

1 submissions we weren't using contrast sensitivity data?

2 DR. BULLIMORE: In attempting to make claims of
3 superiority to alternative technology, I think the sponsor
4 should be allowed to make claims based on any tests that
5 they want. I believe certain tests of contrast sensitivity
6 to be valid and repeatable, and could direct anybody to some
7 seminal work on the topic, but the sponsor should be allowed
8 to submit that data and make those claims.

9 DR. PULIDO: How are we going to look at it if we
10 haven't in the past been able to accept contrast sensitivity
11 data?

12 DR. BULLIMORE: I don't think that is an accurate
13 statement.

14 DR. McCULLEY: You are wrong. I am being
15 facetious. Mark is saying he thinks you are not accurate in
16 your statement. I remember seeing lots of contrast
17 sensitivity data and analysis by FDA. I can't say that I
18 frequently understood it, but I do remember seeing the
19 analyses and the evaluation of those by the FDA.

20 I don't know that we ever used it effectively any
21 more than we ever used effectively topography in our
22 assessments of the studies.

23 DR. PULIDO: So, then, if this data is--what I
24 trying to do is avoid a manufacturer doing all this work on
25 contrast sensitivity and submitting it to us, and us being

1 back in the same point that we were before and saying, gee,
2 I don't know what this means, and looks good, but I don't
3 know. So, what is different now, what makes this different
4 than what we were doing?

5 DR. McCULLEY: But we used contrast sensitivity,
6 as best I remember, in a PMA on a multifocal IOL. So, we
7 have indeed done it, Jose.

8 Dr. Stark.

9 DR. STARK: I am just thinking back to the eye
10 care technology forum, which was attended by the FDA,
11 organized by the National Eye Institute in particular, and
12 industry. There was agreement that there was no agreement
13 on contrast sensitivity data at that particular point. Now,
14 that was about three years ago. Maybe there is some
15 important discoveries since then, but there was not much
16 agreement among the experts in the field that contrast
17 sensitivity data could be used to interpret results or there
18 was really agreement as to what it meant.

19 DR. McCULLEY: I don't know that the contrast
20 sensitivity data relative to PCO would be a measure that
21 might be real world significant, not sure, but it was used
22 within the last--I don't remember timewise--but within the
23 last two years on the multifocal IOL, so since that time
24 that you were talking about, it has effectively been used by
25 the FDA and this panel.

1 MS. LOCHNER: Yes, we have been comfortable
2 evaluating contrast sensitivity data. We are requiring it
3 in some of our studies that are ongoing. It would not be a
4 precedent to require it. If I understand what Dr. Bullimore
5 is saying, I think he may be suggesting that if visual
6 acuity is not sensitive enough to show an effect on visual
7 function, a sponsor might consider contrast sensitivity as a
8 way in which to show differences in visual function.

9 I think the agency would be comfortable evaluating
10 that.

11 DR. McCULLEY: I guess my question here would be
12 if the only variable that one can show a statistically
13 significant difference in were contrast sensitivity, logMAR
14 visual acuity, et cetera, did not, how relevant is that to
15 real world and to whether that lens that does that over
16 nothing else--

17 MS. LOCHNER: I believe it is more sensitive and
18 it would be relevant.

19 DR. McCULLEY: That's my point.

20 Dr. Maguire.

21 DR. MAGUIRE: I think Jose's question is what
22 would the contrast sensitivity study have to show that would
23 lead to a judgment of this panel that the outcome was
24 superior to the other one. I am interested in Dr.
25 Bullimore's comments on that, because I am still unclear,

1 because again, you want to make sure that your measure can
2 show a difference that would be considered clinically
3 significant or reach some other level of significance before
4 you would ask industry to do that.

5 DR. BULLIMORE: You want a number from me?

6 DR. MAGUIRE: I am saying can one generate a
7 number that reasonable people can agree on.

8 DR. BULLIMORE: No.

9 DR. MAGUIRE: Okay. And that gets back to Jose's
10 point.

11 DR. BULLIMORE: The same might be applied to
12 anything else that we discuss as an outcome measure.

13 DR. McCULLEY: Dr. Ferris.

14 DR. FERRIS: It may be an issue of what a primary
15 outcome variable is and what secondary outcome or supportive
16 outcome variables are, and it would seem to me that it might
17 be very reasonable if you had one of these semi-objective
18 measures of capsular opacity that was highly statistically
19 significantly different, and you then came in with support
20 that showed perhaps only trends in visual acuity that were
21 in the right direction, but a statistically significant
22 difference in contrast sensitivity, that that might be a
23 package that we could agree on that says this IOL seems
24 better than the other IOL.

25 So, as part of a package, and I would the visual

1 function questionnaire as another part of that package, we
2 tend to focus on one variable, and we do that for
3 statistical reasons, but at the end of the day for the
4 clinical assessment, I think you want to see a consistent
5 trend across variables, and in that case, I think the
6 contrast sensitivity information, whatever it means--and I
7 agree with the other comments that I don't know exactly what
8 it means--but it does seem to go along clinically with
9 things that mean that it is a useful variable to look at.

10 DR. McCULLEY: What we are discussing now really
11 is a part of your very first question to us. The question
12 here is regarding current methods of PCO analysis, and I
13 think that you mean here analysis of the opacity, some kind
14 of objective qualitative/quantitative analysis of the
15 opacity, correct?

16 DR. BERMAN: That is right. As part of the
17 package here, and I think it is under Tab 2, we tried to do
18 kind of a summary table after doing a quite extensive
19 literature review of some of the available digital analysis
20 methods and computer analysis, and those methods that looked
21 at density of the opacity of those methods that tried to
22 look at density and area, et cetera, and we wanted to get
23 the panel's input as to whether any, or all, or none, or
24 some of these methods would be acceptable, and if they can
25 agree on that, perhaps just which aspects you would find

1 important, going back to Dr. Spalton's discussion this
2 morning, do you want to look at the central 3 millimeters,
3 do you want them to look at the entire, that type of thing.

4 DR. McCULLEY: Let's take the question as it was
5 written and see if Dr. Bullimore would be willing to answer
6 the component.

7 Regarding current methods of PCO analysis, do you
8 consider particular methods acceptable for PCO IOL studies?

9 DR. BULLIMORE: Let me read what I wrote here, and
10 I will talk about clinician grading and image analysis
11 sequentially. Regarding subjective or clinician grading,
12 the standardized photographic scales that have been
13 validated and widely accepted for the grading of cataracts
14 lens opacities, for example, the LOCS III, but to my
15 knowledge, no widely accepted standards have been published
16 for the grading of PCO.

17 I would argue that clinician grading of PCO should
18 not be used unless a valid and repeatable system has been
19 developed that includes photographic standards and not just
20 verbal descriptors. A limitation of using subjective
21 grading systems is the potential for clinician bias.
22 Masking of clinicians would be desirable but may not be
23 feasible if the IOLs under study have other distinctive
24 features.

25 A potentially useful variant of subjective grading

1 is the development of a PCO reading center. Slit-lamp
2 photographs could be taken using established protocols and
3 sent to a reading center. The photos could be graded by
4 trained and masked readers. Other variants like concentric
5 circles could be superimposed on the photographs, so that
6 different regions of the capsule could be graded separately.

7 Regarding image analysis, a number of researchers
8 have developed sophisticated image capture and analysis
9 systems. My impression is that retro-illuminated images are
10 perhaps more appropriate than Scheimflug images just given
11 the extent of the lens that can be captured in one image.

12 It appears that most of the variability arises
13 from image capture rather than the analysis. Thus, any
14 system to be used by a sponsor should be established
15 repeatability using a series of images captured on the same
16 cohort of patients, rather than re-analysis of single
17 images.

18 One advantage of using these systems is that the
19 images can be stored for later analysis. An image may be
20 compared to other images from the same patient or can be
21 graded using a subjective system, again with a masked
22 examiner. A further advantage of image analysis is that the
23 analysis can be limited to a specified area of the capsule,
24 e.g., the central 3 millimeters or 5 millimeters.

25 I don't think I have answered your question, but I

1 just wanted my 15 minutes.

2 DR. McCULLEY: I think you did. The only one that
3 I don't think you answered was, "Regarding the current
4 methods of PCO analysis, do you consider particular methods
5 acceptable for PCO IOL studies," or is that still a can of
6 worms?

7 DR. BULLIMORE: I refer the Chair to my previous
8 statement about wrist slapping.

9 DR. McCULLEY: About what?

10 DR. BULLIMORE: Wrist slapping. I was told that
11 we can't include or exclude certain systems.

12 DR. McCULLEY: Why did you ask us that?

13 DR. BERMAN: I will repeat what I said before,
14 which is that if there are certain methods, certain types of
15 methods, certain categories of methods that the panel feels
16 do not have clinical relevance, maybe the panel feels they
17 are academically interesting, but they are not relevant
18 clinically, or if there are particular areas we are trying
19 to--

20 DR. McCULLEY: So, referring to them by approach
21 rather than by brand name.

22 DR. BERMAN: Right.

23 DR. McCULLEY: You did offer opinion relative to
24 which approaches you thought were better.

25 DR. BULLIMORE: Yes. I stand by what I said

1 already.

2 DR. McCULLEY: All right.

3 DR. BERMAN: It is not clear to me, if you could
4 just get the panel's input as to the area that you would--

5 DR. McCULLEY: He just covered that at the very
6 end.

7 DR. BERMAN: You said 3 millimeters or 5
8 millimeters.

9 DR. BULLIMORE: I threw those out as alternatives.
10 I don't see patients, I don't operate on patients, so I
11 don't know what a typical people size in this population is.

12 DR. McCULLEY: It's an older population. I think,
13 you know, it is going to be in the range of 3 to 4, probably
14 not 5.

15 Walter.

16 DR. STARK: I see a large number of patients that
17 are 40 to 50 with cataracts, they somehow get to me, and so
18 those people can get up to 6 millimeters, so I think that
19 the area under the intraocular lens is probably important
20 for nighttime driving. Those are active people.

21 If you are limiting your decisionmaking to 70-
22 year-olds, then, it is going to be 3 to 4 millimeters.

23 DR. McCULLEY: We have an interesting dilemma here
24 in that relative to any labeling along those lines, I think
25 it still stands that no intraocular lenses are approved for

1 use in anyone under 60, is that not correct?

2 DR. ROSENTHAL: It still stands, but we are hoping
3 to alter that.

4 DR. McCULLEY: It would be a tricky issue to deal
5 with this for an off-label use.

6 DR. YAROSS: Mr. Chairman.

7 DR. McCULLEY: Dr. Yaross.

8 DR. YAROSS: From a HCFA perspective again, for NT
9 IOL, what matters is the Medicare population, which is not
10 going to be that young population.

11 DR. McCULLEY: You are right, and thank you for
12 that input, but we are dealing with overlap. We have got a
13 circle thing going here.

14 Rick.

15 DR. FERRIS: Earlier, we saw a presentation, which
16 I think fairly dramatically showed that you may get
17 different results depending on whether you look at the
18 central 3 millimeters or the entire lens.

19 It seems to me that both are relevant and
20 important, and I would suggest that whoever is submitting
21 this ought to at least measure both, and they may be able to
22 dance around the peripheral one as being less important, and
23 so on, but if you didn't come in with both, I think you are
24 leaving yourself wide open to criticisms, especially if the
25 study is rather short, and the presumption might be that

1 there is peripheral stuff out there which may be going to
2 grow in if you only had another year of follow-up.

3 So, it seems to me if I was going to write a
4 guidance, my general guidance would be you ought to do both,
5 maybe the central is more important or primary, you are
6 going to list that as your primary one, but if you don't do
7 both, you do it at some risk.

8 DR. McCULLEY: And the periphery would be, I
9 thought that what Dr. Spalton was used was the area within
10 the rhexis or peripheral to the optic or the border of the
11 optic where lens overrode capsule, anterior capsule.

12 DR. PULIDO: That is rather vague.

13 DR. McCULLEY: You are a retina doctor.

14 DR. BULLIMORE: I am sure Dr. Pulido appreciated
15 that compliment.

16 Mr. Chair, if it pleases you, why don't I continue
17 and finalize my comments dealing with surgical outcomes, and
18 then I will be quiet.

19 Regarding surgical outcomes, I think a primary
20 consideration is what the patient sees, but from a fiscal
21 perspective, and probably from a HCFA perspective, the most
22 important outcome is whether the patient requires an
23 additional procedure, for example, a YAG, due to the
24 development of "clinically significant PCO."

25 Using this as the primary outcome measure in a

1 clinical trial has huge potential for clinician bias, and it
2 is unclear how people in the literature controlled for this.
3 In one of a number of papers, in one of the St. Thomas's
4 study papers that Dr. Spalton was involved with, they report
5 that none of the patients receiving the polyacrylic IOLs
6 required YAG compared to 26 percent receiving PMMA IOLs, and
7 that has clearly made its way into the product labeling now.

8 Nonetheless, the authors reported no significant
9 differences in visual acuity or contrast sensitivity. So,
10 to me at least, without probably more careful reading of the
11 studies, it is unclear on what basis these decisions to do a
12 YAG were based, and in the clinical trial, they need to be
13 clearly stated.

14 Let me offer an alternative approach, and that
15 would be only to count the number of YAG procedures that
16 resulted in, say, two or more lines improvement in the
17 visual acuity, but again the potential bias still exists,
18 for example, who decides when a patient requires a YAG and
19 on what basis.

20 One way to minimize bias would be to perform YAG
21 on all patients after a given time interval and record the
22 improvement of vision that occurs. I mean that to me would
23 be the gold standard, but you are doing perhaps unnecessary
24 surgery on the majority of the population, and this seems
25 impractical, but in an ideal world.

1 DR. McCULLEY: Rick Ferris. Long first question.
2 Based on review of current literature, the
3 following exclusion criteria are proposed for PCO studies:
4 subjects with pseudoexfoliation syndrome, uveitis, non-age-
5 related cataracts, previous intraocular surgery or laser
6 treatment, diabetes, glaucoma, current use of systemic
7 steroids or topical ocular medications, previous use of
8 cytotoxic drugs or total body irradiation, and previous
9 ocular trauma, and intraoperative exclusions for tear in the
10 capsulorhexis, zonular dehiscence, posterior capsule
11 rupture, vitreous loss, and other unexpected surgical
12 complications which could reasonably be assumed to affect
13 PCO development.

