of
safety and efficacy now, and the follow-up can occur
after it is put on the market. That is different than
this type of approach, which is in addition to the
follow-up of the endothelial cell.

DR. WEISS: So I think what Dr. Rosenthal is pointing out is we've put the cart before the horse.

DR. ROSENTHAL: A little bit.

DR. WEISS: And that if everyone is in agreement that we have no evidence there's stabilization of endothelial cell loss, then is anyone in the panel bothered by the potential of a continued cell loss rate of 2 percent per year in these patients. And if anyone in the panel is bothered by that fact, how do you justify that, or explain that, or accept that?

DR. McCULLEY: Jayne, I've said it before and I'll say it again. We don't have the solid data. We need more data. My sense of this, based on everything including my broad clinical experience and past history with things, is that I would be comfortable enough with this being recommended for approvable. But to further give us assurance and comfort that we follow it post-market.

DR. WEISS: Then I would ask you, Dr.
McCulley, can you explain to the panel why you're comfortable with approval? What factors about this PMA in the face of no documentation of stabilization of the cell loss make you comfortable with approving this?

DR. MCCULLEY: Okay. I don't think there's no documentation. I think there's suggestion that there is, but I don't think there's proof. And the suggestion to me is that we have stabilization in the cell size, variability in shape, and that it does appear that with a limited number of patients that the cell loss between years three and four is leveling off. And I've seen -- and in the absence of any apparent known reason for continued endothelial cell loss, absence of any known mechanism to support continued endothelial cell loss, those give me the degree of comfort that I think this is reasonable. But do I think I have data that would let me nail that down if I wanted to switch sides and argue it the other way? No. But I think that it would be reasonable to try to gather more data to give more comfort to everyone else, and to myself. I could be
wrong. I don’t think I am, but I have reasonable comfort, but I don’t have as solid a data -- if I did, we wouldn’t be having this discussion.

**DR. WEISS:** But the question for the panel really now is whether there should be pre-market data or post-market data, if there’s --

**DR. McCULLEY:** And what I’m saying is, I think we have sufficient assurance now to recommend approvable with continued surveillance post-market.

**DR. WEISS:** Dr. Mathers, and then Dr. Macsai, and then Dr. McMahon.

**DR. MATHERS:** well, finish this discussion. That goes more to Oliver’s question.

**DR. ROSENTHAL:** Finish your discussion about this.

**DR. WEISS:** Finish our discussion, and then go forward.

**DR. ROSENTHAL:** And then we’ll move on.

**DR. MATHERS:** It’s a philosophic point. You’re saying that we don’t know, so let’s go ahead. I would say we don’t know, so let’s make sure before we go ahead. And again I’ll say that I don’t think
that what we say about minus 10 to 15, or 15 to 20
applies to what we say about the 3 to 10. But in the
absence of some indication of safety in this regard,
I think going ahead is not the correct answer.

DR. WEISS: Dr. Macsai.

DR. MACSAI: If you look at my review, I
didn’t make a slide of this – I’m sorry. I did make
a table of the rate of annual endothelial cell loss,
assuming a pre-operative mean count of 2,657, which
was the pre-operative mean endothelial cell count
here. And if we take the average loss, I’m not going
to argue with Mike or Bill Bourne, but if you take the
average loss at .6 percent by natural attrition, that
would mean you’d lose 15.9 cells per year.

In that August ‘02 panel meeting that Dr.
Grimmett did his report on, he said 1.5 percent would
be okay. And that’s 39.8 cells per year. This PMA
has 1.8 percent, which is 48 cells per year. And then
the ANSI Standard is set at 2 percent, which would be
53.1 cells per year, so this PMA lies right smack dab
in the middle between the recommendations of the
August ‘02 panel meeting, and the ANSI - which was 1.5
percent, and the ANSI guidance document referred to, which was 2 percent. So at 1.8 percent, it ain't bad. I just don't know if it's going to be bad in the future, so I think looking at these patients to five years is prudent.

I guess my question to -- I have another question I just want to ask Dr. Schein, since I can't ask him private, is - what if you look at this cohort for five years, this endothelial cell counted cohort for five years to see about retinal detachments, and cataracts, and I forgot what else you said. Would that answer your question? No?

DR. WEISS: Dr. Schein.

DR. SCHEIN: The reason it wouldn't answer the question is, one, sample size; and two, representativeness, the latter being more important. So I would want some sample of patients that are actually getting the device post-market, and some sample of surgeons that are doing it.

DR. MACSAI: Oh, to see who performs the same?

DR. SCHEIN: Absolutely. And also a
larger number, but not for cell counts. That's a different story. That's a longer term issue.

DR. WEISS: Dr. McMahon.

DR. McMAHON: This is to Ralph, and this is sort of a semantics question, because we're dealing with a situation with regard to endothelial cell loss, where we kind of don't know. And so the obligation of the panel of voting on safety and efficacy, one can be that we have to have reasonable assurances that the device is safe, versus reasonable assurance that it's not unsafe.

DR. WEISS: Well, the way it reads is "reasonable safety and efficacy".

DR. McMAHON: Yeah, but I want to know the spirit of that view, because it makes a difference on how I would vote.

DR. WEISS: Well, I'll call on our spiritual counselor, Dr. Rosenthal.

(Laughter.)

MS. THORNTON: Ralph, could you speak into the microphone, please. We want to get this one.

MR. ROSENTHAL: The reasonable assurance
of safety and efficacy.

