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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

Ninety-third Meeting

OPEN SESSION

Friday, October 23, 1998

9:15 a.m.

Lincoln Ballroom
Silver Spring Holiday Inn
Silver Spring, Maryland

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P R O C E E D I N G S

Call to Order

James P. McCulley, M.D., Interim Chair

DR. McCULLEY: I'd like to call to order the Ophthalmic Devices Panel meeting. this is an open session.

I would like to now turn the floor over to Sara Thornton, otherwise known as "Sally," for introductory remarks.

Introductory Remarks

Sara M. Thornton, Executive Secretary

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

Before we proceed with today's agenda, I have a few short announcements to make.

Messages for the Panel Members and FDA participants--information or anything you need--should be directed through Ms. Ann Marie Williams or Ms. Theresa Lewis who are just outside the room here at the registration table, or will be close by, in any case.

I'd like to ask anyone who is participating in the meeting as a Panel Member or a member of the public making comments into the microphone that you identify yourself speak clearly so that we can accurately record your comments.

And, at this time, I'd like to extend a special

1 welcome and introduce to the public the panel and the FDA
2 staff. Three panel participants who have recently joined
3 the advisory committee and are panel participants for the
4 first time: on my left, Dr. Michael Grimmett, Panel
5 Consultant, and he is Associate Professor of Ophthalmology
6 at the Bascom Palmer Eye Institute of the University of
7 Miami School of Medicine in Miami, Florida. He is a
8 specialist in corneal and external disease and a recognized
9 expert on the medical/legal/ethical issues associated with
10 refractive surgery.

11 Also on my left, Dr. Alice Matoba; she's and
12 Associate Professor Ophthalmology at the Baylor College of
13 Medicine in Houston, Texas, and specialist in corneal and
14 external disease and anterior segment surgery. She is
15 recognized for her presentations on many clinical aspects of
16 infectious corneal disease, contact lenses and corneal
17 transplants.

18 On my right, Dr. Ming Wang, Panel Consultant, is
19 an Assistant Professor of Ophthalmology and Visual Sciences
20 at the Vanderbilt University School of Medicine in
21 Nashville, Tennessee, and a corneal and external disease
22 specialist. She also holds a Ph.D. in physical chemistry
23 and has complete postdoctoral fellowships in laser
24 spectroscopy, molecular biology and ocular genetics. She is
25 currently researching laser refractive surgery and the

1 molecular biology of corneal wound healing.

2 To continue, I would like the rest of the panel
3 members to please introduce themselves, beginning with Dr.
4 Yaross.

5 DR. YAROSS: I'm Marcia Yaross, Director of
6 Regulatory Affairs at Allergan, and industry representative
7 to the panel.

8 DR. VAN METER: Woodford Van Meter, private
9 practice in Lexington, Kentucky.

10 DR. BRADLEY: Arthur Bradley, Associate Professor
11 of Visual Science and Optometry at Indiana University.

12 DR. MACSAI: Marian Macsai, Professor of
13 Ophthalmology, West Virginia University School of Medicine.

14 DR. JURKUS: Janice Jurkus, Professor of
15 Optometry, Illinois College of Optometry.

16 DR. BULLIMORE: Bob Bullimore, Assistant
17 Professor, the Ohio State University College of Optometry.

18 DR. SUGAR: Joel Sugar, Professor of
19 Ophthalmology, University of Illinois at Chicago.

20 DR. McCULLEY: Jim McCulley, Professor and
21 Chairman, Department of Ophthalmology, University of Texas,
22 Southwestern Medical School in Dallas.

23 DR. HIGGENBOTHAM: Eve Higgenbotham, Professor and
24 Chair, Department of Ophthalmology, University of Maryland
25 in Baltimore.

1 DR. PULIDO: Jose Pulido, Professor and Head,
2 Department of Ophthalmology, University of Illinois.

3 DR. BELIN: Michael Belin, Professor of
4 Ophthalmology, Albany Medical College.

5 DR. RUBIN: Gary Rubin, Associate Professor of
6 Ophthalmology, Wilmer Eye Institute, Johns Hopkins
7 University School of Medicine.

8 DR. FERRIS: Frederick Ferris, Director, Division
9 of Biometry and Epidemiology, National Eye Institute, NIH.

10 DR. ROSENTHAL: Ralph Rosenthal, Director,
11 Division of Ophthalmic Devices, Office of Device Evaluation,
12 Food and Drug Administration.

13 MS. THORNTON: Okay. I'd just like to make a note
14 for the record that Ms. Lynn Morris, our Consumer
15 Representative, has been called away and won't be attending
16 this session. And Dr. Walter Stark has notified us that he
17 will be late, but he will be here.

18 The notes on the agenda--I'd just like to remind
19 you that our mandated one hour for public hearing
20 presentation was split into two 30-minute periods yesterday
21 and today, and we'll proceed toward that in just a moment.

22 During the meeting, the presentation has built
23 into it opportunities for public comment on particular
24 issues recently under discussion. And the Chair, Dr.
25 McCulley, will recognize those who wish to comment and will

1 determine the duration of the comment period at that time.

2 I'd like to make a note on the agenda: please
3 don't be alarmed. There will be a lunch break. I note that
4 it's not in the agenda, but it will be approximately midday,
5 but depending on the course of the discussion at that time.

6 So I'd like to turn the meeting back over to Dr.
7 McCulley. Thank you.

8 MS. THORNTON: Oh--I'm sorry. I made a mistake.
9 I thought we could do this later, but I need to do it now --
10 the conflict of interest statement for the Ophthalmic
11 Devices Panel.

12 The following announcement addresses conflict of
13 interest issues associated with this meeting and is made
14 part of the record to preclude even the appearance of
15 impropriety. To determine if any conflict existed, the
16 agency reviewed the submitted agenda and all financial
17 interests reported by the committee participant. The
18 conflict of interest statutes prohibit special government
19 employees from participating in matters that could affect
20 their, or their employer's financial interests. However,
21 the agency has determined that participation of certain
22 members and consultants, the need for whose services
23 outweigh the potential conflict of interest involved is in
24 the best interest of the government*.

25 A waiver is on file for Dr. Michael Belin, for his

1 financial interest in firms at issue that could potentially
2 be affected by the committee's deliberations. The waiver
3 allows this individual to participate fully in today's
4 deliberations. A copy of this waiver may be obtained from
5 the agency's Freedom of Information Office, Room 12A-25 of
6 the Parklawn Building.

7 We would like to note for the record that the
8 agency took into consideration other matters regarding Drs.
9 Arthur Bradley, Frederick Ferris, Michael Grimmett and
10 Janice Jurkus. These panelists report past and current
11 involvement in firms at issue, but in matters not related to
12 today's agenda. Since their interests are unrelated, the
13 agency has determined that they may participate in the
14 committee's deliberations.

15 In the event that the discussions involve any other
16 products or firms not already on the agenda, for which the
17 FDA participant has a financial interest, the participant
18 should excuse himself or herself from such involvement and
19 the exclusion will be noted for the record.

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

25 Thank you, Dr. McCulley.

1 have gained considerable experience in both the design and
2 the conduct of clinical trials in the intracorneal
3 environment. And I would like to just make couple of brief
4 comments that I would ask you to consider in your
5 deliberations on the development of guidelines for
6 implantable devices in the anterior segment of the eye.

7 Number one, I think there is a fundamental
8 difference between devices implanted in the cornea and those
9 implanted intraocularly. I'm sure you appreciate that. But
10 it a point that we would like to make. There are different
11 risk considerations, I believe, both surgical and possible
12 device complications in these to environments; for example,
13 intraocular infections, cataractogenesis with intraocular
14 devices. And to me, this would suggest the advisability of
15 different safety endpoints, depending on where the device is
16 implanted. It would also suggest differences in possible
17 risk-benefit ratios.

18 Intracorneal implants--and this would apply to
19 rings, inlays, gels--are essentially additive technology,
20 inducing changes in corneal shape by adding substance, as
21 opposed laser corneal treatment which subtracts corneal
22 tissue to achieve curvature changes. Additive technology
23 offers the possibility of removal or exchange to reverse
24 complications or alter refractive results. The results with
25 additive technology therefore are potentially reversible

1 and/or adjustable in contrast to the subtractive
2 technologies which tend to be somewhat irreversible, at
3 least once the tissue's been taken out it can't be put back.
4 this is particularly true for implants which do not invade
5 the visual axis.

6 Another point is that efficacy endpoints for
7 competing intracorneal technologies would seem to be
8 comparable; that is, the same visual acuity endpoints for
9 lasers, implants. But definition of efficacy "failures"
10 might differ. For example, if an intracorneal implant can
11 be exchanged or adjusted, this might allow for refinement of
12 visual outcome without permanent alteration of the cornea
13 such as occur with other types of so-called enhancements.

14 And just a final point that I would like to make.
15 As has been noted in the literature recently in regard to
16 contrast sensitivity, and that it might be more beneficial
17 to compare contrast sensitivity results preoperatively with
18 the corrected device that patients are using to achieve
19 vision preoperatively to the post-operative devices, such
20 spectacle corrected, contact lens corrected, which would
21 more reflect actual patient conditions.

22 These are the thoughts I anted to share with you
23 this morning, and I'd ask you to consider these as you enter
24 your deliberations. And if I can answer any questions, I'd
25 be happy to do so. Thank you for the opportunity of

1 speaking.

2 DR. McCULLEY: If you would remain at the podium
3 for a moment.

4 Questions from the panel?

5 I think that--you know, one thing that has been a
6 point made repeatedly is that we do need pre- and post-op
7 contrast and halo and glare and the like--pre- versus post-
8 for comparison; that we haven't always had, which I think,
9 if it's not clear to sponsors that we'd like to see that, it
10 ought to be made real clear to them.

11 Gary? Oh.

12 Other questions? Comments--for Dr. Lemp?

13 I have one, Mike--and the claim relative to
14 reversibility is going to be, I guess, the question. How
15 effectively are you going to be able to establish that, and
16 the means by which you intend to that, how convincing it
17 will be. Because that is something you will really have to
18 demonstrate.

19 DR. LEMP: Oh, absolutely. No, it wasn't my
20 purpose to demonstrate any claims in this venue. I just
21 bring o\up the issue as a potential issue in establishing
22 guidelines. THose things surely have to be demonstrated and
23 proven.

24 DR. McCULLEY: Okay. Other questions, comments
25 for Dr. Lemp?

1 Rick?

2 DR. FERRIS: Frederick Ferris.

3 The question I wondered about with regard to
4 developing a guidance--in your experience on the Data
5 Monitoring Committee, reviewing this data for four years, it
6 would seem it would be useful if there were some particular
7 questions or items from the data that you were collecting
8 that were relatively unique to these kinds of devices, to
9 share them with the FDA and, I guess, eventually that gets
10 shared with us. I'm not necessarily suggesting we need to
11 do this publicly now, but it would seem that that would be
12 useful for them. It certainly would be useful for me, as
13 someone who doesn't know much about these, to take the
14 experience of somebody who's been looking at the data for
15 four years and has had an opportunity to decide what was
16 useful and what wasn't.

17 DR. LEMP: Well, I that's a very good point and we
18 have been doing that, Rick. That's--we have an ongoing
19 dialogue with FDA officials, and, like with most clinical
20 trials, anytime you're dealing with adverse events or
21 complications or whatnot, they're always notified--the
22 agency. We deal with it at a series of meetings. And so
23 they've been--they're very up to date on all of the issues
24 that we've dealt with over the years on this.

25 DR. McCULLEY: Other questions or comments for Dr.

1 Lemp?

2 Mike, thank you.

3 DR. LEMP: Thank you.

4 At this time if there are others in the audience
5 who would like to make comment, I invite you to the podium
6 for a time limit of ten minutes.

7 Yes.

8 **Statement of Shirley McGarvey**

9 DR. MCGARVEY: My name is Shirley McGarvey, and
10 I'm an independent consultant in the medical device
11 industry. I have several different clients who are pursuing
12 the development of retractive modalities of--different
13 surgical correction for refractive error. And in looking at
14 the proposal that you're considering today with respect to
15 the guidance, I would just like to make a few comments.

16 We have had a lot of discussions at the Eye Care
17 Technology Forum's sub group that worked to develop the
18 laser guidance document, and made that guidance document
19 very workable for all members who were trying to proceed to
20 approval of their product.

21 I think the same organization could have some
22 beneficial effect in these other areas--in these other
23 modalities--to provide input from industry, as well as the
24 FDA, as well as members of the panel and the professional
25 societies, to collectively come to consensus. It's very

1 difficult to come to consensus when you have different
2 companies pursuing competitive techniques, however the Eye
3 Care Technology Forum has proved very beneficial in the
4 laser guidance development and, I think, could have some
5 bearing here as well.

6 In the context of that work that we did at Eye
7 Care Technology Forum sub group, we saw that as we looked at
8 the different ranges of refractive error that we were trying
9 to correct, that we had some commonality among the safety
10 requirements versus the effectiveness requirements. And we
11 saw yesterday that we had some significant discussion trying
12 to come to conclusion as to what we should change in the
13 current guidance document to accommodate different ranges of
14 refraction to be corrected.

15 Whatever effectiveness criteria are determined to
16 be appropriate for a particular range, I believe should be
17 applied to all modalities of correction in that range,
18 irrespective of whether lasers are used, or radio frequency
19 is used, or inlays are used, or if intraocular lenses are
20 used.

21 So as we look at effectiveness criteria, we have
22 fairly well defined those for the category of less than 7
23 diopters of myopia, and if we are going to use different
24 modalities of correcting that range of myopia, I think those
25 same criteria should be applied to those other modalities.

1 In safety, there are some elements which are
2 common, but they are not call common to all modalities. We
3 se that the loss of best corrected VA should be maintained
4 as a criterion, and it should be the same irrespective of
5 the modality. In adverse events, I think the same things
6 apply. However--the same proportions of incidents apply--
7 however, adverse events will be, in some cases, unique to
8 the modality being used.

9 Safety is the key issue in many of these
10 applications. We have intraocular procedures versus
11 extraocular procedures; intracorneal procedures versus
12 topical, and so you also have reversibility versus
13 irreversibility. The potential for problems that are in the
14 safety category are unique to the modality. And as we look
15 at study design, I believe that we need to take the safety
16 factors into consideration in deciding what should be the
17 dimension of the study, what should be the duration of
18 study, what should be the parameters that are followed, and
19 what should be the criteria on which the safety of the
20 product is based.

21 And so as we look at expansion into the different
22 phases, I believe it is the safety issues that predominate,
23 since effectiveness could be commonly held across all
24 modalities.

25 So as I am looking at the different clients that I

1 have who are trying to design clinical trials, I generally
2 focus in on those safety elements, and I would just propose
3 in the discussions today that as you're looking at the
4 intracorneal versus the intracorneal, that the safety issues
5 with respect to intraocular are not appropriate with respect
6 to the intracorneal--consistent with what Dr. Lemp has had
7 to say here today.

8 In conclusion, I would just to like to again
9 emphasize that maintaining a common standard on
10 effectiveness I think is useful for the practitioners and
11 the patients to be able to have some confidence that
12 whatever their range of correction is that they need,
13 irrespective of the modality of treatment that they will
14 receive, on effectiveness they can have confidence that
15 everybody's held to the same standard; that on the safety
16 aspects, those are unique to the modality, and that whatever
17 considerations need to be given, in terms of parameters, in
18 terms of follow-up, in terms of methods being used, that
19 those will be applied consistently, but not across
20 modalities where they don't have merit.

21 Thank you very much.

22 DR. McCULLEY: Thank you. If I could ask you to
23 remain at the podium a moment.

24 Any questions or comments' from the panel members?

25 There was an issue yesterday that was brought up -

1 -I think Dr. Matoba brought it up--about whether it would be
2 appropriate to balance against effectiveness, increased
3 safety. That came up in the discussion yesterday. Would
4 anyone want to make any comments? You had anticipated it
5 yesterday, did you anticipate it today?

6 DR. BELIN: In theory I agree. One of the
7 problems is that we're dealing with safety issues on
8 relatively small numbers that we're now requiring for these
9 studies, with a high safety profile that we anticipate most
10 of these to have, it's going to take much large numbers to
11 really determine if there really is a statistically
12 significant safety difference. And not that this is
13 comparable, but I think if we--I think Mike Grimmett once
14 did an--I think it was--you did an article comparing sewn-in
15 PC lenses, iris-supported, and AC lenses? Mike--it wasn't
16 you?

17 Okay. There was an assumption that sewn-in PC
18 lenses were going to be a lot safer than AC and graft--I
19 think it was in graft patients. That was the assumption we
20 always went on. Only one or two people ever really did it
21 in a study, and it wasn't held. It wasn't true.

22 I think we can't go into any new device with the
23 assumption that it's going to be safer, and I think the
24 numbers that we're requiring now are not going to allow us
25 to really determine if that's true. I think it will be

1 determined in post-market studies.

2 DR. STARK: Jim --

3 DR. McCULLEY: Dr. Stark?

4 DR. STARK: --could I just, for the record, correct
5 the statement? That was done by Oliver Shein at Harvard,
6 and it was a multi-center trial. The PC--the posterior
7 chamber lenses actually turned out to be a little better
8 visual acuity and less pressurized than anterior chamber
9 lenses--the sutured-in posterior chamber lenses. Oliver
10 Shein, published in the American Journal of Ophthalmology.

11 DR. McCULLEY: Other questions or comments?

12 Thank you very much. Very well thought out and
13 nicely presented comments.

14 Anyone else from audience like to make a
15 statement?

16 The open public hearing session--seeing no further
17 takers--is now closed, and we will now move to the open
18 committee discussion. And unless Sally has something, we
19 will move right on to the Branch Update by Donna Lochner,
20 Chief Intraocular and Corneal Implant Branch.

21 **Open Committee Discussion**

22 **Branch Update**

23 MS. LOCHNER: I just have a few brief comments
24 before we get into the discussion this afternoon--or this
25 morning.

1 First, I'm pleased to announce that PMAP 960034,
2 which is Pharmacia & Upjohn's CeeOn, Heparin Surface
3 Modified UV-Absorbing PMMA IOLs was approved by the FDA on
4 August 12, 1998.

5 I'm also pleased to announce that PMAP 970034,
6 Ophthalmic Innovations International's UV-Absorbing PMMA
7 Posterior Chamber IOLs was approved by the FDA on September
8 25, 1998. This last PMA was not reviewed by the panel, but
9 I thought that you may be interested to know that we have
10 had another PMA approval.

11 And last, a PMA that was reviewed by the panel,
12 P880091, Supplement 14, which is Staar Surgical Company's
13 torque IOL is still under review at the FDA. And this was
14 reviewed at the July '98 panel meeting.

15 DR. McCULLEY: Okay. Now, you have a--well, are
16 there any questions, I guess, at this point?

17 You have a presentation that we have the slides
18 for. Is that what you're going to hop into right now, or do
19 you have--because I want to do one thing before you start
20 your formal presentation --

21 MS. LOCHNER: Right.

22 DR. McCULLEY: If you have other introductory
23 remarks, I'd rather you do those first.

24 MS. LOCHNER: Well, I had some introductory
25 remarks to the discussion, but did you want to --

1 DR. McCULLEY: Since I--why don't you go ahead --

2 MS. LOCHNER: Okay.

3 DR. McCULLEY: --and do you your introductory
4 remarks, and I'll do what I want to do.

5 MS. LOCHNER: As everyone knows, we are going to
6 discuss today preliminary information so that the FDA can
7 develop a guidance document for refractive implants. We
8 wanted to get he panel's recommendations and input before we
9 actually draft a guidance document, and so we've prepared
10 some of the issues that we believe need to be addressed.

11 We had anticipated the format to be that we would
12 give some brief introductory remarks introducing the issue
13 and then opening up the discussion to that one particular
14 issue before proceeding on to the next issue. So instead of
15 us going through all of our slides, we're going to step
16 through them in a sort of piecemeal fashion to get your
17 comments as we go along.

18 I'd also like to acknowledge and thank the people
19 who have worked on this effort. Ashley Boulware, to my
20 right, has been the one responsible, within the FDA, for
21 pulling together all the various viewpoints and preparing
22 the presentation today.

23 Malvina Eydelman has provided us clinical support
24 throughout our reviews and provided a lot of clinical
25 support in preparation for today's meeting.

1 I'd also like to acknowledge Dr. Bernie Lapree,
2 who's been the primary clinical reviewer on these documents
3 that we have--on IDEs that we have so far for refractive
4 implants, and I'd like to acknowledge Don Calagero and
5 Claudin Krozic who have spent a great effort in pulling
6 together information for us and in participating in the
7 discussions for what we believe are the issues for these
8 documents.

9 So with that, that was the only introductory
10 comments I had. Before, I guess, we turn it over to Ashley,
11 Dr. McCulley, do you want to make some statements?

12 DR. McCULLEY: I didn't get to talk to you
13 beforehand, but I did Ashley.

14 I thought, unless you disagree, that it would be a
15 good idea to poll the panel individually about their
16 thoughts relative to the course we're taking. And it really
17 would be one of two broad brush-strokes type approaches.
18 One would be that we would be assuming that the guidance
19 document that was developed for laser corneal refractive
20 surgery would serve as the background and core for any
21 additional guidance relative to implantable devices, and
22 that we would concentrate only in areas where we would think
23 that there should be a deviation from that on the clinical
24 side.

25 The other would be to start from scratch with a

1 guidance document.

2 Now, it appears that you probably are in
3 concurrence with the initial statement; that we would be
4 starting from the guidance document that's been created and
5 is in existence. And I sensed yesterday not a lot of
6 impetus to recommend changes for higher ranges of refraction
7 or different corrective errors, even though there was, you
8 know, discussion; but to use that--but to be a little looser
9 for higher ranges. And--but for this, to take the same kind
10 of approach.

11 And it's been pointed out there are going to be --
12 would we want to change efficacy and predictability
13 standards for these? Not sure. Would we need to introduce
14 new safety guidelines and to use that as a background.

15 Is that your intent?

16 MS. LOCHNER: Yes. I think a lot of our
17 preparation on these issues we would--when we could, we
18 started with the starting point that the refractive laser
19 guidance would be a place to discuss from.

20 Some of these items you may just think there needs
21 to be no change; use the exact criteria that's used for
22 refractive lasers, and some are on the slides, on the table,
23 just as a starting point where you feel there may need to be
24 revisions.

25 So, some of these issues may go through very

1 quickly if you feel they don't need any changes.

2 DR. McCULLEY: Okay. Rather than poll the panel
3 then, let me ask if there is differing opinion from what has
4 been stated?

5 Seeing none, I'll turn it back to you.

6 MS. LOCHNER: Okay. Then we'll turn it over to
7 Ashley Boulware.

8 MS. BOULWARE: Thank you, Donna.

9 I also wanted to make one quick--or two quick
10 statements at the beginning. I wanted to point out that for
11 those interested parties at the next ANSI meeting in New
12 Orleans on November the 6th, there will be a discussion of a
13 possible refractive implant standard, if any of you are
14 interesting in attending. And also that there are a number
15 of studies that are currently ongoing for refractive
16 implants, and we are asking for your recommendations today,
17 mainly for sponsors who either have not yet begun their IDEs
18 or who are in the early states of their IDEs.

19 [Slide.]

20 We've started by dividing refractive implants into
21 two categories: corneal, which are the rings, both solids
22 and gels, and inlays; and chamber implants, which would be
23 posterior chamber IOLs--you may have heard of the incredible
24 contact lens, iris fixated lenses, anterior chamber IOLs,
25 and this would also cover clear lens exchange. We realize

1 that you may have different recommendations for different
2 types of implants, and you may also wish to subdivide the
3 two categories of corneal and chamber into further
4 designations.

5 Also, in our comments today, we've focused on
6 myopic, hyperopic and astigmatic corrections. If you have
7 recommendations for presbyopic corrections we would
8 certainly be interested in hearing those.

9 [Slide.]

10 As Dr. McCulley pointed out, a number of endpoints
11 have been established in the laser guidance document for
12 refractive lasers, and we discussed a number of these
13 yesterday. We did think a number of these might apply to
14 refractive implants. So you see here the stability criteria
15 that you discussed yesterday, with the same definition of
16 stability as you heard yesterday: change of less than or
17 equal to 1.00 D of manifest spherical refraction between two
18 refractions performed at least three months apart.

19 Are there are any comments on whether this is
20 still appropriate?

21 DR. McCULLEY: So what we're going to do as we go
22 through, you're going to ask for comments on specific
23 points, and we're going to address those as we go through--
24 individually.

25 MS. BOULWARE: Yes.

1 DR. McCULLEY: Does anyone think that the targets
2 should be changed?

3 Dr. Bullimore?

4 DR. BULLIMORE: Yes. Point of information.

5 I've got very limited experience with intraocular
6 implants and cataract surgery.

7 What's the panel's feeling on the predictability
8 of refraction following that procedure, since we're
9 considering very similar devices, albeit in the presence of
10 the natural crystalline lens. I'd like some sense of
11 whether they feel that a high standard is set by people
12 performing cataract surgery, in terms of predictability of
13 refraction, and whether we should move in that direction
14 with these devices?

15 DR. McCULLEY: Let me ask Walter a specific
16 question, then.

17 Walter, do you think that, for an implantable
18 phakic lens--intraocular lens--that these expectations and
19 predictability are reasonable?

20 DR. STARK: I think they are. That's probably--we
21 probably do a little bit better with cataract at this time,
22 but--and those data are available. I think Jack Holiday's
23 published--somebody could research the literature and get
24 the data. But that's probably reasonable for cataract
25 surgery.

1 DR. McCULLEY: So, if anything, it would be
2 tighter for cataract surgery.

3 Marian--Dr. Macsai?

4 DR. MACSAI: Dr. Macsai. As far as stability, I
5 think we really had this discussion yesterday--ad nauseam -
6 -and talked about the slope of the mean refractive change
7 between two visits. And would see why that shouldn't apply
8 to these devices.

9 DR. McCULLEY: Okay. So is there a differing
10 opinion that the same standards should apply? It seems that
11 there's consensus on that.

12 Next?

13 MS. LOCHNER: Could I ask a point of
14 clarification?

15 DR. McCULLEY: Okay.

16 MS. LOCHNER: There was discussion yesterday about
17 whether this stability amount of 1.00 D should be lowered to
18 0.50 D because of the stability criteria pre-operatively
19 being that it was within a 0.50 D. And I wasn't totally
20 clear on whether most of the panel felt it should be changed
21 to a 0.50 D or--there was also the discussion that if you
22 put the confidence intervals on the 0.50 D it's actually out
23 to a diopter.

24 DR. McCULLEY: What--Dr. Ferris?

25 DR. FERRIS: Rick Ferris.

1 The data that Doyle Stulting shared with us
2 suggested that one would expect 2.5 percent at 1.00 D, so I
3 think you'd have to be awfully careful. Actually, if you
4 set it to a 0.50 D, I think what he suggested is that
5 everybody would fail that criteria, not based on surgery,
6 but based on reproduceability.

7 So it seems to me that by one or another, we chose
8 something which is pretty reasonable, and that we need to be
9 careful if we're going to raise that bar, because we may
10 raise it to a point that nobody can reach without working on
11 their data a little bit.

12 DR. McCULLEY: Dr. Belin, would you like to
13 suggest we change the pre-op?

14 DR. BELIN: AGain, yesterday he was talking about
15 individual patient variability, not variability of the mean
16 of the population.

17 If we all weighed ourselves yesterday and weighed
18 ourselves today, we all would find that we fluctuate a pound
19 or two one way or the other. However, if you weighed all of
20 us, chances are it hasn't budged a whole lot.

21 We're talking about, here, a mean of the study
22 group. We're not talking about --

23 DR. McCULLEY: Oh, no, no--we're not. We're
24 talking about the individual patient here, Mike. We're
25 talking about 95 percent being within a diopter. We're

1 talking about that individual curve, not the mean change.

2 DR. BELIN: That's not how the document's written,
3 though.

4 DR. McCULLEY: There are two different stability
5 measurements. One is mean, that we don't really have a
6 standard for--relative mean change defining stability. And
7 that's what we were talking about with the slope of the
8 curve. But we do have that 95 percent of people--of
9 individual patients--have to be within 1.00 D three months
10 apart. And that's what we're talking about here.

11 And the only issue is--I mean, we're--it almost
12 seems like we are being inconsistent, that if we have within
13 a 0.50 D change for a year pre-op, that then we say 1.00 D
14 within three months post-op, that there's some inconsistency
15 there.

16 DR. MACSAI: Jim?

17 DR. McCULLEY: Dr. Macsai?

18 DR. MACSAI: I think it might be advisable,
19 because of the individual variation--because of the of data
20 Dr. Stulting--to eliminate that criteria and substitute it
21 with the mean change--the slope of the mean change.