14 Do you suggest any deletions or additions to this
15 list?

16 Let's go with one question at a time. Are you
17 okay with that?

18 DR. FERRIS: Yes. From my perspective, the first
19 set of exclusion criteria up there is designed to exclude
20 groups of patients who have a different risk of PCO than
21 other groups, and you can understand that because of the
22 need to exclude confounding variables.

23 The problem with exclusions, of course, from a
24 clinical trial point of view is that the results may not be
25 generalizable despite the fact that inevitably they are

1 going to be used in those groups.

2 I think that the guidelines should not specify a
3 fixed rule for exclusion criteria. There could be specific
4 reasons for excluding some of these groups. It seems to me
5 reasonable to exclude groups of patients having conditions
6 that are very infrequent and are likely to confound the
7 outcome, and those might be people with previous intraocular
8 surgery or laser treatment that might affect visual acuity,
9 pseudoexfoliation at least in this country is probably
10 fairly unusual, previous use of cytotoxic drugs or total
11 body irradiation where follow-up could clearly be a problem,
12 previous ocular trauma where again function may be difficult
13 to assess.

14 It seems to me that it would certainly be
15 reasonable to exclude those groups. I think it gets more
16 difficult when you get to such things as uveitis and steroid
17 use. Uveitis is infrequent, so in a large trial it may not
18 be part of the trial with sufficient frequency to be able to
19 say anything about it. On the other hand, it is probably a
20 high risk group.

21 An example for uveitis might be that you might
22 relatively easily be able to do a specific trial for an
23 indication of patients with uveitis. That, it seems to me,
24 is something that the company needs to decide, and they
25 might or might not include them.

1 Steroid use can be very difficult to define, and
2 we found that in other trials, people actually in this
3 population not infrequently have steroid inhalers for
4 intermittent asthma, and do you exclude those people or do
5 you include them. I would tend to be on the inclusion side.

6 That goes also for some of the other things that
7 are listed here, such as diabetes, glaucoma, non-age-related
8 cataracts. Diabetes and glaucoma, depending on how you
9 define glaucoma, which I am not going to go there, could be
10 a relatively significant part of the population, and it
11 seems to me that you might want to identify high risk
12 subgroups of patients with glaucoma and diabetes.

13 For example, if you had diabetes with only a few
14 microaneurysms, it is probably reasonable to include such
15 patients. If you have proliferative retinopathy, it is
16 probably reasonable to exclude them, and where you draw a
17 line, I think ought to be up to the company. Similarly,
18 with glaucoma.

19 With regard to the intraoperative exclusion
20 criteria, I believe they are necessary because the
21 intraocular events could confound the assessment of capsular
22 outcome, and because it may make the assessment impossible
23 to assess, if no capsule, no capsular opacity presumably.

24 One way of dealing with that is that if
25 randomization occurs after the surgical complication, these

1 patients can be excluded without any additional data
2 collection because they have never actually been entered
3 into a randomized trial, so you could conceivably do the
4 procedure and then when everything is fine and you are ready
5 to insert the lens, you open the envelope, you have both
6 lenses there and decide which lens to put in or which of
7 three lenses.

8 It can be done and that I think would avoid some
9 of the problems. If the randomization occurs prior to the
10 surgical complication, then, an accounting for these
11 patients is absolutely required. The results could be
12 excluded for certain analyses, but need to be accounted for
13 in other analyses.

14 For example, if a new intraocular lens had
15 characteristics that made PCO less frequent, but also had
16 characteristics that led to more capsular rupture, it would
17 be important to capture this information to assess the risk/
18 benefit ratio of this new lens.

19 The study protocol needs to assure that once a
20 patient is randomized, there will be an accounting for this
21 patient and all analyses. For some analyses, such as
22 proportion with PCO opacity, this would mean that the
23 patient was accounted for as "non-assessable."

24 Other analyses can be performed to demonstrate any
25 differences in complication rates between the lenses

1 studied. There should be no opportunity for the clinician
2 or others to exclude a patient because of a complication
3 after randomization.

4 DR. McCULLEY: Are there comments to Rick's answer
5 to the question? Dr. Weiss and then Dr. Stark.

6 DR. WEISS: I just wanted to know, Rick, why you
7 would like to include patients who are on steroid treatment.

8 DR. FERRIS: It is more that I don't necessarily
9 think they have to be excluded. I think a company could
10 come in and exclude any or all of those things. When they
11 do, however, I wonder about why they are doing it.

12 I mean if they are doing it because they think
13 steroid use increases the risk of capsular opacity, which I
14 presume might be the reason, and steroids are used in a
15 relatively high group of patients, I would think you would
16 like to know whether that was true or not.

17 The problem is that inevitably if--let's say it's
18 5 percent of the population and you had 300, that is 15
19 cases. You are not going to be able to get much information
20 at all. However, if they are included in the trial and set
21 up in advance as a subgroup that we are concerned about, if
22 they are in the trial, at least you have some opportunity of
23 looking at the--well, if it's a 300-patient trial with 150
24 in each arm and a 5 percent event rate, even though it is
25 only eight patients in each group, you might have an

1 opportunity to look to see if there was some particularly
2 unusual thing that was going on in them, like all eight went
3 on to have opacities.

4 It seems to me that there is a little bit of
5 opportunity for a warning that off-label use in this or use
6 in this subgroup may not get you the same results as the
7 overall group.

8 I think such exclusion criteria are always a dicey
9 issue. From the scientific point of view, often we like to
10 have the narrowest, cleanest group to look at, and from the
11 clinical point of view, we inevitably want to know, well,
12 what about the patients that weren't in it, are we to
13 extrapolate to them or do you have any information on them,
14 and I don't think there is a right answer here.

15 DR. McCULLEY: Would you agree that those patients
16 with these risk factors, concern factors, should be reviewed
17 separately as a subgroup, and that when you are comparing
18 the two groups, that there be not an imbalance?

19 DR. FERRIS: I think it is perfectly reasonable
20 for a study to be designed saying that the primary analysis
21 is going to be in the group that excludes perhaps all of
22 these patients, but we are going to do other analyses.

23 The problem is that there is nothing in the
24 company to do that, because they are better off doing the
25 sort of the normal group and assuming that this thing is

1 then going to be used off-label in everyone else.

2 There is nothing to be gained because the only
3 thing that is likely to come out is that it's demonstrated
4 that it may be worrisome in some subgroup.

5 DR. McCULLEY: The one diagnosis that I recall
6 that was brought up by others to include in the exclusion
7 group was retinitis pigmentosa. I don't recall that there
8 were any others, but I can be corrected if there were.

9 Dr. Stark.

10 DR. STARK: Well, if visual acuity were going to
11 be used an endpoint, then, I would say we should probably
12 exclude people with age-related macular degeneration, and
13 probably people with diabetic retinopathy, any diabetic
14 retinopathy, because if you are using an indication for YAG
15 laser capsulotomy as a reduction in vision, sometimes it is
16 a little difficult to determine is this a capsule that is
17 opacified with some fibrosis or is it the age-related
18 macular degeneration getting worse.

19 DR. McCULLEY: Dr. Bullimore.

20 DR. BULLIMORE: I would like to remind everybody
21 that we are assuming that this is going to be a randomized
22 clinical trial, and there are some advantages to setting
23 broad eligibility criteria and letting the randomization
24 take account of any other confounding variables like IRM,
25 like diabetes, things like that.

1 DR. McCULLEY: Okay. Dr. Matoba.

2 DR. MATOBA: I don't think Dr. Ferris specifically
3 mentioned topical medications, but that was the thing that
4 really jumped out at me as a thing that shouldn't be
5 excluded. A lot of people use antihistamines and all sorts
6 of medications, and so I would remove that, and under
7 certain circumstances, certain topical medications may be
8 excluded, but generally, I don't think that that broad a
9 category should be included among the exclusion criteria.

10 DR. McCULLEY: Dr. Pulido.

11 DR. PULIDO: Just to further define Dr. Stark's
12 idea of including as an exclusion ARMD, probably it should
13 be patients with exudative ARMD, wet ARMD, or high risk dry
14 ARMD, because a few drusen is common and the chances of
15 progression are probably small in that group.

16 As far as diabetic retinopathy, I agree with Dr.
17 Ferris that mild diabetic retinopathy probably should not be
18 an exclusionary criteria because the chances of progression
19 into development of clinically significant diabetic macular
20 degeneration over a time period of a year or two in the
21 presence of just mild diabetic retinopathy probably wouldn't
22 be sufficient to exclude these people.

23 DR. McCULLEY: Other comments along either Dr.
24 Matoba's or Dr. Pulido's and Stark's comments? Dr. Weiss.

25 DR. WEISS: Some authors have also put high myopia

1 in the exclusion list.

2 DR. FERRIS: I guess I would like to address that.
3 In my sense of this, any of these fairly unusual ocular
4 events that could have an effect on acuity or function, it
5 seems to me it is reasonable to exclude them.

6 I worry more about the more common things. You
7 know, when you start doing a trial in the population and you
8 have a fairly high rate, for example, of diabetes in this
9 population, to exclude them certainly makes your trial
10 harder to do.

11 It seems arbitrary to me, especially for people
12 when we can sort of go down the hierarchy, if they have no
13 demonstrable retinopathy, it seems to me silly to exclude
14 them especially if they are a Type 2 patient who is on diet
15 alone. If they have one or two microaneurysms that you have
16 to hunt around for, it starts getting more problematic, and
17 where you draw the cut point is fairly arbitrary, but it
18 seems to me there is some point where you would like to draw
19 the cut point, and the same with age-related macular
20 degeneration, retinitis pigmentosa seems silly to include,
21 and some of these other things that are very rare, they only
22 add noise.

23 Randomization doesn't give you any solace because
24 they are unlikely to be enough. Just even one or two, when
25 you are looking at fairly low event rates here, like 10

1 percent could make a difference.

2 So, I think it is, in general, the sense of what I
3 am trying to say is that exclusion criteria are appropriate,
4 anything that is on this list could be an exclusion, that
5 the company has to decide that there is some tradeoffs, and
6 in general, from the consumer's point of view, being
7 inclusive gives you a little bit more information.

8 So, from the consumer's point of view, more is
9 better; from the trialist point of view, more defined is
10 better, and exactly where you make that cut point is I think
11 sort of arbitrary.

12 DR. McCULLEY: Dr. Coleman.

13 DR. COLEMAN: I agree with Dr. Ferris in terms of
14 not in general excluding glaucoma patients. I think it is
15 important to include them, once again based on certain
16 criteria how they want to define it, but not to exclude
17 them.

18 DR. McCULLEY: Have we provided you with what you
19 need? Does the panel think there is anything else we need
20 to drive home to FDA? Okay.

21 Rick, your next question was regarding time points
22 for PCO assessment, FDA guidance for IOL studies suggests
23 scheduled follow-up at day 1, week 1, month 1, months 4 to
24 6, and years 1, 2, and 3. What time points do you suggest
25 for PCO assessment? Do you suggest follow-up beyond 1 year?

1 If so, at what intervals and for what duration?

2 DR. FERRIS: My sense of this is that the schedule
3 for IOL studies has worked well in the past and that these
4 visits are appropriate, not necessarily for PCO assessment,
5 but for assessment of other complications of any IOL. So, I
6 think the visits are appropriate, but assessing PCO at all
7 of these visits seems to me to be superfluous.

8 Because the overall event rate for PCO at one year
9 is around 10 percent, then assessment out at one year might
10 be appropriate. I am not sure you care whether it happened
11 at 6 weeks or 1 month or 6 months, however, I think the
12 assessment at the 4 to 6 month visit is likely to be
13 worthwhile and individual investigators I think should
14 consider that, especially after what we saw this morning,
15 that at least some measures of PCO outcome assessment may be
16 quite predictive of longer term outcomes, and time to those
17 events might be a very sensitive way of looking at
18 development of PCO.

19 If early assessment is not performed, then
20 mechanisms must be in place to document the severity of PCO
21 prior to any surgical intervention. The concern here I
22 think is fairly obvious, that is, that if you allow YAG
23 without documenting that a PCO has occurred, that is a real
24 problem, and that allows bias into the trial, and I think
25 that has to be avoided in one way or another.

1 I think long-term follow-up is desirable because
2 most surgical interventions tend to occur after one year. I
3 would think a minimum duration of a study would be one year,
4 and I think at least some 2-year data ought to be available.

5 DR. McCULLEY: Comments? Dr. Stark.

6 DR. STARK: Were you including the 4-week, Rick,
7 because you need a point there to document what is left over
8 from the cataract operation. Unless you have got
9 pseudoexfoliation, weak capsule or trauma, your capsule is
10 going to be either clean or somewhat hazy, but that is going
11 to be the same after surgery at a month. It is not going to
12 change a lot within that month unless there is weak zonules
13 or some other thing. So, there ought to be some
14 documentation at about a month as to what you are starting
15 out with. Before that, one day, it may be difficult to do.

16 DR. FERRIS: That is fine with me.

17 DR. McCULLEY: I would agree with that, some early
18 point like a month, but not too early.

19 Other questions, comments? I think that was
20 pretty straightforward.

21 Rick, your next question. What factors are
22 critical to be standardized within a PCO study? Across all
23 studies, e.g., surgical techniques such as incision size,
24 capsulorhexis size, post-op medications, and capsule
25 polishing, as well as measurement techniques, et cetera.

1 DR. FERRIS: I have sort of a general answer, and
2 that is that I think it is critical that the surgical
3 techniques do not differ in any important ways between IOL
4 groups, and that list probably includes potentially
5 important differences, because if the surgical techniques
6 are different, it will be impossible to determine if the
7 differences are a result of the lens or the surgical
8 technique. That seems pretty obvious.

9 Standardization within studies I think in my
10 experience standardizing surgical techniques is difficult,
11 across studies it is useless or impossible. So, I think it
12 is very important to understand that looking at historical
13 controls because of that may be very difficult or dangerous,
14 and--dangerous seems like a strong word--will be difficult
15 to interpret.