DR. WEISS: Okay. So with this in mind, since it seems -- from what I understood from the vote before, most of the panel members didn't feel the stabilization was -- the data showed stabilization.

Do most of the panel, even with that fact, would most -- those panel members who would feel that there is still -- this is still reasonably safe to have a post-market study, and go ahead with approval under any means, or we're not talking about what type or whatever, in terms of labeling or other issues. What number -- if you could raise your hands.

DR. ROSENTHAL: Excuse me, Dr. Weiss. It's a post-market follow-up of the existing IDE subjects.

DR. WEISS: Fine.

DR. ROSENTHAL: That's very different than a post-market study of another group of patients.

DR. WEISS: So we're talking post-market study in order to get further data, and approval with the information we have at the present. At the present point, and we haven't gone through the other
issues, the members of the panel who would -- yes.

DR. BRIGHT: Well, I have a presentation that goes over what's appropriate for pre-market, what's appropriate after the device is allowed on the market, what you can get in a pre-market setting versus condition of approval, versus post-market. And that might short-circuit some of the questions.

DR. WEISS: Okay.

DR. McCULLEY: Jayne, can I say one thing, and I do want to hear what she has to say.

DR. WEISS: Yes.

DR. McCULLEY: In response to Bill's philosophical question, the issue is do we have reasonable assurance of safety and efficacy. I think we do. I don't think we have absolute, and I would like to go ahead and get the absolute. That's the reason for requesting additional surveillance. I think we have reasonable, but it's not absolute.

DR. WEISS: Would I be able to -- just in the interest of time, would you be able to show whatever that you have that speaks specifically to the choice of studies the panel might have, as opposed to
the background information that you might have, that
we could look at concrete stuff as far as what our
choice in terms of studies that we might recommend?

DR. BRIGHT: Well, I have two concrete
choices, but I want to lead up why I got there, if
that's okay.

DR. WEISS: If you can make a quick
lead-up.

DR. BRIGHT: I'm covering many slopes.
Okay. Well, the disclaimer is that just because I'm
presenting about those market studies, doesn't mean
that I think it's approvable right now, but it would
apply even if there was a later discussion about
approvability.

The reasons for doing post-market
assurance would be that the study population for the
pivotal study is small, and not large enough to detect
the potentially serious adverse events. And the study
population for the pivotal study is highly selected.
It doesn't include vulnerable sub-populations.

The study duration is typically shorter in
real-world exposure, so we've been talking about the
3 and 4 year effects, versus 30 and 40 years. And it can detect problems due to improper or unskilled use of the device in the real-world. And study centers -- but the study centers that you already have the data from are typically highly skilled and motivated.

And another general reason is to detect adverse events due to drug-device, or device-device interactions that would not be detected in controlled studies. So questions that might need to be addressed for this particular device are the longer term decline in endothelial cell count, long term development of cataract. Dr. Schein mentioned some other outcomes.

Some issues for phakic IOLs is the prior history in the 1980s with an implantable lens that was associated with safety concerns after 10 years of use, so we would want -- might want an earlier warning system. And PIOLs could be implanted in a large number of young adults with moderate vision problems. And, therefore, in the worst case scenario, there's a potential for a large number of middle aged to elderly adults needing corneal transplants.

So what are the three authorities we have...
for requiring studies? We have the pre-market authority, the study has to be done in order for the device to get to market. But the disadvantage is a small sample size and short follow-up time. The condition of approval study is one where the approval is conditional until the results of that study are satisfactory, but you have to order it before the device even gets the conditional approval. And the post-market surveillance study, we can order that study any time, but patient and physician approval is the most difficult during that time because the device is freely available.

So in considering the type of conditional approval study, it has to be least burdensome. We can consider any appropriate study design, and it does not need to be simply an extension of the pre-market study. The sponsor could be asked to report progress and results to the panel each year if the panel desires, and the sponsor can use the results to change the labeling and marketing.

So there are two main types of observational study designs. There's case control and
follow-up. The advantage of the case control study is you can be more efficient with a smaller sample size, but in this instance, I think it's impractical because I think the use of this device is likely to be relatively uncommon. And you also have to decide in advance what outcomes you're going to look for.

But in the follow-up study, you can enroll patients as they get the PIOL, so if it's vastly popular, you get your cohort up and running very quickly. If it takes longer, then it takes longer to accrue, but that's fine because it's affecting a smaller portion of the population anyway. You get flexible follow-up time, and you can discover new outcomes that weren't anticipated. But the disadvantage is that you need to minimize the drop-out rate, and you need a large number of patients.

We worked out two options. There's nothing required about any of these, but they're basically discussion and talking points. The first option was called registry, so you could ask patients at less than one year intervals whether they had an
ophthalmic visit for a problem. And we said less than a year because if we use the mail system, which is considered least burdensome of different kinds of ways you could contact patients, they're forwarding interval is one year. And you could ask a very simple question, did you have to go to the ophthalmologist. And then if they say yes, ask for the details for getting their records. And you could follow as many patients as possible for a decade or more, whatever time period the panel is interested in.

The advantages are, you can readily describe and identify the population of users in the event that some kind of regulatory intervention is needed. And it's a relatively inexpensive study. The disadvantage is that there's no early warning of impending problems. You get the warning when somebody has the problem that's bad enough to go to the ophthalmologist.

The other option that could be considered is something called a nested cohort, where you could build on the existing clinical trial population, and then sample some new patients, collect cell counts at