22 DR. McCULLEY: We're fine with 1.00, Marian. We
23 don't need to take both out.

24 DR. MACSAI: I didn't--we weren't going to take
25 both out.

1 DR. McCULLEY: I mean, we need both. We need the
2 mean --

3 DR. MACSAI: The mean is not in there right now.

4 DR. McCULLEY: That's right. That's what we were
5 unable to arrive at: whether--I mean, Rick made a suggestion
6 of what the slope could change--.1, .2, .3--and be
7 acceptable for the mean change. But we do need the
8 individual patient as well. And that's been set at 1.00 D.

9 But what's different--where the inconsistency
10 comes, as I see it--is that we have--for a patient to enter
11 the study, they have to have no more than a 0.50 D change in
12 refractive error within the preceding year.

13 DR. MACSAI: Correct.

14 DR. McCULLEY: Dr. Wang?

15 DR. WANG: Ming Wang.

16 It seems now we're discussing two things. One is
17 the slope change and one is the diopter change. If we focus
18 on diopter change, as I remember from yesterday's
19 discussion, there are two feelings. One, the noise,
20 individual variability, is approximately 0.50 D pre-op.
21 Two, 1.00 D perhaps is too loose. So perhaps somewhere in
22 the middle.

23 DR. MACSAI: Yes. .75.

24 DR. McCULLEY: Rick?

25 DR. FERRIS: Rick Ferris.

1 Two issues regarding this. One is I'm not sure
2 it's totally inconsistent to say that you would like a 0.50
3 D as an eligibility criteria, but that you're going to look
4 at 1.00 D within the study. In fact, if I was doing the
5 study, if I had people that were bouncing around with
6 refraction, and recognizing that I'm going to exclude maybe
7 five out of --or maybe, in this case, if you said 0.50 D
8 maybe you're going to exclude 10 or 20 or 30 percent of your
9 potentially eligible patients, that's not as concerning to
10 me as saying that we want to demonstrate stability. In
11 fact, it may--presumably it would help you demonstrate
12 stability because there are a lot of reasons people have
13 fluctuating refractions, not just that their true refraction
14 is fluctuating. Some people have trouble doing the exam,
15 for example.

16 I said yesterday that I was concerned about making
17 seat-of--the-pants recommendations with regard to this slope
18 and so on--talking about stability. And as I've thought
19 about it some overnight, part of the reason why I was
20 concerned became more clear to me, and that is: are you
21 going to take the point-estimate of the slope, or are you
22 going to say that the slope has to be statistically
23 significantly less than something? And both are
24 problematic.

25 The bigger your sample size is, the more likely

1 you are to have a statistically significant worsening slope,
2 so that's suggesting to a company, "Don't get your study too
3 big--" --

4 DR. MACSAI: Right.

5 DR. FERRIS: --"--you might demonstrate that this
6 is worsening over time." So that's a problem.

7 And I'm not--I think it just points out that this
8 is a difficult issue. And I'm not sure what the best answer
9 is. The one thing I am sure of is that we ought to look at
10 the slope. And from--the data are much more revealing, I
11 think, about what's going on than arbitrary standards, and
12 that if you see a decreasing slope with some standard errors
13 around it, it's either going to raise concern or not.

14 And I'm not sure how to set up a line-in-the-sand
15 guideline with regard to that.

16 DR. McCULLEY: Okay, we don't have it, and I think
17 we're right back to where we were yesterday, with the added
18 benefit of Rick's comments that we're not so uncomfortable
19 with the entry criteria being .5 and the post-op being 1.00
20 D. So he's brought logic to that.

21 Dr. Bradley, anything more to add?

22 DR. BRADLEY: Yes, just to clarify. I'm not
23 talking about stability, I'm talking about predictability.
24 And I'd like to really reiterate what several people have
25 said already: that there are two factors that will influence

1 what percentage of patients will have a refraction within
2 some dioptric criterion value, like 1.00 D, or 0.50 D. That
3 is essentially the error in the measurement--the refractive
4 accuracy, or the refractive repeatability, and also error in
5 the procedure.

6 And I think when these sort of numbers that we
7 have up here are presented, essentially we, from experience,
8 are appreciating that both of those sources of error are
9 combined here. And I think, in the end, it would be nice to
10 have some standard based upon the error of the procedure,
11 which is what we would really like to hold up to a high
12 standard.

13 We have data in the literature telling us the
14 likely error in refractive data. So if we now what that is,
15 we ought to be able to estimate, for example, the percentage
16 of people who would be within 1.00 D, 0.50 D, 0.25 D if the
17 procedure itself had zero error. If the procedure had zero
18 error--you produced exactly the refraction that you intended
19 to--still you would only have a certain percentage of the
20 patients to be within some dioptric criterion, simply
21 because of the error in the refractive measurements. You
22 can then add your procedural error to that. And,
23 essentially, there are two sources now, and you can add it.

24 And we might discuss, for example, what the
25 refractive procedural error we would tolerate might be.

1 Would that be 0.50 D, would that be 0.25 D, would that be
2 1.00 D? That, itself, will then add, in a statistical way,
3 to the underlying error in the refraction data. And I think
4 several people have sort of talked around that topic.

5 DR. McCULLEY: I think, in effect, we've done that
6 with these numbers. If it's plus/minus 0.50 D
7 reproduceability, then we want 50 percent to be dead-on and
8 we will allow another percentage to be within 0.50 D for the
9 0.50 D of noise.

10 But I think we've kind of done that. Not very
11 eloquently, but.

12 DR. BRADLEY: I agree. I think that's what we're
13 trying to do here, and I wonder whether the FDA should be
14 specifying standards in terms of specifically procedural
15 error.

16 DR. McCULLEY: I guess we'd leave that to them.
17 WE've built the noise in form them. If they want to take the
18 noise out, then they can do it.

19 Dr. Grimmett?

20 DR. GRIMMETT: I agree with Dr. Bradley regarding
21 the concept of systematic and random error. Dr. Stark
22 mentioned, regarding predictability data for cataract
23 surgery--when I reviewed the data a number of years ago,
24 it's approximately 80 percent plus or minus 1.00 D, 95
25 percent plus or minus 2.00 D, and 99 percent plus or minus

1 3.00 D. So the numbers up here, at least for our current
2 regression formulas for cataract surgery appear very
3 reasonable to me for that circumstance.

4 DR. McCULLEY: Rick? And keep in mind we've got a
5 lot to do. So if it's going to add to the discussion and
6 potentially change direction or cement, then please comment.
7 Otherwise, we really are going to need to --

8 DR. FERRIS: This is a general comment, not a
9 specific comment. And that is that it seems to me that the
10 guidance that was developed has worked well, and that if
11 it's going to be changed I think there needs to be a
12 compelling reason.

13 I don't know why we tripped into 1.00 D as a
14 working guideline, but it seems to have worked pretty well.
15 It set a bar for refractive surgery that--I'd like to go
16 back to something I said yesterday, and that is that it
17 seems to me that the paradigm with the FDA is that there's a
18 treatment now that has been shown to be safe and effective.
19 And it was shown to be safe and effective using this
20 guidance. Other treatments--they don't have to be laser
21 treatments--other treatments that want to treat the same
22 disease--if I was doing diabetic retinopathy the bar would
23 be photocoagulation. They need to be able to show that
24 they're at least comparable to--well, in my--from a clinical
25 point of view--I'm not talking about the FDA's point of

1 view, I'm talking about from a clinical point of view, they
2 need to be comparable.

3 And at least from my sense of this, this guidance
4 has worked pretty well. So we should look to that as the
5 kind of standard that we would like to see others adhere to,
6 except for where there's special circumstances, and the
7 special circumstances are going to be discussed.

8 DR. McCULLEY: You know, in our collective wisdom,
9 even though we didn't always have scientific data, what we
10 did seems to have stood the test of the marketplace. So it
11 could be argued about how we developed some of these things,
12 but in our collective wisdom, they seem to have worked well.

13 And--Mike, you had your hand up before. Did you -
14 -

15 DR. BELIN: Just a quick comment on that, and I'm
16 going to--this is a question, more.

17 I don't think any of the currently approved lasers
18 were approved under this guidance document. Is that
19 correct?--by the FDA?

20 MS. LOCHNER: We're getting nods. Yes.

21 DR. BELIN: Excuse me?

22 MS. LOCHNER: We're getting nods.

23 DR. BELIN: Right. So I mean, that's--you can't
24 make that statement, that they were not approved by this
25 guidance document.

1 Two is just a real quick comment on that pre-op,
2 post-op --

3 DR. McCULLEY: But it was in development in our
4 heads, and there were criteria we applied. But that's
5 irrelevant here. Same criteria.

6 DR. BELIN: In my recollection there were a
7 little--that's okay.

8 The pre-op, post-op comment--the only, the one
9 concern I have is that post-op refractive stability is done
10 under a controlled study using a standardized refraction
11 technique, using EDTRS, using 8 feet, 20 feet, whatever it
12 is. Pre-op eligibility, we're looking at past records,
13 someone else refracting, someone else's technique, and we're
14 asking for more strict criteria in an uncontrolled
15 comparison than in a controlled.

16 DR. McCULLEY: Okay. Dr. Pulida?

17 DR. PULIDO: I disagree with the comment that the
18 wheel isn't broken so don't fix it.

19 We already saw that the wheel is partly broken
20 when it comes to hyperopic considerations. For myopic
21 considerations, it looks like the wheel --- our guidance
22 document--works well. But when it comes to hyperopic
23 considerations, there can be a 0.50 D change at each visit,
24 and as long as it's within a 0.50 D change, it's still
25 within stability criteria.

1 So I think we do need to add that second part to
2 the stability criteria about the slope change, and that
3 there be very little slope change. And that's not within
4 the guidance at this time.

5 DR. McCULLEY: What's not there is a standard for
6 the slope. I mean, we want the slope. And, as Rick said,
7 we certainly want to look at it, but he's till reluctant, as
8 a person who is expert in clinical trials, to put a number
9 or a standard on the slope at this time. But we definitely
10 want the slope.

11 Okay --

12 DR. FERRIS: We have some sort of standard, don't
13 we? I mean, --

14 MS. THORNTON: Dr. Ferris, could you please
15 identify yourself?

16 DR. FERRIS: I'm sorry--Dr. Ferris.

17 There is some sense that you don't want long-term
18 drift. And the problem with putting a number on the nine-
19 month, one-year data is that we have no idea how predictive
20 that is of long-term drift. But it would seem to me that
21 anybody that had a slope that looked like at two or three or
22 four years out you were going to be changing by more than
23 several diopters, certainly that would be problematic.

24 DR. McCULLEY: Okay. I'm going to assume that
25 this is one of the more ticklish points, and probably, in a

1 way, some of the more important ones, and that each of the
2 issues won't take as long, otherwise, bring your pup tents.

3 Let's go on to the next issue.

4 MS. BOULWARE: Could we clarify--just before we
5 move on?

6 DR. McCULLEY: Yes.

7 MS. BOULWARE: We realized yesterday, in terms of
8 the higher corrections, that the decision seemed to be to
9 keep what we've got in the laser guidance and to consider
10 them on a case-by-case basis. Is there anything different
11 about implants, for correction effectiveness, that would
12 change your decision?

13 DR. McCULLEY: I think you've heard the opinion to
14 be no.

15 MS. BOULWARE: Okay. Thank you.

16 DR. McCULLEY: Is that incorrect? No. Okay.

17 [Slide.]

18 MS. BOULWARE: Continuing on the effectiveness
19 endpoints, you see the endpoints here are also 85 percent
20 20/40 or better is from the refractive laser guidance.

21 I assume that your answer for the higher ranges of
22 correction may be the same as for the predictability. Would
23 you recommend a 20/20 benchmark?

24 DR. McCULLEY: Okay. There is a two part to this
25 question, just to be sure I don't skip over anyone who has a

1 differing opinion.

2 Relative to 20/40, the benchmark--the suggestion
3 is it would be the same? Yes?

4 We don't have a 20/20, even though there was a
5 20/20 in the initial that Mike suggested when this was first
6 thrown on the table. Should there be a 20/20 now for the
7 implants?

8 Dr. Macsai?

9 DR. MACSAI: I think as we look at the higher
10 ranges of myopia, there will be patients who cannot achieve
11 20/20. But if you separate out the data of those who can
12 achieve 20/20 and see where they end up, that's important
13 information for patients.

14 DR. McCULLEY: Now, one can put it in general
15 terms that it would be obtaining post-op what was obtainable
16 pre-op.

17 DR. MACSAI: Correct.

18 DR. McCULLEY: Dr. Wang?

19 DR. WANG: Ming Wang.

20 85 percent 20/40 or better for low range
21 uncorrected vision seems to be low. And that percentage may
22 be more accurate for high range correction. I understand
23 most of the PRK data shows that 20/40 or better is in the
24 range of 95 or even 98 percent by some of the studies.

25 DR. McCULLEY: That really isn't what's on the

1 table now. And if we--unless we stay to what is on the
2 table, we're going to be in real trouble today.

3 Dr. Sugar?

4 DR. SUGAR: I don't think we should add a
5 criterion for 20/20. We do have criteria for loss of best
6 spectacle-corrected vision, and the patients are up-front--
7 effectively, in the package insert, notified what the
8 expectation is for the specific device for 20/40 or better,
9 they effectively buy into it. And if they don't lose best
10 spectacle-correct vision, we don't need a standard for
11 20/20.

12 DR. McCULLEY: Good point. So we have safeguard
13 built in.

14 MS. BOULWARE: Great.

15 DR. McCULLEY: Satisfied?

16 MS. BOULWARE: Yes. Thank you.

17 [Slide.]

18 This is also an issue that came up yesterday, and
19 this may be very quickly addressed in terms of astigmatic
20 corrections. We initially proposed that you might want to
21 recommend a benchmark for residual astigmatism, but we did
22 have Dr. Bullimore's proposal yesterday for a target value
23 for the amount of correction achieved: CMD/IRC greater than
24 or equal to 70 percent.

25 What would your recommendations be for astigmatic

1 corrections?

2 DR. McCULLEY: Dr. Bullimore?

3 DR. BULLIMORE: This is Dr. Bullimore.

4 Let me ask you a question. Do you foresee devices
5 that do have an astigmatic component, or are we dealing
6 purely with spherical devices?

7 MS. BOULWARE: We anticipate that we will see
8 implants that correct cylinder as well as sphere.

9 DR. BULLIMORE: Then I think we should at least,
10 in the absence of any conflicting data, retain the same
11 standard that we've discussed for other devices.

12 MS. BOULWARE: Dr. Belin?

13 DR. McCULLEY: Dr. Belin--I'm sorry.

14 DR. BELIN: Just a quick comment. We probably
15 need to have both. You may find--well, let's say--I'll use
16 a laser example, a laser manufacturer where currently they
17 are only approved for 0.75 D or more. They try to lower
18 that limit by doing a study for low levels of astigmatism.
19 And, as we said already, it would be unrealistic to expect,
20 if you're coming in with 0.75 D, to try to get a 70 percent
21 correction. So you may want to have a residual astigmatism
22 -- I'll throw out a number of 0.50 D, or an amount
23 correction achieved of CMD/IRC of greater or equal to 70
24 percent. Otherwise, you're going to have no one try to get
25 those lower corrections. They'll be physically impossible.

1 Does that make--Mark is nodding is head.

2 DR. McCULLEY: Agreement? Disagreement?

3 Agreement. Disagreement. Make up your mind.

4 DR. FERRIS: This is Rick Ferris. I mean, except
5 for the absurd, if you start with 0.50 D, presumably you'll
6 wind up with at least 0.50 D.

7 DR. McCULLEY: Dr. Belin?

8 DR. BELIN: There are some--I don't know whether
9 they're published or not, but there are some--at least I
10 think, Ray Stein and Bruce Jackson have some data suggesting
11 low levels of astigmatic corrections improving on corrected
12 visual acuity. I don't know this from the top of head, but
13 we may be presented with some data to expand the range into
14 lower levels. And we need to have criteria for that.
15 That's what we're trying to do. We're trying to cover all
16 potential bases.

17 DR. McCULLEY: Do you need that restated by
18 anyone?

19 MS. BOULWARE: I don't think so. Thank you.

20 [Slide.]

21 MS. BOULWARE: We've divided the safety endpoints
22 into those that could be evaluated at the first post-
23 operative year and the longer term safety.

24 I'd like to start with those that could be seen in
25 the first post-operative year.

1 In terms of adverse events, we've proposed that
2 existing aphakic IOL grid rates be used as target values for
3 the chamber implants and that the less than 1 percent per
4 type of adverse event target be used for the corneal
5 implants, and the less than 1 percent comes from the
6 refractive laser guidance.

7 Any comments?

8 DR. McCULLEY: Dr. Macsai?

9 DR. MACSAI: Actually, I thought the grid was
10 being revised.

11 MS. BOULWARE: It is, and it would be the updated
12 grid--which actually isn't all that different from the
13 older grid.

14 DR. McCULLEY: Other comments?

15 Dr. Stark?

16 DR. STARK: Just the comment that I would want to
17 look at that grid before making that decision that's
18 acceptable. Because we're dealing with--for the higher
19 myopia--or for these people, presumably, would be higher
20 myopic--if you correct 10 D, you should gain a line of
21 visual acuity. You should gain 20 percent improved
22 resolution; a line of best corrected visual acuity.

23 So I just--when we're dealing with cataracts,
24 we're taking people 20/50, 20/70, 20/80 and trying to make
25 them 20/20. So would need to add into that a specific point

1 about loss of best corrected visual acuity, assuming they
2 need one line of visual acuity. You wouldn't want to see a
3 lot of people losing one or two lines of visual acuity, and
4 that would have to be in that for the intraocular lenses.

5 DR. MACSAI: Unless they're hyperopic.

6 DR. STARK: Well, hyperopic would be the opposite.

7 MS. LOCHNER: This point is only speaking to
8 adverse events.

9 MS. BOULWARE: We have additional slide --

10 MS. LOCHNER: We have another slide for what
11 you're just discussing.

12 DR. McCULLEY: Gary?

13 DR. RUBIN: Gary Rubin.

14 The grid that we're talking about is based on
15 primarily cataract surgery, and that's a different age
16 group, I would presume, than the ones being considered for
17 this procedure. And I would think that the adverse events--
18 complications, etcetera--might be quite different in an
19 older age range. The expectation might be different in an
20 older age group than in the younger age group being
21 considered for these procedures.

22 DR. McCULLEY: The expectation might be. I'm not
23 sure that the complication rate in this circumstance would
24 not be somewhat comparable. But I would agree with Walter
25 that we would want to see the revised grid before we sign

1 off on it as the guideline. So I think that would be our
2 only comment here, is that we'd like to see--we want to see
3 that revised grid anyway. But before we agree that it would
4 be applied here, we'd like to see it.

5 MS. LOCHNER: You have seen that at a previous
6 panel meeting.

7 DR. McCULLEY: We've seen a draft. That's what
8 the final's going to be?

9 MS. LOCHNER: I think what we would do is once
10 release it in final we would, of course, show you it.

11 But you've basically seen it. It's not any
12 different.

13 DR. McCULLEY: Okay.

14 MS. LOCHNER: The numbers weren't vastly different
15 from the old grid, if you recall from a couple years--I
16 guess last year, I think it was, when we presented it. They
17 weren't widely different.

18 I think, speaking to the point of age, the
19 complication rates that we're talking about are very, very
20 low already. So I don't know whether to--you know, I
21 thought the inference was in the younger population you
22 might want to be a little --

23 DR. McCULLEY: Stricter.

24 MS. LOCHNER: --stricter, but they're already quite
25 low.

1 DR. McCULLEY: Dr. Matoba?

2 DR. MATOBA: I just have a quick question about
3 this statement--less than 1 percent per type of adverse
4 event. Does that mean that--less than 1 percent infection,
5 less than 1 percent hemorrhage, etcetera, etcetera. But is
6 there a statement about aggregate--total number of adverse
7 events?

8 MS. BOULWARE: Not in the refractive laser
9 guidance as it stands, to my knowledge.

10 DR. MATOBA: So does that mean that it's
11 potentially possible for a procedure to have a very high
12 complication rate, but only a very few of each type so that
13 they would pass this rule but actually be quite hazardous?

14 DR. McCULLEY: Yes, that would be the--in the
15 guidance that would be true. But if there was an implant
16 that had multiple ones, then our thoughtful approach to that
17 would come in. So it might sneak by on an individual line,
18 but under consideration, I don't think either the FDA or the
19 panel would let something like that find that kind of
20 loophole.

21 DR. MATOBA: Okay, but--so you don't need--feel a
22 need to --

23 DR. McCULLEY: An aggregate?

24 DR. MATOBA: Mm-hmm.

25 DR. McCULLEY: We haven't felt that way in the

1 past. That's where the human component comes in--both FDA
2 and panel.

3 MS. LOCHNER: It's a good comment, but I don't
4 know that we could come up with a number. So, at this point
5 in time, we're pretty much doing it on the--bring it to the
6 panel for their consideration kind of basis.

7 DR. McCULLEY: Dr. Bradley?

8 DR. BRADLEY: The point was just raised about the
9 procedures we're now talking about are different from
10 historical implant procedures in that they're generally
11 going to be performed on younger people. But I think the
12 issue is not that they're younger, I think the important
13 issue is this is an elective procedure for which a non-
14 hazardous alternative does exist. And I believe that
15 because of that, the adverse event rates should be mandated
16 to be lower, I think, because this is an elective procedure.
17 We shouldn't tolerate such high adverse event rates.

18 So it's not an age issue, it's an elective
19 procedure issue.

20 MS. LOCHNER: My only concern with that is that
21 there seems, from over the years of updating the grid and--
22 you know, basically updating it as the years go by, there
23 seems to be like an inherent low level rate that is just
24 associated with the surgery itself, that it's almost as if
25 patients who are choosing this elective procedure have to

1 assume that risk because they are having surgery.

2 I think if our rates were higher than they were
3 now, you know, I would agree totally with your statement.
4 But I almost feel that we're to the point where it's at that
5 noise level, or whatever; that surgical rate that you can't
6 obviate.

7 DR. McCULLEY: Dr. Macsai?

8 DR. MACSAI: I have to echo Dr. Bradley's comments
9 also in that not only is this elective, we're talking about
10 a much younger population, so that the potential for the
11 complications to get worse as the population ages are
12 significant. So I think Dr. Matoba has a good point in that
13 the overall risk of adverse events maybe needs to be
14 separated as to the morbidity of the events.

15 For example, if a patient develops endophthalmitis
16 or expulsive hemorrhage, or--I mean horrible intraoperative
17 events; hyphema, chronic angle closure, chronic intraocular
18 complications, that's very different than an adverse event
19 of a loss of one line best corrected visual acuity because
20 of the morbidity associated, and also because of the
21 longevity of the people who are going to be treated with
22 these devices.

23 So that I think both of these points are quite
24 valid.

25 MS. BOULWARE: I think the grid rates are very

1 low, and I would echo what Donna said in terms of the
2 chamber implants. Perhaps, for the corneal implants, the
3 less than 1 percent--I agree with Dr. Matoba's statement
4 also that the less than 1 percent per type does, I think,
5 open it up more than the grid rates would. I think you're
6 going to have--I think the grid rates are a little tighter,
7 actually. Whether the morbidity of adverse events
8 associated with corneal implants is the same, I can't say.

9 MS. LOCHNER: Yes, and there are a few grid rates
10 that certainly would cause pause. I mean, there's secondary
11 surgical reintervention of 2 percent. Now that might
12 definitely cause pause in these type of procedures, but I
13 think what we were sort of suggesting is, you know, first of
14 all, this is just a guideline and it's more or less a
15 starting point. And we expect for many years these types of
16 implants will be going to the panel; that it's really just a
17 guideline. And--but I also think that, you know, the point
18 of tightening up some of these like, you know,
19 endophthalmitis, for example, is at .1 percent. It's very
20 hard to tighten than any more with reasonable sample sizes.

21 So I think I appreciate your comment. I'm not
22 disagreeing with it. I just don't know where--the
23 implications of that are much broader than just tightening -
24 -you know, you're talking about huge sample sizes.

25 DR. McCULLEY: Well, it's a valid philosophical

1 point.

2 MS. LOCHNER: Right. And I think it's part of the
3 deliberations.

4 DR. McCULLEY: And it's hard sometimes to put a
5 philosophical point, or to replace it with a number.

6 MS. LOCHNER: Yes.

7 DR. McCULLEY: Dr. Van Meter?

8 DR. VAN METER: Even though these patients are
9 younger and healthier that would undergo refractive surgery,
10 there are over a million implants done a year, and the
11 surgical procedure for implants for cataract surgery is
12 pretty standardized.

13 Most of the complications that seem to be coming
14 up with phakic implants have to do with the surgical
15 procedure of cutting on the eye, trying to put an implant
16 in. There's a risk of glaucoma because you've got a lot of
17 material in the anterior chamber that sometimes can block
18 aqueous flow. There's a risk of cataractogenesis from
19 putting a foreign body on top of the crystalline lens.

20 And I think it's probably reasonable to leave it
21 like this, because even though these patients are healthier,
22 the complication rate that we anticipate is going to come
23 from the procedure of implanting the lens, and I don't think
24 that that's going to get much lower* because we're using
25 pretty standardized technique for putting these lenses in.

1 DR. McCULLEY: I guess, you know, that with these
2 implants there are going to be some complications that we'll
3 worry about more: development of cataract, glaucoma,
4 uveitis, hemorrhage.

5 Now, those are the ones that seem to me just
6 immediately off the top of my head that would be the biggest
7 concern, that we would not want to accept very much. Are
8 we--even though I've read this twice--are we going to come
9 back and address those issues specifically --

10 MS. BOULWARE: Yes.

11 DR. McCULLEY: --subsequently?

12 MS. BOULWARE: Yes.

13 DR. McCULLEY: So that we don't have to continue
14 to address those now.

15 MS. BOULWARE: Yes. The long-term--glaucoma,
16 induction of cataract, cell counts are all addressed in a
17 separate section.

18 DR. McCULLEY: Okay.

19 DR. STARK: And are we going to go over that too--
20 today?

21 MS. LOCHNER: Yes. It's a couple slides away.

22 DR. McCULLEY: Because that's, you know, where I
23 think some of our biggest concerns are.

24 Dr. Wang?

25 DR. WANG: Ming Wang.

1 I have a quick comment. I think, rather than
2 comparing with cataract surgery, this refractive implant
3 will always be held against existing refractive procedures.
4 Therefore--like PRK and LASIK which has, for example, almost
5 nil endophthalmitis chance. So I think a tighter--I'd like
6 to second Dr. Macsai's feeling--tighter rate standard for
7 these intraocular complications would be important, because
8 this procedure will not be compared with cataract; will be
9 compared and LASIK.

10 DR. McCULLEY: My sense on this is that we're not
11 going to be of much more help to you unless you put in front
12 of us the grid where we can say, "This needs to be
13 tightened; that doesn't need to tightened." We're not going
14 to be able to do it based on memory.

15 MS. BOULWARE: All right. Thank you.

16 DR. McCULLEY: So how do you want to deal with
17 that?

18 MS. LOCHNER: We can move on.

19 DR. McCULLEY: Well, no. I mean, that doesn't
20 deal with it.

21 MS. LOCHNER: Well, as I said earlier, we
22 definitely will show you the grid --

23 DR. McCULLEY: Okay. Then --

24 MS. LOCHNER: --and I think we actually. I
25 probably should have said this in the introductory remarks--

1 we don't anticipate this is the last time were going to
2 bring the issue of guidance development for refractive
3 implants to the panel.

4 DR. McCULLEY: Okay.

5 MS. LOCHNER: Once we get your input today, we'll
6 actually draft a guidance, and then I anticipate that we
7 would bring that back to you. So this isn't your only
8 opportunity to make the pass on this.

9 DR. McCULLEY: To comment on the grid, we need to
10 have the grid in front of us, and then we can do it
11 effectively. And knowing how sometimes things work, I guess
12 our specific request is: relative to our consideration, IOL
13 grid rates for chamber implants being the same or different,
14 we would like that to come back to us specifically with the
15 grid in front of us.

16 Dr. Ferris?

17 DR. FERRIS: This is Rick Ferris.

18 I have a general comment with regard to the grid,
19 and I think that I've already heard enough to know that
20 those rates in this grid are below the conceivable rates
21 that--unless we're going to suggest that the study sample
22 sizes need to be dramatically increase--although all of us
23 have the concerns that Drs. Bradley and Macsai mentioned,
24 the ability to confirm event rates like .1 percent is beyond
25 the scope of the study.

1 However, I suspect if those events happen--even
2 one of those events happens, it will have a chilling effect
3 on the ability to use this procedure when there's other
4 procedures around in competition.