16 There are certainly going to be important
17 confounders across trials, and trying to limit that within
18 the trial by attempting to standardize technique and say
19 this is what our operative technique in general is going to
20 entail, and then hoping that randomization will help smooth
21 out the rough edges, because inevitably, from patient to
22 patient, there will be some differences, but I think
23 attempting to standardize the technique is important.

24 I think that the outcome assessment definitely
25 should be standardized and, to the extent possible, masked,

1 and the outcome measures, as Dr. Bullimore was discussing,
2 need to be reliable and reproducible so that investigators
3 can be assured of finding a difference when one exists, and
4 that the assessment of outcome measures should be
5 appropriately masked so that the reviewers can be assured
6 that they are witnessing a difference that is due to
7 treatment rather than bias.

8 DR. McCULLEY: Dr. Sugar.

9 DR. SUGAR: I agree with what Rick said, but there
10 are conceivably situations where the surgical technique is
11 part of the lens. For example, techniques where you would
12 do a small capsulorhexis, aspirate the lens contents, and
13 inject a material that solidifies in the lens capsule has
14 been a suggested means of replacing lenses, and the
15 technique, in and of itself, is part of the lens, so that we
16 shouldn't be too dogmatic about comparing that to a standard
17 incision or clear corneal incision technique.

18 DR. FERRIS: I guess my comment is that the
19 procedure ought to be specified and standardized in both
20 arms, and where there are differences, that needs to be
21 apparent, and if, as you say, that is part of the lens,
22 then, so be it, that is part of the difference, and at the
23 end of the day, trialists look at approaches, not just the
24 specific lens, and so it is kind of the intention to treat
25 analysis.

1 DR. McCULLEY: Other comments? Dr. Stark.

2 DR. STARK: Even though there is a standard
3 technique, the capsulorhexis size may make a difference, so
4 you just want to make sure it is documented, and it could be
5 at that month visit, is the capsulorhexis anterior to the
6 lens, is it peripheral, or is it fibrosed under the lens,
7 because we have situations where maybe a little weakness of
8 the zonules allows it to be more floppy, the capsule will
9 come under the lens and fibrose under the lens.

10 That may be different than fibrosing outside the
11 diameter. It may be different from being on the anterior
12 surface of the intraocular lens, and those are all important
13 things to document.

14 DR. McCULLEY: Dr. Yaross.

15 DR. YAROSS: I believe Dr. Ferris called out
16 postoperative medications in his review, but I believe
17 intraoperative medications also need to be standardized.

18 DR. McCULLEY: Other comments?

19 Rick, your last question is, if a sponsor wishes
20 to claim reduction in YAG capsulotomy rate, what
21 standardized clinical criteria would you suggest for
22 performance of capsulotomy after objective documentation of
23 PCO, i.e., specified number of lines decrease and/or minimum
24 threshold level of BCVA, contrast sensitivity, glare effect,
25 subjective complaints, PCO grade level, or any combination

1 of these? Do you feel that all PCO studies should evaluate
2 both outcomes, YAG capsulotomy rate and PCO incidence?

3 DR. FERRIS: I will answer the last one first, and
4 that is, it seems to me it is important to document
5 intervention, so that for sure you would need to count the
6 number of YAG capsulotomies.

7 The concern with the capsulotomies we have
8 discussed already, and that is, that there is potential for
9 bias and that it is apparent that capsulotomy rates vary by
10 surgeons, so that needs to be controlled for in some way.

11 There are two ways that I can see. One is that
12 you document the severity of the PCO before it is operated
13 on, and hopefully you have a defined event outcome, and if
14 it has reached that event outcome, then, you don't care that
15 the capsulotomy occurred.

16 The other thing that you can do to try to sort out
17 the potential for bias is to use some of the functional
18 outcomes, either decreased before the capsulotomy or
19 improvement after the capsulotomy, to help assure that these
20 are not being done trivially, but that every one that is
21 being done or some high proportion of those that are being
22 done have some functional outcome.

23 In particular, if it is a randomized trial, then,
24 you can look between groups to try to assess whether there
25 is a bias. For example, if you see lots of improvement in

1 the control group and less in the treated group, you might
2 worry that there is a bias--well, I said that backwards--if
3 you were trying to show that a lens was effective, but I
4 think you see the point, that there is a potential for bias
5 to be the reason for this, whereas, if the functional
6 outcomes are the same in the two groups, then, it says,
7 well, using the capsulotomy rate may be a pretty good way of
8 looking at the amount of capsular opacity that occurs in
9 each group.

10 DR. McCULLEY: Comments? Dr. Bullimore.

11 DR. BULLIMORE: This is as question for Rick and
12 the rest of the panel. What do you think about the
13 possibility of having a centrally based, masked examiner
14 that had to be presented with all the clinical data before
15 deciding whether this person deserves a YAG?

16 DR. McCULLEY: Your idea about a reading center.

17 DR. BULLIMORE: Yes, but maybe not necessarily a
18 reading center for subjective rating of opacity, but
19 somebody who is presenting with visual acuity data,
20 opacification data, visual function questionnaire data, and
21 basis of decision to do a YAG on that rather than leaving it
22 to the individual clinician and individual center.

23 DR. McCULLEY: And what would be provided to that
24 person for them to be able to assess?

25 DR. BULLIMORE: Well, that is the second question.

1 Let me just say they get visual acuity data, visual function
2 questionnaire data, opacification percentage data.

3 DR. McCULLEY: Rick.

4 DR. FERRIS: Let me comment on that. We have used
5 thresholds like that before in other trials. There are two
6 issues here. One is that at the end of the day, it is up to
7 the patient and the physician as to whether this occurs.

8 You can try to cajole the study investigators into
9 holding off on doing surgery until an outcome or an event
10 has been stated to happen. For example, if you had the kind
11 of measurement that we saw this morning, of PCO opacity, and
12 you said that it had to be a certain amount before you were
13 going to call that a significant opacity, as I said
14 previously, if they have reached that amount, then, I don't
15 care whether you have the capsulotomy or not.

16 If they haven't reached that, then, it is a
17 concern and you could say to the investigators, well, we
18 would like you not to do capsulotomy until this has been
19 reached.

20 I actually do have a problem with giving a reading
21 center the visual acuity information and the other
22 functional outcome information because potentially, that
23 then biases their assessment of the posterior capsular
24 opacity.

25 So, I would like that event assessment

1 independently done from any other information regarding the
2 patient. I think the study investigators have to understand
3 that if these capsulotomies occur before events are
4 declared, it is potentially damaging to the overall study,
5 and it is in their interest, if they are interested in the
6 study, to try to come to an agreement that we won't do
7 capsulotomies unless events are occurred, recognizing that
8 inevitably, a patient is going to demand a capsulotomy and
9 you are going to have to do it just because if you don't do
10 it, somebody else is going to do it.

11 DR. McCULLEY: Further comments? Does that
12 adequately answer the last question for you?

13 DR. BERMAN: Yes.

14 DR. STARK: I read in one of these where the
15 observer was going to be masked as to the type of
16 intraocular lens. Is that part of your recommendation,
17 Rick, and if it was, one can tell the difference between the
18 lenses by looking at it, so there is going to be bias at
19 that particular point.

20 DR. FERRIS: I agree with that comment, and I
21 think there might be ways, for example, in a photographic
22 reading center, of obscuring the lens. If the thing is
23 measured by a machine, for example, then, it may be less
24 important. However, if a person is making the outline of
25 where the capsulorhexis is, that potentially could affect

1 the outcome.

2 So, other methods for trying to mask the IOL might
3 be considered. For example, somebody in advance goes in and
4 blacks out the area.

5 DR. STARK: I wasn't talking about masking the
6 IOL. One can tell, if you are comparing an acrylic with a
7 silicone, the observer, the doctor can tell the difference
8 between the lenses.

9 DR. FERRIS: In the retroillumination photo?

10 DR. STARK: Yes--by the clinical examination, yes,
11 the clinical exam, not by the retroillumination photo.

12 DR. FERRIS: The one I would care about is if you
13 are using a retroillumination photo as your outcome
14 assessment, and you could tell the difference in that, then,
15 I think you need to do something about masking it. If you
16 can't tell the difference in that, and I can imagine
17 situations that either could occur, you either do have to
18 worry about further masking or not.

19 It seems to me if you are doing the trial, and the
20 observer of the event can tell the group that the patient is
21 in, then, you need to worry about trying to solve that
22 problem, because otherwise, you will never have an adequate
23 answer to the critic who says, well, I think there was
24 observer bias.

25 DR. STARK: Then, if the outcome is going to be,

1 if the observer is going to determine the outcome, then,
2 that has to be addressed, because I can look at the lens and
3 tell if it is an acrylic or a silicone, and I can tell the
4 difference between the two acrylic lenses by just looking at
5 the edge.

6 DR. McCULLEY: Are there further comments?

7 DR. BERMAN: Dr. McCulley, may I ask one question
8 just as a point of clarification? You may not be able to do
9 this, but in the panel's clinical experience--again, I
10 realize this would be guidance, and it is not something that
11 the companies would be held to--but can the panel make any
12 recommendation at all as to a clinical--you had mentioned
13 the threshold level that would have to be met, for instance,
14 best corrected acuity of 20-blank or worse before
15 intervention or the patient has been dropped from X number
16 of lines before YAG, can you make any recommendations at
17 all?

18 DR. McCULLEY: Dr. Sugar, do you want to touch
19 that one?

20 DR. SUGAR: I think we touched on that in the
21 discussion of the first question in my section, and the
22 answer is no, that it is a combination of one from group A
23 and one from group B or whatever, that there are some visual
24 acuity issues that can be singularly determinants, and there
25 is some opacification issues in the face of good acuity that

1 can be singularly determinants in the face of certain
2 symptoms. So, I think it would be very hard to put it out,
3 that you could put out patient subjective, visual acuity,
4 and then whatever objective measures we have, and any of
5 those, you know, one from each of those three or whatever,
6 you could set up a schema. I don't think we can do it here.

7 DR. McCULLEY: Rick?

8 DR. FERRIS: My preference, you could probably
9 tell from what I said earlier, was that you picked some
10 assessment of posterior capsular opacity that is done in a
11 masked way that is likely to be early enough that it would
12 occur before you would want to do capsular surgery.

13 If you can't do that, then, that is a potential
14 problem. I think once you get into these functional things,
15 as we heard today, 20/20 means a lot different to somebody
16 who is used to 20/10 compared to somebody who has had a
17 cataract for years and is used to 20/40 vision.

18 DR. McCULLEY: Does that address everything?

19 DR. BERMAN: Yes.

20 DR. McCULLEY: We have your summary question.

21 Having reviewed the PCO study discussion paper, are there
22 any areas for which you have additional suggestions?

23 That is a very open-ended, I think we have covered
24 extensively. Is there anything that either you would like
25 us to cover that we have not, "you" being FDA, or that any

1 panel member would like to bring up that we have not yet
2 covered?

3 DR. BERMAN: No.

4 DR. McCULLEY: What I would like to do is have our
5 next open public hearing session, and specifically invite
6 Dr. Chambers to make some comments. If anyone else wishes
7 to make comments, you will be invited to the podium after
8 Dr. Chambers makes his comments.

9 **Open Public Hearing**

10 DR. CHAMBERS: Wiley Chambers, Food and Drug
11 Administration, Center for Drug Evaluation and Research.

12 I think it is important that the panel should know
13 that the particular topic, although not related directly to
14 the effect of intraocular lenses, but related to posterior
15 capsular opacification, is not an issue limited to the
16 Center for Devices. There are drug products and biologic
17 products that have also considered claims of preventing
18 opacification.

19 The Center for Drugs and Center for Biologics have
20 had to make cuts on what is a legitimate endpoint a number
21 of years ago. A lot of the discussion you have had today
22 was also done at that point. Some of the science has
23 changed, but relatively little of it has changed in that
24 period of time.

25 Based on the discussions that you have had so far,

1 the largest potential disagreement between policies right
2 now in the Center for Drugs and Biologics, and what you have
3 discussed revolve around the amount of change that would be
4 considered clinically significant.

5 The Center for Drugs and Biologics have used 3-
6 line change as opposed to a 2-line change. It is possible
7 to argue that there are differences in benefits to risk for
8 adding additional drug products or biologic products as
9 opposed to putting an intraocular lens in, which you are
10 putting in for other reasons, and there may be reasons to
11 have a higher or different, not necessarily higher, but a
12 different criteria.

13 It would be useful for people on the panel to
14 comment how strongly there is a belief that for intraocular
15 lenses, that there should be a 2-line versus a 3-line. This
16 is not an attempt to go and ask you to change your opinions
17 based on a consistency with the Center for Drugs and
18 Biologics. They were made on different calls and on
19 different information. But it would be I think worthwhile
20 to hear how strong you feel about 2 lines as opposed to any
21 other measure, or whether that should be continued to be
22 discussed.

23 DR. McCULLEY: Dr. Sugar.

24 DR. SUGAR: I think again we discussed that
25 earlier, that even 2 lines is not hard and fast, and may be

1 even too many lines, it may be even less than 2 lines, that
2 it has to fit into the whole combination of subjective and
3 functional assessment of the patient, and that was the whole
4 point of the discussion earlier.

5 DR. McCULLEY: Dr. Bullimore.

6 DR. BULLIMORE: I think it is also important to
7 consider the context in which we are using the criteria of 2
8 lines or 3 lines. Are we talking about the proportion of
9 patients that lose or gain 2 or 3 lines, are we drawing a
10 line in the sand and saying that a device has to, on
11 average, produce a 2-line improvement? What are you saying
12 here?

13 DR. CHAMBERS: We have actually left the option
14 open. We have said any of the following are acceptable, and
15 these will all have to be pre-defined prior to the protocol
16 going on, but you could pre-define any of these, and they
17 would all be acceptable: a mean change in 3 lines between
18 the groups, a difference in the percentage of people that
19 had lost 3 lines, or the third, a difference in the
20 percentage of "justifiable" YAGs, justifiable YAGs being
21 those where after the YAG, the vision was taken, the YAG was
22 performed, and the vision after the YAG was 3 lines or more
23 better than it was prior to the YAG being done, tested, also
24 either in normal light settings or in high light settings.

25 DR. McCULLEY: Dr. Bullimore, continue.

1 DR. BULLIMORE: So, in essence, you wouldn't
2 regard--let's suppose a sponsor came in with a randomized
3 clinical trial, 100 patients in each group, and they found a
4 mean difference of 1 line of acuity between the two groups,
5 that wouldn't pass muster under your guidelines?

6 DR. CHAMBERS: That is correct.

7 DR. BULLIMORE: Then, I would suggest that your
8 criterion is too rigid for this particular panel.

9 DR. McCULLEY: Dr. Weiss.

10 DR. WEISS: Three lines will increase the duration
11 of the study because you are going to wait for the capsular
12 opacity to get worse, so I think, also clinically, 2 lines
13 is visually significant, that you are going to want to
14 intervene, so on both of those bases, I would support 2
15 lines rather than 3.

16 DR. McCULLEY: Other comments? Dr. Ferris.

17 DR. FERRIS: I understand Wiley's point, and I
18 think 3 lines is a level where you can say that is a
19 documented decrease in visual acuity that is not due to
20 chance or variation from exam to exam.

21 The difficulty that I see with this, in this
22 study, is the practicality of taking Americans and telling
23 them that they have to wait until their visual acuity gets
24 to 20/40 before they have their capsular surgery.

25 That gets to the point we were discussing earlier,

1 because I worry just as much about the bias of the capsular
2 surgery as I do about the 3-line loss. You can take the
3 perspective that, well, you can have your surgery, you are
4 just never going to get counted as an event, but it makes
5 the trial very difficult to do.

6 DR. McCULLEY: Dr. Pulido.

7 DR. PULIDO: I see your point, because--

8 DR. McCULLEY: "Your" meaning?

9 DR. PULIDO: --Wiley Chambers' point--because now
10 you are adding a pharmacologic intervention over and above
11 what would normally have been done, which is putting in the
12 posterior chamber implant.

13 So, because you are adding something else to the
14 surgery or even possibly chronic medications afterwards, I
15 would like to see a substantial change using that
16 pharmacologic therapy as opposed to a prosthetic device that
17 we were going to be putting in anyway.

18 So, I think a 3-line change for a pharmacologic
19 intervention, especially a chronic pharmacologic
20 intervention, would be very reasonable.

21 DR. McCULLEY: Dr. Grimmitt.

22 DR. GRIMMETT: I would just add this panel has
23 used a 2-line cutoff in part because prior data including
24 the PERK study and NEI-funded study has found that in
25 unoperated eyes, from visit to visit, patients can change 9

1 letters or less, especially in those who are testing better
2 than 20/20 on an ETDRS chart. Hence, a 2-line cutoff, I
3 believe is appropriate for what at least this panel has
4 always considered clinically significant.

5 DR. McCULLEY: Thank you, Wiley. Do you have
6 anything else you would like to say, Wiley?

7 DR. PULIDO: But what is our consensus on this, is
8 this a different situation than what we are dealing with?

9 DR. McCULLEY: I think that was the consensus.

10 DR. CHAMBERS: Actually, what I heard was that
11 there are reasons to potentially have differences.

12 DR. McCULLEY: Right.

13 DR. STARK: But our consensus, I don't think was
14 that it required even 2 lines, because 2 lines is still a
15 loss of the resolving power of the eye, and so we are not
16 requiring that, and I can understand why you have done that,
17 but that is 50 to 60 percent loss of resolving power of the
18 eye before they can have that YAG laser.

19 DR. McCULLEY: We reached a consensus before.
20 Wiley then had an issue that was 3 lines as opposed to 2.
21 Our consensus is that his situation is different, so thank
22 you for your input.

23 Is there anyone else in the audience that would
24 like to make a comment?

25 [No response.]

1 DR. McCULLEY: This closes the open public hearing
2 session.

3 Does the panel have anything additional to add to
4 the topic of posterior capsular opacity? Dr. Yaross.

5 DR. YAROSS: Just one point. We have discussed
6 the fact that there is a lot of variability regionally,
7 technique, et cetera. I think some consideration should be
8 given to requiring the results to be in more than one
9 clinical setting, so not a single investigator, a single
10 site.

11 DR. McCULLEY: Dr. Bullimore.

12 DR. BULLIMORE: I am not sure that should be--I
13 don't accept that as a uniform requirement because it
14 clearly depends on the outcome measures you are going to
15 use. If you are going to use YAG rates as the outcome
16 measure, then, that might be desirable, but I could make an
17 argument for using the single clinical center.

18 DR. McCULLEY: I think there has always been the
19 issue of transferability. How many times do you use a
20 single site for any major study?

21 MS. LOCHNER: For the primary pivotal study, it is
22 extremely rare, and a sponsor would actually have to justify
23 it. For some studies that are used to support claims, I
24 really don't have a good feel, but it is not as rare as the
25 pivotal.

1 DR. McCULLEY: Any other comments on PCOs? Then,
2 that concludes our deliberation on PCOs.

3 Ms. Thornton has some announcements to make, and
4 then I think probably what we should do would be to break
5 for lunch and then come back for our second topic, unless
6 there is strong, which there does not appear to be. After
7 Ms. Thornton's concluding remarks, we will break, take an
8 hour for lunch.

9 [Whereupon, at 12:25 p.m., the proceedings were
10 recessed, to be resumed at 1:25 p.m.]

AFTERNOON PROCEEDINGS

[1:25 p.m.]

DR. McCULLEY: We are reconvening the second portion of the Ophthalmic Device Panel's meeting on the second day, and our second and last topic is discuss is refractive implants. Ashley Boulware is in charge of this, so let me ask you to introduce this.

TOPIC B: REFRACTIVE IMPLANTS**Introduction**

MS. BOULWARE: Thank you, Mr. Chairman.

I would also like to thank Dr. Malvina Edylman for her assistance in addressing some of these issues.

What I would like to do is to begin with an overview of the materials you received which outlines the clinical study design that we are proposing for these refractive implants, and then to go through the questions that you receive in your panel memo.

[Slide.]

The scope of the document is that it applies to any ocular implant whose primary indication is the modification of the refractive power of a phakic eye to improve distance and/or near uncorrected visual acuity.

This document would also apply to any intraocular lens intended for clear lens exchange.

[Slide.]

1 Safety endpoints. Maintenance of endothelial cell
2 counts. This would be both measured cell loss between
3 preoperative and Month 3 exams, and that loss should not
4 exceed 10 percent.

5 The endothelial cell loss between Month 3 and
6 Month 36 exams should not exceed 4.125 percent, which is
7 equivalent to 1.5 percent per year rate of loss.

8 [Slide.]

9 In terms of maintenance of best corrected visual
10 acuity, these should look fairly familiar to you. Less than
11 5 percent of eyes should lose 2 lines or more BSCVA, less
12 than 1 percent of eyes should have BSCVA worse than 20/20 if
13 they started out 20/20 or better pre-op.

14 We have included a recommendation that sponsors
15 may wish to consider performing best contact lens visual
16 acuity on patients with high myopia and high hyperopia to
17 increase the accuracy of both their preoperative refraction
18 and their power calculations for these implants.

19 [Slide.]

20 Induced manifest refraction cylinder. For those
21 implants that are not intended to correct pre-existing
22 cylinder, less than 1 percent of eyes should have an induced
23 manifest refractive astigmatism of greater than 2 diopters.
24 Rates of adverse events, including cataract formation,
25 should be reported.

1 [Slide.]

2 In terms of efficacy endpoints, predictability of
3 refraction, 75 percent of eyes should achieve predictability
4 of MRSE plus or minus 1. Fifty percent of eyes should
5 achieve predictability of MRSE within plus or minus half.

6 In terms of uncorrected visual acuity, 85 percent
7 of eyes should achieve an uncorrected acuity of 20/40 or
8 better, for those that began with a best corrected acuity of
9 20/40 or better preoperatively.

10 [Slide.]

11 In terms of the study design, the pivotal safety
12 and effectiveness study would consist of 300 subjects, and
13 this sample size was set up to be adequate to evaluate rates
14 of adverse events that would be associated with refractive
15 implants.

16 Endothelial cell counts substudy with a sample
17 size of 200 subjects, and this would be adequate to detect a
18 yearly endothelial cell loss of 1.5 percent or greater and
19 also to demonstrate linearity of the cell loss over time.

20 [Slide.]

21 The contrast sensitivity/low contrast acuity
22 substudy - 125 subjects. This would be adequate to detect a
23 0.3 log unit difference between preoperative and
24 postoperative measurement.

25 The study duration would be 3 years. We have

ajh

1 recommended a phased enrollment based on the amount of
2 initial information the company has about a product, and we
3 have recommended that bilateral implantation be phased in
4 once 50 eyes with 6 months of follow-up has been submitted
5 and reviewed by the agency.

6 [Slide.]

7 Just to point out a couple of the notable
8 inclusion criteria. We have asked that myopic subjects be
9 greater than 18, less than 45 ideally, or less than 50 years
10 of age to try to avoid age-related cataracts as a
11 confounding variable.

12 Hyperopic subjects, we have opened this to between
13 18 and 60 years of age, given the average older age of
14 hyperopes and difficulties in enrolling these patients.

15 We have also added uncorrected VA 20/40 or worse
16 as an inclusion criteria with the thought that if
17 uncorrected VA of 20/40 or better is an endpoint, you should
18 certainly be worse than that to begin with before you enter
19 in one of these investigational studies.

20 [Slide.]

21 Additional inclusion criteria. Subjects between
22 21 and 45 should have a minimum endothelial cell count of
23 2,500. Subjects older than 45 should have a minimum cell
24 count of 2,000, and this is to ensure that patients have
25 sufficient cell counts, such that at the time that they may

1 need cataract surgery as elderly patients, they would have
2 sufficient corneal health to undergo that surgery.

3 Also, subjects that have significant cylindrical
4 error, who would be receiving refractive implants that only
5 provides spherical correction should be given the
6 opportunity to experience his or her best spectacle vision
7 with spherical correction only and still be willing to
8 proceed with the surgery.

9 [Slide.]

10 The reporting periods you will see on the screen,
11 ranging from preoperative to Month 36.

12 [Slide.]

13 We have set out a number of evaluations. You have
14 seen these before, and we have incorporated your comments
15 from previous panel meetings.

16 [Slide.]

17 Additional evaluations. These are to be performed
18 on all subjects.

19 [Slide.]

20 On a subset of subjects, you see the specular
21 microscopy substudy, as well as the contrast sensitivity/low
22 contrast acuity substudy. For the contrast sensitivity/low
23 contrast acuity, that would be under both mesopic and
24 mesopic with glare conditions.

25 [Slide.]

1 We have made some initial recommendations in terms
2 of data analyses. Accountability analyses according to our
3 draft accountability guidance that is available. Stability
4 of MRSE, both change of less than or equal to 1 diopter
5 between refractions 3 months apart, as well as change of
6 less than or equal to 0.5 diopter between refractions 3
7 months apart.

8 Additionally, the mean change in MRSE between
9 visits as determined by a paired analysis.

10 Obviously, the analyses of the safety and
11 effectiveness endpoints that were laid out earlier.

12 Given this brief overview, I would really like to
13 just get to the questions that we have for the panel, so
14 that you can give us your input.

15 We asked Drs. Ferris, Weiss, and Pulido to be
16 prepared to at least begin the discussion on these
17 questions.

18 The first question to you is the current scope of
19 the document includes ocular implants intended for
20 implantation in a phakic eye, as well as IOLs intended for
21 clear lens exchange.

22 Do you agree that IOLs intended for clear lens
23 exchange should be included in the scope of this document?

24 DR. McCULLEY: Were there any specific assignments
25 or just to the three?

1 MS. BOULWARE: Just to the three in general to be
2 prepared to throw out a comment if something was needed to
3 get the discussion started.

4 DR. McCULLEY: We can start with any one of those
5 three to jump forward. If you volunteer, great; if you
6 don't, I will call on somebody. And other panel members, as
7 well, please jump into this.

8 One of the three of you who gave additional
9 thought to the first question, do you have a response?

10 **Panel Discussion of Questions**

11 DR. STARK: Could I just get one point of
12 clarification? Are we talking about clear lens extraction
13 for people with uncorrected vision to 20/40 or worse? I
14 didn't understand exactly what you said. You said
15 uncorrected vision of 20/40 or worse. Are we going to
16 condone a study that would do clear lens extraction for
17 20/40 uncorrected vision?

18 MS. BOULWARE: One of the next questions is that
19 if you agree that the scope should include clear lens
20 exchange, you may wish to impose additional inclusion
21 criteria or exclusion criteria for devices for that
22 indication. That might be something you want to add.

23 DR. McCULLEY: When we discussed this before, I
24 did not realize that we were including in the discussion
25 implants associated with clear lens extraction.

1 MS. BOULWARE: We have not previously discussed
2 this topic with the panel, but it has become more and more a
3 topic at issue, there are more papers on clear lens
4 exchange, and this is just clear lens exchange, not clear
5 lens extraction where no lens is placed. This is simply
6 where a clear lens is extracted and then an IOL is put in
7 place, and we have not brought this to the panel before.

8 DR. McCULLEY: Right. I mean this opens up a
9 whole completely different issue that I am not sure--I guess
10 your question is a simple one, can this be lumped in all of
11 a sudden with the phakic IOLs or is it sufficiently
12 different that it needs separate consideration.

13 MS. BOULWARE: That is certainly an option.
14 Lumping it in with this guidance doesn't mean it gets lumped
15 in and nothing is different than the phakic IOL study. I
16 think we can handle it in this guidance with additional
17 provisions, either additional inclusion criteria, additional
18 evaluations. If you feel that it is significantly different
19 and deserves its own guidance, we can do that, as well.

20 DR. McCULLEY: Well, the way we approached it
21 before, my understanding was that the assumption was we were
22 going to deal with that as a separate issue, not lump it
23 into this.

24 Now, there may be different views from the panel
25 that thinks we can make your life a little easier by lumping

1 these in together. I have an opinion, but let's see what
2 others think about this.