5 So it seems to me we need to keep track of those.
6 I'm not sure we need to go--of course, we want to see these
7 grids, but we need to keep in mind that for some of these
8 terrible outcomes, a rate that's below what we can possibly
9 confirm would inevitably make the procedure non-viable.

10 DR. McCULLEY: Dr. Rosenthal?

11 DR. ROSENTHAL: Dr. Rosenthal.

12 The other issue is, of course, is that if a
13 company comes up with results in which they say, "Well, it
14 meets the grid standards," we are going to have difficulty
15 saying--without our panel, saying, "Well, that's quite all
16 right. You may meet the grid standards, but that's not good
17 enough."

18 And I think that's the sense of what we want from
19 you, is that if, in our judgment, even though you meet grid
20 standards, it is clinically unacceptable to not--to have
21 that complication rate, then we shouldn't be approving the
22 device.

23 DR. McCULLEY: Right. And what we're asking --

24 DR. ROSENTHAL: If I'm making myself clear.

25 DR. McCULLEY: Yes, you've made yourself very

1 clear. And I think--I hope we have, too--is that what we
2 are saying is that we'd like to see the grid in front of us.
3 We'll go down it line by line to say, "We think this is
4 okay" or we don't, and whether it should be tightened or
5 not.

6 Dr. Macsai?

7 DR. MACSAI: I just want to respond to Dr.
8 Rosenthal's comment.

9 If there is such a device, perhaps, that meets
10 these standards in the guidance document and it does come
11 before the panel, and if we clinically think it's not safe
12 or effective, we sort of have our hands tied. Because we
13 have to tell you what they can do to make that device
14 approvable. And even if we don't think there's anything
15 they can do, we're stuck with--those are our choices.

16 So that I think when you design this guidance
17 document, we have to allow for that potential possibility,
18 so it doesn't happen.

19 DR. McCULLEY: Other comments?

20 Do you have any further questions on this item?

21 MS. LOCHNER: No, I don't think so.

22 DR. McCULLEY: Okay.

23 [Slide.]

24 MS. BOULWARE: I think these are fairly
25 straightforward. This deals with the loss of BSCVA, and

1 each of these is from the refractive laser guidance
2 document.

3 DR. McCULLEY: Questions?

4 Yes, Gary?

5 DR. RUBIN: Gary Rubin.

6 Is the first one correct, or is it supposed to be
7 .5 percent? It's .5 percent, I think, in the laser
8 guidance.

9 MS. BOULWARE: I'm being told that it is 5
10 percent.

11 DR. McCULLEY: Because the "2 lines" we're
12 starting down in the 20/12, 20/10 range. It is 5 percent.

13 DR. BULLIMORE: This is Mark Bullimore.

14 I think there is a--I think, from memory, there is
15 another value relating to loss of 2 lines of visual acuity
16 and worse than 20/40.

17 DR. McCULLEY: It's less than one percent have--
18 well, it's stated here. I mean, these are the--what's in
19 the current guidance.

20 Is there any disagreement that this should not
21 stand?

22 Seeing none, do you need further clarification?

23 MS. BOULWARE: No, thank you.

24 [Slide.]

25 MS. BOULWARE: Two last safety sheets here on the

1 first postoperative year: induced manifest astigmatism (when
2 only a spherical correction is intended). This is also from
3 the laser guidance document. And then the loss of mesopic
4 contrast sensitivity. We're really looking for contrast
5 sensitivity losses, in terms of a safety concern. We
6 anticipate, in most cases, contrast sensitivity data will be
7 included in the labeling.

8 DR. McCULLEY: Dr. Pulido?

9 DR. PULIDO: The most recent guidance document,
10 though, how does it deal with the contrast sensitivity
11 issue?

12 MS. BOULWARE: The laser guidance document? The
13 laser guidance document stipulates that if you include a
14 warning in your label regarding the, I believe, difficulties
15 with vision in dim lighting conditions, then you're not
16 required to perform contrast sensitivity testing.

17 DR. PULIDO: Because we've had problems with
18 dealing with the contrast sensitivity data before. So why
19 is it magically all of a sudden we can deal with it now?

20 DR. MACSAI: Because we'd have pre-op and post-op.

21 MS. BOULWARE: In this Branch we have a history of
22 requesting this type of data, and we have gained, I would
23 say, considerable experience in looking at this data and
24 find that it's been helpful when included in the labeling,
25 and it's also helping for looking for large losses. And we

1 anticipate that some of these devices--for example, an
2 anterior chamber type lens with a small optic diameter
3 definitely has a potential to cause a glare situation, and
4 could cause large contrast sensitivity losses that we may
5 only pick up, not through Snellen acuities but through this
6 type of testing. And, in fact, we've had devices that
7 companies chose to redesign because of problems that were
8 identified through this type of testing.

9 MS. LOCHNER: Yes, and I think you have to bear in
10 mind that this is--as Ashley had said, it's sort of like a
11 gross screening. It's looking for very large losses. And
12 we have had the experience in the past that we've been able
13 to stop certain studies where there were very gross losses.

14 DR. McCULLEY: Dr. Macsai?

15 DR. MACSAI: I think this is a great benefit, this
16 identification of the mesopic contrast sensitivity, both
17 pre-operative and post-operative, and I think it would be
18 very helpful to everyone.

19 I would recommend, though, that that "greater than
20 2.0 D of absolute cylinder power be reduced to 1.0 D.

21 MS. BOULWARE: Dr. Eydelman did remind me that the
22 refractive laser guidance document also states that the
23 reviewers may ask for contrast sensitivity data if it's a
24 new type of ablation, or a new type of laser for which they
25 feel that there may be a risk of loss of contrast

1 sensitivity.

2 DR. McCULLEY: Okay. You've clarified a previous
3 point. Now we'll go back to Marian's point.

4 Her recommendation is that 2.0 is too high.

5 Rick?

6 DR. FERRIS: This is Rick Ferris again.

7 Two points. One, I think you just clarified it.

8 You said you were not requiring contrast sensitivity in some
9 circumstances?

10 MS. LOCHNER: The laser --

11 DR. FERRIS: For laser--right, but any new --

12 MS. LOCHNER: Refractive implant we have been
13 requiring it.

14 DR. FERRIS: And although I still have a sense
15 that contrast sensitivity is looking for a niche in life, I
16 think that your point about big differences being--you can
17 demonstrate big differences, and big differences are
18 concerning, and they have been useful suggests that we
19 should second your stance: that all new devices should do
20 contrast sensitivity, despite the fact that some lasers
21 don't have to do it any longer.

22 The point about less than 1 percent, less than 2.0
23 D--we're back to this 1 percent. And astigmatism is not
24 necessarily reproducibly assessed either.

25 DR. McCULLEY: Two diopters?

1 DR. FERRIS: But 2.0 D--I'm just saying, when you
2 get to 1.0, you may start to push the reproducibility. So I
3 agree with the overall point. I don't know whether it's 1.0
4 or 2.0. Certainly you want to look at the data. But we
5 have to keep in mind that 1 percent may be around the
6 reproducibility of, certainly, subjective refraction and
7 maybe even automated refraction.

8 DR. MACSAI: But this is "induced."

9 DR. FERRIS: Well, how do you measure the induced?
10 You take the pre and the post, presumably. And so it's the
11 -- reproducibility again becomes an issue.

12 DR. McCULLEY: Okay. Yes--I mean, 2.0 diopters is
13 fairly reproducible, but it's hard to reproduce .5 or .75.

14 Dr. Stark?

15 DR. STARK: Two points. One, about the
16 astigmatism: we've just looked at a large number of patients
17 with a 3.5 mm incision--a little bigger than what you'd make
18 here. Probably this is going to be a 3 mm incision for
19 cataract. I always thought that I induced about 0.50 D or
20 it could change--it averages out at 1 in my hands in over
21 300 cases. So I think you need to leave it at 2, otherwise
22 you're not going to approve any of these.

23 The second point is--I agree with Rick--that we'd
24 like to figure out a place for contrast sensitivity and
25 glare testing but, more importantly would be the subjective

1 questioning of the patient. And I would like to request
2 that all refractive surgery procedures have a standardized
3 mechanism for asking the patient about glare at night. For
4 example, if you have 20 percent of the people that have a
5 severe or disabling glare at night prior to the procedure,
6 but 50 percent of the people have it afterwards, it's easy
7 enough to tabulate that and to present those data to us.
8 That will probably alert us to optic size problems or other
9 things that are causing glare. And that's a problem I'm not
10 sure we've addressed adequately, especially for the
11 correction of high myopia, when you're getting down to small
12 optic size, or volti zone size, and it's something that we
13 need to look at and have reported to us--the subjective
14 problems; difficulty driving at night because of glare would
15 be one question I would like to see asked of all refractive
16 surgery patients.

17 DR. McCULLEY: Would it be reasonable for us to
18 make a recommendation that the FDA, with whatever help you
19 need or don't need, develop a standard pre and post-
20 operative questionnaire for patients? I mean, this keeps
21 coming up repeatedly.

22 MS. LOCHNER: Yes, I think that's a very good
23 idea.

24 DR. McCULLEY: Now, has there been --

25 DR. FERRIS: The NEI--this is Rick Ferris--the NEI

1 is currently sponsoring development of myopic--or myopia--a
2 refractive error questionnaire similar to the NEI FVQ, and
3 it's being done --

4 DR. McCULLEY: Are you going to let the FDA use
5 it, Dr.--Rick?

6 DR. FERRIS: Of course.

7 [Laughter.]

8 DR. FERRIS: It's being done in the same way the
9 NEI VFQ did with the Rand Corporation and its focus groups,
10 and trying to identify the problems that people with myopia
11 have. And I think industry has also felt the desire to have
12 a standardized questionnaire. So the issue is just when
13 that's going to happen, and what do you do in the meantime,
14 because that's still more than a year or so away, and people
15 are doing these now. And as Walter pointed out, you need
16 the change on the questionnaire. You can't just insert this
17 questionnaire at the end as productively.

18 DR. McCULLEY: Dr. Rosenthal?

19 DR. ROSENTHAL: There are two refractive surgical
20 quality of life questionnaires already out; one in
21 Australia?

22 DR. MACSAI: Yes, Australia.

23 DR. ROSENTHAL: And for England, Australia or
24 somewhere.

25 DR. MACSAI: Australia.

1 DR. ROSENTHAL: One, certainly, in this country,
2 developed by Oliver Shein at Johns Hopkins.

3 DR. MACSAI: Right.

4 DR. ROSENTHAL: And the third, which will, I hope,
5 be operational before the end of this year, coming from the
6 NEI.

7 Now, we cannot require companies to use specific
8 questionnaires --

9 DR. McCULLEY: But you can provide guidelines for
10 the questionnaires --

11 DR. ROSENTHAL: But we can provide in our guidance
12 that--you know, a choice of which questionnaires that we
13 feel would be reasonable for them to use.

14 DR. McCULLEY: Okay.

15 DR. ROSENTHAL: But, again, we cannot require it
16 of them.

17 DR. McCULLEY: A specific one.

18 DR. ROSENTHAL: A specific one.

19 DR. McCULLEY: But you could set standards for the
20 questionnaire --

21 DR. ROSENTHAL: Yes.

22 DR. McCULLEY: --and I think that's what we're
23 asking.

24 DR. ROSENTHAL: Correct.

25 DR. McCULLEY: Yes, I've got a cue here.

1 Dr. Higginbotham?

2 DR. HIGGINBOTHAM: My comment, several questions
3 ago, was related to quality of life, because I agree that
4 contrast sensitivity really doesn't have a significant
5 scientific role here, and the quality of life would
6 certainly help it.

7 DR. McCULLEY: Oh--Dr. Bradley. I'm sorry, he was
8 ahead.

9 DR. BRADLEY: Thank you.

10 A comment on measuring mesopic contrast
11 sensitivity. I think there are two issues here that need to
12 be separated. One is that you are measuring mesopic vision-
13 -low light-level vision; and, two, you're using a test that
14 happens to be contrast sensitivity. And I agree, there are
15 some arguments back and forth about the relative merits of
16 which test one should use; should you use contrast
17 sensitivity, visual acuity or any other number of tests?
18 I'm not going to comment on that.

19 I'm commenting on the fact that you are testing
20 under mesopic conditions, and there are sound optical
21 reasons to do this. The optical reasons are that under
22 mesopic conditions, younger adults will dilate their pupils.
23 And if you predict, based on the optical device you're
24 using, that a larger pupil will result in a slightly
25 different optical system being active--and the obvious

1 example is if the implant has a small diameter and pupil
2 dilates to a larger diameter than the implant, you
3 effectively have a bifocal optical system at that point.

4 So combine that with the reports from patients
5 that the primary problem in the past has been vision at
6 night--there was nothing inherently important about night
7 vision. My suspicion is it's purely vision with large
8 pupils. Its the optical change that occurs when the pupil
9 dilates with the small diameter devices.

10 And I think if there is some belief that the
11 device is of limited size and therefore the effective
12 optical system will change when the pupil dilates. It is
13 really incumbent upon the FDA, I think, to demand that some
14 sort of evaluation be done with a large pupil; whether this
15 be done with a cycloplegia refraction, or whether you dilate
16 the pupil simply by lowering the light level, I'm not sure
17 that's particularly important. But it is important to
18 actually evaluate visual performance with a realistically
19 dilated pupil that patients may be using. Again, which test
20 to use? Contrast sensitivity may be as good as any other.

21 DR. McCULLEY: Thank you.

22 Dr. Grimmett?

23 DR. GRIMMETT: Thank you. Michael Grimmett.

24 Dr. Bradley made one point I was going to make. I
25 just echo that measuring contrast sensitivity as a function

1 of entrance pupil size I think is key, and that is the
2 primary issue there.

3 I would also like to echo that subjective quality
4 of life questionnaires I think are vitally important for the
5 evaluation of these patients; the mention of Oliver Shein's
6 refractive surgery vision profile--RSVP profile--I think is
7 important. Literature has shown that our outcome
8 measurements, such as contrast sensitivity and other
9 standard measures do not correlate very well with subjective
10 questionnaires. So I think that is an additional piece of
11 information that is vitally important in order to evaluate
12 the quality of life for these patients.

13 DR. McCULLEY: Dr. Macsai?

14 DR. MACSAI: I was just going to add to Dr.
15 Rosenthal's comments, because there is the Oliver Shein
16 questionnaire, there's the Australian-Michael Lawless
17 questionnaire. And I would say you just need a validated
18 questionnaire, and that solves it.

19 DR. McCULLEY: Okay. Thank you.

20 Dr. Yaross?

21 DR. YAROSS: Yes. I'd like to second what Dr.
22 Macsai just said. I think validation is more important than
23 the specific instrument. And I'd also like to comment that
24 while I would agree--and I think most of industry would
25 agree--that we need to get patients' subjective complaints

1 and that's a very important part of the safety profile, I
2 think, in terms of going into quality of life, unless a
3 sponsor is looking to make specific quality of life claims,
4 we need to not confuse that with safety and efficacy.

5 DR. McCULLEY: Thank you.

6 Dr. Stark?

7 DR. STARK: Just one other point. A simple
8 question: "Would you have the procedure again or not?" I'd
9 like to see added to whatever questionnaire the
10 manufacturers use.

11 DR. McCULLEY: Okay. So I think the point's been
12 made.

13 Do you have any further questions about the issues
14 you have on the screen?

15 MS. BOULWARE: No. Thank you.

16 DR. McCULLEY: Okay.

17 [Slide.]

18 MS. BOULWARE: Based on just these safety issues
19 we have just finished discussing--these are the first post-
20 operative year--we've proposed a sample size of 420 total
21 subjects, with a PMA cohort of at least 300 subjects seen at
22 each form or visit, with a maximum lost-to-follow-up rate of
23 10 percent. And this is consistent with our current
24 guidance for studies of aphakic IOEs, and you have seen this
25 before. And just as a reminder, in terms of what you can

1 detect with this sample size, we've listed some effect sizes
2 for several adverse events.

3 And as a point of clarification, the effect size
4 is the minimum difference between the rate observed in the
5 test population and the expected rate that is statistically
6 significant. For example, to determine that an
7 endophthalmitis is statistically significantly different
8 from .1 percent, the test population would have to have a
9 rate of .7 percent in a population of 300 subjects.

10 Are you comfortable with the 300 sample size?

11 DR. McCULLEY: Okay. I'd like to go straight to
12 where I know the expertise to be. Rick? Arthur? Gary? On
13 these kinds of things--you deny expertise?

14 [Laughter.]

15 DR. McCULLEY: What--are you comfortable with
16 these sample sizes from a statistical standpoint? From a
17 gut clinical standpoint, I'm --

18 DR. FERRIS: This is Rick Ferris --

19 DR. McCULLEY: --reasonable.

20 DR. FERRIS: This has been the sample size that
21 we've suggested people need to use.

22 I gather from some of the comments that I've heard
23 that there may be some people on this panel who will have a
24 tolerance of endophthalmitis considerably below 2 out of
25 300. If two people come in with endophthalmitis for a

1 myopia treatment--two people come in--let's go back to this
2 combined outcome. Any study that has two blinded people,
3 it's probably going to be a non-starter. And I suspect the
4 company knows that as well. So that, in general, I think
5 the sample size is--as all sample sizes are--a reasonable
6 compromise between what a company can do and what you would
7 like to know the truth.

8 So I'm comfortable with this sample size,
9 recognizing that for these very adverse effects, we have a
10 good chance of missing it. I mean, there's a--the other
11 side of looking at this data is that you have a very good
12 chance of missing a .1 percent endophthalmitis rate, given a
13 sample size of 300. And I think that's--we just have to
14 recognize that risk and understand that post-marketing, I
15 assume, these serious outcomes are still going to be
16 watched. I can't imagine them not being published, in any
17 event. So I'm comfortable with this sample size.

18 DR. McCULLEY: I don't think you can make those
19 latter two assumptions.

20 DR. FERRIS: Well, it's the requirement of the
21 agency, isn't it, that they do some sort of post-marketing
22 surveillance. Whether--no?

23 MS. LOCHNER: They're required to report --

24 DR. FERRIS: Serious --

25 MS. LOCHNER: --adverse events.

1 DR. FERRIS: --adverse events?

2 MS. LOCHNER: Yes, serious adverse events.

3 Certainly and endophthalmitis rate greater than their
4 labeled rate, which is usually right around zero or .1
5 percent would be required to be reported.

6 DR. McCULLEY: But that requires reporting, and
7 doctors just plain don't do it.

8 MS. LOCHNER: Correct.

9 DR. FERRIS: I agree with that. Correct.

10 DR. McCULLEY: So do you have a recommendation,
11 taking your two assumptions away?

12 DR. FERRIS: I still think that this sample size
13 is appropriate, and we have to--at least I hope that
14 ophthalmologists that observe serious outcomes will adhere
15 to the law.

16 MS. LOCHNER: Well, you assume that if they don't
17 contact--that at some rate they would contact the company
18 and any company with a rate that goes quite higher than that
19 I think would not want to continue to sell the product until
20 they understood the cause. I mean, they would take it as
21 seriously as the FDA.

22 So there are deficiencies in the fact that, you
23 know, a reporting system is based on whether people report.
24 But there is as much of an --

25 DR. McCULLEY: I don't doubt that the company

1 would take it seriously. My doubt is that the physician
2 would notify the company or the FDA, unless they think there
3 was specifically a problem with the device.

4 So a random case, I --

5 MS. LOCHNER: Yes, I agree. I mean, and you
6 don't--you wouldn't find it out quite as fast. But I think
7 eventually, if there were a problem with a device, the
8 doctor would report it--if he suspected the device--to the
9 company.

10 DR. McCULLEY: Okay, Ralph. You're jumping up and
11 down. Then I'm going to go to Dr. Higginbotham.

12 DR. ROSENTHAL: Well, it's just that you know--Dr.
13 Rosenthal. There is no device that I know of in which there
14 is a low rate of complication during a study in which you're
15 not going to have the potential of putting it out into the
16 marketplace and having a different rate being seen.

17 I mean, the same is true of the drugs. I mean,
18 it's true of everything that's done in a clinical trial.
19 Once it's out in the community and being used, then its real
20 rate--quote "real rate"--can be determined, if you have any
21 mechanism of determining it.

22 The other comment is that we do, when there are
23 major issues related to devices, we do hear about them. And
24 I think that if there were a major issue, we would hear
25 about it. It would be incumbent--I mean, I don't really

1 think that the industry, or the practitioners would withhold
2 the information.

3 DR. McCULLEY: Okay.

4 Dr. Higginbotham.

5 DR. HIGGINBOTHAM: Given the concern that's been
6 raised just in this last discussion about knowing the
7 significant adverse events, I think--and considering the
8 fact that it's a younger group, elective procedures,
9 etcetera--having only 71 percent of the forms required at
10 each time point I think seems to be an underestimation of
11 what we should be asking for.

12 I would suggest something, certainly, higher.
13 Looking at the previous slide--the "PMA cohort of at least
14 300 seen at each form or visit"--one consideration would be
15 to increase that to a higher number so we can at least
16 capture whatever adverse events we can capture while we have
17 the device under surveillance. And I'll just throw a number
18 out: at least 85 percent.

19 DR. McCULLEY: At each time point.

20 DR. HIGGINBOTHAM: At each time point. Currently
21 you're only asking for 71 percent and it's compared to
22 aphakic IOLs, and I'm sure a lot of those patients that had
23 aphakic IOLs were older, and certainly couldn't make all the
24 visits.

25 DR. McCULLEY: What's our standard for refractive?

1 Do we have it? We juste have the 90 percent. Do we have
2 per-visit standard set?

3 MS. BOULWARE: No, I don't believe so.

4 DR. McCULLEY: So is there--before we move off of
5 this, those of you who are wishing speak, do you want to
6 speak to the point that is now on the table?

7 Okay, Dr. Bullimore.

8 DR. BULLIMORE: Point of clarification. These
9 numbers in the right-hand column, are they total event
10 rates? Or are they event rates different from the first
11 column?

12 MS. BOULWARE: I'm sorry, could you --

13 DR. BULLIMORE: I mean, are we looking at the
14 total event rate for iritis of 1.3 percent, or 2.3 percent?

15 MS. BOULWARE: 2.3 percent.

16 DR. BULLIMORE: 2.3. So we're drawing--well,
17 we're setting the bar at 2.3 percent, or seven cases of
18 iritis in 300.

19 MS. BOULWARE: It would be significantly
20 different, yes.

21 DR. BULLIMORE: Okay.

22 Considering --

23 DR. MACSAI: Where did 2.3 come from?

24 DR. BULLIMORE: It's the first column plus the
25 third column.

1 MS. BOULWARE: The numbers under "300"--the .6
2 percent, the 1.3 percent and 1.8 percent--are the effect
3 sizes that you would need--that's the difference you need
4 between the expected rate and the observed rate.

5 DR. BULLIMORE: So that's--I just want to make
6 sure where we're putting the bar. So for endophthalmitis,
7 we're putting it at .7, which is 2 out of 300.

8 MS. BOULWARE: Correct.

9 DR. BULLIMORE: For iritis, we're putting it at
10 2.3 percent, which is 7 out of 300. And if we were to see
11 any persistent CME, it would be set at 4 percent.

12 MS. BOULWARE: That's correct.

13 DR. BULLIMORE: Question for my colleagues on the
14 panel: can someone give me an operational definition of
15 iritis?

16 DR. McCULLEY: Dr. Stark?

17 DR. STARK: And I'd like to address that further.
18 Because as I reviewed the literature on phakic IOLs, iritis,
19 depending on how you measure it, can be a significant
20 problem. And Pierre Santonja and others have--there's
21 literature using fluorophotometry showing a chronic iritis
22 with some of the intraocular--the phakic IOLs; more so with
23 some than others.

24 And I think that as we get into that, we need to -
25 -that's going to be an issue that comes up during the

1 review, and so we need to standardize what we want for
2 iritis or chronic flare by flaremeters, or measures of
3 aqueous turbidity. That will all come up. And it's better
4 to bring it up now and make the requirement than two years
5 from now, when there's a question. And, yes, we can get the
6 subjective impression from the investigator, but I'd like
7 some documentation, since there already is a literature
8 indicating that there's a chronic, mild iritis in some of
9 these patients.

10 MS. BOULWARE: I believe, actually, the panel
11 meeting when we discussed the aphakic IOL guidance document
12 we did ask for panel input on a number of definitions. I
13 can't recall off the top of my head what we had settled on
14 for iritis, but we could certainly include a list of
15 definitions in this guidance document and, you know, we
16 would ask for your comments that they were still appropriate
17 for these implants.

18 DR. STARK: Walter Stark, again.

19 I think it's going to be different to aphakia
20 diseased eyes than it will be for young people with myopia.
21 And I will be happy to supply you with references on the--on
22 phakic IOLs that's know today. And it may be that we'd want
23 to--I can't remember where Santoja--and I'm probably no
24 pronouncing it right--is from, but we may want to find out
25 what work they're doing, and what experience they have to

1 date.

2 Because this will come up, and this will be a
3 stumbling block. And if we don't have that information,
4 it's going to be one of those things that--the companies
5 will say "Why didn't you ask for it before?" "Well, we're
6 asking for it now." And we'd like to know: do these lenses
7 cause chronic inflammation. And that's going to be my
8 largest concern with phakic IOLs, is what will chronic
9 inflammation over a period of 40 years do to an eye?

10 MS. BOULWARE: Any information you can give us
11 will be great.

12 DR. McCULLEY: Okay. What if--I understand what
13 Walter is saying. In the past we have accepted subjective
14 measurement. You're suggesting that we should now request
15 an objective measure.

16 MS. BOULWARE: Right.

17 DR. McCULLEY: And that's going to be a broader
18 issue that you probably need to deal with and have some kind
19 of homework assignment to specific people.

20 You're an expert on this, Ralph.

21 DR. ROSENTHAL: There is only one objective way--I
22 mean, purely objective--and that is using the aqueous flare-
23 meter, but it has not been, as you know, totally accepted
24 that it is totally accurate.

25 But one can, actually--to be fair to the

1 clinician--determine whether or not there's flare or cells
2 in an anterior chamber.

3 DR. McCULLEY: Okay.

4 DR. ROSENTHAL: And I'm not sure putting this
5 extra burden on the company to measure it with this flare-
6 meter would give us any more information than good clinical
7 evaluation, having looked at large numbers of uveitis for a
8 large number of years.

9 DR. STARK: Let me just--Walter Stark, again.

10 Ralph, if you or Doug Jabbs were the ones looking
11 at the eye, I would accept that. There's investigator bias.
12 Every investigation we do we want to work. Otherwise we
13 wouldn't get involved in it. And so to take out
14 investigator bias--which is natural--I would like to see
15 some objective measure of this. And it may--one could use
16 the other eye as control, or age-match control.

17 But I think it's something that's going to come up
18 two years from now, and we might as well have the
19 information. We may find it doesn't make any difference;
20 that it's not interpretable. But I think it's easy enough
21 to set up when we're talking about 20 year and 25 year old
22 people getting an intraocular procedure, that we're going to
23 call--someday, hopefully--reasonably safe and effective.

24 DR. BULLIMORE: The reason I --

25 DR. McCULLEY: Dr. Bullimore.

1 DR. BULLIMORE: This is Mark Bullimore, again.
2 The reason I asked the question was not an attempt
3 to throw more technology at the problem, but just as someone
4 who doesn't spend a lot of time looking at eyes, I want to
5 know what an iritis is. Is it flare in the anterior
6 chamber? Is it flare plus a red eye? Is it something
7 requiring treatment?

8 Now, we've got here 7 cases per 300. I don't know
9 what--seven cases of what? Now is it something that--it's a
10 low-grade, chronic inflammation? Or is it something that
11 required, you know, the use of a steroid? That's what I
12 want to know.

13 DR. McCULLEY: No. To me, as a clinician,
14 anything that would be more than what I would pass as the
15 rare cell I might see passing by is iritis.

16 DR. ROSENTHAL: I don't want to get into
17 definitions. What is glaucoma, we could get into--I mean,
18 you know.

19 [Laughter.]

20 MS. BOULWARE: I was waiting for that.

21 DR. ROSENTHAL: This is Dr. Rosenthal.

22 I understand your concern. And I think we should
23 address it now. And I think--I mean, we should begin to
24 address it now. And I think we should certainly begin to
25 look at ways of doing it.

1 It's difficult to use a control eye, which might
2 be the best way if you're going to do bilateral implants,
3 which is what the patients are going to be pushing for if
4 they have a successful unilateral implant, and which you'll
5 be discussing later on. So that is a very difficult thing
6 to do.

7 I'm not totally convinced that an aqueous flare-
8 meter, in a bilateral situation, will give you any more
9 information than a good clinical exam.

10 Dr. Macsai did say something about a sub study,
11 and I think may that would be a rather important issue to
12 begin to think about, of the small number that might have it
13 in one eye, and compare it to the second eye it it's going
14 to be a long-term thing.