3 Walter.

4 DR. STARK: I am sorry, I haven't read this over,
5 but I can comment. It is a much, much bigger procedure, and
6 certainly has many more risks for clear lens extraction.
7 You might be able to use some of the guidelines for phakic
8 IOL, but they are going to have certain restrictions for
9 clear lens extraction, I would think.

10 DR. McCULLEY: Jayne.

11 DR. WEISS: I think it is sufficiently different
12 that you probably will want a different document. If we put
13 it in the same document for ease, it is going to essentially
14 be a different document than included in the same document,
15 because it is a different procedure.

16 DR. McCULLEY: Dr. Pulido.

17 DR. PULIDO: Just to play the devil's advocate in
18 this situation, the concerns at least from a retina person's
19 point of view are the great chances of retinal detachment, I
20 guess from a glaucoma point of view, pigment dispersion,
21 glaucoma.

22 So, they both have these same concerns. Why
23 should there be a different document if both have similar
24 adverse events that we are all concerned about?

25 DR. McCULLEY: A priori, I am not sure that I

1 would agree that both have similar adverse events. I think
2 it is something we would need to, quite honestly, work
3 through. There is not going to be the issue of
4 cataractogenesis, which is a major issue with the phakic.
5 That is not going to be an issue.

6 With the phakic IOLs, as long as nothing else goes
7 wrong, there should not be an increased risk that I would
8 envision relative to the retina, whereas, if you are doing a
9 clear lens extraction and putting an implant in, that there
10 are new issues there.

11 I think in fairness to us in addressing this
12 issue, I think we would have to go with this with the
13 implantable phakic lenses, and we would also have to have
14 very thorough, in-depth discussion about clear lens
15 extraction and implants, and then once that is gone through
16 very thoroughly--and I agree with the others that rather
17 than the devil's advocate--that if once we have gone through
18 that, indeed, it can be brought back in, okay, but I don't
19 think to try to tack it onto the phakic implants that we
20 have discussed in the past in depth is appropriate.

21 MS. BOULWARE: If that is the consensus of the
22 panel, can you still give us guidance as a place to start on
23 a separate document, so that we might put together a
24 beginning to bring back to you for discussion?

25 DR. McCULLEY: What we could do would be to give

1 you our major increased concerns that relate to that
2 procedure as opposed to the phakic implants.

3 Dr. Yaross.

4 DR. YAROSS: I agree that the issue as related to
5 phakic implants are different than using an IOL in a clear
6 lensectomy or refractive lensectomy. One opportunity, since
7 what those IOLs used in clear lens exchange are most similar
8 to the IOLs used for cataract surgery, it may be possible
9 that an addendum could be done to the existing IOL guidance
10 to address the additional concerns relevant to a different
11 patient population for devices that we have a great deal of
12 experience with.

13 DR. McCULLEY: We are dealing within circles
14 again. We have got some overlap. I agree with Marcia that
15 the issues related to intraocular lenses, period, and some
16 related to refractive state.

17 Dr. Bullimore.

18 DR. BULLIMORE: I am going to line up with the
19 devil on this one because I have yet to be convinced that
20 for the scope of a guidance document, which is really
21 dictating how the study should be done, and not making any
22 statements about the criteria for success, you anticipate
23 the rates of certain complications and adverse events would
24 be higher for one type of device than the other, but the
25 information to be collected is going to be the same.

1 You know, we are going to measure visual acuity,
2 we are going to measure refraction, we are going to record
3 adverse events, we are going to take note of retinal
4 detachments, glaucoma, regardless of which they are, and I
5 think there is a need to sort of lump these together and
6 have a document that all the technologists can move forward
7 together on.

8 My impression is that what is happening here is
9 that there is a greater knee jerk about this clear lens
10 extraction approach, because we are taking out a perfectly
11 clear lens in most of the time a young or relatively young
12 eye, but nonetheless, the outcomes I think that need to be
13 assessed will be the same or at least similar or
14 sufficiently similar that they can be covered by a single
15 guidance document.

16 DR. McCULLEY: We are getting differing opinions.

17 DR. SUGAR: Right now this is a practice of
18 medicine issue using an approved device for an off-label
19 indication.

20 MS. BOULWARE: That is correct.

21 DR. SUGAR: And it can continue that way, but
22 should a company come to the agency requesting this is a
23 label indication, I think it makes sense for that to be an
24 addendum using the criteria for intraocular lenses, but
25 probably with some modifications.

1 There is no reason to think that the endothelial
2 cell count is going to be different in these patients than
3 in elderly patients. I mean the count may be different, but
4 the effect on the endothelial count shouldn't be any
5 different, and I think that this should be an addendum to an
6 already approved device, and I think that you have some
7 standards for numbers for modifications. Certainly, you
8 won't need 300. I presume you won't need 300 patients.

9 MS. BOULWARE: It depends on what you are looking
10 for. If you are looking for rate of retinal detachment that
11 is, say, less than 1 percent, you may need more than 100
12 patients to detect that.

13 DR. SUGAR: What we are looking for is a change
14 from the present 0.075 or three-quarters of 1 percent. 0.75
15 percent to a higher rate, and presumably, that would be
16 seen, if it is substantial, if it is the 7 to 9 percent that
17 has been reported in Europe, then, you will see that with
18 certainly less than 300 patients.

19 DR. ROSENTHAL: May I just comment? I think it is
20 rather important that the issues related to this problem be
21 addressed today because we may be faced with an application
22 in which a company requests this for an indication which
23 heretofore has been off-label, and I would like to hear the
24 panel's comments and concerns, and the main issues.

25 I agree, the issues are very similar, but they

1 seem to be put in a different perspective when you take out
2 a clear lens, and therefore, I would like to have your
3 general viewpoint. I mean do you think it is perfectly
4 acceptable to do this under an IOL guidance document type of
5 a study? You do.

6 DR. SUGAR: Yes.

7 DR. McCULLEY: The risk-benefit ratio is a little
8 bit different than taking out a cataractous lens that is
9 interfering with vision.

10 DR. BULLIMORE: I know, but if you use the IOL
11 document, and the IOL guidance document, you essentially use
12 the IOL guidance document, or does it require--

13 DR. McCULLEY: I think it requires certain things.

14 DR. BULLIMORE: The informed consent requires
15 modification, but what else, I mean other than endpoints?
16 You certainly have to look at refractive--

17 DR. McCULLEY: You are also presumably taking
18 patients that are higher risk for retinal complications.

19 Dr. Stark.

20 DR. STARK: We are talking about lumping phakic
21 and clear lens IOLs. Now, we are lumping it onto the IOL
22 guidance document. I wouldn't mind taking either one and
23 see where you want that information and add it on, but
24 operating on younger people, I mean younger males have a
25 higher risk of retinal detachment even if they are not

1 myopic.

2 When you start getting myopic up above an axial
3 length of 25 millimeters, which means it's as long eye, your
4 rate of retinal detachment in our group, in our study we
5 did, was 5 percent at about two years. Joseph Colin showed
6 a very low rate of retinal detachment at one year, 1 to 2
7 percent, 3 to 4 percent at three to four years, but it is up
8 to 8 to 9 percent at five years. So, I mean there are big
9 different issues.

10 Also, the aspect of being able to document what is
11 accommodation and what near vision do people have, so we can
12 report to them afterwards, you lose your ability to
13 accommodate, a detailed evaluation of the vitreous in these
14 younger people, and the thing that concerns me, when you put
15 that uncorrected vision of 20/40 up, is I see people around
16 our area advertising for patients for phakic IOLs, you know,
17 FDA-approved studies.

18 So, it makes it sound good, and I want people to
19 understand the risk of an IOL exchange. I don't want them
20 thinking, well, this is an FDA-approved study. It could be
21 harmful, because I think clear lens extraction could be
22 harmful, especially in the younger people in the lower
23 myopia range.

24 DR. McCULLEY: Rick.

25 DR. FERRIS: I guess that people have figured out

1 that, in general, I am a therapeutic nihilist and a skeptic,
2 and as a retina person, maybe I shouldn't be commenting on
3 this, but I find the whole thing extraordinary that you take
4 out a clear lens, and I guess I would like to echo Walter's
5 complications, except he said we don't know whether there
6 will be complications.

7 I think we do know there will be complications, we
8 just don't know what the rates are, and I think talking to a
9 20-year-old about the possibility of retinal detachment
10 sometime in the next 25 years is virtually impossible, and
11 we are never going to get information on that.

12 Maybe this is an informed consent issue more than
13 the document issue. I guess if you are going to experiment
14 and people are willing to do this, that is their business,
15 but I think that there are surely complications. As someone
16 who has had a retinal detachment 25 years after cataract
17 extraction, I am particularly sensitive to the idea that
18 that is a risk, that there is no way you are ever going to
19 fully inform a 20-year-old about that risk, especially since
20 there is no way we will ever know what it is. We just know
21 it is there, and we just don't know the magnitude of it.

22 So, I think it is a real concern when you are
23 doing something like this. I have said enough. I am
24 appalled.

25 DR. McCULLEY: Leo.

1 DR. MAGUIRE: I would just like to reinforce that.
2 We have done some epidemiologic work at Mayo and have found
3 the same thing, that once you are pseudophakic, your risk of
4 retinal detachment increases with time and increases with
5 the amount of preoperative myopia.

6 On the other side of it, on the hyperopes that
7 have these small eyes, you are going to have a certain
8 number of people that have enophthalmus [?] and other things
9 in crowded chambers. They are technically more difficult to
10 work with, and if you are doing it on young people, you have
11 got a more dense, dangerous vitreous if you happen to drop a
12 nucleus or something else in the process of the procedure.

13 Again, it gets back to our discussion yesterday of
14 outliers. This is where a thing where it can generally be
15 quite safe and effective, but the complications are so
16 devastating for the people that they occur to, that you have
17 to approach it with significant caution.

18 The issues involved with doing an intraocular
19 procedure of that type versus a phakic intraocular lens are
20 very different. You have to worry about uveitis, long term
21 endothelial cell loss, cataractogenesis, the whole concept
22 of removing a phakic intraocular lens, and differences in
23 lens design about how easy they are to move, increased
24 endothelial cell loss there, extra manipulation, then, doing
25 the cataract procedure and putting a lens implant in, a

1 double shot on exposure for cystoid macular edema from two
2 separate procedures, and so on, I think these two things
3 should be separate.

4 DR. PULIDO: I think what we are showing is our
5 bias, and we have strayed from the initial question, which
6 is does this document reflect a reasonable approach if one
7 is to do a study, of looking at the things that need to be
8 looked at. Believe me, I hate them as much as you all do,
9 because I have to deal with the problems afterwards, but,
10 you know, they look at, under adverse events, they do look
11 at pupillary block, they do look at retinal detachment rate,
12 they do look at endophthalmitis, they do look at uveitis, so
13 this document is a reasonable working document for these
14 people to try to develop a study to prove to us that this
15 isn't a bad thing, and, you know, we have to separate
16 ourselves out from the bias that we all are coming in with
17 that it is a bad thing, we have got to develop a different
18 document. This document is not a bad document.

19 DR. STARK: I am basing mine on scientific fact,
20 my statements--just kidding, a little bias there. I guess
21 it was the 20/40 that got me. I wouldn't mind seeing a
22 company come in and apply for the extremes of myopia and
23 hyperopia where contact lens failure and people over 12
24 diopters, where LASIK is not a good procedure maybe, or over
25 5 to 6 diopters of hyperopia, and so I think that is a

1 reasonable place to start.

2 The numbers are small, it is going to be hard to
3 get 300 in those groups, but that is an area where if they
4 are contact lens failures and feel disabled by their
5 glasses, that it should be started.

6 I would not want to be associated with an FDA
7 study, approved study, that allowed people with 20/40 vision
8 to get either a phakic IOL or a clear lens extraction.

9 DR. McCULLEY: You are talking about 20/40
10 uncorrected.

11 DR. STARK: Uncorrected.

12 DR. McCULLEY: One of the things we are dealing
13 with here is with the phakic IOLs we are dealing with
14 unknown complications and rates. With clear lens extraction
15 and IOL insertion, we are, to a large degree, dealing with
16 somewhat known complication rates, somewhat.

17 DR. PULIDO: I disagree. I think there is as
18 pretty high rate of retinal detachments in the phakic
19 refractive IOL situation, too. I mean there is one article
20 I found that was 5.8 percent versus possibly 2 percent.

21 I think the problem that I have with this
22 document, like Walter was saying, was the level at what you
23 are starting with. Maybe the level for phakic would be a
24 little less than that for clear lens, but overall I am very
25 concerned about doing either procedure for patients that

1 have better than, let's say, minus 7 diopters of myopia.

2 DR. McCULLEY: Less than minus 7.

3 DR. PULIDO: Less than minus 7, yes.

4 DR. McCULLEY: Dr. Bullimore.

5 DR. BULLIMORE: Mr. Chairman, I don't think we are
6 going to reach any immediate resolution on this. I mean if
7 I were a sponsor or potential sponsor sitting in the
8 audience, I would be scared off by now for clear lens
9 extraction because clearly, there is sufficient concern
10 about the procedure that it is not going to be smooth
11 sailing to get a PMA approved by the kind of people that sit
12 on this panel.

13 I mean that is really what we are saying. We are
14 hypothesizing about what the adverse event and complication
15 rate is likely to be and saying how uncomfortable we are
16 about that rather than concentrating on what we should be
17 measuring here.

18 Can we just table that part of the discussion and
19 move on with the guidelines, and then come back to it again?

20 DR. McCULLEY: That's fine with me. The question
21 I have, I guess it is twofold, are we prepared to discuss
22 the clear lens extraction, IOL insertion for refractive
23 corrective purposes, and if we are prepared to do that, do
24 we think that today, then, the only way we could do it today
25 would be if we would be making recommendations relative to

1 the existing--or to do it in any depth--to the existing
2 phakic implants.

3 DR. ROSENTHAL: Dr. McCulley, may I usurp your
4 position--

5 DR. McCULLEY: Absolutely.

6 DR. ROSENTHAL: --and make some sort of a
7 decision. I think the issue is so complicated that it
8 requires another meeting. What we would like to do is get a
9 refractive guidance document out, at least for phakic IOLs
10 right now. We know the sense of the panel's feelings,
11 divergent from one to tack it onto IOL, to leave it in here,
12 but I think, you know, the issue is important enough that we
13 may bring it back to you as a specific topic to be discussed
14 at a future time.

15 DR. McCULLEY: That is exactly where I think I
16 was. You usurped well, and where Dr. Bullimore wanted us to
17 be, as well.

18 So, we will recommend that we not deal with these
19 issues directly today. I think we would all agree that it
20 is of sufficient importance that we would welcome having it
21 come back to panel for input, but as a separate, specific
22 topic, and then you can decide whether you have a separate
23 document or incorporate it with another one.

24 MS. BOULWARE: We would certainly be happy to hear
25 any brief comments if there are areas that would be

1 significantly different, that would give direction to go.

2 DR. McCULLEY: Some of those have come up. We can
3 start throwing them out. The retinal complication rate.

4 MS. BOULWARE: Is that more often evaluations you
5 would want to see or is there a separate endpoint you would
6 like to see?

7 DR. McCULLEY: With all due respect, I don't think
8 we want to go into great detail. If you want things thrown
9 out as areas to consider, I think we can and should do that,
10 but I don't think we should go into any greater detail. I
11 don't think we would do you a service, and we are going to
12 paralyze the rest of our discussions.

13 MS. BOULWARE: Thank you.

14 DR. McCULLEY: There is the loss of accommodation,
15 there is the retinal detachment or the retinal complication
16 issue, what else?

17 DR. BULLIMORE: I think what Ashley is trying to
18 do is to get you to say what you would do differently, and
19 you are very skillfully, I might add, avoiding answering her
20 questions--

21 DR. McCULLEY: I am.

22 DR. BULLIMORE: --in case you would agree with my
23 distinguished colleague to your left. We understand they
24 are different devices, but if the types of complications and
25 adverse events are sufficiently different that they require

1 a different protocol, say so.

2 DR. McCULLEY: Ashley, we are not going to do
3 that. He usurped. We are going to stay with his usurption.

4 DR. ROSENTHAL: Ashley has worked so hard on this
5 that I don't want us to get bogged down into this
6 discussion. I would like to leave it right now. I think we
7 can think up most of the issues.

8 MS. BOULWARE: Consider it left.

9 DR. ROSENTHAL: But maybe I am wrong, I am being
10 usurped by my staff.

11 DR. McCULLEY: I have heard in the wind a
12 suggestion I like very much. I would like for us, unless
13 there is tremendous and majority panel disagreement, I would
14 like for us to leave the issue of clear lens extraction and
15 implantation at this point.

16 Is there disagreement to that? Dr. Yaross.

17 DR. YAROSS: I would just like to bring one minor
18 point to the panel's attention before we move on. This
19 panel has looked at some other technologies that were being
20 performed under the practice of medicine and felt that there
21 was benefit in bringing them in through the FDA process in
22 order to adequately describe to the public and to the
23 patient population the risks and benefits.

24 So, I would suggest that that same consideration
25 be given to refractive lensectomy, which we do know is being

1 performed as practice of medicine.

2 DR. McCULLEY: I don't think you are disagreeing
3 with what we said, that we think it is important, it should
4 come back, but we are not going to proceed with our
5 discussion today.

6 DR. YAROSS: That is fair.

7 DR. McCULLEY: Okay. Any other definite strong
8 opinions?

9 Okay. Let's go on then to your other questions,
10 which next come under the heading of endothelial cell
11 counts.

12 MS. BOULWARE: Yes. As I described earlier, we
13 propose a substudy of 200 subjects with cell counts measured
14 preoperatively and at 3 or 6 months, 1, 2, and 3 years. The
15 purpose of the substudy is to demonstrate the rate of
16 surgical loss, which would be pre-op to 3 or pre-op to 6
17 months, sponsor's choice, and also the rate of chronic loss
18 of endothelial cells over time.

19 To begin with, I just want to touch on the
20 surgical loss. We suggested a maximum rate of surgical loss
21 of 10 percent. Your guidance to us in the past has said
22 that this a reasonable target. We wanted just to confirm
23 that this is still a reasonable target for surgical loss.

24 DR. McCULLEY: Dr. Grimmett.

25 DR. GRIMMETT: I believe that the 10 percent

1 figure is reasonable for the initial insult, yes.

2 DR. McCULLEY: Is there disagreement to that?

3 None. Dr. Pulido.

4 DR. PULIDO: What is the reasonable target for
5 chronic?

6 MS. BOULWARE: That is next slide here.

7 [Slide.]

8 A rather lengthy slide, but basically, what it
9 says is assuming a standard deviation of 5 percent, which
10 was taken from a collection of literature article, a sample
11 size of 200 subjects should allow the detection of a rate of
12 chronic loss greater than 1.5 percent per year.

13 Based on also some of the literature information,
14 we have estimated that a patient who receives a refractive
15 implant at age 21, has a 10 percent loss due to surgery and
16 then has a 1.5 percent per year chronic loss, will still
17 have 1,000 cells until approximately age 88.

18 So, given this, is the rate of 1.5 percent per
19 year a reasonable target?

20 DR. McCULLEY: Dr. Pulido

21 DR. PULIDO: The problem, and I would like my
22 corneal colleagues to answer that, is if this is a 3-year
23 study, you are going to have at 1.5 percent per year, a 4.5
24 percent difference, and from my being on the panel before,
25 4.5 percent is within the error of the measurements, so is

1 this reasonable to just do a 3-year study?

2 MS. BOULWARE: If I might address Dr. Pulido's
3 question, the statistics not only take into account the fact
4 that there are four measurements, either 3 or 6 months, 1,
5 2, and 3 years, and we are also recommending that repeated
6 measurements be taken, so two measurements would be taken at
7 each visit, which would reduce the variability of the method
8 and would allow 200 subjects to be adequate to detect the
9 1.5 percent rate of loss, but it does require those four
10 measurement periods over the 3-year study, and having
11 repeated measurements, having two measurements at each exam,
12 which is not an onerous thing to do, we have been told, gets
13 you there.

14 DR. McCULLEY: Dr. Bullimore.

15 DR. BULLIMORE: Just to express confidence, I have
16 confidence in these numbers, so they are reasonable. One
17 thing that should be noted throughout this guidance
18 document, wherever you are talking about numbers of cells, I
19 think what you mean is cell density, and cells should be
20 changed to cells per millimeter squared.

21 MS. BOULWARE: You are exactly correct. Thank
22 you.

23 DR. McCULLEY: Dr. Grimmett.

24 DR. GRIMMETT: In follow-up to Dr. Pulido's
25 comments, I believe in January of '99, at a prior panel

1 meeting we discussed normal and cell loss rates per year,
2 and please correct me if I am remembering this incorrectly.
3 My memory is fuzzy on these. But I believe normal rates for
4 unoperated eyes are 0.6 percent per year, and I believe
5 there was a figure thrown out that after cataract surgery,
6 and I am pretty sure that the age range was older, it was
7 2.4 percent per year.

8 Given those rates, I believe and agree with Dr.
9 Bullimore that these figures are reasonable up here. If
10 putting a lens in is in accordance with what we know about
11 status post-cataract surgery, a threshold of 1.5 should
12 catch that higher rate. So, I agree with 1.5 percent.

13 DR. McCULLEY: Other comments? Okay. Your next
14 question.

15 MS. BOULWARE: We have recommended that for
16 corneal and anterior chamber refractive implants, that both
17 central and peripheral counts should be taken, however, we
18 would like your recommendation for the location of the
19 peripheral counts, whether that be 3 millimeters from center
20 or directly over the implant, if it is a corneal implant.
21 We would like some feedback from you on this topic.

22 DR. McCULLEY: Thoughts? Dr. Sugar.

23 DR. SUGAR: I don't have the exact location, but
24 Hank Edelhouser had a posterior this year, and had a report,
25 I think, at the Academy last year, that was expanded,

1 showing that the endothelial cell density is actually
2 greatest at the knee, in the mid-periphery, and I don't know
3 if that was 3.5 millimeters from the center or exactly what,
4 but I think that that could be readily looked up, Hank
5 Edelhouser at Emory.

6 MS. BOULWARE: Thank you.

7 DR. SUGAR: I guess the reason it would be
8 appropriate, I would assume, to look at that area of
9 greatest density, as well as the central cornea.

10 DR. McCULLEY: You brought up another issue,
11 though, that was related to the lens in the periphery.

12 Dr. Grimmett.

13 DR. GRIMMETT: Dr. Edelhouser was previously
14 commenting at a panel meeting that the further out you go,
15 it does become more difficult to image these cells
16 accurately, and I believe they are using a Conal endothelial
17 machine, and as we all know, clinically, it does become more
18 difficult doing that.

19 DR. McCULLEY: Rick.

20 DR. FERRIS: I am not sure I understood what Dr.
21 Grimmett said earlier. Did you say that the rate of cell
22 loss after cataract extraction was 2.4? So, that would be
23 more than this 1.5 threshold. So, if this procedure was the
24 same as cataract surgery, this panel would then think that
25 that is unacceptable?

1 DR. GRIMMETT: No, I didn't make a determination
2 about whether it is acceptable or not. If we know that
3 implanting an intraocular lens in that age group, whatever
4 that data was, was 2.4 percent per year, and if this newer
5 procedure had a similar rate, which it may, it may not, if
6 it does, setting up a study that would have a threshold of
7 1.5 may be able to catch what we are sort of expecting from
8 prior data. Whether it is acceptable or not, I don't know.

9 MS. BOULWARE: You might be interested to know
10 that if you had a rate of 2.5 percent per year, and started
11 out at 21, receiving this implant under the same condition,
12 you would be down to 1,000 cells by the time you reach 60.

13 DR. FERRIS: I figured that out all by myself, and
14 it is pretty scary.

15 MS. BOULWARE: Which is why we wanted to set the
16 threshold below that.

17 DR. McCULLEY: The acceptable threshold.

18 MS. BOULWARE: The threshold to be detected. We
19 would seek panel guidance at the time of the PMA application
20 as to what rate that had been demonstrated was acceptable.

21 DR. McCULLEY: Dr. Sugar.

22 DR. SUGAR: Those figures, I think from Bill
23 Bourne, they were 10-year follow-up of cataract extraction
24 patients, and probably that means their surgery was done 14
25 or more years ago, so it is not comparable, and we need

1 actually concurrent data on cataract patients.

2 DR. STARK: I think the other point is that the
3 three-year follow-up isn't going to pick this up. Are you
4 requiring 5- and 10-year follow-up?

5 MS. BOULWARE: We are requiring 3-year follow-up
6 before the submission of a marketing application. If a PMA
7 came to the panel, certainly one of your recommendations may
8 be long term follow-up, endothelial cell count, but before
9 the PMA comes in, we are asking for 3 years of follow-up.

10 DR. McCULLEY: Leo.

11 DR. MAGUIRE: I just want to make one comment on
12 the Mayo data. It was extracapsular, cataract extraction,
13 but the rates of endothelial cell loss in that study were
14 among the lowest ever reported for extracapsular, cataract
15 extraction, so they may, in fact, apply.

16 DR. McCULLEY: Dr. Matoba.

17 DR. MATOBA: I agree with the thresholds that you
18 proposed for the study, but I think that it might be useful
19 to have them stratify some of the results by age because I
20 think it is conceivable that older patients will have a
21 greater loss rate than younger patients, even if they
22 undergo the same procedure and have the same levels or
23 comparable levels of endothelial cells pre-op.

24 DR. McCULLEY: Other comments? Then, your next
25 question.

1 MS. BOULWARE: For the analysis of endothelial
2 cell counts, we have recommended that sponsors look at both
3 the mean rate of cell loss over time, which is what we have
4 just been talking about, calculated via a paired analysis,
5 and then also look at a frequency analysis examining the
6 percentage of subjects who lose greater than 10 percent of
7 cells between Month 3, or Month 6, and Month 36 of the
8 three-year exam.

9 Are you in agreement with these recommendations?
10 Are these additional analyses that should be performed? I
11 assume from your previous discussion that you agree that the
12 first analysis is valid. I guess I am asking, is the
13 frequency analysis worthwhile, and is 10 percent a decent
14 target to look at?

15 DR. McCULLEY: Leo.

16 DR. MAGUIRE: Since I am the outlier advocate at
17 this meeting, I think it is a good place to start. I think
18 the more important concept is to identify outliers and the
19 degree variability that you see in this, because that is
20 going to have significant public health implications. If we
21 have a minus 15 myope, that ends up needing a penetrating
22 keratoplasty, as well as a cataract extraction because of
23 endothelial decompensation, even if that happens once in a
24 while, that needs to be taken into consideration.

25 DR. McCULLEY: Other comments?

1 MS. BOULWARE: Moving on to cataractogenesis, we
2 recommended that the crystalline lens be evaluated both
3 preoperatively and at each of the postoperative visits using
4 a standardized grading system and photographs.

5 Do you agree that the LOCS III and Oxford grading
6 systems are adequate for this evaluation? Would you
7 recommend other grading systems or have other additional
8 recommendations about this evaluation?

9 DR. McCULLEY: Dr. Bullimore.

10 DR. BULLIMORE: I would add the Beaver Dam eye
11 study/age-related eye disease study, whatever it is called,
12 system to that list.

13 DR. McCULLEY: Leo.

14 DR. MAGUIRE: I would also suggest that at a
15 minimum, the FDA investigate over the next few years, wave-
16 front aberration, that aberrometers be looked at. There is
17 good information coming out of Japan now on the increase in
18 higher order aberrations in the lens over time, and I think,
19 with that baseline data in the population started, we might
20 be able to compare what we see in the phakic intraocular
21 lens with that, and that may give us potentially a more
22 sensitive indicator.

23 I am not saying every place should do that, but
24 maybe similar to what we are doing with endothelial cell
25 counts here, at least one of two sites be identified as

1 people to do a substudy on wave-front aberration to see if
2 we can detect changes in the optical function of the lens at
3 an earlier stage than is possible by standard physical
4 examination because we all know from refractive surgery that
5 a cornea can look good after surgery, and still show optical
6 aberration, and certainly the same thing may apply to the
7 crystalline lens.