15 If it's going to be sort-term thing, it's really
16 of not much value, I hope you will agree.

17 DR. McCULLEY: Okay. So we'd get back to a
18 validated--should we ever have a validated method for
19 objectifying iritis, we'd like to see that.

20 DR. ROSENTHAL: Well, I mean, iritis--Dr.
21 Rosenthal--iritis isn't a--I mean, iritis you can tell; a
22 good clinician. You're talking about chronic flare, aren't
23 you? Low-grade flare, which could lead to the long-term
24 complications of intractable elevation of intraocular
25 pressure due to damage in the angle, etcetera, etcetera,

1 etcetera.

2 DR. McCULLEY: Okay.

3 Dr. Yaross.

4 DR. ROSENTHAL: Which I'm sure Dr. Higginbotham
5 has seen --

6 DR. McCULLEY: Dr. Yaross.

7 DR. ROSENTHAL: --without lenses.

8 DR. YAROSS: Marcia Yaross.

9 I think if we have standardized definitions and
10 rating scales in the guidance document that will be helpful
11 to the investigators and to the companies.

12 I also wanted to just touch real briefly on Dr.
13 Higginbotham's point about sample size.

14 DR. McCULLEY: We've gotten multiple points on the
15 table here, even though I tried to keep us to the one about
16 sample size--unsuccessfully.

17 DR. YAROSS: Yes. Let me just touch briefly on
18 that.

19 The 300 versus 420. The 300 has been established
20 as the number of completed cases. And 420 is what sponsors
21 are allowed to enroll in order to get 200 cases, after
22 allowances for the lost-to-follow-up. But it's not that
23 it's any 70 percent of a 420 number.

24 DR. McCULLEY: The way this is written, it could
25 be interpreted that way.

1 Dr. Higginbotham?

2 DR. HIGGINBOTHAM: Well, Dr. McCulley, I didn't
3 know if you wanted to get into definitions at this point.
4 So certainly I can wait until we start looking at each of
5 these definitions --

6 DR. McCULLEY: Okay.

7 DR. HIGGINBOTHAM: --but for the moment, I'll just
8 simply state that IOP elevation is not glaucoma.

9 [Laughter.]

10 DR. McCULLEY: Now, what I'd like to do is go back
11 to your original point, which related to sample size and
12 number of patients seen relative to the total enrollment at
13 each visit; which is what I think that Dr. Higginbotham
14 brought up, then we got off on iritis.

15 Dr. Ferris?

16 DR. FERRIS: Rick Ferris.

17 With regard to the 300 versus the 420, I think 70
18 percent is a rather low overall rate. On the other hand, I
19 also think as long as we have 90 percent at the last visit,
20 missed visits may not be so serious with regard to
21 complication rates, because presumably you're capturing all
22 the complication rates that were in the intervals, even if
23 they missed a visit.

24 I don't mind raising the bar, I just think we have
25 to remember that we have some experience, I think, with

1 these companies saying that these patients who are perfectly
2 healthy, don't have any ropes on them and are free-living,
3 ranging human beings, it's very difficult to get them in at
4 every visit. So I think we need to keep that in mind.

5 More concerning to me is something that Dr. Van
6 Meter said earlier, which I happen to agree with, and that
7 is that there is an underlying risk of intraocular surgery.
8 An this sample size that was set up was set up with an
9 overall sense that--I think, what the underlying risk of
10 extraocular surgery was.

11 If this group believes one of two things: one--and
12 perhaps most importantly--that the observed risk of
13 intraocular surgery does not preclude intraocular surgery
14 being used as a method for correcting myopia--because I
15 think Dr. Van Meter is correct, that you're not--well, you
16 would have to prove that your procedure was better than the
17 current intraocular surgery risks. If that's what we're
18 saying, then we need a much large sample size than this to
19 document that the risk rate is lower than seen for cataract
20 surgery today.

21 If the committee felt that--and I think it's very
22 important for companies to know this up front. I mean,
23 before they spend a lot of money on something, if this group
24 is going to--or the FDA is going to say that this is not
25 tolerable; that the rate of complications for cataract

1 surgery is not tolerable for young people who have myopia as
2 their only problem, they need to know that in advance--I
3 think.

4 And if that's the rate--if that's where the bar is
5 going to be set--the current intraocular risk of surgery, if
6 that's where the bar is going to be set, this sample size
7 isn't adequate to demonstrate that you're at that level--I
8 don't think. But I would have to--again, it's a seat-of-
9 the-pants stuff. But my guess is, without doing the
10 numbers, that these sample sizes aren't enough to show
11 equivalence to current cataract surgery.

12 DR. McCULLEY: What would be the correct sample
13 size?

14 DR. FERRIS: I don't know off the top of my head,
15 but there are tons of statisticians and so on --

16 DR. McCULLEY: And so the message--would it be
17 then, is there consensus that we would want to see a sample
18 size that would allow one to have statistical confidence
19 that the complication rate is no greater than that seen by
20 whatever grid adjustments we finally agree to, once we go
21 down the grid?

22 Dr. Matoba?

23 DR. MATOBA: Alice Matoba.

24 Does that mean you're going to differentiate
25 between the intraocular procedures and the corneal rings?

1 DR. McCULLEY: Yes. Because we set two standards.
2 One was the grid for intraocular, and the 1 percent was for
3 intracorneal, yes.

4 Dr. Macsai--is there--do you want to address that
5 question on the table?

6 DR. MACSAI: I want to address that point.

7 DR. McCULLEY: Not that point, the one I brought
8 up.

9 DR. MACSAI: Yes, about the sample size. Isn't
10 that what we're talking about?

11 DR. McCULLEY: Okay. Well, we're talking about:
12 is the recommendation--the specific question at the moment
13 is: does the panel recommend that the sample size be set at
14 whatever the level the statisticians determine is necessary
15 for us to be able to determine that the complication rate is
16 statistically no greater than that seen--at least no greater
17 than, and if we adjust the grid tighter--at that level,
18 relative to cataract surgery, for the intraocular implants?

19 DR. MACSAI: Yes.

20 DR. McCULLEY: Do you want to --

21 DR. MACSAI: Bear in mind--well, I was just going
22 to say, bear in mind that if you look at the slide with the
23 effect sizes, a 300 sample size population will show that
24 you're not statistically significantly different than the
25 grid, to the level shown in the slide.

1 Now, you can increase it to 500 and bring the
2 rates down a little bit. You can increase it to 1,000 and
3 bring it closer into the grid. But that's what you're
4 talking about --sort of narrowing down your confidence
5 interval.

6 DR. McCULLEY: That--Dr. Macsai had the floor.
7 Dr. Macsai.

8 DR. MACSAI: Well, my question, Donna, is if in
9 the intraocular lens studies that were done for cataract
10 surgery originally, a cohort size of 500 was required.

11 MS. LOCHNER: Right.

12 DR. MACSAI: Why would we lower that? I don't
13 understand that. We're talking--

14 MS. LOCHNER: We --

15 DR. MACSAI: --wait, wait. Let me finish this.
16 Because we made mistakes, and we should learn from those
17 mistakes. We implanted ORCs, we implanted LISKIs, we've
18 implanted lenses that were recalled. And if we know that
19 from 500 we didn't get sufficient data to know what would
20 happen in the future--and we're talking about putting
21 implants in younger people who do not have cataracts--why
22 would we lower that bar, and potentially create another
23 situation like --

24 MS. LOCHNER: Well, I'm sure most of the people
25 who are on the panel today were probably not at the panel

1 meeting when we brought this issue. We brought this issue
2 of lowering the sample size from 500 to 300. And at that
3 time we showed the effect sizes for 300 and 500.

4 Now, I certainly don't remember the numbers off
5 the top of my head, but going from 500 to 300, there were
6 not great differences; I mean, like, I'm just throwing this
7 out, but instead of it being .6 it would be like .7 or
8 something.

9 DR. MACSAI: But those were for --

10 MS. LOCHNER: Very, very small differences. And
11 so at that time the panel agreed that lowering the sample
12 size to 500 didn't significantly lower the power of the study'
13 the ability to detect, within that confidence interval.

14 DR. MACSAI: But that was for people with
15 cataracts. That's what we were talking about when we set up
16 that grid.

17 MS. LOCHNER: Right. Right. And we are just --

18 DR. MACSAI: This is a totally different
19 situation.

20 MS. LOCHNER: Right. We are only offering this as
21 a talking point. We are not saying this has to be the
22 criteria for refractive implants. But we're starting as a
23 starting point: what do we require for cataracts? And we're
24 open to your comments if you believe it should be raised,
25 but I think you have to raise that in the context of how

1 significantly does that change the effect size and that
2 that's important.

3 DR. McCULLEY: Yes, I put a question on the floor
4 a minute ago. And Marian seemed to agree.

5 Dr. Bullimore?

6 DR. BULLIMORE: I'm going to disagree with the
7 statement that you made about, really, what is showing
8 equivalence between some benchmark and some new device.

9 You're going to be up in the five figures very
10 quickly, in terms of sample size, and while that may be
11 scientifically desirable, and we may ultimately get that as
12 the result of grid or meta-analysis once these devices have
13 matured, it's totally unreasonable, I think, to ask that of
14 a contact lens manufacturer, an intraocular lens
15 manufacturer, or anybody else.

16 We're here to provide a reasonable assurance of
17 safety and efficacy, and the emphasis is on the word
18 "reasonable." And whether you go to 300, 500--you know, we
19 know the confidence with which we're using the word
20 "reasonable," and I think that's what we have to use.

21 DR. McCULLEY: Okay. What would you suggest is
22 reasonable? The 420?

23 DR. BULLIMORE: I think where we are. You know, I
24 would like us to have the same playing field for all of
25 these technologies--be they intraocular devices,

1 intracorneal devices, or traditional contact lenses or
2 lasers. I think we're--if we start changing the numbers,
3 we're going to get ourselves in all sorts of messes.

4 DR. McCULLEY: All right.

5 Dr. Yaross, you were next.

6 DR. YAROSS: I think my point's been made. Thank
7 you.

8 DR. McCULLEY: Okay.

9 Dr. Belin?

10 DR. BELIN: I think I'm going to agree pretty much
11 with what Mark just said. I think statistics are great
12 until you try to use them.

13 [Laughter.]

14 DR. BELIN: And the problem is, as the procedure
15 gets safer and safer, if you follow that line of thought
16 you're going to require greater and greater number of
17 patients to make it statistically significant. And then, if
18 you're going to hold to that 90 percent follow-up, you
19 become--we're using 90 percent, which isn't a statistically
20 significance. We all know that if you have three times more
21 patient population, you can show significance in smaller
22 number of patients. So we're using a fixed number on one,
23 and not using statistical significance on the other.

24 So, again, going to a huge population is not going
25 to allow us to hold to that 90 percent. It's going to be

1 physically impossible. Do you want a number--I agree with
2 Marian. I think we should not lower it from the 500. This
3 is a new procedure. It's not a new cataract lens. It's a
4 different application.

5 DR. McCULLEY: Dr. Macsai, and then Dr. Stark.

6 DR. MACSAI: I just wanted to echo something Dr.
7 Belin said. If you're assuming safety--you know, the first
8 excimers--I think there were 700, and--oh, gosh. You could
9 correct me. I mean, there was in excess of 700 eyes. We
10 can't assume safety. It's a false and dangerous assumption.
11 That has not been proven.

12 DR. McCULLEY: Dr. Stark?

13 DR. STARK: Yes. As I remember back, I think we
14 required 500 minimum, so maybe 700 PRK cases; the
15 intraocular lenses were 500.

16 I would say--I would let Rick Ferris make the
17 final decision after analyzing the data and thinking about
18 it. But I would vote for 500 on a new procedure; and
19 especially an intraocular procedure.

20 DR. McCULLEY: Okay.

21 Dr. Bradley?

22 DR. BRADLEY: I guess I'm going to reiterate some
23 of what Dr. Ferris and Dr. Belin have said. It's sort of an
24 almost impossible task to try and identify the sample size
25 you're going to need to statistically distinguish a

1 significant change from some other procedure for a very rare
2 event. And the particular events that I'm most concerned
3 about here are sight-threatening events. And, again,
4 because this is an elective procedure, it seems to me almost
5 as a starting point there should be zero tolerance for
6 sight-threatening events.

7 The idea that we should be comparing it to rates
8 for current IOL implants for cataract patients is sort of
9 inappropriate, it seems to me. I mean, this is a procedure
10 we're doing for people who have myopia, and they have
11 innumerable options available to them.

12 If there's examples here of whatever--several
13 within 300 having sight-threatening events, I consider that
14 unacceptable. I mean, I just don't know why it's a
15 statistical argument. And it seems to me that this should
16 be absolute numbers here, and they should be zero,
17 basically, for sight-threatening events.

18 DR. McCULLEY: Okay. Let me be sure that--I have
19 trouble keeping up with so many hands going up. Was there
20 another one on this side?

21 Dr. Ferris?

22 DR. FERRIS: Rick Ferris.

23 I apologize for bringing it up, but that's exactly
24 the reason that I brought it up. And if the tolerance is
25 going to be close to zero, there are two ways of approaching

1 it statistically.

2 One is to say that this procedure has to be better
3 than current cataract surgery. And I haven't done the
4 sample size calculations, but I can tell you by the seat of
5 my pants that that's going to be 10,000 or something. It's
6 not going to happen. If that's what the requirement is, the
7 companies can't do it.

8 If the requirement is that we, in general, have an
9 overall intolerance for blinding complications, and we think
10 that there is a reasonable probability with intraocular
11 surgery that that rate may be as high as 1 percent, which we
12 think is intolerable--and maybe even lower would be
13 intolerable.

14 The one thing about moving from, for example, 300
15 to 500--the overall power to show a difference from cataract
16 surgery doesn't change at all. Your probability of finding
17 blinding events roughly doubles. So if you went from 300 to
18 600, it would double. And saying that, that's like saying
19 your probability of winning the lottery doubles by buying
20 two tickets.

21 [Laughter.]

22 DR. FERRIS: And that's true, too.

23 So you have to realize that you still have a high
24 probability of missing blinding complications even at 600.

25 DR. McCULLEY: Okay. We have idealism and

1 practicality here.

2 What would you recommend as a number--since we
3 have to agree, or we should try to agree on a number to
4 recommend. What are we going to be.

5 DR. FERRIS: If previously 500 was used for
6 intraocular lenses, I think that it is reasonable to say,
7 "We're going to go to a higher standard than we're going to
8 use for extraocular surgery, but we're not going to go out
9 of the ballpark of what's feasible." And 500 seems like a
10 reasonable compromise; recognizing that we're risking
11 missing some significant blinding complication. But it's a
12 compromise.

13 DR. McCULLEY: Okay. So you're saying 500 to
14 replace the 300.

15 Is there consensus in that regard? This is--are
16 we talking about both the intracorneal implants and the
17 intraocular device here--on the cohort? Just intraocular,
18 you're saying.

19 DR. MACSAI: Just intraocular.

20 DR. McCULLEY: So intraocular. So we're saying a
21 cohort of at least 500 seen at each visit.

22 DR. MACSAI: At least.

23 DR. McCULLEY: Is there disagreement to that?

24 Dr. Yarros, you want to speak for industry.

25 DR. YAROSS: I guess I'd just like to put back on

1 the table that a number of years ago there was a careful
2 analysis, and the power of 300 studies was considered to be
3 quite a good compromise, in terms of the types of events.

4 With these intraocular implants, the types of
5 events are fairly well known. And as a result, I think
6 serious consideration should be considered to that as part
7 of an overall look at the issues of parity here.

8 DR. McCULLEY: Okay. That's industrial's
9 perspective.

10 Dr. Macsai?

11 DR. MACSAI: Well, I just have to respectfully
12 disagree with Dr. Yarros --

13 DR. McCULLEY: Okay.

14 DR. MACSAI: --because I'm not sure we know all the
15 information.

16 DR. McCULLEY: Well, she worded it carefully. She
17 said "types of."

18 DR. MACSAI: Okay.

19 DR. McCULLEY: Incidence, we don't know. And our
20 tolerance for incidence is going to be less in this than it
21 is in a surgical procedure returning vision to a patient who
22 has cataracts.

23 DR. MACSAI: Right.

24 DR. McCULLEY: And, again, I get so darned
25 confused when we start getting into statistics. It's so

1 difficult to try to make logic out of some of the
2 statistical approaches for a clinician. I'm sorry.

3 Gary?--at least for this clinician.

4 DR. RUBIN: Gary Rubin.

5 I just want to address a small point, and that is
6 the issue of whether it's each visit or some important
7 visits. If our real interest right now--you sample-size for
8 safety. I don't think that the "each visit" standard needs
9 to be quite that high. It's 500 seen at the end of the
10 study. Because if we miss an adverse event sometime during
11 the middle of the study but we pick it up later, we still
12 catch the adverse --

13 DR. McCULLEY: Maybe for adverse events, but for
14 stability and things of the sort --

15 DR. RUBIN: No, that's a different issue.

16 DR. McCULLEY: --it gets to be--right. But we're
17 going to have to come up with a number that has to apply to
18 everything. We're not going to have --

19 DR. RUBIN: But I thought we were setting the
20 higher sample size standard because of safety issues only.
21 I thought we agreed that the lower sample size was actually
22 adequate for stability and all. Therefore something like
23 300 seen at each form or visit would be adequate for
24 efficacy, but --

25 DR. McCULLEY: Maybe, but if we have 500 for the

1 other, we're going to have the patients evaluated for
2 safety at each visit. So I'm missing the --

3 DR. RUBIN: I'm saying we can allow missed visits,
4 and that won't impair our ability to determine safety.

5 DR. McCULLEY: Okay. And this would get back to
6 the original point that Dr. Higginbotham brought up.

7 Dr. Higginbotham?

8 DR. HIGGINBOTHAM: I really have a concern,
9 because this is the second comment I've heard that we could
10 miss some of the visits early on. I mean, we could miss a
11 transient intraocular pressure elevation; transient iritis.
12 I think it's important to know those early events, because
13 this will be a procedure that's being used electively in the
14 community.

15 So I would suggest, if you're increasing the
16 sample size to 500, I would still set the bar rather high--
17 at least 85 to 90 percent of the cohort should actually be
18 seen, at least at some of the early visits.

19 If you want to define some key visits early on,
20 and allow missed visits, then you're getting a little bit
21 complicated.

22 DR. McCULLEY: I've seen other studies where we've
23 had, you know, not the same patients followed all the way
24 through. Really, it brings up all sorts of problems.

25 Dr. Belin?

1 DR. BELIN: Could we back up one slide?

2 MS. LOCHNER: Sure.

3 DR. STARK: And while they're doing that, can I
4 ask: are we talking about one or two years' follow up?

5 MS. BOULWARE: We haven't gotten there yet.
6 We'll be discussing that.

7 MS. LOCHNER: Also, be clear whether you're
8 talking about 500 total enrolled, or 85 percent of 500 seen
9 at the --is that the point you're --

10 DR. McCULLEY: Well, we were talking about the 300
11 --

12 MS. LOCHNER: 500 equals 85 percent, so that you'd
13 enroll more than 500--right.

14 DR. McCULLEY: Yes--to get the 500 at each visit
15 is where we've got.

16 DR. BELIN: The question I had, because I know
17 sometimes in the past, when we've looked over some laser
18 studies, we've thrown out as not having follow-up, those
19 patients that missed any appointments. I just want to make
20 sure we're all saying the same thing. Even though we agree
21 that we're going to change the sample size here, what we're
22 saying is: 420 subjects, at least 300 seen at each form or
23 visit. They don't have to be the same patients. That's not
24 real clear.

25 You can have 420 people, but 300 of them are seen

1 at each visit, but at the last visit, you've lost no more
2 than 10 percent of follow-up. That's different than what I
3 think we're all saying. So this needs to be cleared up.

4 In other words, 420 people, 300 at each point--
5 those 300 can be any of the 420. But at the endpoint--so
6 it's 90 percent at each visit.

7 MS. BOULWARE: I think that's what Dr.
8 Higginbotham was addressing earlier by her asking for 85
9 percent of the total enrolled, which is different than
10 what's on that slide.

11 MS. LOCHNER: So instead of 420 and 300, we've
12 read 420 and 85 percent of 420.

13 DR. BELIN: Okay. The--300--420 is below 85
14 percent.

15 MS. LOCHNER: And then I think you can live with
16 the fact that it's not the same people if the percentage of
17 the total goes up at each visit.

18 So you're suggesting we replace the 300 number
19 with 500, so we obviously have to allow the companies to
20 enroll more than 500 to attain 500.

21 DR. McCULLEY: I think that's the sense. Is it?

22 MS. LOCHNER: And are we with the 85 percent
23 standard, basically? Because we can figure out what it is.

24 DR. BELIN: The 500 should be maximal lost-follow-
25 up of 10 percent. So we want 90 percent to be 500. Or do

1 you want 500 at every--that's a difference. That's why I'm
2 bringing it up.

3 MS. LOCHNER: No, you want 500 to be the number
4 that are seen at the last visit. So you add a little bit
5 more to allow for the 10 percent lost-to-follow-up.

6 DR. McCULLEY: Right--and at each time point, no
7 more than 15 percent not seen at that form/visit.

8 DR. BELIN: So it's 550 enrolles if you're only
9 going to allow --

10 DR. McCULLEY: Well, they can figure the numbers
11 for the total. But the principle--let me try to state it
12 just to be sure. And if I'm not stating it correctly, it
13 won't be the first time I've been wrong today.

14 We want at least 500 patients to complete the
15 study, with no more than 15 percent at each form not being
16 seen. Does that state it simply? And then you, then, have
17 to do the math to figure the total number.

18 Dr. Belin?

19 DR. BELIN: I thought the third part was a maximal
20 lost-to-follow-up at final exam of 10 percent.

21 DR. MACSAI: That's right. So it's not 500 at
22 final. It's actually like--the amount you'd have to enroll
23 is close to 600.

24 DR. McCULLEY: Well, if we say--yes, if we said
25 500, allowing no more than 10 percent lost-to-follow-up, and

1 not more than 15 percent not seen at each form/visit.

2 MS. BOULWARE: I think we're clear on what you
3 want. We'll check on the numbers.

4 DR. McCULLEY: All right. So is what I said
5 agreed?

6 Dr. Higginbotham?

7 DR. HIGGINBOTHAM: I agree with that, but I think
8 the discussions--it was my interpretation that the
9 discussion was that you guys wanted 500 at least at each
10 form visit.

11 So I think--but that's not what you just said.

12 DR. McCULLEY: I know. I --

13 DR. HIGGINBOTHAM: But I agree with what you just
14 stated it as, because I think there hasn't been a compelling
15 reason, from our resident statistician, that there is a
16 significant difference between 500 and 600, in terms of the
17 sample size, given what we're doing here.

18 DR. McCULLEY: Yes, our discussion was along the
19 lines as though we would have had 500 at each visit. I then
20 softened that, based on all the other discussions. But,
21 yes, you're right. We discussed one thing and then I stated
22 what I hoped was a compromise consensus just a moment ago.

23 Dr. Ferris?

24 DR. FERRIS: Rick Ferris.*

25 Just to make sure we know what we're asking for,

1 in the early treatment of diabetic retinopathy, say for
2 example, where we have full-time coordinators and I think
3 diseased people, the rate at each visit that we had follow-
4 up--and I think the same is true with the age-related eye
5 disease study now--it's about 90 percent; between 85 and 90
6 percent.

7 And that's under those conditions. These
8 conditions--we're making--we're setting this bar very high
9 for these companies. And I'm not --

10 DR. McCULLEY: It's a guideline, Rick.

11 DR. FERRIS: Well, if it's a--well, I'm not sure
12 whether it is a guideline.

13 DR. ROSENTHAL: Well, no, it's--this is Dr.
14 Rosenthal--it's a guideline. But I also want to get back to
15 the point about the percentage. And Dr. Abrams is
16 absolutely right. You know, if you see, say, 75 percent of
17 this group, the number of patients who have iritis or
18 elevated intraocular pressure, you're going to have a good
19 handle on that. Seeing those extra 25 patients is not going
20 to make a big difference.

21 DR. FERRIS: No--this is Rick Ferris, again--and
22 it gets even worse, or even better than that. And that is,
23 if you have 90 percent at the final visit--and I think I
24 would emphasize that the final visit that the percentage has
25 to be higher than the 70 percent. Because I don't missing

1 the interim visit, but I definitely mind the final visit.

2 And I would put out one other thing for
3 consideration and that is if you're worried about blinding
4 complication s, there are visits and then they're totally
5 lost from contact, and I think that you could have an even
6 higher bar from totally lost from contact; that you could
7 say that we are not tolerant of 5 percent totally lost from
8 contact.

9 In the age-related eye disease study, for example,
10 we have less than 1 percent totally lost from contact after
11 five years. So it's not that it can't be done. And you do
12 have the opportunity to call people up and say, "Did this
13 procedure blind you? Even if you're not coming into the
14 clinic." And there may--blinded people may have a tendency
15 not to come back to the --

16 DR. McCULLEY: Okay. So how would you adjust the
17 statement I made? Would you have a recommendation to adjust
18 what I said? Which basically was: 90 percent at final visit
19 --

20 DR. FERRIS: Yes.

21 DR. McCULLEY: --with a minimum number of 500 being
22 seen at last visit --

23 DR. FERRIS: Right.

24 DR. McCULLEY: --with no more than 15 percent not
25 seen at each form/visit.

1 MS. BOULWARE: We have those numbers, if you'd
2 like to know. It would be 550 enrolled; 500 at the last
3 visit; and 468 at each visit, minimum.

4 DR. FERRIS: If I was going to relax anything, I
5 would relax the "at each visit" to even 80 percent. But --

6 DR. McCULLEY: Okay. Is there a consensus for
7 that? I'm trying to get panel consensus here. Dr. Abrams?
8 Rubin. Whatever--I'm sorry, Gary.

9 DR. RUBIN: I'm agreeing with --

10 DR. McCULLEY: To relax it to 80 percent.

11 DR. RUBIN: I'm agreeing with relaxing to 80
12 percent, because if the issues are not transient events but
13 permanent safety events --

14 DR. McCULLEY: So we relax 15 to 20 percent.

15 Is there agreement to that? Is there disagreement
16 to that?

17 Is there agreement with the statement with that
18 relaxation in it? Is there disagreement? There's none
19 seen.

20 Should we--that, then finishes this point, right?
21 Or do you have another question?

22 MS. BOULWARE: Only in the case of corneal
23 implants, where endophthalmitis and the grid rates are not
24 part of the safety discussion; the safety--your lowest rate
25 really is your 1 percent adverse event rate.

1 And the same sample size calculations basically
2 apply. With a sample size of 300 your effect size is 1.3
3 percent. So you'd have to have an adverse event rate for a
4 particular type of adverse event of 2.3 percent to be
5 statistically different than the 1 percent. Are you
6 comfortable with that--for corneal implants.

7 DR. McCULLEY: Okay. For the implants, do we go
8 with what they have written here, what we stated for
9 intraocular implants, or something different?

10 Dr. Macsai?

11 DR. MACSAI: I know this won't be popular, but I
12 would vote for the same as the intraocular implants, since
13 we haven't had reversibility and safety proven.

14 DR. McCULLEY: What is it for the laser now--laser
15 corneal.

16 MS. BOULWARE: I believe the guidance just says
17 between 300 and 400 patients, and asks the sponsors to do
18 their own system of calculations.

19 DR. McCULLEY: Should it be any different for an
20 intracorneal implant than it is for laser? Is there any
21 logic to that?

22 DR. MACSAI: My point is that the original laser
23 studies were at about 700. And after we had the laser
24 verified by two different--three different sponsors, you
25 know, then this guidance was written, and the bar was

1 lowered. That's my point.

2 DR. McCULLEY: Okay.

3 Dr. Belin?

4 DR. BELIN: Well, I agree totally.

5 DR. McCULLEY: Say it in the mike.

6 DR. BELIN: I agree totally. We haven't
7 established safety, and that's what was initially done by
8 the laser manufacturers. And the first time we look at any
9 new technology we probably need a higher sample size.

10 DR. McCULLEY: Okay. So this puts, then, the
11 intracorneal implant into the same principle as the
12 intraocular implant. That's what Dr. Macsai suggested.

13 Is there agreement, disagreement to that?

14 Dr. Belin, then Dr. Ferris.

15 DR. BELIN: Even so, I think my recollection, when
16 we even discussed that, is we even made the stipulation that
17 if a new laser came along that substantially was different -
18 -a new wave length, other type of modality--that that lower
19 sample size would not apply.

20 DR. McCULLEY: Is that clear currently in the
21 guidance document, and in the minds of the FDA and in
22 industry?

23 DR. EYDELMAN: Actually, there is no such--Dr.
24 Eydelman here--there is no such stipulation in the guidance.
25 The 300 to 400 is based on the safety endpoints as listed in

1 the guidance, and that was a 300 to 400 range.