8 DR. McCULLEY: Rick.

9 DR. STARK: I think if you are going to use the
10 systems as a surrogate for clinically significant lens
11 opacity, that it is almost a requirement that you have sort
12 of control group, because you are going to find some sort of
13 progression on these scales plus their error, and these are
14 actually fairly noisy systems.

15 I don't know how a panel would be able to
16 interpret the 1 and 2-year and 3-year event rates because of
17 both the noise and the natural progression of lens opacities
18 which isn't very great in a younger population, but if some
19 of these patients are older, it will be.

20 DR. McCULLEY: Dr. Pulido.

21 DR. PULIDO: I agree with Dr. Ferris, and that
22 leads me to one of the problems that I have with the
23 document, among many. The other was the level of refractive
24 error that this should be allowed for, but under bilateral
25 implantation, it says, "At the time that expansion to Phase

1 III is approved, sponsors may wish to allow implantation of
2 the fellow eye under the following conditions: no adverse
3 events in the initially implanted eye with a waiting period
4 of 90 days between eyes."

5 That is only three months, and it doesn't give a
6 lot of time to look at adverse events, and it doesn't allow
7 for using the fellow eye as a control.

8 MS. BOULWARE: Our particular difficulty with the
9 bilateral implantation issue has been that we have been
10 successfully able to encourage sponsors to enroll at least
11 the beginning subjects that are contact lens tolerant,
12 however, when the studies are opened up, once they have done
13 the first 50 and have six months follow-up, we allow them to
14 move to Phase III assuming there are no problems, and
15 usually the study is 3- or 400 patients.

16 A good many of these patients are going to be
17 contact lens intolerant and will have significant
18 anisotropia. If you correct one eye, especially if they are
19 minus 8, minus 10, minus 12 myope, and won't have anything
20 else in the fellow eye, and we felt that at the time that we
21 had at least some limited data that, with informed consent
22 that specifically lays out the risk of bilateral
23 implantation, it would be appropriate to allow that if the
24 sponsor wanted to allow it in their protocol, but to require
25 that a year or two years worth of follow-up be completed

1 before the fellow eye could be done, sponsors have told us
2 that it would be very difficult to enroll patients in this
3 study.

4 DR. PULIDO: How does the panel feel about a
5 situation where after only 50 eyes with six-month follow-up
6 only, they will allow bilateral implantation?

7 DR. McCULLEY: Dr. Weiss.

8 DR. WEISS: I think a lot of this speaks to
9 Question 3(c), and there are other refractive procedures
10 available, and if we are talking about patients who are
11 above minus 12, minus 15, they are a special subset, for
12 those who are less than that, they could easily be contact
13 lens intolerant, but have LASIK on the other eye.

14 That also would allow for a better study and an
15 internal control to see the rate of cataract formation in
16 the LASIK eye versus the rate of cataract formation in the
17 implantable eye.

18 So, I would agree with Dr. Pulido, and I think it
19 doesn't have to be an excessive burden on the patient or the
20 sponsor, because they could have a different refractive
21 procedure in the second eye.

22 DR. McCULLEY: What order would you recommend
23 performing the refractive procedures?

24 DR. WEISS: I don't know if you would have to
25 determine that. You might allow patients to enter the study

1 who have had LASIK in one eye, and you might allow them to
2 go the other direction, but actually, I don't really have
3 any thoughts on that initially, which direction must you go
4 in.

5 DR. McCULLEY: Dr. Coleman.

6 DR. COLEMAN: Yes. I wanted to go back to 3(a).
7 We didn't finish talking about the cataract. We moved from
8 3(a) to 3(c), but I just wanted to go back and recommend
9 that they just put a standardized cataract grading system,
10 because different individuals are using--some people use the
11 LOCS III, some people use the Oxford, Wilmer has theirs,
12 Beaver Dam has theirs--instead of having a specific one,
13 just having one that has reproducibility and repeatability
14 data available.

15 MS. BOULWARE: So simply just say that a
16 standardized method be used at all the sites. We just
17 wanted to recommend some because some of the sponsors that
18 are getting into this don't have a lot of experience with
19 it, and come to us to ask us, well, what do you recommend,
20 and it is helpful if we can put literature references in the
21 document to point people in the right direction.

22 DR. BULLIMORE: The reason I was adding Beaver Dam
23 in particular is that what would be nice, given Dr. Pulido's
24 concern about--no, it was Dr. Ferris' concern about lack of
25 controls with Beaver Dam and I think with LOCS III, there

1 may be historical data on cataract incidence and
2 progression, maybe in a slightly older population, but
3 something against which a future panel could compare data.

4 DR. PULIDO: It's an older population, and it is
5 not the myopic population, so it doesn't hold to this.

6 DR. BULLIMORE: But in reference to that, I think
7 asking people to be unilaterally corrected for a substantial
8 period of time or corrected in the other way, with LASIK, is
9 just fraught with difficulties for the sponsor, and in an
10 ideal world, we do that, but I just don't think that is
11 practical and reasonable.

12 MS. BOULWARE: There also may be effects on, for
13 example, visual symptom questionnaire data if the patients
14 have varying refractive surgery in the other eye. You may
15 not be able to discern, if patients have difficulty driving,
16 it may be difficult to discern whether it is due to the
17 refractive implant or due to the LASIK, that got glare halos
18 or something, and were at minus 10.

19 DR. McCULLEY: Dr. Yaross.

20 DR. YAROSS: In addition, regarding the bilateral
21 question, often we find in clinical studies, if the
22 physician really thinks that this person is an appropriate
23 LASIK candidate, they may choose to do LASIK, and put into
24 the studies the people for whom they feel it is best suited,
25 so I think, in addition to the confounding issues that Ms.

1 Boulware has brought, I think that there are real practical
2 problems in saying these patients cannot have this modality
3 in their second eye until after it is approved. I don't
4 think that is something that the investigators would find
5 acceptable.

6 DR. McCULLEY: Rick.

7 DR. FERRIS: I don't think we need to require how
8 they do this study design. I still believe that they need
9 some sort of concurrent control group, whether they have
10 LASIK, whether they are myopes that aren't having LASIK, and
11 the better that they can do to have the control group
12 equivalent, the more able the panel is going to be able to
13 assess whatever kind of lens opacity progression that we
14 see, because without the control group, actually, I think it
15 is going to be worse for them if there isn't a control
16 group.

17 MS. BOULWARE: So, you are recommending a control
18 group to look at simply the cataractogenesis progression of
19 lens opacities in an age-matched control group?

20 DR. FERRIS: Or fellow eye. I mean it is up to
21 them to come up with an appropriate control group, but for
22 this, unlike the endothelial cell density where you were
23 using a standard that they had to compare against, for this
24 they need some sort of control group, and I think the panel
25 might recognize the difficulty of using a fellow eye, and I

1 don't think we should necessarily require that. If they
2 want to use that, that is fine, but they should be given the
3 freedom to come up with the best control group that they
4 can, recognizing that they may be criticized. In fact, for
5 sure they will be criticized by somebody, but they can do
6 the best they can.

7 MS. BOULWARE: Dr. Ferris, you are absolutely
8 correct in that it is very difficult to set a target or a
9 baseline as we have attempted to for the endothelial cell
10 count, but the problem comes back with the control group
11 because in order to tell the company what size control group
12 they need, you have to tell them what kind of difference are
13 you looking for, are you trying to make an equivalency
14 determination, and with what precision are you making an
15 equivalency determination, and I think that will vary for
16 each of these grading systems, and the differences in the
17 grading systems, what is the significant difference, is it a
18 change from plus 1 to a plus 2?

19 We could certainly use your help, if that is your
20 recommendation.

21 DR. McCULLEY: Are we not looking for an
22 equivalency comparison?

23 MS. BOULWARE: Ideally, you would like to see no
24 lens change between pre-op the 3-year endpoint. We were
25 hoping that should there be something greater than zero,

1 that at the time the document came before the panel, that
2 that would be an item we would get your guidance on.

3 If there is a rate of 1 percent of some lens
4 opacity appearing between pre-op and post-op, is that too
5 much? If it's a rate of 5 percent or if it's a rate of 1
6 percent of significant lens opacity and a 5 percent rate of
7 any lens change, is that acceptable?

8 We don't have a good feel at the moment for what
9 is an acceptable rate of lens change, be it a clinically
10 significant or a not clinically significant lens opacity.
11 So, it is a very difficult issue.

12 DR. McCULLEY: Do you want to address that, Joel?

13 DR. SUGAR: Partly. I don't know that we can
14 answer that, but there is a definite literature that there
15 is an increased incidence of nuclear sclerotic cataract in
16 high myopes, so that without a control, you would expect, in
17 the operated eye, to see progression of lens change over
18 time. If you are talking about lens change not specific,
19 there is going to be progression of lens change over time in
20 any population, but more so in the nuclear sclerotic
21 cataracts in myopes.

22 I think that the European literature suggested
23 that lens changes are anterior cortical, anterior
24 subcapsular in the people who have had posterior chamber
25 phakic implants. So, the specific type needs to be looked

1 at, and I think there has to be a control if you are going
2 to look at nuclear sclerotic cataracts.

3 What is acceptable is partly a judgment call. How
4 bad is it to be a minus 20 myope and how much risk are you
5 willing to take, and are you willing to take the risk of
6 putting the implant in, having them get a cataract, take the
7 cataract out, or should you upfront take the clear lens out
8 and put in an implant, and you may end up in the same place
9 either way.

10 MS. BOULWARE: Without having any idea of what is
11 acceptable, we can't set the size of the control group.

12 DR. SUGAR: I understand in terms or you are
13 prospectively trying to determine numbers, but I don't know
14 what the answer is.

15 MS. BOULWARE: Nor do we.

16 DR. SUGAR: If you pick a number out of the air, I
17 would say 5 percent is certainly a lot, 5 percent visually
18 significant cataract in the operative population.

19 DR. McCULLEY: Rick.

20 DR. FERRIS: Just the grading, regrading of these
21 lens opacities, a one-step change on this scale is going to
22 be about 5 percent. That is why I said the control group is
23 actually something that the company needs to protect them,
24 otherwise, it is going to look like they have 5 percent
25 progression if, in fact, they had nothing.

1 DR. McCULLEY: Dr. Weiss.

2 DR. WEISS: I would just go back to the suggestion
3 of an internal control. We can just make suggestions here,
4 the company can decide to do whatever they want, but
5 obviously, if you have an internal control, you take out a
6 lot of these questions, and you have a much stronger study,
7 and if they opt not to do that because of other
8 considerations, then, that is up to them. But it makes it a
9 much weaker study.

10 DR. McCULLEY: Other comments? Do you need
11 anything more there?

12 MS. BOULWARE: No.

13 DR. McCULLEY: Go on to the next question.

14 MS. BOULWARE: I will move on. We have
15 recommended two analyses of this information. One is the
16 percentage of subjects with lens changes, and that would be
17 any change in the appearance of the lens with stratification
18 by the type of change, and the percentage of subjects with
19 clinically significant lens opacities, and our working
20 definition is opacities leading to the loss greater than 2
21 lines of BSCVA with glare as compared to preoperative levels
22 that have been adjusted for magnification or minification
23 effects.

24 Our question to you is: Do you agree with these
25 recommendations? Are there additional analyses we need to

1 do?

2 DR. SUGAR: When you say with glare, you are
3 talking about they dropped 2 lines on the day of the
4 examination or with glare they are 2 lines worse than they
5 were preoperatively?

6 MS. BOULWARE: With glare, they are 2 lines worse
7 than they were preoperatively.

8 DR. SUGAR: So, then I would say with or without
9 glare, either way.

10 MS. BOULWARE: Yes. If you are 2 lines worse
11 without glare than with glare, you will be more than 2 lines
12 worse. That is why we wrote it that way, but you are
13 correct.

14 DR. SUGAR: No, no. There are people who get
15 better with a smaller pupil.

16 DR. McCULLEY: Other comments? Rich.

17 DR. FERRIS: I understand the concept, but I would
18 remain concerned that the 3-year rate of a level of vision
19 loss that, in this country, is probably getting most people
20 cataract surgery, or at least consideration of cataract
21 surgery. Somehow built into this, as was mentioned before,
22 is going to have to be some sort of long-term follow-up
23 because you could easily pass this hurdle and still have an
24 epidemic down the road.

25 DR. McCULLEY: Other comments? Your next

1 question.

2 MS. BOULWARE: I will move to 3(c) here, which has
3 to do with the age limits that we had placed in the
4 inclusion criteria, to point out that there was a difference
5 for the hyperopes versus the myopes, because the hyperopes
6 tend to be of an average older age when they become
7 symptomatic and seek out this surgery, and therefore, there
8 is a smaller number of them available if you limit the
9 inclusion criteria to 50, and we would like to hear what
10 your comments are on this.

11 DR. STARK: I personally would not set the upper
12 age limit because you might want to look at those patients.
13 You know, 60-year-old patients sometimes don't have a
14 cataract. They may want this technology, and it may be that
15 they all develop a cataract within a year, and so you would
16 get some information. It could be age stratified later on.

17 DR. FERRIS: I would like to say I am a lot less
18 worried about the 60- and 70- and 80-year-olds who are at
19 risk of having their lens out anyway, and who don't have to
20 worry about the 20-, and 40-, and 50-year follow-up of
21 having this thing in their eye.

22 So, I am not sure I care about an upper age range.

23 DR. PULIDO: That is true if there is a control,
24 but otherwise, if there is no control, then, the company
25 could say that's just the natural progression of their

1 cataract, so I agree with you, Walter. Again, it emphasizes
2 the importance of some kind of control in this study.

3 DR. STARK: I may have a little concern with the
4 hyperopes, because I think hyperopes tend to let their--they
5 get a thicker lens, because they get less hyperopia, at
6 times they are getting a little cataract, and it is my
7 impression, I mean that is what shallows their chamber, plus
8 they start off with a more shallow chamber, so as you pick
9 older hyperopes, you are going to run a greater risk of
10 pushing this iris up against the cornea, of if the lens
11 rotates and blocks an iridectomy, getting a pupillary block,
12 so there is a risk in doing older hyperopes.