2 DR. McCULLEY: So a new laser comes along, it
3 would be 300 to 400.

4 DR. EYDELMAN: Correct.

5 DR. McCULLEY: I don't see any logic, I'm sorry,
6 in --

7 DR. MACSAI: No, that's if a new laser is
8 considered to be biologically equivalent, right?

9 DR. McCULLEY: No. No. It doesn't say that.

10 MS. LOCHNER: There some of those stipulations
11 that affected the guidance is what Malvina just said.

12 DR. EYDELMAN: The guidance is for excimer lasers.

13 DR. MACSAI: Right. It's for excimer lasers.

14 DR. McCULLEY: Okay. So the logic here would be
15 this is something substantially different from the excimer
16 laser that we have experience with.

17 DR. MACSAI: Right.

18 DR. McCULLEY: So you would use the principle that
19 we'd be using for intraocular implants, which is also new,
20 but also has some added risk factors.

21 Dr. Ferris?

22 DR. FERRIS: This is Rick Ferris.

23 This is not just laser, this is LASIK. There are
24 some pretty rude things being done to the cornea in some of
25 these procedures that aren't all that different than the

1 implantable things. So I guess I'm--I'm not sure I see the
2 logic between the--I see some logic in separating
3 intraocular from extraocular. I'm not sure I see the logic
4 of saying that some of these extraoculars only need 300, and
5 some of them need 500. I'm not sure I follow that.

6 DR. MACSAI: Well, in the--Dr. Macsai--in the
7 first two LASIK applications we looked at, the numbers were
8 in the thousands. So you can say it violates the cornea,
9 but we're talking about safety in something that has not
10 been established.

11 DR. McCULLEY: Other thoughts? I see both sides
12 to the point. Other thoughts?

13 Dr. Rosenthal, would you like to try to--I mean,
14 so there's sentiment that it should be the same for
15 intraocular devices because it's a completely new approach.
16 There's sentiment that it should not be any different from
17 the excimer laser because it's extraocular and in the
18 cornea.

19 DR. ROSENTHAL: Could we hear from some of the
20 other members of the panel?

21 DR. McCULLEY: Please.

22 Dr. Belin?

23 DR. BELIN: Yes. Let me just have everyone turn
24 to page 16 on the guidance document. 3.2.7.1 "A sample size
25 for studies with refractive surgical laser which ablate

1 tissue within 200 u of the endothelium, or for lasers with
2 fluencies greater than 230, or for lasers with raise other
3 safety issues should be calculated based on the expected
4 rate of adverse--"--etcetera, etcetera.

5 It's clearly stating that that sample size of 300
6 to 400 does not apply for other lasers that we are not yet
7 familiar with. Okay. Simple.

8 MS. BOULWARE: The problem comes in in that 300 to
9 400. I mean it's--how closely do you want to be able to
10 detect something that occurs at a rate of 1 percent? You
11 can have not very good assurance of detecting something that
12 occurs at 1 percent with a sample size of 100. You can have
13 very good assurance of detecting something that occurs at a
14 rate of 1 percent with 1,000. It's really your comfort
15 level, and how closely can you detect it? And what are the
16 chances you might miss it?

17 And that's what drove the numbers up, to try to
18 detect that .1 percent endophthalmitis rate. That's why we
19 got to 500, with the--you know, the 1 percent is the value
20 we have. You know, if the corneal implants, for any one
21 particular adverse event, you don't need the numbers you
22 need to detect a 1 percent rate that you need to detect a .1
23 percent rate.

24 DR. McCULLEY: Dr. Wang, you had your hand up.

25 DR. WANG: Ming Wang.

1 I think there is a difference between a procedure
2 which goes into the eye every time--intraocular procedure -
3 -or intracorneal procedure which may, by accident, cut into
4 the eye. So I think probably, for intracorneal procedures,
5 it's reasonable, giving both sides of the argument, somewhat
6 relaxed, but still pay attention to these rare
7 complications.

8 DR. McCULLEY: Dr. Pulido?

9 Dr. PULIDO: I disagree with the comment that
10 corneal procedures may need to have a more relaxed adverse
11 event, or sample size numbers, because they can turn into
12 intraocular procedures down the line. For instance, the
13 article by Dr. Siler that Dr. Stark gave us yesterday showed
14 that three patients that had purely intracorneal procedures
15 turned out to be intraocular procedures subsequently.

16 So I don't think we can decrease the bar for new
17 procedures because one is intraocular and one is
18 extraocular.

19 DR. McCULLEY: Okay. What I'd like to do is go
20 around the panel, since we have a lot of people that haven't
21 spoken. And if I give you two choices, is this fair? Do we
22 set the 500 number that we set for intraocular, or do we set
23 the 300 that was on the previous slide here?

24 Is that fair to do? And will that be helpful to
25 you? Because I feel like we're--I'm not sure what the

1 consensus is.

2 MS. LOCHNER: Yes. By "the 300" you mean the
3 criteria set for lasers.

4 DR. McCULLEY: Yes--yes, excimer.

5 MS. LOCHNER: Yes, excimer lasers.

6 DR. McCULLEY: Yes. So the criteria set for
7 excimer, or the criteria set for intraocular. And if you
8 disagree with either one of those, just say you want
9 something different, and we'll try to figure out what the
10 difference is if there's enough sentiment to try to figure
11 that out. Fair?

12 Dr. Stark?

13 DR. STARK: I didn't understand. You're going to
14 say--you're saying 500 for a new procedure --

15 DR. McCULLEY: No. Sorry. Let me re-state it. I
16 said it poorly.

17 We either set the same standard that we have set
18 for excimer, which is in the 300 to 400 range; we set the
19 same standard that we just set for intraocular implantable
20 devices, which is 500 at the last visit, with all the other
21 qualifiers; or do you think it should be something very
22 different, but if there's a sentiment to look for something
23 very different, then we'll come back to that in group
24 discussion. Otherwise, we will not.

25 Fair? Helpful?

1 DR. MACSAI: Yes.

2 DR. McCULLEY: Let's start with Dr. Yaross. Pick.

3 DR. YAROSS: This is a very tough one, because I
4 think parity is important, and level playing fields are
5 important. But I think that it should be set based on what
6 can be anticipated as the complications.

7 So --

8 DR. McCULLEY: Now, you have to pick. Right now
9 all I want you to do--no soliloquies, no discussions, no
10 nothing. I want you to pick

11 DR. MACSAI: Why don't you just vote?

12 DR. McCULLEY: Okay, we'll vote, then.

13 All right. How many think it should be set at--
14 thank you--good suggestion--at the--with the same principle
15 as the excimer laser.

16 DR. STARK: Jim --

17 DR. McCULLEY: Okay. Dr. Stark, for
18 clarification.

19 DR. STARK: Excimer was 500, now it's 300.

20 DR. McCULLEY: It's 300 to 400.

21 DR. STARK: But it was 500. So if we go --

22 DR. McCULLEY: I'm saying where it is now.

23 DR. ROSENTHAL: May I make this a little easier,
24 and that is--this is Dr. Rosenthal--vote between what you've
25 decided on the intraocular implants, and what has been

1 suggested for the intraocular lenses, because that we have
2 good workup on. 420 and 300. Well, you know, that comes to
3 about the same thing.

4 DR. McCULLEY: I tried that one before, and that
5 one didn't fly, Ralph. But --

6 DR. ROSENTHAL: Well, 300 to 400 is --

7 DR. McCULLEY: Okay. So we really have--okay we
8 have four different things, really. I know--it makes it
9 worse. But we do. And if we don't get the four out, then
10 it gets to be a bigger mess.

11 We've got the--what we decided for intraocular
12 phakic implants; we have what we started off with excimer,
13 which was suggested at around 500 completed, which is very
14 similar to what we set for intraocular implants--so not
15 substantially different. So let's take that one out of
16 there.

17 We have the one that is currently existent for
18 excimers, which is in the 300 to 400 range.

19 DR. STARK: Can I just make one --

20 DR. McCULLEY: And then we have the other, which
21 is --

22 DR. STARK: Can I make one suggestion. It may
23 simplify it.

24 I'd like to vote on new technology for the
25 correction of myopia, and I'd like to then say that we have

1 the option for lowering that bar after we feel comfortable
2 with that technology in general.

3 DR. McCULLEY: Would you make a motion?

4 DR. MACSAI: I second that.

5 DR. McCULLEY: Speak into the mike, Walter, and
6 say it again--in the form of a motion.

7 DR. STARK: Well, I would move that we make a vote
8 on the number of eyes required for new technology for
9 correction of myopia.

10 DR. McCULLEY: And would you recommend that number
11 to be --

12 DR. STARK: 500.

13 DR. McCULLEY: --the number that we established
14 for, and the principles we established for phakic
15 intraocular implants.

16 DR. STARK: I just heard you say the number is
17 500.

18 DR. McCULLEY: Well, it was 500 the last visit,
19 and it was 550, and then the 20 percent at each visit; no
20 more than 10 percent lost-to-follow-up, and so forth. So
21 the principle that we established.

22 DR. STARK: Correct.

23 DR. McCULLEY: Is--well, we've already --

24 DR. MACSAI: Second.

25 DR. McCULLEY: For all new technology--that we

1 would say that would apply to all new technology is the
2 motion, although I guess we're not supposed to be--I don't
3 know if we're supposed to be taking votes.

4 Okay. Is there a second to that motion?

5 DR. MACSAI: Second.

6 DR. McCULLEY: All in favor--is there further
7 discussion on the motion?

8 Dr. Bradley?

9 DR. BRADLEY: Just a point of clarification. The
10 wording would include new spectacle technology, so I think
11 it needs to be just --

12 DR. McCULLEY: Refractive surgical technology.

13 DR. BRADLEY: Thank you.

14 DR. McCULLEY: Any further discussion?

15 All in favor of that principle, raise your hand.

16 [A show of hands.]

17 DR. McCULLEY: Fourteen.

18 All opposed.

19 [A show of hands.]

20 DR. McCULLEY: Fourteen to one. That
21 recommendation carries.

22 Now, the question then would be for--to get off
23 the dime on this--we've set that for the intraocular
24 implant, do we think that--how many* think that the bar
25 should be lowered for intracorneal --

1 DR. MACSAI: We just voted on that. It's done.
2 Let's move on. He said "surgical techniques for myopia"--
3 refractive surgical techniques.

4 DR. McCULLEY: All right. Walter had initially
5 said, but with the understanding the bar could be lowered.
6 So we're saying we're not lowering the bar.

7 DR. MACSAI: Not until we establish safety.

8 DR. BELIN: For new.

9 DR. McCULLEY: For new. Okay. All right.
10 Got it?

11 MS. BOULWARE: Thank you. Yes.

12 DR. McCULLEY: Okay. Can we--is there a sentiment
13 for a break, or do we charge on through. I know there were
14 people who wanted a break before. I was trying to reach a
15 stopping point. We finally reached one. Do we keep going?
16 I don't hear a sentiment.

17 We can say five minutes, but it will be 10 or 15.
18 So what do you want? Do you want to keep going? How many
19 want to keep going?

20 DR. STARK: We're going to break for lunch in
21 about an hour.

22 DR. McCULLEY: We'll break for lunch in about an
23 hour.

24 DR. BRADLEY: Could the chair give us an estimate
25 of how much work we still have to do?

1 DR. McCULLEY: We are, by page, about a third of
2 the way through the work that we have to do. But,
3 hopefully, the hardest part is over.

4 DR. PULIDO: I would make a motion to keep going.

5 [Laughter.]

6 DR. MACSAI: Second. Second.

7 DR. McCULLEY: I for one have to take a break in a
8 minute. But we'll just keep going. We'll take individual -
9 -we'll have to go to the bathroom alone.

10 [Laughter.]

11 DR. McCULLEY: Okay. Any other comments on this -
12 -we're through with that now, right?

13 Okay. Next point.

14 [Slide.]

15 MS. BOULWARE: I don't know if what you said is
16 true about the hardest part being past, because the next
17 part to discuss is some of these long-term safety issues,
18 which include loss of endothelial cells and possible corneal
19 decompensation, which could occur in both corneal and
20 chamber implants; the induction of cataract; induction of
21 raised intraocular pressure. And we do have that defined--
22 from your previous comments, Dr. Higginbotham. And Dr.
23 Rosenthal has also suggested aqueous flare as a long-term
24 issue to consider.

25 First I want to discuss the endothelial cell loss.

1 In the past, sponsors have generally performed a sub-study
2 that was sufficient to detect a 10 percent loss at the one-
3 year exam. Do you consider a 10 percent loss to still be an
4 appropriate clinically significant endpoint for corneal and
5 chamber implants, and should this endpoint at the one-year
6 timeframe or at the end of the study?

7 I guess I'll recognize you Dr. Macsai.

8 DR. MACSAI: Well, thank you, Dr. Boulware.

9 I have some comments on this endothelial cell
10 loss. I think that --

11 MS. THORNTON: Marian, excuse me. I think it
12 would appropriate to wait until Dr. McCulley gets back.

13 DR. MACSAI: Oh.

14 MS. THORNTON: I know we'd like to move on, but he
15 will be back.

16 Do you have any more clarification?

17 DR. FERRIS: Is everyone taking a break?

18 DR. STARK: Can I just say something endothelial
19 cell studies --

20 MS. THORNTON: No. I think it would be better to
21 wait until he gets back, because he has to be able to--to
22 deal with you individuals.

23 DR. MACSAI: So do I still get to say it when he
24 comes back? We've decided that he shouldn't be alone.

25 [Laughter.]

1 MS. THORNTON: I f you could please try to be back
2 in the room in five minutes.

3 [Recess.]

4 DR. McCULLEY: Okay. Marian informed me she was
5 first up. I went to the bathroom alone before the group.
6 So I missed the last few words said. So --

7 MS. BOULWARE: I had simply brought up the--some
8 of the long-term safety issues you wanted to address, and
9 the first of those was endothelial cell loss; and that, in
10 the past, we've asked sponsors to conduct a sub-study that
11 was sufficient to detect a 10 percent at one year. And our
12 questions are whether 10 percent an appropriate endpoint,
13 for both corneal and chamber implants, and whether this
14 endpoint should be at one year or at the end of the study.
15 And Sally rightfully pointed out that I could not recognize
16 Dr. Macsai in your absence.

17 DR. McCULLEY: Okay.

18 Let me just tell you what the game plan is.
19 Through all of the endpoints--endothelial cell count loss,
20 cataracts, raised IOP--takes us to the first break for
21 public comment on issues that we are in the process, or that
22 we have just discussed, only. My goal is for us to get to
23 that point and finish the public comment, and then take a
24 lunch break.

25 Okay. Dr. Macsai?

1 DR. MACSAI: I wanted to comment on the
2 endothelial cell loss, and bring to the agency's attention
3 some of the problems with what's proposed.

4 Yesterday, Dr. Stark reviewed some of the
5 literature regarding endothelial cell loss, and brought to
6 our attention two good studies; one by Proeme, and one by
7 Perez-Santoya, demonstrating that with discontinued contact
8 lens wear, there may be an increase in the central corneal
9 endothelial density. So that if you have a measurement of
10 the central endothelial corneal density, and that's what you
11 use--exclusively--and demonstrate a 10 percent loss at one
12 year, it may, in fact, be a 17 percent loss. Or you may
13 have a 3 percent loss that's actually a 10 percent loss.

14 So there's an inherent problem with this
15 measurement. But what's important is, to me, one: how we
16 fix this problem for measuring it in these individuals. I
17 don't know what the appropriate control would be.

18 But, number two is if you indeed had a 10 percent
19 loss per year, and you started out with 2,500 cells per
20 square mm, it would only take 14 years for your cornea to
21 decompensate--assuming there's no aqueous flare; assuming
22 there's no elevated intraocular pressure, etcetera, etcetera
23 --no compounding factors. So that if you had this device,
24 whatever it is, at age 30, by age 44 you'd be seeking a
25 corneal transplant.

1 And, therefor, there's a big inherent problem
2 here, and there's a lot of reasons that a cohort will need
3 to be studied much longer than one year.

4 MS. BOULWARE: Maybe I should show my next slide,
5 which addresses progressive endothelial cell loss. We also
6 had questions about progressive cell loss, and maybe you
7 should see both of these.

8 DR. STARK: While you're getting that slide, can I
9 make a comment about that?

10 DR. McCULLEY: Yes, I think--okay.

11 DR. STARK: Okay.

12 One of the ways to solve the problem--and from my
13 review yesterday, it is apparent that if you wear contact
14 lenses you can have decrease in cells. You take them off
15 and, it seems to me the literature would support that maybe
16 there's a 7 percent increase after taking off the contact
17 lenses. One of the ways to solve this problem would make
18 sure they have adequate studies on people who have not worn
19 contact lenses--or separate, for sure, those that have worn
20 contact lenses up to the point of their surgery, and those
21 that have not--don't have a history of long-term contact
22 lens use.

23 And also I'll say that 7 percent--Bill Bourne told
24 me that he has a paper in preparation that would support
25 that apparent decrease of 7 percent from wearing the contact

1 lenses.

2 DR. McCULLEY: How long does it take for that 7
3 percent to recover?

4 DR. STARK: I don't know, but we could ask Bourne.
5 I'm sure he's--and I referenced the two other groups.

6 DR. SUGAR: Three months it would take.

7 DR. STARK: Three months?

8 DR. McCULLEY: Okay. Let me remind everyone
9 please to speak directly into the microphone. Some of us
10 are not speaking as directly into it. So please get right
11 into it, otherwise the transcriptionists are not picking up
12 comments, and it's going to mean I'm going to have to repeat
13 a whole lot, and that's going to take time.

14 So, please, everyone speak into the mike. And if
15 you're not, I'll start reminding you.

16 Dr. Wang had his hand up, next.

17 DR. WANG: Ming Wang.

18 I have one comment not related to endothelial cell
19 loss, and maybe at the end of your presentation, whenever
20 you think it's appropriate. Do you want me to comment now?

21 DR. McCULLEY: Why don't you go ahead and make
22 your comment now, yes.

23 DR. WANG: This was the issue just past, prior to
24 the break, and I was the one who voted no, and there was a
25 motion that all new refractive surgical procedures, extra or

1 intraocular, should be held in the same high standard as
2 intraocular with regard to the sample size. And the reason
3 that I just wanted to comment that I voted no is because I
4 feel if someone comes up with anterior corneal--another
5 procedure--and we know intuitively, and it should have much
6 less chance of, say, endophthalmitis compared with
7 intraocular procedure, and we require the company to collect
8 the same large number of patients high safety standard as an
9 intraocular, I don't feel that's very reasonable, and that's
10 why--it could cause extra, undue amount of financial and
11 time loss. And that's why I voted no.

12 DR. McCULLEY: I'm sorry, I thought we--okay. My
13 misunderstanding.

14 Comments on endothelial cell count?

15 Dr. Ferris?

16 DR. FERRIS: I would like to essentially, I think,
17 second what Walter just said, and that is that, as I
18 understand it, these endothelial cell counts are on 10
19 percent of the overall population. And I suspect that it --

20 DR. McCULLEY: Into the mike, Rick.

21 DR. FERRIS: I suspect that it is certainly not
22 too difficult to identify 10 percent that didn't--have not
23 been chronic contact lens wearers in the last three months;
24 some such thing.

25 I also think that collection of the information on

1 history of contact lens wear is important in looking at this
2 when the data is analyzed to make sure that there isn't any
3 confounding of cell loss with history of contact lens wear.

4 So I think there's a potential way around this
5 apparent confounding.

6 MS. BOULWARE: These have been sub-studies in the
7 past, because large numbers were not required to get to this
8 10 percent loss. When you address the issue of progressive
9 loss, that may change.

10 DR. McCULLEY: Is there anyone that is prepared to
11 make a suggested recommendation to resolve this issue,
12 relative to endothelial counts? And they are sub-studies.

13 Dr. Stark?

14 DR. STARK: I think I made--the suggestion I would
15 make is they have adequate number of patients who have not
16 worn contact lenses within three or six months.

17 DR. McCULLEY: Speak louder, please, Walter.

18 DR. STARK: That they have--that those companies
19 provide adequate number of patients for their endothelial
20 studies on patients who have not worn contact lenses within
21 three to six months of the pre-operative evaluation for the
22 laser.

23 DR. FERRIS: Well, maybe, could the--and this is
24 Rick Ferris. It seems to me that there was a sample size
25 determination that's already been made as to what the number

1 is that are necessary to detect a 10 percent loss at the
2 one-year exam. And I thought that was--it was less than a
3 hundred, wasn't it?

4 MS. BOULWARE: It is. It is. We detect a 10
5 percent loss at one year.

6 [Slide.]

7 MS. BOULWARE: This next slide was talking more
8 about what Dr. Macsai brought up, and that is the
9 possibility of progressive cell loss.

10 DR. McCULLEY: Okay. Let's deal with the first
11 slide first.

12 MS. BOULWARE: Sure.

13 DR. McCULLEY: And is there agreement that the 10
14 percent is an appropriate level to detect? And should the
15 endpoint of 10 percent loss be at one year or at the end of
16 the study--or both?

17 DR. MACSAI: Are we accepting a 10 percent loss?
18 Is that --

19 DR. McCULLEY: That's what I just asked: if you
20 did or didn't. Are you now going to belatedly speak up?

21 DR. MACSAI: I don't think it's belated, Jim. I
22 don't accept a 10 percent loss.

23 DR. McCULLEY: Okay. Well, then, what would you
24 recommend?

25 [Pause.]

1 What's the error in measuring endothelial count
2 from one time point to another in the same patient? Isn't
3 it roughly in the range of 10 percent?

4 DR. YAROSS: Mr. Chairman? I have that paper in
5 front of me, and this is a paper by Bourne, Nelson and
6 Hodge, 1997, and shows specular microscopic measurements
7 method is reproducible within 7 percent.

8 DR. McCULLEY: Within 7 percent.

9 DR. YAROSS: 7 percent.

10 DR. McCULLEY: So, given that, Marian, what would
11 you recommend?

12 DR. MACSAI: Well, I would recommend an acceptable
13 loss at one year after the procedure of perhaps 7 or 10
14 percent. However, not at two years, and not at three.

15 DR. McCULLEY: Of progressive. Okay. Okay.

16 DR. MACSAI: I'm separating out the two issues.

17 DR. McCULLEY: We're going to come to
18 progressive in just a minute. We're separating out multiple
19 issues here.

20 DR. MACSAI: A small incision --

21 DR. McCULLEY: We're going to come back to the
22 progressive loss on the next slide in just a minute.

23 So the question here: is the 10 percent mark
24 reasonable--which takes into account the variability in
25 measuring within one patient? And is that at one year? And

1 we're going to come, still, to the progressive loss issue.
2 We're not there yet.

3 DR. MACSAI: Well, my thoughts on this are as
4 follows. If 10 percent is acceptable with
5 phakoemulsification at one year, then a procedure where
6 you're just--you're not phakoing, you're not doing anything,
7 you're just sticking something in the anterior chamber,
8 should be less.

9 DR. McCULLEY: Is there agreement on that,
10 considering the 7 percent variability?

11 MS. BOULWARE: Mr. Chairman --

12 DR. McCULLEY: Yes.

13 MS. BOULWARE: We've seen literature with a value
14 of 11 percent for non-contact spectromicroscopy.

15 DR. McCULLEY: For variability in the same
16 individual.

17 Dr.--Woody.

18 DR. VAN METER: Woody Van Meter.

19 I would favor having the information collected as
20 long a period of time as possible, and with fairly tight
21 standards. But there are tow problems that I would point
22 out.

23 Number one is we have no pre-operative evaluation,
24 and the obvious inference, if you see a young, healthy
25 patient who's losing endothelial cells is maybe they were

1 losing cells beforehand. So you can't rule out pre-existing
2 endothelial microscopic pathology.

3 DR. McCULLEY: Don't we have pre-op in--

4 DR. VAN METER: Right, but you don't have
5 longitudinal counts.

6 The second problem is that even if someone loses
7 endothelial cells, a more critical issue is how the cells
8 are working. And I would introduce that maybe post-
9 operative and pre-operative phakometry would be helpful to
10 see how the corneal function is working, because that's a
11 more accurate determinant, I think, of corneal function than
12 cell counts.

13 DR. McCULLEY: Agreed.

14 Other suggestions?

15 Dr. Matoba.

16 DR. Matoba: Alice Matoba.

17 I agree with Dr. Macsai's comment that we should--
18 that if we accept 10 percent as cell loss at one year as
19 being acceptable for phako, that it's not acceptable for
20 this type of procedure, and I would want to set the bar
21 higher.

22 Dr. Ferris alluded to the fact that there was
23 information that they had already computed the number of
24 patients you would need to look at in order to detect a 10
25 percent loss at one year? And isn't that--in that

1 computation, was this variability for endothelial cell
2 count--the variability--wasn't that already taken into
3 account?

4 MS. BOULWARE: Yes, that's in the refractive laser
5 guidance document. However, I would also point out that 10
6 percent loss was considered the clinically significant
7 endpoint for excimer laser procedures.

8 DR. McCULLEY: Again, this is at one year. We're
9 going to talk about progressive in a moment.

10 Dr. Belin?

11 DR. BELIN: On any procedure that we feel is more
12 susceptible to cell loss, one thing you may want to consider
13 is delaying second eye treatments and using the first eye as
14 a control.

15 DR. McCULLEY: Mike, can you speak more directly
16 and louder into the mike?

17 DR. BELIN: Sorry. On any procedure that we feel
18 may be susceptible to cell loss, you may want to delay
19 second eye treatments--which is something we've always
20 discussed; when you can do second eyes, to use the first eye
21 as a control.

22 DR. McCULLEY: Okay. We're going to come to
23 second eyes in a minute.

24 Dr. Wang?

25 DR. WANG: I agree with Him that it's important to

1 figure out what's the noise. Is there a consistent noise
2 into the variability of measurement of endothelial cell
3 count?

4 MS. BOULWARE: WE've seen literature with 11. I
5 have not seen the article that Dr. Yaross is referencing.

6 DR. McCULLEY: Yes. I have stuck in my mind 10
7 percent, which is roughly, I think, in the same ballpark
8 that we're talking about. And we're probably not going to
9 fine tune it any better than that. So if you have a 10
10 percent variability, is that going to wash going up and down
11 if you take the group? And if you have a big enough group,
12 and then what would we accept, then, as--with that assuming
13 to be a wash up-down in the 10 percent range, then what
14 would we take as significant cell loss at that first point?
15 Which is our first safety point. And then we're going to
16 have other safety points for continued loss.

17 Dr. Ferris?

18 DR. FERRIS: But that's what that calculation did.
19 It said "We're going to rule out 10 percent or more loss at
20 one year. And this is the number of people we need to do
21 it, given a variance of--"--whatever--7 or 11, whatever they
22 chunked into that calculation, and out comes a number that
23 you need which, as--I don't really remember what it was. It
24 was like 89, or some number like that, which was do-able,
25 and meant that you had to do pre-op and post-op. It seems

1 to me that you can easily at least try to deal with the
2 contact lens issue by saying that we want people who aren't
3 chronic contact lens wearers or, if you are, maybe you have
4 to stop for three months before we do this procedure. And
5 those are details that it seems to me the agency can work
6 out with a company.

7 The more difficult issue is this follow-up issue,
8 and I don't know whether you want to --

9 DR. McCULLEY: We'll come to that in a minute.
10 But it was 10 percent for refractive guidance document, as
11 well as intraocular lenses. So we've already established
12 that standard to be the same, even though it's different.
13 Is that not correct?

14 MS. LOCHNER: We don't have that in intraocular
15 lens guidance.

16 DR. McCULLEY: You don't have that in the
17 intraocular lens.

18 DR. McCULLEY: Okay. But in the refractive
19 guidance document it's 10 percent.

20 MS. BOULWARE: That's correct.

21 DR. McCULLEY: Okay.

22 Gary, you had your hand up, and then Dr. Matoba.
23 Dr. Matoba?

24 DR. MATOBA: On the next slide, with the sample
25 size of 300 you can detect a loss of 3 percent.

1 DR. McCULLEY: These are done as sub-groups. Not
2 every patient is required to have specular--or hasn't been
3 in the past. But let's see.

4 Yes, that comes back, then, to the longer term.
5 We'll come back to that.

6 The question here is: is 10 percent going to be
7 our bar, I think, is it not?

8 MS. LOCHNER: For the first year.

9 DR. McCULLEY: For the first year. So, is that
10 agreed, that 10 percent for the first year is where the bar
11 is set?

12 DR. FERRIS: Yes.

13 DR. McCULLEY: Marian says no. Anyone else--okay,
14 all that think it should be at 10 percent at a year, raise
15 your hand.

16 [A show of hands.]

17 DR. McCULLEY: All that do not.

18 [A show of hands.]

19 DR. McCULLEY: Okay. The majority is that the bar
20 at 10, but there are three people who disagree with that.

21 Do you want me to fine tune that more, or is that
22 enough?

23 MS. LOCHNER: No, I think by going on to the other
24 questions we may fine tune that.

25 DR. McCULLEY: All right.

1 Let's go on, then to the next.

2 [Slide.]

3 MS. BOULWARE: The questions we've posed here, in
4 terms of progressive cell loss are: what is the maximum
5 amount of change between time intervals that can be
6 considered acceptable to demonstrate stabilization of cell
7 loss? And then, by answering that question, you also need
8 to define what the minimum time interval is. Is it one year
9 to two years? Is it six months to 12 months?

10 And simply for your information, you see that to
11 determine progressive loss, you get into very big numbers.
12 With a sample size of 300, you can still only detect a
13 progressive loss between time intervals of 3.1 percent,
14 which adds up fairly quickly.

15 DR. McCULLEY: Dr. Sugar?

16 DR. SUGAR: I don't know what you mean by
17 stabilization cell loss, because there's always cell loss.
18 And there's a paper by Bill Bourne, I think in this month's
19 Ophthalmology--is that right?--where he showed a 0.6 percent
20 loss per year in normals, and a 2.6 percent loss per year in
21 people with posterior chamber intraocular lenses, and a
22 massively higher loss for people who had had keratoplasty.

23 So if you consider 2.6 percent the standard for a
24 post-cataract extraction intraocular lens, and .6 percent
25 normal, I would hope we would search for something between

1 those numbers, but I don't think we have the ability to
2 detect it if we're only measuring a hundred patients.

3 MS. BOULWARE: And I do have some more numbers for
4 other sample sizes if you'd like to see them.

5 DR. McCULLEY: Gary?

6 DR. RUBIN: I'm not sure what the statistical
7 assumptions that were used in these sample size
8 calculations, but I think they're incorrect, in that I think
9 that they are not done on the basis of repeated measures
10 within an individual, but as--am I correct? Were they done
11 as repeated measures or as independent measures between
12 subjects?

13 MS. BOULWARE: Repeated. Here you see the
14 assumptions: the two-sided alpha of .05, 80 percent power;
15 and then this was assuming the standard deviation of 11
16 percent--the non-contact--based on the article that we had.
17 And you see what the effect sizes are. And this is between
18 time intervals.

19 DR. McCULLEY: I think one of the real concerns is
20 going to be progressive endothelial cell loss in these
21 patients. And they're young. And it's an elective
22 procedure. So I think that legitimately is a major concern.

23 Dr. Bullimore?

24 DR. BULLIMORE: How much of our endothelium can we
25 use before it has a functional significance?

1 DR. McCULLEY: It varies. But cell density alone
2 does not predict function, or functional reserve. It's not
3 that clean. We had always hoped that we could say that this
4 is the number of cells you have to have to keep the cornea
5 detergessed, but there's broad spread. It's 800, plus-minus
6 400.

7 VOICE: 60 to 80 percent loss.

8 DR. BULLIMORE: 60 to 80 percent loss. So even at
9 3 percent, it's going to take you over 20 years to get to a
10 50 percent loss.

11 DR. McCULLEY: You're 21, you have an implant. At
12 41, you have a transplant.

13 DR. BULLIMORE: Yes. I'm just trying to get a
14 perception of what we're dealing with here before I
15 determine how excited I get about the issue.

16 DR. MACSAI: Well, you know, a transplant is not
17 something that carries no --

18 DR. McCULLEY: Into the mike, Marian.

19 DR. MACSAI: I think it's important that we--since
20 many of us at this table are transplant surgeons, that a
21 transplant carries significant risk to a patient.

22 DR. BULLIMORE: This is Dr. Bullimore again. I'm
23 not one of those people who has that immediate benchmark, so
24 I'm trying to --

25 DR. MACSAI: Right.

1 DR. BULLIMORE: --educate myself on line.

2 DR. McCULLEY: Right. And I think those of us who
3 are on the corneal transplant side think this is a very
4 serious consideration.

5 DR. BULLIMORE: Okay.

6 DR. McCULLEY: Am I wrong, Dr. Stark? Dr. Macsai?
7 Dr. Wang?

8 DR. MACSAI: No.

9 DR. McCULLEY: And you were wanting to speak, Dr.
10 Wang?

11 DR. WANG: Ming Wang.

12 I was just wondering, is there a reference of
13 phako? And I think, if anything our standard should be
14 equal or higher.

15 DR. McCULLEY: Oh you mean get reference for phako
16 and endothelial loss with the surgical procedure?

17 DR. WANG: Yes.

18 DR. McCULLEY: There are all sorts of data.

19 DR. WANG: Just see whether we can get a sort of
20 consensus ballpark. And I think for refractive procedure,
21 it would be equal or better.

22 DR. McCULLEY: This is at the one--okay, we're
23 already past that; the surgical intervention. That's pre-
24 op, to post-op to one year. So we've already deal with that
25 at 10 percent.

1 Now we're looking at one year, two year, three
2 year to see if there's progressive endothelial cell loss.
3 And we would not want 10 percent for year two.

4 DR. WANG: So that was point. Is there any
5 reference for progressive?

6 DR. SUGAR: Brill Borne's is 2.6 percent; 2.6
7 percent per year in normals.

8 DR. MACSAI: In normals it's .6

9 DR. SUGAR: And 2.6 --

10 DR. MACSAI: If you have a PC IOL it's 2.6.

11 DR. SUGAR: It's 2.6, right. Yes. That's right.

12 DR. MACSAI: So you want less than 2.6.

13 DR. SUGAR: Yes.

14 DR. MACSAI: Closer to .6.

15 DR. SUGAR: Per year.

16 DR. McCULLEY: And it takes 300 to get 3.1--to
17 detect 3.1. And you're saying you want detection that would
18 pick up less than 2.6.

19 Rick?

20 DR. FERRIS: Rick Ferris.

21 One possible suggestion would be that anyone doing
22 a study--I think, again, we're talking about a new, either
23 intraocular or extraocular refractive procedure--has to do
24 that initial one-year study, but would be required to
25 continued to follow those patients--I would say at least

1 three years. And I think that if there was continuing
2 evidence of decrease over the three years, that they should
3 be required to follow that cohort for five years. In fact,
4 I think, clinically and ethically, they would be--it would
5 be irresponsible not to follow them if you saw continuing
6 decrease.

7 DR. McCULLEY: It's all going to be part of the
8 PMA?

9 DR. FERRIS: I don't know whether it's possible to
10 require long-term follow-up in a sub-group, but it seems to
11 me that it's ethnically responsible to do that. Whether you
12 can legally --

13 MS. LOCHNER: Yes, we can.

14 DR. FERRIS: --require them, I don't know.

15 MS. LOCHNER: Yes, we have the authority to
16 require that. It's sometimes difficult to get those studies
17 to succeed, but we can impose them.

18 DR. McCULLEY: Do you have similar requirements
19 for aphakic, pseudophakic, intraocular lenses now that are
20 three years of stability or more, on endothelial cell count
21 to be a part of the PMA?

22 MS. LOCHNER: No. We have a three-year follow-up
23 on anterior chamber lenses, but it doesn't specifically look
24 at endothelial cell counts.

25 DR. McCULLEY: Rick?

1 DR. FERRIS: My point here--Rick Ferris--is that
2 it's much more valuable to have three-year data on 100
3 patients than one-year data on 1,000. Because you have no
4 idea what's going to happen after one year. You've got that
5 one-year rate nailed down, but you don't know what's going
6 to happen beyond that. And I think that's the concern, and
7 I think it's a legitimate concern, given the past history of
8 other intraocular things.

9 DR. McCULLEY: Okay. Here, we've got some real
10 problems with ideal and practical.

11 Walter?

12 DR. STARK: And I think as a corneal surgeon, who
13 follows a lot of people with, say, Fuchs corneal dystrophy,
14 I find, as Dr. Van Meter, indicated and others echoed, that
15 corneal thickness is an important finding, and it can be
16 done on a higher number of patients, even in specular
17 microscopy.

18 What's important clinically is that the corneal
19 can thicken 20 percent. It can go from .52 to .62 mm, with
20 a progressive loss of endothelial cell function, and still
21 the vision is maintained at 20/20. So those people will be
22 considered successes, even though their cornea's thickened
23 by 20 percent. But when it thickens to about 25 percent--
24 when it goes to .64 or .66--in that range--.66 mm--then
25 vision begins to fall off.

1 So what we want to make sure is that we're not
2 missing a progressive deterioration in endothelial cell
3 function by several measures. One would be endothelial cell
4 count. And we could look at hexagonality and the junctions.
5 But, also, I would add that, for the length of those studies
6 we should look at corneal thickness, measured in a
7 standardized fashion. Because if we see a trend over time,
8 that may alert us to a problem that might occur ten years
9 later.

10 DR. McCULLEY: But corneal thickness isn't going
11 to kick in until you get below the critical cell density.
12 It will stay detergessed at a normal thickness until you
13 reach whatever that individual's critical mass is going to
14 be. But I think it's a good idea to have endothelial cell
15 count as well as corneal thickness measurements over time.

16 MS. BOULWARE: We do plan requesting phakimetry.

17 DR. McCULLEY: Dr. Wang?

18 DR. WANG: Ming Wang.

19 I'd like to second Dr. Ferris's comment. As I
20 understand that in an attempt to achieve compromise between
21 practical and ideal, is perhaps develop a guideline say, at
22 one year if the endothelial cell loss exceeds this
23 particular threshold. Then for that subset of companies,
24 they will require to do second and third year. But this
25 requirement may not be applicable for all companies,

1 therefore seeking compromise between what's practical and
2 what's idea.

3 DR. McCULLEY: I hear a voice. I didn't tie it to
4 a body. Other comments?

5 Dr. Bullimore?

6 DR. BULLIMORE: Dr. Bullimore again.

7 I think, given the level of concern on the panel,
8 it would be prudent at this stage to encourage manufacturers
9 to take endothelial density measurements on all subjects
10 rather than it being a sub-study. I think having data on
11 all of the subjects at one year or two years, depending on
12 the duration of the study, will clearly give us a much
13 better ability to make decisions when the PMA comes to
14 panel.

15 I think we've taken this out of the sub-study
16 range. We've taken this as something that has to be done on
17 all the subjects.

18 DR. McCULLEY: There are two issues. One is what
19 happens with doing the surgical procedure--the cell loss
20 that occurs with that, and whatever might occur in a year.
21 And the other is, is there a progressive higher rate of
22 endothelial cell loss? There are two--you know, there are
23 two major issues. And I'm not sure how we're going to end
24 up resolving it.

25 But we also have to be practical. It's very

1 difficult to do the specular, and it adds a lot of expense,
2 and a lot of difficulty for industry to do that. And that's
3 why we've gone to the sub-study. And I'm not sure that I
4 wouldn't rather see a manageable--100 would answer the first
5 year, but if they're going to have to have more to give us
6 the progressive loss at a lower rate, then I would apply
7 that same number for the year, obviously, because it's going
8 to be done.

9 Dr. Ferris?

10 DR. FERRIS: Two things. One is I believe there
11 were two reasons to go to the sub-study, one of which was
12 that you didn't need the full number to show this 10 percent
13 difference, and the second was that not everyone does
14 endothelial cell counts equally well, and that you were
15 better off picking the sites that were practiced and good at
16 it, and doing it in those sites than throwing in a lot of
17 garbage --

18 DR. McCULLEY: Noise.

19 DR. FERRIS: --if you will.

20 The second thing is that if you think about the
21 three-year study--and the reason I said at least three and
22 maybe five--again, I haven't done calculations, and I can't
23 do them sitting right here--but I suspect that at three
24 years you could have pretty much the same power of saying
25 that there's not a continuous 3.3 percent decrease over the

1 three-year period; that the standard error of the
2 measurement at three years says that you can rule out a 10
3 percent difference at three years. So that's an average
4 worsening of 3.3 per year.

5 Now, I suspect that that's not the way this
6 process works; that at least one would imagine, certainly in
7 the intraocular procedures, that there's a fall-off
8 initially, and then the question is is there a continued
9 fall-off. And if the issue is that you want to assess the
10 continued fall-off after the first-year period, then you'd
11 go down to something like 5 percent per year is your
12 threshold for being able to do anything.

13 Now, Ming Wang made, I think, a reasonable point
14 to consider. And that is, at three years you're going to
15 see the data. And, depending on the data, you might say,
16 "Well, that's enough," or you might say, "You know, it's
17 still going down. We need more--longer follow-up on this
18 cohort."

19 DR. McCULLEY: Okay. So would you agree with the
20 suggestion that we say that there be at least a three-year
21 study--so one year is the 10 percent issue we've dealt with,
22 and measure at two years and measure at three years, and
23 follow-up--to answer the time interval--and that it be set
24 at, well, between 100 and 300 patients?

25 DR. FERRIS: Yes, the 100 or the--whatever that

1 number was, which I think was around 100 --

2 DR. McCULLEY: That was the 10 percent for one
3 year.

4 DR. FERRIS: Right. Well, I think the 100 will
5 give you a pretty good estimate --

6 DR. McCULLEY: Okay. So --

7 DR. FERRIS: --as to what's going on over a three-
8 year period.

9 DR. McCULLEY: --100 would give us the --

10 DR. FERRIS: Because you have repeated measures
11 there. These sample size calculations in some ways, I
12 think, are relatively conservative in describing what's
13 happening to the same population followed three times.
14 That, I don't think, is built into this, that you're getting
15 repeated measures on the same patient.

16 So there's more power here than --

17 DR. McCULLEY: Okay. So would your recommendation
18 be 100 patients followed for a three-year period?

19 DR. FERRIS: That would be my--

20 DR. McCULLEY: As part of the PMA submission.

21 DR. FERRIS: Yes, that if it's a new device, you
22 have to provide us with at least some three-year data and
23 recognize that--I believe it's--I'm sure it's true--that the
24 excimer people have already provided, or had already
25 provided some long-term--longer-term--follow-up.

1 DR. McCULLEY: I don't remember how many years we
2 had on excimer. I don't think we had three year. We maybe
3 had two year.

4 Dr. Yaross?

5 DR. YAROSS: Marcia Yaross.

6 Can I ask Dr. Ferris for a clarification, in terms
7 of what would be the difference in power between 50 subjects
8 over three years and 100? And the reason I ask that is with
9 a phased approach you will have a 50 patient group that's
10 enrolled fairly early. And if you're able to get those
11 patients followed over the long term there's some advantage
12 over that. So is there much power difference there?

13 DR. McCULLEY: Isn't it on the slide there?

14 DR. YAROSS: But he was saying with repeated
15 measures it gets better.

16 DR. McCULLEY: Well, it would be the same ballpark
17 as on the slide--isn't it? So you'd drop from 5.4 percent
18 detection to 7.6? You'd drop from 100 to 50?

19 DR. FERRIS: I believe that the power changes as
20 the square of the relative difference, and so it's--you lose
21 about 25 percent power by current the sample size in half.
22 And I don't think it's fair to ask me to do these sample
23 size calculations sitting here.

24 But as I said to Marian earlier, I won't be put in
25 the position of saying that more isn't better, because it's

1 always better. And the issue here is trying to find some
2 reasonable compromise.

3 DR. McCULLEY: Right.

4 DR. FERRIS: And you make a good point that you're
5 enrolling people over time, and having 50 people out at five
6 years would provide a lot more power.

7 DR. McCULLEY: Dr. Grimmett?

8 DR. GRIMMETT: Michael Grimmett.

9 I think one issue to be brought up again if the
10 sample size decreases is if we're going to take out those
11 patients that have not worn contact lenses, like Dr. Stark
12 has suggested, and that obviously will come into play
13 regarding the sample size calculation. Whether 50 would
14 truly be enough if you have a subpart of that that have not
15 worn contacts or those who have.

16 SEcond point I'd like to make is getting back to
17 the measure of phakimetry. I don't believe these a
18 sensitive enough outcome variable for what we're really
19 looking for. These patients are young, had a high count
20 going in. I don't think there's really any way we could
21 detect a meaningful increase in corneal edema, certainly, in
22 this patient subset early.

23 DR. McCULLEY: Dr. Matoba?

24 DR. MATOBA: Somebody had' asked a question about
25 he excimer lasers and endothelial cell counts. In

1 deliberations, the panel had recommended that because these
2 treatments were only a one-time trauma to the cornea, that
3 the issue of progressive cell loss was not likely to be an
4 issue. And that's why long-term data was not required of
5 the excimer lasers.

6 DR. McCULLEY: Right. This is a new issue for us.

7 Dr. Stark?

8 DR. STARK: Who recommended that? Who indicated
9 that?

10 MS. BOULWARE: I believe, the panel.

11 DR. STARK: No, I think that may be a mistake.
12 Because there's a potential, with intraocular lenses,
13 especially anterior chamber, and maybe the angle supported,
14 that there could be a progressive endothelial cell loss.

15 DR. McCULLEY: This is keratorefractive, Walter.

16 DR. STARK: Well, you know, you don't know for
17 sure--you know, the ultraviolet damage to the endothelium--
18 you don't know for sure. But I think we've been assured by
19 the studies so far, with VISX and Summit, that there's no
20 progressive loss apparent.

21 DR. MACSAI: Right. But this is a different can
22 of worms.

23 DR. STARK: Yes.

24 DR. McCULLEY: Okay. Does anyone have a
25 suggestion as to what we should recommend here? We're

1 talking around it. So let's try to get the point.

2 Dr. Macsai?

3 DR. MACSAI: My point would be that we learn from
4 history and base our practices on scientific data. Dr.
5 Bourne's paper that just came out is a pretty well-done
6 article demonstrating that with a posterior chamber lens
7 there's a 2.6 percent loss per year.

8 I don't think we should accept anything higher
9 than that.

10 DR. McCULLEY: Okay. That would mean that we
11 would have to have somewhere around 500 patients followed
12 for three years to detect that.

13 MS. BOULWARE: Actually, you could look at 150
14 patients from the one-year timepoint to three years, because
15 if it was a, say, 2.5 percent loss a year, that would be 5
16 percent over two years, and you would be able to detect that
17 with 150 patients over that two-year time interval.

18 DR. SUGAR: It would probably be less than that
19 because of the repeated measures in the same patient.

20 DR. McCULLEY: Okay. So let's come to a number
21 then. Let's come to a number to recommend.

22 DR. MACSAI: I would leave that number to the
23 statisticians.

24 MS. BOULWARE: Yes, I think if you take the 2.6
25 percent rate, we could then back --

1 DR. MACSAI: We accept nothing --

2 DR. McCULLEY: All right. So you will set it so -

3 -something that would pick up --

4 MS. BOULWARE: The 2.6.

5 DR. McCULLEY: --something less than 2.6.

6 DR. MACSAI: Because at 2.6 percent, it takes
7 about 50 years for your cornea to decompensate. So if we've
8 accepted that for cataract and we're going to use the grid,
9 etcetera, that's okay.

10 DR. McCULLEY: Okay. I could keep this going by
11 saying we've got a young population here with an elective
12 procedure that --

13 DR. MACSAI: 20 to 70.

14 DR. McCULLEY: --if we kick them into 2.5 percent
15 endothelial cell loss per year it's a very different kettle
16 of fish to a 65, 70 year old person with a PC IOL with a
17 non-really elective vision-saving procedure, who's not going
18 to live as long as that young person.

19 DR. MACSAI: I guess--but, Jim, you'd also have to
20 take into account to actuarial tables, you know, honestly of
21 a 20 year old to 70. And I don't know that --

22 DR. McCULLEY: In terms of how far down below 2.6
23 you would be comfortable going?

24 DR. MACSAI: Right .

25 DR. McCULLEY: Dr. Matoba?

1 DR. MATOBA: Alice Matoba.

2 This is just a question, but is it know whether
3 there's an accelerated rate of endothelial cell loss as we
4 get older and, if so, we may want to go below the 2.5, since
5 the intraocular lens data we're looking at is for an older
6 population than the ones that we're going to be dealing
7 with.

8 DR. McCULLEY: Where do you want to--they can--FDA
9 can set the--can figure the numbers. Where do you want to
10 set the bar? You've said less than 2.6.

11 DR. BULLIMORE: 2.5 percent per year.

12 DR. McCULLEY: 2.5 percent per year? Is there
13 agreement to that? Disagreement to that?

14 Dr. Bradley?

15 DR. BRADLEY: A question for the chair. We're
16 setting this bar at this point based on very long term
17 projections on cell loss; your own comments about these
18 people are quite young. Do we have actual data long term?
19 5, 10, 20, 30 years? Or is this pure speculation on our
20 part about what's going on in 20 years' time?

21 DR. McCULLEY: Are you talking about in the normal
22 population?

23 DR. BRADLEY: In any population.

24 DR. McCULLEY: Yes. I mean, that was what Dr.
25 Sugar's been talking about. .6 --

1 DR. MACSAI: Is normal.

2 DR. McCULLEY: --loss per year in you and me
3 sitting here, assuming we're normal; and 2.6 in those that
4 have had cataract surgery and have a PC IOL.

5 DR. BRADLEY: You can come up with cell loss per
6 year by doing a two-year study. We're talking 40 years into
7 the future. Have they done --

8 DR. McCULLEY: How long--what was the length of
9 the study --

10 DR. MACSAI: Ten years.

11 DR. McCULLEY: Ten- year study from the Mayo
12 Clinic. So I think we're--reasonable number.

13 DR. MACSAI: What about 2 percent?

14 DR. McCULLEY: Anyone want to go for 1.9?

15 [Laughter.]

16 DR. McCULLEY: Dr. Matoba?

17 DR. MATOBA: Well, how about we ask the
18 statisticians to give us the numbers we would have to look
19 at to detect 2, versus 2.5; take a couple of numbers that
20 we're comfortable with and then come back and look at it
21 after we --

22 DR. BULLIMORE: I can give you the numbers, just
23 looking at the screen there.

24 If you did a two-year study, you'd be able to find
25 --

1 DR. McCULLEY: Three year. Three year.

2 DR. BULLIMORE: If you did a two-year study on a
3 100 patients you would probably have adequate statistical
4 power to detect a 2.5 percent loss per year. If you did a
5 three-year study on 50 people you'd probably have an
6 adequate statistical power to detect 2.5 per year.

7 Those numbers that I was just giving you are based
8 on what's up there, and as Dr. Ferris has already said,
9 they're probably conservative. Because when you take
10 multiple measures, if you're measuring these people every
11 six months, you're trying to determine the slope of a
12 function, so you borrow--or you add some statistical power,
13 just by the virtue of the repeated measures. So it's--we're
14 not presenting--I don't think we're presenting the sponsor
15 with an insurmountable task here by requiring measurements
16 and setting that bar.

17 Rick's going to disagree with me now.

18 DR. McCULLEY: Yes, maybe in terms of numbers.
19 But we're setting a real obstacle for the sponsor in terms
20 of time.

21 Dr. Ferris?

22 DR. FERRIS: Well, that's tough--I don't think
23 there's any way around--it's Rick Ferris.

24 If you're concerned about long-term cell loss,
25 there's only one way to do it, and that is you need some

1 information. And I think there's enough in the literature
2 that would say intraocular procedure, certainly there's
3 reason to believe that there may be long-term cell loss.
4 And I think it's almost irresponsible to not look after one
5 year. And I think, in some ways, if we go--if you just
6 figure out the numbers, asking them to do the sample that
7 they originally identify, to then follow them up at two and
8 three years is the same number or fewer endothelial cell
9 loss counts than if they had done the whole population at
10 baseline.

11 And I guess what I would like to ask is the
12 statisticians to say, "Given that scenario, what is our
13 power to find change over time?" So work backwards. Here's
14 the sample size that you have. You're going to follow them
15 for over three years, or five years, and what's the power to
16 show differences over that period--of cell loss over that
17 period of time? And if we think that power is reasonable
18 and it will give us a pretty good estimate of what the rate
19 of cell loss is, that's enough.

20 DR. McCULLEY: Okay. So --

21 DR. FERRIS: So my recommendation is to turn this
22 back to the agency; that, at least--well, my personal
23 recommendation is that they take that cohort that they had
24 to do anyway at one year, and follow them for three, with
25 the idea that that will give us power to see roughly a third

1 of that one-year rate over three years.

2 DR. McCULLEY: Okay. So--and we would want to be
3 able to detect at least 2.5, if not 2 percent, change or loss
4 of endothelial cells per year.

5 MS. LOCHNER: With a sample size of 100?

6 DR. McCULLEY: Well, you'd decide the sample size
7 to reach that requirement.

8 MS. LOCHNER: Well, if you want us to figure the
9 power, we have to --

10 DR. MACSAI: You determine the sample size.

11 DR. BULLIMORE: This is Dr. Bullimore again.

12 We have to be very careful in the way we word
13 this. Okay? If we want the ability to detect 2.5 percent
14 per year, that will give us one number. If we want some
15 assurance that it is no greater than 2.5 percent per year,
16 that's a very different number. It's a higher number and
17 would involve a longer follow-up. Okay? And that's why it
18 needs to be, I think, passed back by the statisticians in
19 the agency to come up with the sample size or, if you're
20 going to fix the sample size, to give us some indication of
21 what the statistical power is.

22 MS. LOCHNER: What if we worked it out a couple
23 different ways and then showed you those numbers.

24 DR. McCULLEY: I think it's clear to you, I think
25 --

1 MS. LOCHNER: The issues.

2 DR. McCULLEY: --from what's being said, at least a
3 three-year study.

4 MS. LOCHNER: Right. And if there's loss, out to
5 five years. If it's still progressing.

6 DR. McCULLEY: Yes. And with Dr. Wang's
7 additional comment. Okay.

8 MS. BOULWARE: Great. Moving on.

9 DR. McCULLEY: The next is going to be cataracts.

10 [Slide.]

11 MS. BOULWARE: Here we go. Induction of
12 cataracts.

13 We'd like to know--I'll read it first--whether the
14 inclusion criteria should be written to address age-related
15 lens changes. In other words, how do you address the fact
16 that you will have age-related lens changes? Should you
17 exclude a certain portion of the population from your study
18 to address this?

19 Secondly, how should cataract formation be
20 measured? Subjectively, by the investigator, or by using a
21 more objective method such as a slit-lamp photography-type
22 method?

23 And, finally, what rate of cataractogenesis over
24 the population norm for that age group would trigger the
25 need for longer follow-up?

1 DR. McCULLEY: Okay. Let's take them a question
2 at a time.

3 Should the inclusion criteria be written to
4 address age-related lens changes? I could just say yes to
5 that.

6 DR. MACSAI: Yes.

7 MS. LOCHNER: And, if so, how? So what would be
8 the upper --

9 DR. McCULLEY: Then we get--is the next--how
10 should cataract formation be measured, which is really the
11 second question.

12 MS. LOCHNER: Well, can we do a 1-b--if we should
13 limit the age entry into the study. Do you have any idea on
14 what the upper limit entry should be?

15 DR. McCULLEY: I don't know how you'd do that, no.
16 I think you have to--there's sufficient individual
17 variability in lens changes with age that that would be very
18 difficult to do.

19 MS. LOCHNER: Okay. But you say, should the
20 inclusion--so you're just saying that they should just be
21 excluded, basically, if they have any evidence of age-
22 related lens changes--regardless of their age.

23 DR. McCULLEY: Well, everyone has evidence of age-
24 related lens changes--unless they're dead.

25 MS. LOCHNER: Okay, well I mean, I misunderstood -

1 - DR. McCULLEY: Because as we age, we get age-
2 related lens changes.

3 MS. LOCHNER: The question was, should the
4 inclusion criteria be written to address age-related lens
5 changes. And your answer was "yes."

6 DR. McCULLEY: Right.

7 DR. SUGAR: I think the implication is that we
8 should record that. We should, you know, have an estimate
9 of what's going on with their lens at entry and
10 subsequently.

11 MS. LOCHNER: Okay. That's what I was getting at.

12 DR. SUGAR: And whether you use the Lochs
13 classification or whatever, you use some standardized
14 measure.

15 MS. LOCHNER: Okay. That's what I was getting at.
16 Thank you.

17 DR. ROSENTHAL: And should there be an exclusion
18 based upon significant--I mean, based upon a defined --

19 DR. McCULLEY: Probably yes.

20 DR. ROSENTHAL: --abnormality.

21 DR. McCULLEY: I think if a person had what
22 appeared to be more than lens changes related to age, they
23 would be excluded. I think if a patient were sufficiently
24 far along the age-related line, that cataracts are apt to be
25 visually significant within a reasonable period of time,

1 that they would be excluded. But then to put --

2 DR. ROSENTHAL: No--with the greatest respect--you
3 can't just make these etherial definitions. I mean, you've
4 got to know: do they have 2+ nucleus score--I mean, the
5 Lochs--and we can pick areas within the Lochs, or within the
6 Oxford Grading system, if these are what you feel should be
7 done, in which a cutoff would be--that above that, the
8 answer would be they'd be excluded, and below that the
9 answer would be they'd be included.