13 DR. MAGUIRE: I think you can make a case for
14 having separate studies for younger and older patients,
15 because what you want to know is, is what groups does it
16 apply to, and it is reasonable to address questions like
17 what Dr. Stark is talking about in the hyperopes, and it is
18 also important in the high myopes to ask is the rate of
19 cataract progression more rapid in people who have phakic
20 intraocular lenses placed at a later stage in life, because
21 it is still going to be a more complex procedure to remove
22 the lens, do the cataract extraction, and so on.

23 There is a separate set of risk factors in younger
24 people that we have already discussed, things having to do
25 with more thickened vitreous, and so on. I am not sure if

1 it is better to group them all in one or to consider looking
2 at two different age groups, or if we are going to stratify,
3 at least make sure that the study population is large enough
4 that we don't end up with the same problems we have when we
5 are evaluating the refractive procedures, and we don't have
6 enough numbers in the higher levels of stratification to
7 make good statistical decisions on what is going on.

8 MS. BOULWARE: That may be difficult if you open
9 it up, for example, in the hyperopes and the older patients,
10 you may not get very many over 60 who don't have a cataract,
11 and want to have a correction done.

12 I was also going to ask if you would want the age
13 stratified by decade or is there some median age where you
14 would want above and below, and is it different for
15 hyperopes versus myopes.

16 DR. MAGUIRE: Those things are obviously
17 arbitrary, but you could obviously think of either
18 stratifying by decade or by 20-year periods, people aged 20
19 to 40, 40 to 60, or something like that.

20 I mean that can be worked out, but I certainly
21 think that that is worthwhile. Others may disagree.

22 DR. McCULLEY: I think 20-year stratification is
23 probably too broad.

24 Yes, Mark.

25 DR. BULLIMORE: I like the idea of having an upper

1 limit. I am not sure whether 50 is where I would put it,
2 but I think having an upper limit makes sense. If a sponsor
3 chooses not to have a control group, it limits--it may not
4 eliminate--but it limits the possibility of confounding
5 factors of age-related cataract formation rather than the
6 device.

7 I would also like to float the idea about having a
8 lower limit, as well. I saw the age 21 in the guidelines
9 here. How do people feel about moving that up to 30, given
10 the fact that we really don't have good data on endothelium
11 at the moment? Keeping the very young out of this study
12 might be prudent. I mean talking about people running out
13 of endothelium or running out of viable endothelium at the
14 age of 60, I think having entry criteria at the moment or
15 initially as 30 and above.

16 DR. FERRIS: Or 60? I am being facetious.

17 DR. McCULLEY: Dr. Jurkus.

18 DR. JURKUS: I would agree with Dr. Bullimore that
19 at age 30, the hyperope probably will not have as much
20 accommodation left, so will be easier to find, and then also
21 having the upper age limit will definitely give us an idea
22 of which group we are looking at.

23 DR. BULLIMORE: I think it is important, though,
24 when we are thinking about these, that we remember we are
25 dealing with people with high refractive errors. I would

1 like to bring up the issue of range of eligibility, maybe
2 restricting this, if it is not already.

3 MS. BOULWARE: It has not been restricted. The
4 sponsor does have to address the risk-benefit in their risk
5 analysis they submit for their IDE application, but we have
6 not restricted the range in general for these devices.

7 DR. BULLIMORE: I think maybe we should.

8 DR. McCULLEY: This came up before about the
9 limits, you know, the lower limits that the panel thought
10 was appropriate. Is there a consensus among the panel that
11 there should be a lower limit?

12 DR. STARK: When and if these get approved, if we
13 limit it to 30 years, we will have no data between 20 and
14 30, and it will be an off-label use, so I would just as soon
15 try and get the data now.

16 DR. McCULLEY: If you look at a potential benefit,
17 the younger, active people being free of optical external
18 devices, the potential benefit to them might be the greatest
19 during that decade. I don't know that that is important or
20 not.

21 DR. STARK: Also, with the vitreous attachment
22 stronger, the risk may be greater, too, but we will
23 hopefully find that out with a well-designed study.

24 MS. BOULWARE: Just for the panel's information,
25 we are currently working on a proposal to take the aphakic

1 IOL indications down to 21 and older.

2 DR. McCULLEY: For people with cataracts.

3 MS. BOULWARE: Yes.

4 DR. FERRIS: So, they can finally get cataract
5 surgery.

6 MS. BOULWARE: Yes.

7 DR. McCULLEY: As if they haven't been getting it.
8 Are there any other comments on this last
9 question?

10 DR. SUGAR: I agree that there should be some
11 lower range, whether it is minus 10, minus 12, it should be
12 in that range because these are people who become outliers
13 in laser refractive surgery, and if they are contact lens
14 intolerant, are handicapped by their spectacles.

15 So, I think we should set either minus 10 or minus
16 12, or that range, no maximum for the myopes. For the
17 hyperopes, I think it should be in the range of 5 to 6 and
18 higher.

19 MS. BOULWARE: Should a sponsor want to
20 investigate a device to treat the lower amounts of myopia,
21 would they have to receive PMA approval for the higher
22 amounts of myopia or hyperopia before they could begin a
23 clinical study in the lower range?

24 DR. SUGAR: Yes, I think that that makes sense
25 especially when we are talking about substantial risks in

1 terms of cataractogenesis and endothelial changes, which
2 shouldn't be that much different between the minus 14 and a
3 minus 6, and if it turns out that there is this epidemic
4 caused by this procedure, I think at least we should have it
5 in a population where there hasn't been another good
6 refractive surgical treatment.

7 DR. McCULLEY: Let me stab at a philosophical
8 description of this, and that would be that we would prefer
9 seeing safety data where there are no alternatives that have
10 been shown to be safe before looking at safety and efficacy
11 in the range where we already have safety and efficacy data.

12 DR. PULIDO: Dr. McCulley, the only problem with
13 that is going back to a Phase I study, safety study, is 50
14 patients, 6 months. That is not enough. So, are you
15 saying, then, that you would allow, after six months, in
16 patients between minus 10 and greater, if they are looking
17 okay at 6 months, that you would let this go on to minus 1?

18 DR. McCULLEY: No. Actually, what I was implying
19 until we had safety and efficacy data after Phase III in
20 effect, not to bring the range down.

21 DR. PULIDO: So, it is more than just Phase I and
22 Phase III.

23 DR. McCULLEY: More than 6 months, it's 3 years.

24 DR. PULIDO: Three years for the whole group.

25 DR. McCULLEY: I was trying to state what I

1 thought I was sensing, and, yes, it would be not after the 6
2 months, that it would then drop to the lower range.

3 DR. STARK: Correct me if I am wrong, Jim, but I
4 think that they are already out for minus 8, aren't they, or
5 7.5?

6 MS. BOULWARE: That was going to be my comment,
7 that there are studies that are being performed now for
8 refractive implants well below the minus 7, minus 8, down to
9 minus 4, minus 5, I believe, on the myopia side, down to
10 maybe plus 2 or plus 3 on the hyperopia side, and, in fact,
11 we approved the Care Vision intacts for low levels of
12 myopia, so this document is intended to apply to all
13 refractive implants, not just phakic IOLs. This would be
14 corneal inlays.

15 DR. McCULLEY: I think we have been talking more
16 today about intraocular than anything. It has been the
17 position from which most of our statements have been made.

18 MS. BOULWARE: There are four or five IDE studies
19 that we expect will come to PMA, that will include both
20 these lower ranges, as well as patients 21 and older, that
21 will be coming to you.

22 DR. McCULLEY: Those things that you have already
23 done, then, you just need to state as facts, so we don't
24 beat ourselves to death about issues that have already been
25 decided.

1 DR. STARK: I would think it would behoove the
2 companies to not bring all their data in with a minus 4 or
3 5. I was surprised that they could put them in people with
4 as low a myopia as minus 4, and I don't know what the range
5 is now. I was surprised that it went down to minus 8 when
6 it got started, but the companies, I would think that the
7 companies may have trouble getting through this panel with
8 most of the patients concentrated in the minus 4 to minus 8
9 or 9 range, where there is already a safe and effective
10 alternative, to be approved.

11 DR. McCULLEY: Dr. Pulido.

12 DR. PULIDO: My concern also about having that
13 data for minus 4 and minus 8, we know that the greater the
14 myopia, the greater the chances of retinal detachment, and
15 we want to catch those patients with the greater chances of
16 retinal detachment.

17 So, if they show a low level of retinal detachment
18 from minus 4 to minus 8, that is not going to tell us a
19 whole heck of a lot. This is going to be problematic.

20 DR. YAROSS: Again, the risk-benefit ratio has to
21 be looked at in terms of the specific device modality.
22 Corneal implants, one has already been recommended for
23 approval by this panel in a low range, and therefore, found
24 to be reasonably safe and effective.

25 I don't think we should cast this guidance

1 document based on the concerns for what is perceived as the
2 riskiest form without due consideration to the fact that
3 others may be able to be shown to be safe and effective in a
4 broader context, in a broader population.

5 MS. BOULWARE: I think it is important to remember
6 that while there is certainly considerations during the
7 study, and informed consent issues, where there are other
8 safe and effective modalities for treatment, when a PMA is
9 submitted to the agency, we have to take that PMA on its
10 own, and in the absence of other products that are out there
11 when we make our safety and effectiveness determination, it
12 stands on the data that are in the application.

13 So, if a sponsor comes in to show that a device is
14 reasonable safe and effective, they don't have to be safer
15 or more effective than something that is already out there,
16 it is simply a safe and effective, reasonable assurance of
17 safety and effectiveness of that product based on that data,
18 and we cannot make comparisons in our evaluation.

19 DR. McCULLEY: Leo.

20 DR. MAGUIRE: For a lot of things, that makes
21 sense, but we know, let's say, from the radial keratotomy
22 experience, that was originally declared safe and effective,
23 and it turned out to be safe and effective over the short
24 term.

25 DR. McCULLEY: It was never approved.

1 DR. MAGUIRE: I am not saying FDA, but I am just
2 saying if you look at the literature. What I am saying is
3 the concern with this, because it is an intraocular
4 procedure is, is it going to be safe and effective over the
5 long term, and we have long-term data on other procedures,
6 and so it seems like you would want to stay at the higher
7 end.

8 DR. McCULLEY: That horse is already out of the
9 barn, so there is no point in us discussing that. So, let's
10 drop it, but please make clear to us in discussions what has
11 already been decided, that we should not be addressing, so
12 we don't address it. It is a waste of time and then it's
13 frustrating.

14 MS. BOULWARE: I agree.

15 DR. McCULLEY: Rick.

16 DR. FERRIS: It is now my understanding that there
17 may be three levels of these. One is the guidance document
18 that is already out there, about LASIK and other--would
19 these other ways of mucking about with the cornea without
20 actually getting into the eye, all fall under that guidance.

21 DR. McCULLEY: No, there is some mucking with the
22 implants in the cornea.

23 MS. BOULWARE: Not in that guidance document, no.

24 DR. McCULLEY: In a different guidance document,
25 in this guidance document.

1 DR. FERRIS: Well, that is the question that I am
2 trying to sort out and make sure I understand. Are we
3 saying that putting something inside the cornea is going to
4 have the same guidance as putting something inside the
5 anterior chamber, because it seems to me those are different
6 levels.

7 We backed away from the lensectomy because we said
8 that was a different level. In the anterior chamber, to me,
9 seems like a different level than something inside the
10 cornea, which may or may not have an effect on the
11 endothelial cells.

12 DR. McCULLEY: You are right, but we discussed the
13 corneal implants and intraocular implants in the past, so we
14 have covered some background there rather than opening a new
15 can of worms with the other, and they are very different.

16 Dr. Pulido.

17 DR. PULIDO: Jim, deja vu all over again. I
18 remember you mentioning at a previous meeting where they
19 were trying to lump corneal inlays with intraocular surgery,
20 that you did not, and emphatically said we don't want to
21 lump these two together, and yet now it seems like they have
22 both been lumped together.

23 DR. McCULLEY: That is what happens when you turn
24 your back. I think they have been put together, and they
25 are very different, and the risks are very different.

1 MS. BOULWARE: But the evaluations are very much
2 the same. The cataractogenesis evaluation may not be
3 applicable for corneal implants, but the evaluations in
4 terms of the endothelial cell counts are the same, the
5 evaluations for the visual acuity, predictability,
6 stability--

7 DR. McCULLEY: But the levels of myopia are
8 different that we would allow.

9 MS. BOULWARE: We had not set any limits on the--
10 that is why you see no difference between the corneal and
11 the intraocular type of implants.

12 DR. McCULLEY: This is kind of the same principle
13 of let's not get into things that have already been decided,
14 whether we like them or not.

15 Are there any other comments on this last
16 question? Ashley, do you need anything more on this last
17 question?

18 MS. BOULWARE: No, thank you.

19 DR. McCULLEY: Dr. Matoba.

20 DR. MATOBA: So, it has been decided that it is
21 all going to be under one guidance document, and we can't
22 ask for it to be undecided?

23 DR. McCULLEY: Corneal implants and intraocular
24 implants?

25 DR. MATOBA: Yes.

1 DR. McCULLEY: I don't think it would be of great
2 benefit to try to pull apart what has been put together. I
3 mean if they have managed to meld them together enough and
4 done the in-house work to do that, even though there are
5 differences that apparently have been taken into account and
6 are recognized, I don't think it would be beneficial to try
7 to go backwards now.

8 MS. BOULWARE: If Dr. Matoba has some specific
9 issues she would like to see separated out, we would
10 certainly be willing to take comments either now or some
11 other time to try to address those.

12 DR. STARK: That would be a perfect place for the
13 age issue. I would not want to see these phakic IOLs
14 approved for minus 2 to 6. I think the risk is higher than
15 LASIK, I believe, but the studies will show that, but we
16 need to do it where there is less of an alternative, safe
17 and effective alternative.

18 DR. McCULLEY: Walter, I think they have told us,
19 if I understood them correctly, that they are already
20 allowing intraocular implants below minus 6.

21 DR. ROSENTHAL: The panel gives recommendations,
22 and we have heard your recommendations.

23 DR. McCULLEY: We have to remember. We are asked
24 to advise and provide advice, recommendations on things that
25 the agency wishes to bring to us. They then choose to do