10 Because I'm sure you know that a lot of high
11 myopes, which is what a lot of these patients are, have lens
12 changes at a very early age.

13 So I'm quite happy to accept the recommendation to
14 use a standardized grading system, and to somehow come back
15 with a cutoff level by which a patient would be excluded,
16 and also by which the patient could be then continually
17 measured who were included.

18 Is that fair enough?

19 DR. McCULLEY: Yes. There' no disagreement there,
20 I don't think.

21 Dr. Stark?

22 DR. STARK: I think it would behoove the companies
23 to exclude people who have visually significant cataract.
24 And so you would look at--they don't want to be putting
25 lenses in people with cataract and then having it blamed on

1 the intraocular lens.

2 So I would look over the--and Rick could provide
3 for us, from the NIH, some of the classification of
4 cataracts--how they're classified, whether or not you want
5 to go to Scheimpflug photographs on some of the patients.
6 Maybe it would be worthwhile on a small subset of the
7 patients.

8 But you're right, Jim. A lot of high myopes, when
9 they get in their forties, begin to get nuclear cataracts,
10 and they also have a higher risk of glaucoma. So those are
11 things that need to be taken into consideration.

12 MS. BOULWARE: I think what we're concerned about
13 is if there's a rate of cataract formation at the end of the
14 study, whether the sponsor can say, "Well, half of this rate
15 is due to natural age-related lens changes and not due to
16 our device." Or "All of it is due to age-related lens
17 changes and shouldn't be held against device." And how do
18 we tell?

19 DR. McCULLEY: Dr. Ferris?

20 DR. FERRIS: Rick Ferris.

21 As some of you know, I'm the chairman of a study
22 called "The Age-Related Eye Disease Study," cataract being
23 one of the two age-related diseases we're studying.

24 This is going to be a very difficult area.
25 Cataracts, in general, progress at glacial speed, which

1 means that they're very difficult to document that they're
2 progressing, even when you know they are. And we're looking
3 at people in their sixties and seventies; I know they're
4 having lens changes progress, but they're difficult to
5 document.

6 Clinically, given the variability of clinical
7 assessment, your chances of documenting lens changes related
8 to this treatment verges on nil, I think, over a one-year
9 period, because of the variability of the assessment and not
10 having a control group. Having a control group would make a
11 big difference in being able to show lens-related changes.

12 Even photographically, it's difficult, short of
13 going to Scheimpflug, which I think is out of--it might be
14 wonderful, but it's not practical. So I think it's a very
15 difficult question.

16 Visual acuity, of course, is sort of a summary
17 measure of what's going on in these patients, and any
18 progressive loss of visual acuity is important. The problem
19 is that they can have significant lens opacity progression
20 and not have visual acuity progression.

21 So this is, I think, is going to be a very
22 difficult area to say, with any assurance, that we can rule
23 out cataractogenesis in a one-year study.

24 DR. McCULLEY: What would you suggest as the
25 solution to the difficult problem?

1 DR. FERRIS: Well, for some studies where I've
2 thought that lens opacities--although you would worry about
3 them, there wasn't a high probability of it. It was really
4 a secondary outcome, or a tertiary outcome--that maybe the
5 clinical assessment, even given its gross variability, with
6 a control group, would be a reasonable approach. Here, I
7 think the clinical assessment--you could try it, but I think
8 it would be very difficult to utilize.

9 Photographic assessment can be done. Even that
10 we've found--it has not been easy to get standardized lens
11 photos, even in just 11 pretty well-defined clinics.

12 So you're either left with looking at visual
13 acuity and doing the clinical assessment, or with trying to
14 force standard photos. And I would think you'd almost have
15 to do it on all of them. So it gets to how worried you are
16 about the outcome.

17 And for sticking little lenses next to the lens, I
18 would be pretty worried.

19 DR. McCULLEY: Dr. Pulido?

20 DR. PULIDO: Certain interventions cause
21 cataractogenesis relatively quickly. For instance,
22 vitrectomy in cases of macular hole, 70 percent have
23 cataracts--visually significant cataract within one year.
24 So, clinically, if it's a really severe situation, you can
25 see it very quickly.

1 On the other hand, the situations where it may
2 cause the cataracts to come on more slowly--as you said, it
3 may be difficult. One thing that I guess they are following
4 is the contrast sensitivity. Would progressive change in
5 the contrast sensitivity be a good proxy for
6 cataractogenesis?

7 DR. McCULLEY: Contrast sensitivity experts step
8 forward.

9 Dr. Stark?

10 DR. STARK: I've done work with Gary on contrast
11 sensitivity. That's not going to pick up an early cataract.

12 I was going to make the point Jose mentioned: it's
13 usually over three years after a vitrectomy they'll get a
14 cataract. Everybody will get a nuclear cataract. But as
15 one who sees a lot of cataracts, one of the earlier
16 findings, even before you can pick it up on the slit-lamp,
17 is progressive myopic. As that nucleus thickens and goes
18 from totally clear to a little opalescent, they'll get a
19 little more myopic.

20 And so, for me, that's a good indication: when
21 people come in at 40 to 45, with something unusual, and
22 they're getting more myopic, that's--I look very closely at
23 the lens. And I think that may be one of the measures.
24 It's certainly one that we should look for.

25 I'd like to turn it back to Rick. He shook his

1 head when I said "Scheimpflug." But is Scheimpflug
2 principal on a limited number of patients? Is that a
3 reproducible photographic technique that will document small
4 changes in the lens?

5 DR. FERRIS: This is Rick Ferris.

6 I think it is for pure nuclear cases. And if you
7 start getting combined opacities, it gets more problematic.
8 Perhaps you could do that in a sub group.

9 The problem with myopia as a surrogate is that it
10 wouldn't be surprising, in a group of people that you were
11 doing surgery for myopic that there was some increasing
12 myopic over time after the surgery, and it would be totally
13 confounded, between cataract--you know, is that cataract, or
14 is that just regression from the procedure.

15 DR. STARK: From an intraocular, it should be
16 stable. I mean, you should not get progressive myopia. And
17 to indicate--when you get progressive myopia and you're in
18 your fifties, you're getting a cataract. That's what--it's
19 not from elongation of the eye.

20 The other point.

21 DR. FERRIS: No, I agree with that. But --

22 DR. STARK: Let me just make one point, because
23 what you said may be an option.

24 If it's good for nuclear cataracts--we use it for
25 nuclear cataract--our slit-lamp examination is very good for

1 posterior subcapsular cataracts. As a clinician, by
2 retroillumination, you can see little vacuoles forming, and
3 you can pick up very early posterior subcapsular cataracts.

4 Where you have trouble is the early nuclear
5 cataract; determine is that a little opalescence or not.
6 And that's going to be the hardest one to pick up. And if
7 Scheimpflug would pick that up, then a combination of
8 retroillumination photographs of the posterior aspect of the
9 lens, to pick up posterior subcapsular cataracts, and
10 Scheimpflug, to pick up nuclear. And then, I guess,
11 photographs also for anterior subcapsular.

12 DR. McCULLEY: But what kind of cataract are you
13 expecting to see? What would we anticipate the lens change
14 to be if it's going to be induced by this implantable lens?

15 DR. STARK: It could be an anterior subcapsular in
16 posterior chamber lenses. If there's trauma to the lens,
17 most likely it will produce a posterior subcapsular
18 cataract. So we're not talking about nuclear.

19 But intraocular trauma, though, can produce that
20 nuclear cataract. If you have a vitrectomy, you'll get a
21 cataract within three years--a nuclear cataract. It's--and
22 no one understands exactly why, but that's been shown for
23 years.

24 DR. McCULLEY: So we have to expect that we'd have
25 to deal with all forms of cataract changes.

1 DR. SUGAR: Joel Sugar.

2 My understanding from the literature is that there
3 are transient anterior cortical vacuoles and anterior
4 cortical vasification, but that was not looking
5 prospectively at the nucleus and everything else--in Bykoff
6 and those cases.

7 DR. McCULLEY: Okay.

8 Dr. Wang?

9 DR. WANG: Ming Wang.

10 I thought a key question to address after your
11 question is: how should cataract formation be measured, and
12 how can we follow?

13 And I think one suggestion could be, let the
14 company focus to address that particular question on a group
15 of younger patients--say, 20 to 30, or 20 to 40. We know
16 naturally they have very little cataract formation without
17 any surgical intervention. So assume that's negligible,
18 just to simplify the matter. Have them follow this younger
19 subset of patients over x-number of--period of time, and if
20 that younger subset study for which we know naturally do not
21 have significant cataract formation, demonstrate appreciate
22 cataract formation, now we are reasonably can conclude that
23 is probably due to the device.

24 DR. McCULLEY: Dr. Bradley?

25 DR. BRADLEY: A related comment that also stems

1 from what Dr. Ferris mentioned.

2 It seemed as though he was arguing that because of
3 the glacial speed of cataract development, this poses a
4 problem. But in some ways it seems to me that's the
5 advantage; that normally it is so slow for any reasonable
6 sample of people undergoing this treatment for myopia, we
7 might over one-year to not be able to pick up any cataract
8 development.

9 So that seems to me to be an advantage. Because
10 if you see any, you now have a direct indication that it is
11 due to the procedure.

12 DR. ROSENTHAL: This is Dr. Rosenthal.

13 May I add, for someone who also has a fair amount
14 of experience with glacial cataract development, that the
15 Locks or the Oxford Grading System are very competent
16 clinical ways of measuring early cataract and changing
17 cataract. They've been documented to be reproducible. It's
18 a lot of work to learn how to do it, but you can do it with
19 a slit-lamp and photographs. And I just wanted to--and
20 without having a \$50,000 machine, which is what the --

21 DR. McCULLEY: Well, it sounds like, from what
22 you're saying, that practicality and logic here would be to
23 say--to take one of those approaches and apply that in this
24 study.

25 DR. ROSENTHAL: Well, we're asking if the panel

1 feels it is worthwhile. It's a lot of work to do. Dr.
2 Ferris can tell you. It is a lot of work on the basis of
3 these investigators.

4 DR. McCULLEY: Okay.

5 Rick?

6 DR. FERRIS: Rick Ferris.

7 As an experiment, as part of the age-related eye
8 disease study, and recognizing that cataract development is,
9 not just for this, but for lots of new procedures or drugs,
10 a question of interest. We tried to assess a reduced
11 version of the Lochs. We used a slightly different
12 Wisconsin system. There isn't ten cents worth of difference
13 between the ones we're talking about here and any would be
14 reasonable to use.

15 Now, we have purposely done this experiment with
16 our--mostly--retina people, and we wanted to see how
17 reliable, how reproducible, this was, without tremendous
18 training efforts--with sort of the efforts that you might
19 expect in a study such as the ones that we're talking about,
20 without going to heroic means.

21 To say that some of the results were surprisingly
22 poor would be fair. And whether it can be used at all, I
23 don't know. Now, many refractive surgeons are going to be
24 much more careful about this assessment than the retina
25 people who, I must say--one of them said, "Well, I only

1 assess the lens through the indirect ophthalmoscope."

2 [Laughter.]

3 DR. FERRIS: So I take the point that this may not
4 be the ideal subgroup to do it in. I was looking at it from
5 the other way. If we can get them to do it, we can probably
6 get corneal people to do it.

7 I do not think it's useless, and I think that it
8 is far matter than nothing. And the problem is that the
9 next step up is extraordinarily expensive, with maybe a
10 marginal gain. Furthermore, if there really start to be
11 lots of cataracts developing in these patients, regardless
12 of whether people report it or not, I think we're going to
13 know it.

14 So it seems to me that it is worth asking the
15 companies to do some sort of clinical lens assessment, and
16 there are several available. And we can discuss whether you
17 wanted to demand photographic. But I would think clinical
18 might be sufficient.

19 DR. McCULLEY: Okay. I think what you last said
20 seems to be the key to what you said: is that a clinical
21 assessment on the part of the investigator --

22 DR. ROSENTHAL: A formalized clinical assessment,
23 or --

24 DR. McCULLEY: Using one of the systems.

25 DR. FERRIS: Well, I would use standards.

1 DR. McCULLEY: Okay. So your critical assessment
2 --

3 DR. FERRIS: Based on the Locks, or based on the
4 age-related eye disease study standards, or --

5 DR. McCULLEY: Okay. Fine. Okay. Is there--
6 relative to this part of the question, are there any other
7 clarifying comments to be made?

8 Dr. Macsai?

9 DR. MACSAI: I would also hope that we would hear
10 about both visually significant and visually non-significant
11 changes.

12 DR. McCULLEY: Sure. I mean, okay.

13 Anything else?

14 DR. PULIDO: And I would like any disparaging
15 remarks about retina people taken out of the record.

16 [Laughter.]

17 DR. McCULLEY: That's impossible. We'd have to
18 expunge the whole thing.

19 Do you want us to address further the last point
20 in this--rate of cataractogenesis over the population norm
21 for that age group would trigger the need for longer follow-
22 up? I would think any. I mean, we really don't want to see
23 this device causing speed-up in a significant way of
24 cataract change.

25 DR. STARK: Jim, are we thinking--I would say we

1 take three years as the final point on that. Steroid
2 induced cataracts, the trauma from vitrectomy, others, tend
3 to show up by three years.

4 DR. McCULLEY: Okay. So a three-year follow-up
5 relative to lens changes.

6 DR. STARK: You know, that may preclude approval,
7 but it's--one or two years, whenever you want. But I think
8 you ought to require a three-year follow-up for that and
9 also inflammation.

10 DR. McCULLEY: Okay. Well, and we had that for
11 endothelial cell count. And the way I read these things, I
12 don't see how, if we don't have the three-year data, how a
13 PMA could be considered.

14 MS. LOCHNER: We have a slide for that. If you
15 want we hold that off until we get to the follow-up slide.

16 DR. McCULLEY: Okay.

17 DR. STARK: But you can consider the PMA before
18 three years.

19 MS. LOCHNER: Right, we can. And that's one of
20 our questions: at what point we could --

21 DR. McCULLEY: Okay. We'll come back to that.
22 You have those triggered for that, so we'll do that.

23 So now we're going to go to induction of raised
24 IOP.

25 MS. BOULWARE: And as I mentioned earlier, this

1 definition is from Dr. Higginbotham's comments and the
2 consensus of the panel at the October of '97 meeting, so
3 that's a consistent definition. And we really would like
4 just to know at what rate does induction of raised IOP
5 either a significant safety concern, or require longer term
6 follow-up.

7 DR. McCULLEY: Dr. Higginbotham has promised she
8 can answer this question succinctly for us so that we'll all
9 agree with.

10 DR. HIGGINBOTHAM: I've been waiting for this
11 question for a day--so.

12 [Laughter.]

13 DR. HIGGINBOTHAM: Since you already said there's
14 no controversy on the first issue, I agree with the first.

15 Regarding the second, considering that in the out-
16 study we have untreated patients in that study up to a
17 pressure of 32 that we'll be following for five to 10 years,
18 I think certainly, given the fact that these are young
19 patients, and assuming the eligibility criteria took into
20 account excluding patients that didn't have moderate or
21 severe glaucoma, and if they did have physiologic cupping
22 that is was proven not to be glaucoma, and there are now
23 ocular hypertensives that these investigators would want to
24 have in this cohort--assuming all those provisos, there is
25 only a 1 to 2 percent chance, based on the literature that

1 we have to date, that within one year they may have a field
2 change.

3 So, assuming that we have Q 3-month forms in
4 follow-up--is that right?--that if there's an elevated
5 pressure that's untreated--I assume that you're also talking
6 about untreated --

7 MS. BOULWARE: Yes.

8 DR. HIGGINBOTHAM: --within two consecutive visits,
9 then that should be reported, just from a safety concern,
10 because that means that six months--and this was a problem
11 that wasn't actually noted prior to this elective procedure.

12 MS. BOULWARE: And at what rate is that a problem?
13 1 percent?

14 DR. HIGGINBOTHAM: I would make it consistent with
15 everything else, I think: less than 1 percent. I mean,
16 there's going to be some noise here, considering that these
17 are surgical procedures.

18 DR. McCULLEY: Dr. Pulido?

19 DR. PULIDO: Just a question for Dr. Higginbotham.
20 Considering that the pressure within the central retinal
21 vein is about 28 mm/Hg, would you rather have--would you
22 rather stay with 30 mm/Hg, or 28, which is closure driven.

23 DR. HIGGINBOTHAM: This is Dr. Higginbotham.

24 Considering you have 800 people in this country
25 that are being followed with pressures up to 32--and these

1 are young patients--I have no problem with this high end of
2 30.

3 DR. McCULLEY: Other comments from panel or from
4 FDA--well, let's see--panel?

5 FDA?

6 MS. BOULWARE: One last issue that was raised
7 during the discussion this morning, and that was about
8 aqueous flare as a long-term concern, and it was mentioned
9 that--I believe Steven Foster has developed a method for
10 detecting aqueous flare --

11 DR. ROSENTHAL: Measuring --

12 MS. BOULWARE: Measuring--sorry--aqueous flare
13 that does not involve very expensive equipment.

14 DR. ROSENTHAL: Clinically--clinical. He has a--
15 sorry, this is Dr. Rosenthal.

16 Just like the Lochs--I mean, he has a method of--I
17 was told from someone in the audience--a method of looking
18 at flare clinically.

19 DR. McCULLEY: We all do. But he has a
20 quantitative machine--apparatus?

21 DR. ROSENTHAL: I --

22 DR. McCULLEY: Can we leave that? I think where
23 we got before was that relative to flare, if we went beyond-
24 -cell and flare iritis beyond the clinical observation, that
25 if there were a validated, quantitative machine, that

1 that's--or apparatus--

2 DR. ROSENTHAL:

3 DR. McCULLEY: --or method--that we would like to
4 see that included.

5 Other--does that? We dealt with that?

6 Now, we have built into the day three different
7 times for public comment related to the portion of this
8 draft that we have just discussed.

9 **Public Comment**

10 So if anyone has--if there's public comment that
11 relates to what we have discussed to this point, I will
12 recognize people coming to the podium.

13 Come to the podium.

14 And these must be, again, brief comments.

15 MR. FESHBACH: My name is Matt Feshbach, and I'm a
16 consumer. I have the Staar ICLs bilateral, I guess is what
17 the technical word for that is.

18 Anyway, the points I wanted to make were that
19 before I got the ICLs I was a minus-10, basically in both
20 eyes. And I was desperate to get the lenses because it
21 definitely severely affected the quality of my life. And,
22 in retrospect, I'm not sure I would have considered it an
23 elective procedure.

24 The only--when I decided to do these lenses, I did
25 quite a bit of research, and the only concern or risk I felt

1 I had was cataracts. And I've heard comments about that
2 here today, and I felt that the comments that have been made
3 today have overemphasized that concern, the reason being
4 that I was far worse off with the--with my natural vision
5 than I would have been if I had gotten cataracts. And
6 there's been no sign of any cataracts to date. I've had
7 them for over a year. And I'm 20/15 in both eyes. I've had
8 no glare, no--basically, no side effects whatsoever.

9 The last point I wanted to make was that, again, I
10 was so desperate to get these that I got one as part of the
11 FDA trial, and I went out of the country for a second one,
12 just because wearing the contact in one eye was just not a
13 viable way to go.

14 And, finally, I think that not--when I heard the
15 comments about not being allowed to wear contacts for up to
16 three months before you got the procedure--I think that that
17 would have also been sort of severely restrictive and
18 unnecessary.

19 So--anyway, I love these things, and I think that
20 the panel should be looking at it from the viewpoint of how
21 can you get these into the hands of consumers faster,
22 because I do think that they're--from my experience, they're
23 extremely safe, and extremely effective.

24 DR. McCULLEY: Thank you.

25 DR. BULLIMORE: Just one question--this is Mark

1 Bullimore. Do you have any potential for conflict of
2 interest with any of the companies involved?

3 MR. FESHBACH: I'm not a shareholder of any.

4 DR. BULLIMORE: Thank you.

5 DR. McCULLEY: Good point--to--Dr. Waring is, I
6 think, in line next--to identify yourself and any conflicts
7 that you might have. And, if none, state none.

8 DR. WARING: I'm George Waring, Professor of
9 Ophthalmology at Emory University. I'm a paid consultant
10 for Bausch and Lomb in the field of intraocular contact
11 lenses, and I've investigated for other companies
12 previously. I have personal experience implanting all three
13 current styles of phakic intraocular lenses, as well as
14 intracorneal rings.

15 I would like to make two kinds of comments to the
16 panel. One, generality, and the two or three specifics
17 about the things that we discussed this morning.

18 The generality is to plead that the FDA agency,
19 and that the panel, remain in the world of reality as they
20 wrestle with these very difficult problems of safety and
21 effectiveness. Our goal is to bring safe and effectiveness
22 technology to the American public in a timely fashion.

23 I have just finished, as principal investigator of
24 an investigational device exemption, a study that's just
25 about to receive its final PMA. We have our approvability

1 letter. Once the labeling is done, we'll have our final
2 PMA. To my knowledge, this was the first physician-
3 sponsored IDE to be allowed by the FDA. The specific topic
4 is the Emory system of laser in cytokeratome uses.

5 At the time we received our approvability letter,
6 which was many, many months before we will approval, the
7 technique that was approved was totally out of date. We
8 will never use it. We have no interest in using it. And,
9 in a sense, we wasted our time.

10 The point of my personal testimony in that regard
11 is that I believe the agency must attend to the rate at
12 which new technology is propagated and allowed to go.

13 DR. McCULLEY: George, will you come to a point
14 about what we just finished discussing, please?

15 DR. WARING: Yes. That has to do with the
16 discussions, Jim, of the questions of the--of where the bar
17 is set.

18 DR. McCULLEY: Okay.

19 DR. WARING: My conclusion there is, the higher we
20 set the bar, the more cost and the more patients, the slower
21 the technology goes.

22 DR. McCULLEY: Okay. Point taken.

23 DR. WARING: My specific points are: I believe the
24 contrast sensitivity adds very little to the assessment,
25 based on our appearances before the FDA.

1 I believe that endothelial cell assessments should
2 be done in two stages, and that one can assess endothelial
3 cell loss at three months from surgery. It's not necessary
4 to wait a year after surgery to figure out how much the
5 surgery damaged the endothelium. I think that can be done
6 much quicker, and then we wrestle with the problem of the
7 long-term loss.

8 I would like to express an opinion against using
9 slit-lamp photography in the assessment of cataracts,
10 because of what Rosenthal says--it is very complicated, and
11 very expensive, and very difficult, based on our previous
12 experience.

13 And, finally, if we're using visual acuity
14 outcomes, I think those outcomes--for example the percent of
15 eyes 20/20 or better uncorrected--must be a subset of eyes
16 that had 20/20 vision pre-operatively and, of course,
17 exclude monovisions and intentional undercorrections.

18 Thank you.

19 DR. McCULLEY: Thank you, George. Thank you for
20 making your last points.

21 I want to re-emphasize that the purpose of this
22 session is for points to be made relative to what we have
23 been discussing; not testimonial, not other areas to be
24 delved over into, please.

25 Dr. Sanders?

1 DR. SANDERS: [Technical difficulties with audio
2 pick-up.] Don Sanders. I'm the Acting Medical Monitor for
3 the Staar Surgical Implantable Contact Lens Study, which has
4 been in clinical trials for approximately two years.

5 And what I'd like to do is address some of these
6 endpoints.

7 First of all, of the cases that have been done in
8 the United States, the average refractive error is over 10
9 D, and it can back to, to date, over 17 D. So we're dealing
10 with a very highly myopic population. And I think that some
11 of the topics that have been set down are elliptic for this
12 sample. For instance, uncorrected acuity of 20/40 or
13 better, and it's going to be [inaudible].

14 I think 75 percent plus or minus 1 D, in a 15 D
15 myope is a different standard than one would attempt to do
16 between 1 and 7. And I will challenge any other technology
17 to anywhere near approach even 50 percent plus or minus 1,
18 when you're dealing in the double-digits [inaudible].

19 [Inaudible] is same issue. If you can't get that
20 level of predictability--and I've had some [inaudible] for
21 phakic eyes, and [inaudible] complicated in some ways,
22 that's a standard that's even difficult for orthocular lens
23 calculation, at least from the data I've seen.

24 I think, with regard to the standard of 80 percent
25 of patients at each visit, my experience with clinical

1 trials in a number of these studies have indicated that in
2 some respects, we're [inaudible] the ability to get patients
3 at each visit, and with this highly mobile population,
4 that's something that the company should attempt, but I
5 think that you're going to find that it's going to be very
6 difficult, and that the major [inaudible], as brought out by
7 Dr. Ferris--to make sure these patients come back and that
8 you know that they are [inaudible] any serious adverse
9 reactions by the end of the study. So I think you ought to
10 be aware of it.

11 About the cataracts, I think that there are two
12 issues: one, even in the highly myopic population, as many
13 of you are aware, the alternative to using a phakic IOL had
14 been [inaudible] extraction. So what some of these phakic
15 IOLs do is they offer an alternative to maintain
16 [inaudible], even if there is a higher incidence of
17 cataract formation. With cataract formation, also, I think
18 we ought to bear in mind that there is a certain amount of
19 surgical trauma involved in putting them in, and it can vary
20 according to the surgeon and so on.

21 So what we need to do is also bear in mind a
22 certain level that might be expected due to surgical trauma,
23 and then the ongoing issue, which is what has been discussed
24 here.

25 Thank you

1 DR. McCULLEY: Thank you for your viewpoints.

2 Dr. Schanzlin, you've been shuffling around back
3 there. Do you want to speak?

4 DR. SCHANZLIN: Thank you. Dave Schanzlin,
5 University of California at San Diego and Professor of
6 Ophthalmology. I've spent the last 20 years in academic
7 medicine, and have been primarily involved with designing
8 clinical trials.

9 I do have a relationship with KeraVision, in that
10 I serve as a consultant to them. I have no stock in their
11 product.

12 But my comments really are from the academic side.
13 And what I have heard in the last several hours is really, I
14 think, a concern that you all have with being sure that
15 these techniques are safe as well as effective. But let's
16 not forget the science of statistics. And what I have heard
17 here is constantly pushing, one, more and more safety. And
18 yet is any one of us designed a clinical trial and submitted
19 it to a peer review, such as the NIH, they would come back
20 and say, "Your sample size calculation tells you two things:
21 1) what's the minimum number of patients you need to prove
22 the point you want to make?" And that, of course, will come
23 back to you as a budget cut if they think you can get away
24 with fewer patients. And budget are important if we want to
25 keep technology here in the States.

1 But there's another side to it that we shouldn't
2 forget. We should never expose more patients than necessary
3 to an experimental surgical procedure. So if we're going to
4 get very minimal gain by doing 500 cases versus 420 cases,
5 we've essentially put 80 patients at risk, because some
6 procedures may come through the FDA that are dangerous. And
7 these protocols may not get stopped in time before that's
8 realized. So the flip side to having enough cases is that
9 having too many cases to prove scientific significant could
10 be a risk to patients.

11 Thank you.

12 DR. McCULLEY: Thank you.

13 Are there any other comments on what we have
14 discussed today so far? We're going to have two other
15 options, but they must be restricted to what we have been
16 discussing.

17 Yes?

18 MS. FANT: My name is Barbara Fant, and I'm an
19 independent consultant and I represent several clients who
20 have LASIK under investigation, and a client that also has a
21 phakic refractive lens; it's a posterior chamber lens.

22 I've done extensive analysis with LASIK, and I
23 just finished an analysis for this client on their
24 international data for the phakic refractive lens, and I can
25 say that the efficacy criteria that we have for LASIK

1 translates very well to at least the phakic refractive lens.

2 The safety criteria is a different story because
3 you're looking at a different procedure. And what we've
4 seen from the safety side of it is that you really need to
5 separate out adverse events that occur due to the surgery,
6 to the implant procedure itself, versus the long-term
7 adverse events that occur to the device itself; and that
8 adverse events that occur early in the learning curve--in
9 other words, when a surgeon is first implanting that lens
10 for the first time--versus adverse events that occur after
11 there's some experience with the lens. So I would just like
12 to make those points.

13 Also, in looking at uncorrected visual acuity data
14 we need to remember that when we look at uncorrected visual
15 acuity with the implant, we're not looking at true
16 uncorrected visual acuity. There is correction with that
17 implant, and that needs to be taken into account; and also
18 looking at what these patients are able to achieve, in terms
19 of uncorrected visual acuity. So if you have somebody who
20 counts fingers preoperatively without uncorrected visual
21 acuity, what can they achieve post-operatively with the lens
22 in place? That does need to be taken into account.

23 We've looked at stability and predictability, and
24 stability can be analyzed very easily, and it's very easy to
25 meet the target criteria that were discussed today.

1 Predictability is an issue if you're looking at
2 cylinder correction versus non-cylinder correction, and when
3 you look at predictability versus LASIK, in most cases
4 you're allowing for cylinder correction, and in many cases
5 with the implants or the other modalities there is no
6 cylinder correction. So that needs to be borne in mind when
7 you look at efficacy criteria, as well.

8 Contrast sensitivity--my LASIK experience with
9 contrast sensitivity is that patients that are highly myopic
10 have difficulty doing contrast sensitivity pre-operatively,
11 so you don't get a good baseline reading when you're trying
12 to do post-op evaluation.

13 And, basically, for sample size, I think many of
14 the points that have been discussed earlier are valid
15 points, and our experience with LASIK is that the normal
16 population, without much prompting, you get about a 70
17 percent return of your patients coming for your post-
18 operating evaluations. If you start reminding patients and
19 do a lot of work to get these patients in, you can get an 80
20 to 85 percent follow-up at the post-operative visits.

21 Getting the 90 percent follow-up at the last post-
22 operative visit takes an extreme amount of work from the
23 investigator's standpoint because these are normal healthy
24 people and they don't feel that they're sick and they need
25 to come in for these evaluations. And my particular clients

1 that have been working toward these 90 percent evaluations,
2 they have to devote a considerable amount of resources, in
3 terms of personnel, to get these people in for these 90
4 percent evaluations.

5 I think 80 to 85 percent--the 80 percent is
6 reasonable at each evaluation. I think 90 percent at the
7 evaluation is reasonable, but it takes a lot of work to get
8 it.

9 DR. McCULLEY: Thank you.

10 Anyone else wish to be recognized?

11 [No response.]

12 DR. McCULLEY: We will break for lunch now, seeing
13 no other people wishing to speak. And let's take 30 minutes
14 for lunch. So look at your individual watch, since we don't
15 all have the same time, and we will reconvene in
16 approximately 30 minutes which, by my watch, will be about
17 eight minutes before 2:00.

18 [Whereupon, at 1:25 p.m., a luncheon recess was
19 taken to reconvene at 1:52 p.m., this same day.]

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

[2:16 p.m.]

1
2
3 DR. McCULLEY: If we could begin, again. I would
4 like to call the session back to order. There are a number
5 of people that I'm being told will have to leave prior to 5
6 o'clock. I think our anticipated expectation with the
7 document today probably does not fit reality. This has
8 ended up being a very difficult, from my perspective,
9 document and assignment to address. I think everyone has
10 given it their darndest, and we'll keep doing that as long
11 as we have enough people here. At some point, I guess you
12 will have to decide whether you want, if the group to
13 discuss gets smaller, whether you want to continue with a
14 smaller group or whether you want to leave some of the
15 issues to be addressed later.

16 Dr. Rosenthal?

17 DR. ROSENTHAL: Before you start, Dr. McCulley,
18 I'd like to introduce to--the panel has met Dr. Berman, our
19 new medical officer, but I wanted to introduce her to the
20 public, who may not have been here yesterday. So even
21 though that public has not come back from lunch--

22 [Laughter.]

23 DR. ROSENTHAL: Dr. Berman, you are being
24 introduced to a public that may not be here. But Sherri
25 Berman is a new medical officer in the division, and we

1 wanted you to see her, so that when you have to deal with
2 her, you will know that there is a person behind the name.

3 DR. McCULLEY: We'll begin with the next issue.
4 Just an appeal that let's try to keep our restating, either
5 what we've already stated or what someone else has stated,
6 to a minimum. There are situations where that is very
7 valuable, and I don't know how to tell, before the fact,
8 which it is.

9 So everyone just please try to use your best
10 judgment relative to readdressing issues that have already
11 been addressed by either yourself or someone else and try to
12 keep comments, please, to the point, not that you haven't
13 been doing that already, but it makes me feel better to say
14 it.

15 Let's start now with the next issue, Study
16 Design.

17 MS. BOULWARE: The next issue is study design, and
18 the first area we'd like to discuss is power formulas. One
19 aspect of the study design is the power formula recommended
20 prescribing range, and power formulas may be unique to a
21 particular device, since the formulas that currently exist
22 for aphakic IOLs cannot be used. It should be recognized
23 that the power formula and associated constant will be an
24 integral part of the device that is ultimately PMA-approved.

25 Our initial proposal, at this time, is to ask

1 sponsors to include the recommended power formula in their
2 IDE. The IDE should also include a basis for the formula,
3 theoretical or foreign clinical data. And, finally, we
4 would strongly recommend that sponsors allow the formula to
5 be personalized; that we would also recommend that the case
6 report forms be modified to collect data on the formula
7 used, a constant use, if applicable, and any personalization
8 that was applied.

9 We would like any comments you might have on this.

10 DR. McCULLEY: You realize we did not have this in
11 our handout.

12 MS. BOULWARE: This was the one slide that was
13 added.

14 DR. McCULLEY: Walter, you're expert on power
15 formulas. Were you listening? Were you paying attention?

16 [Laughter.]

17 DR. STARK: We're organizing a dance.

18 [Laughter.]

19 DR. BULLIMORE: I think what Walter wanted to say
20 is it's okay.

21 DR. McCULLEY: Any comments about this? Thanks,
22 Fred.

23 [Laughter.]

24 DR. McCULLEY: Dr. Bullimore's comment stands.

25 Jose?

1 DR. PULIDO: So what I would understand then is
2 that, as time goes on and they learn more whether their
3 initial power formula works, we're going to get different
4 data and better accuracy with time. So going back to what
5 we had originally required, which was a certain percent
6 within plus or minus one diopter, the initial patients
7 wouldn't be able to achieve that, what they originally--what
8 we're requiring for the patients. The original set of
9 patients wouldn't be able to achieve that kind of accuracy.

10 MS. LOCHNER: I think our experience has been that
11 companies have been able to at least, when they come up with
12 the initial power formula that they propose, I think they're
13 pretty close to being able to meet that. We haven't seen
14 any problems with them meeting that. I think it does result
15 in a little bit of fine-tuning, and we would do that as the
16 study goes on, but I don't think, initially, that would
17 necessary be a problem.

18 DR. McCULLEY: I would agree. We already know who
19 some of their consultants are.

20 MS. BOULWARE: Moving on to phase-in, we have
21 historically had a slow phase-in, but we found those
22 approach has been beneficial in several cases. So this
23 would be our proposal. Phase 1 of ten subjects followed
24 for six months, and we're really just looking for disasters
25 at this point; a Phase 2, with 100 additional subjects

1 enrolled, and then a report on 50 subjects with six months
2 of follow-up to the agency to provide some additional safety
3 data and some initial effectiveness results; and then a
4 Phase 3 would be the remainder of the study population--and,
5 obviously, that number will have to be adjusted based on our
6 discussions this morning.

7 We'd like your comments on our proposal.

8 DR. McCULLEY: Walter?

9 DR. STARK: It seems reasonable.

10 DR. McCULLEY: It seems reasonable to me. Anyone
11 differ?

12 [No response.]

13 MS. BOULWARE: We may be through earlier than we
14 thought.

15 DR. McCULLEY: I don't know that, but we'll give
16 time to where we need it, but where we don't need to spend
17 time, we won't, and I don't want it to seem like we're in a
18 rush.

19 Dr. Sugar?

20 DR. SUGAR: Responding to the comment that I don't
21 know if Dave Schanzlin and George made about speed, can
22 those ten subjects be acquired outside of this country?

23 MS. BOULWARE: Yes.

24 DR. SUGAR: So that the first six months or even
25 the first 12 months could be obviated with foreign patients.

1 MS. BOULWARE: If they're followed to a very
2 similar protocol.

3 DR. McCULLEY: Next point?

4 MS. BOULWARE: We've also had sponsors who wished
5 to pursue multiple indications; for example, both myopia and
6 hyperopia, and our concern is the total number of eyes that
7 are exposed to a new device early in the investigation.
8 We've also recommended that sponsors keep these protocols
9 separate due to differences in testing measurement, whatnot.

10 So our proposal, when multiple indications are
11 desired, is a Phase 1 of 20 subjects--that's ten for each
12 indication followed for six months; Phase 2 of 150 subjects
13 with no more than 100 for any one indication, and then a
14 report to the Agency when 50 subjects of the same indication
15 have six months of follow-up; and then Phase 3 would allow
16 the rest of the population to be enrolled.

17 DR. McCULLEY: It seems perfectly reasonable to
18 me. Any differing comment, Fred, Woody?

19 DR. VAN METER: That's fine. It seems to me that
20 there's such a difference between myopia and hyperopia that
21 we found, clearly, those two indications needed to be
22 studied separately. I wonder, in this particular example,
23 if anybody else on the panel thinks it's reasonable to hold
24 them to two separate indications.

25 MS. BOULWARE: There would be two separate

1 protocols. If the two protocols are being run at the same
2 time for a new device, we're trying to limit the total
3 number of eyes exposed to the device, no matter the
4 indication. So the protocols would be separate.

5 DR. McCULLEY: But the implication is that you
6 would not allow three protocols or is it ten per protocol,
7 whether there's two, three, four, or five?

8 MS. LOCHNER: We hadn't considered more than the
9 myopia and hyperopia at this point. But I think it's the
10 same issue, more or less, and it's sort of an untested
11 device and how the device will work in the eye, if there's
12 any gross concerns in limiting the phase-in, initially.

13 DR. BULLIMORE: This is Mark Bullimore. When we
14 had the laser, when we were doing sort of different shaping
15 things to the anterior cornea, there were obviously very
16 different concerns for ablation in the central area or this
17 sort of mid-peripheral thing that people do for hyperopia.
18 Here I think our primary concern is the safety issue of
19 putting something inside the eye. And whether it's a plus
20 lens or a minus lens, I think we can get away with this or
21 we can live with this.

22 DR. McCULLEY: Any differing opinion?

23 DR. VAN METER: Woody Van Meter. I would just add
24 to that, that the shape of the lenses is going to be
25 different and will fit differently in the eyes, and we know

1 that there is a big difference between highly myopic eyes
2 and highly hyperopic eyes. There's enough difference it
3 would concern me. But I agree with the Agency's decision to
4 not put too many eyes at risk.

5 DR. McCULLEY: You can have mild hyperope with or
6 without astigmatism. So you could very easily expand to
7 four. So that was the question about limiting it to two
8 indications.

9 MS. LOCHNER: Generally, the protocols, if they
10 are myopia, they allow up to a certain amount of
11 astigmatism. So that's all sort of handled in one. We
12 haven't had devices yet that specifically correct the
13 astigmatism.

14 DR. McCULLEY: We did with lasers, and we just saw
15 intraocular lenses, Forex intraocular lenses. So a company
16 could propose starting a myope, a hyperope, a myope with
17 astigmatism, a hyperope with astigmatism trial all at once,
18 theoretically.

19 MS. LOCHNER: Right.

20 DR. McCULLEY: So the question is are you going to
21 allow that or are you going to limit them to two studies
22 initially; is that your intent?

23 MS. LOCHNER: I don't think we have quite gotten
24 that far.

25 DR. McCULLEY: Okay. Something to think about.

1 Mike?

2 DR. BELIN: This document we're looking at is not
3 just for implantable IOLs. It's also for potentially
4 intracorneal inlays, rings, et cetera. Particularly, if you
5 think about intracorneal inlays, there may be very different
6 safety risks to a thin-centered minus lens versus a thick
7 plus-plus lens. I would think we should handle like we've
8 always handled it, as two separate indications.

9 DR. McCULLEY: Any other comments?

10 [No response.]

11 MS. BOULWARE: Our next question has to do with
12 ranges of refractive correction, and considering some of the
13 safety issues we've discussed today, what are your
14 recommendations for the range of refractive errors that
15 should be treated in the early phases of an investigation;
16 that would be Phase 1 and 2, for the indications we've
17 listed. We realize you may wish to make separate
18 recommendations for different types of implants.

19 DR. McCULLEY: Dr. Stark has left, not to return?

20 DR. MACSAI: It appears so. His briefcase is
21 gone.

22 DR. McCULLEY: I know he's not there. Is he
23 returning? Not returning?

24 MS. LOCHNER: No, Dr. McCulley, he told me he had
25 to leave at 2:30 today.

1 DR. McCULLEY: He left ten minutes early.

2 [Laughter.]

3 MS. LOCHNER: We'll have to get him for that.

4 DR. McCULLEY: And he had comments specifically on
5 this yesterday that he didn't make. But I think the gist of
6 his comments, as I understood them, was that for implantable
7 lenses in the eye, that the greatest interest on the
8 clinician's part is in the higher range, where we don't have
9 alternatives, and we're most interested in seeing safety and
10 efficacy data in the higher ranges, where we don't really
11 have alternatives to try to get people to emmetropia. I
12 think that was what he was stressing.

13 DR. MACSAI: That was his point.

14 DR. McCULLEY: Which I would echo.

15 MS. LOCHNER: Are you suggesting then that if a
16 company has an intraocular lens, for example, and they want
17 to go from, let's say, 4 to 20, should we limit them in the
18 early stages to the higher myopes?

19 DR. McCULLEY: My gut response to that would be
20 yes because we have viable alternatives in the lower range,
21 so that those patients already know established risk, and so
22 in learning what are unknown risks, that it would be
23 advantageous I think all around to have the initial study
24 patients be in the very high range, where we don't have
25 viable alternatives.

1 MS. BOULWARE: Would you care to put a number on
2 that?

3 DR. McCULLEY: Well, the upper limit, in terms of
4 ability to aim for emmetropia, if we set 250, and we have a
5 160 plate, it depends on the patient's pre-op corneal
6 thickness, and that is going to be somewhere in the range of
7 a minus 12 to minus 14 spherical equivalent. So above that,
8 so I would say--and then there's the issue of where will the
9 advantages shift over, whether they are opinions at 10 to
10 12. I certainly would put it, I would probably say above a
11 minus 14. But that's going to vary a little bit with the
12 patient's corneal thickness. They are minus 12s that you
13 can't fully correct. They don't have a very thick cornea.

14 MS. BOULWARE: It may be difficult for sponsors to
15 find a significant number of patients between 14 and 20 to
16 fulfill the first two phases of their study.

17 DR. McCULLEY: What if we dropped it to minus 10.
18 Mike had his hand up first, that I saw, anyway.

19 DR. BELIN: To a large degree, my preference would
20 be to leave this up to the company that's doing the IVE.
21 Again, some of this I think we're putting our own bias about
22 what we anticipate to be the safety profile of a new
23 procedure. My guess would be is that you're not going to
24 have companies putting in intraocular lenses in the minus 2s
25 and minus 3s, because if that's all the data they're going

1 to provide, then their indications are going to be limited
2 up to minus 2 and minus 3, where they know their market is
3 not going to be. So I think it's going to be somewhat
4 determined by the company submitting the IDE.

5 DR. McCULLEY: My opinion is not bias-driven, it's
6 ignorance-driven.

7 DR. BELIN: I won't say it's the same thing, but--
8 [Laughter.]

9 DR. McCULLEY: Ouch.

10 DR. BELIN: That came out wrong.

11 DR. McCULLEY: Janice?

12 DR. JURKUS: This is Janus Jurkus. I would
13 suggest considering possibly a minus 10. We know that the
14 majority of our refractive surgeries are used for people
15 under a minus 10 range, and contact lenses and other options
16 become more limited over that amount, but yet still the
17 population should have enough subjects available to it for
18 inclusion in the study.

19 DR. McCULLEY: Marian, I saw your hand next. Do
20 you still have it up?

21 DR. MACSAI: I would even accept down to minus
22 seven.

23 DR. McCULLEY: Woody?

24 DR. VAN METER: This is all fine, but there is
25 legitimate data that comes from safety in efficacy in all

1 ranges, and I think if we leave it up to the companies and
2 ask for reasonable stratification of the data, there's
3 useful information to be gained.

4 What concerns me is recruitment of patients in the
5 high ranges is going to be more difficult. And, certainly,
6 if these lenses work better than procedures that change the
7 shape of the cornea, that we'd like to know that, even in
8 the moderate ranges.

9 DR. McCULLEY: There's no question about that.
10 It's where to start to try to find out, to bring into the
11 known range what is currently unknown.

12 DR. VAN METER: I'd leave it to the companies.

13 DR. McCULLEY: Marcia, you had your hand up. Do
14 you still want to say something?

15 DR. YAROSS: Yes. I was going to say that I think
16 that sponsors need to be able to make their case for
17 whatever indication may be appropriate.

18 DR. McCULLEY: Ming?

19 DR. WANG: Ming Wang. I think it's agreed that we
20 do not know the profile of the new technology. But the
21 question is, as I understand Dr. McCulley's point, is
22 fairness to the patient. If minus 3, you have very
23 satisfactory--fairly satisfactory refractor procedure today.
24 It may not be fair to these patients to subject them to
25 experimental procedure. So it's really only consideration

1 on behalf of patient, maybe a lower limit can be set.

2 DR. McCULLEY: Mike?

3 DR. BELIN: Again, right now I think we're
4 fixating on intraocular implants. This document is also for
5 corneal rings and inlays, where the potential refractive
6 profile is totally, totally different. I don't want to be
7 specific, but there's one that we know that we're going to
8 be looking at soon, and if we say you have to come in with
9 minus seven and above, they're going to have nobody.

10 DR. McCULLEY: You are right. It does need a
11 point of clarification. Our discussion was going along the
12 lines, as though we were talking about intraocular implants
13 and the requirement for that, and that clearly would not be
14 the requirement for intracorneal implants.

15 Jose?

16 DR. PULIDO: I would have to stress I would want
17 to also leave it to the companies to make the decision.
18 Because if you, from the start, take those patients that are
19 minus 10 or above, those are also the patients that have a
20 higher incidence of developing spontaneous retinal
21 detachments. And if you see a greater number of retinal
22 detachments in this group, are you going to say it's because
23 of the procedure that you did? So I would rather leave it
24 to the company to make the decision*.

25 MS. BOULWARE: Just a point of clarification--

1 excuse me. Go ahead.

2 DR. ROSENTHAL: Excuse me. This is Dr. Rosenthal.

3 The company proposes a limit, I mean, a range, and
4 we decide whether or not we feel it's appropriate. We don't
5 leave it up to the company to decide where they're going to
6 start. We make that decision. We need your advice whether
7 or not you feel we should limit it, at a certain point, or
8 we should allow them to have an entire range.,

9 DR. McCULLEY: And that's what we're discussing.

10 MS. LOCHNER: Especially in the early phases.

11 DR. ROSENTHAL: In the early phases. We're not
12 talking about the Phase 3. We're talking about the early
13 phases of a new implantable device inside the eye.

14 DR. McCULLEY: And we've heard 14, 10, 7, and
15 nothing, and I will come back to that.

16 Ashley, you had something?

17 MS. BOULWARE: Yes. I wanted to clarify that we
18 do have requests for very large ranges from minus 2, minus
19 3, up to minus 20, and from minus 1/1.5, I mean, plus 1,
20 plus 1.5 to plus 20. So there will be requests for the
21 entire range very early on.

22 DR. McCULLEY: I understand. And the question is
23 whether in the very early phases, while you are really
24 concentrating on unanticipated, as well as anticipated,
25 safety issues, that my perspective is that you should go to

1 the ranges where there aren't already known risk safety
2 issues.

3 Rick?

4 DR. FERRIS: This is Rick Ferris. It seems to me
5 this is a guidance document and that it would be perfectly
6 reasonable to put in a guidance document that, as I think is
7 true for almost anything--new drugs, new devices--that this
8 first Phase 1 you tend to take patients who are more severe
9 disease and who have sort of more to gain in the Phase 1
10 trials. They have more to risk at this point because you
11 don't know what the risk profile is. It strikes me that in
12 a guidance document that you would put that in there.

13 Now I said my favorite number was 8.375. I'm not
14 too sure that we need to pick a number here. But it seems
15 to me that the sense of the discussion is that you ought to
16 start at the higher end of your spectrum at the beginning
17 and expand to the rest of the spectrum as time goes on, and
18 that you should submit that plan to the FDA. If you're
19 going to do something different than that, you better have
20 a good explanation as to why, and maybe that's enough.

21 DR. McCULLEY: If that satisfies the FDA, and you
22 don't have to have a number or don't really want a number
23 from us. Dr. Grimmett?

24 MS. LOCHNER: That's fine.

25 DR. GRIMMETT: Michael Grimmett. I was just going

1 to make the point that if it's restricted to just the higher
2 end of the range, those are also the patients where there
3 may be more trouble with predictability and all of those
4 other stringent criteria we set up.

5 DR. McCULLEY: Mike?

6 DR. BELIN: I'll be quick. Again, on the higher
7 end, if the initial Phase 1 is a safety analysis, we do a
8 procedure--and, again, we'll take let's say putting a lens
9 in the eye that subsequently has to come out, we risk a
10 patient population that is now at greater risk for
11 complications due to the surgery of removing the IOL.

12 In addition now, if you do something with an
13 intracorneal implant on a high level and have to take it
14 out, and you have to do something to correct that, we don't
15 have a procedure to correct it. So it could be made a
16 safety argument to limit it in the range where we currently
17 have alternative treatments.

18 DR. McCULLEY: Ming.

19 DR. WANG: Ming Wang. I'd like to second Dr.
20 Farris' point that if I'm in a, say, chemotherapy and
21 somebody come up with brand new drugs, no safety guidance at
22 all, it would not be fair to subject to patient with low-
23 grade tumors, where we have more effective treatments.
24 Perhaps for these patients who are really at the end of the
25 line, so to speak. So I think insofar as safety, early

1 phase, is more reasonable to have some sort of limit.

2 DR. McCULLEY: Marian?

3 DR. MACSAI: If it's really a new device and
4 there's real safety issues, do it in blind eyes, and then
5 determine it's safe, like they did for all other new things,
6 and proceed.

7 DR. McCULLEY: I am not sure. Sometimes I'm
8 really unclear whether you want us to keep driving to a
9 final point or whether you want broad information from us.
10 The risk is, from our perspective, if we leave it broad,
11 then our influence, if we did want it to go to a specific is
12 lost. So it's what the panel wants and what the FDA wants
13 as well. We've left this, from our standpoint so far,
14 you've heard arguments at both ends of the spectrum.

15 MS. LOCHNER: I think on this particular issue we
16 can work with what you've given us, and bear in mind that
17 you will see the draft guidance when we release it. So
18 you'll have an opportunity to comment again.

19 DR. McCULLEY: Again, my caveat to the panel is,
20 if we leave it there, then we've lost some of our potential
21 influence. If we have a group opinion, we need to state it
22 clearly.

23 Jose?

24 DR. PULIDO: In terms of what Dr. Macsai said, I
25 have a problem about putting an intraocular lens in a blind

1 eye to see if it's helpful or if it doesn't cause harm. So
2 I would hold from that point.

3 DR. McCULLEY: Yes. I mean, unexpected
4 sympathetic, but I agree with you. I think an intraocular
5 procedure in a blind eye for investigational purposes I
6 would have trouble supporting.

7 DR. VAN METER: Sensing the Agency's request for a
8 number, I like Marian's number of seven. May I throw that
9 out? That eliminates the low myopes that have other
10 alternatives.

11 DR. McCULLEY: This is an intraocular implantable
12 device. Is there consensus on seven? All who think seven
13 is the best number raise your hand.

14 [Show of hands.]

15 DR. McCULLEY: Put them up or down. Don't wave at
16 me.

17 [Laughter.]

18 DR. McCULLEY: All who think it's not?

19 [No response.]

20 DR. McCULLEY: So seven seems to be the best
21 consensus number for intraocular implantable devices for
22 myopia.

23 MS. BOULWARE: Do you want to make a
24 recommendation for hyperopia?

25 DR. McCULLEY: Do you want to make a

1 recommendation for hyperopia?

2 DR. VAN METER: Four.

3 DR. McCULLEY: Four for hyperopia, all in favor?

4 [Show of hands.]

5 DR. McCULLEY: All opposed?

6 [No response.]

7 DR. McCULLEY: Sold.

8 MS. BOULWARE: Thank you very much.

9 DR. McCULLEY: But that, again, is for intraocular
10 implantable devices.

11 DR. BRADLEY: Mr. Chair, it might be worth
12 pointing out for the record that the majority of the people
13 did not vote. So there seems to be a certain degree of
14 uncertainty about this.

15 DR. McCULLEY: Right. There was a large number,
16 in the latter vote for hyperopia, most people abstained.
17 For myopia the majority did vote I think. The majority did
18 not vote on hyperopia.

19 Dr. Higginbotham?

20 DR. HIGGINBOTHAM: A very quick comment.

21 Hyperopia is a little bit more difficult, obviously. But
22 from a glaucoma standpoint, you are going to have a greater
23 tendency for angle closure and all other complications. So
24 that's why I abstained.

25 DR. McCULLEY: Duration of study?

1 MS. BOULWARE: We've talked about a number of
2 issues already that might impact follow-up. Are there any
3 that we haven't discussed today that would impact the length
4 of follow-up? I think we started off with a proposal of
5 maybe two years for most and three years for anterior
6 chamber, phakic IOLs, in terms of follow-up, but we've had
7 discussions already today that lean towards three.

8 DR. McCULLEY: For all.

9 MS. BOULWARE: And then in terms of how much
10 follow-up is needed prior to PMA submission or approval.
11 And depending on what your answer is for that, would you
12 recommend post-approval studies to address long-term
13 concerns?

14 DR. McCULLEY: This is tougher. The sense I got
15 was that for us to be able, for the panel to be able to feel
16 comfortable to recommend, that we would want to see three-
17 year data. Is that an incorrect sense, Rick?

18 DR. FERRIS: This is Rick Ferris. First, as a
19 question, can a company come in for review whenever they
20 want to come in for review?

21 MS. BOULWARE: Yes.

22 DR. FERRIS: So the issue is, is there a sense of
23 this panel that would suggest to a company don't bother to
24 apply until you have a certain amount of data. If that's
25 the question, it seems to me that it may be somewhat data-

1 driven. If, for example, you had one-year data that showed
2 not one endothelial cell had ever been lost in this study,
3 everybody was improving in vision, this was the best thing
4 since sliced bread, and that was one year, I don't think
5 that we could say for sure that you shouldn't come until
6 three because we want to see the three-year endothelial cell
7 data. So there may be circumstances where one is enough.

8 I can't imagine where less than one would be
9 enough, and I can imagine circumstances where one wouldn't
10 be sufficient.

11 DR. McCULLEY: How about cataracts, Rick? I mean,
12 that was the magic number picked before for cataracts. So
13 we've got--

14 DR. FERRIS: For three years?

15 DR. McCULLEY: Yes, for an intraocular device.

16 DR. FERRIS: It's the company's risk. If they
17 think their data is compelling enough and they have clean
18 enough evidence that there's no cataract, I don't see how
19 you can keep them from coming in.

20 DR. McCULLEY: As I understand it, the company can
21 come in. The FDA decides whether the PMA is acceptable or
22 not and whether, then, to bring it to panel. So they have
23 internal issues before us.

24 DR. ROSENTHAL: This is Dr. Rosenthal. I'm sure
25 you aware that the first of a kind would come to panel, and

1 it would be unfair to say to a company this is data-driven
2 and then have them come here and say we want two more years.
3 You can't have it both ways. I think you've got to lay down
4 the--it's a guidance anyway. It's a guidance. And things
5 could change either way. But I think it's only fair to give
6 us a sense of what you think might be required and then a
7 sense of what is required because they're the ones who are
8 at the mercy of the panel.

9 DR. McCULLEY: Rick?

10 DR. FERRIS: This is Rick Ferris again. As was
11 pointed out earlier this morning, by the time you have one-
12 year data on everybody, you probably have three-year data on
13 at least some subset. So I think it's fair to say that--
14 well, you have two-year data probably.

15 MS. BOULWARE: You might have two-year data, but
16 it's very unlikely that you would have three-year data.
17 These studies tend to enroll fairly quickly.

18 DR. FERRIS: Point taken. My point was that
19 you're going to have some longer data as well. It seems to
20 me that if you're going to come in with less than three-year
21 data on lens opacity and endothelial cell count, which I
22 think were the two--and corneal thickness--points of major
23 concern, that you better have pretty compelling data that
24 three-year data aren't necessary. But, in general, I guess
25 the sense of this group is that you would need the three-

1 year data on at least the--

2 DR. McCULLEY: I think you stated it well; that we
3 would want to see three-year data unless there is compelling
4 data to suggest that we would not need the three-year data.
5 Is that stated in an acceptable way?

6 DR. ROSENTHAL: This is Dr. Rosenthal. May I just
7 make a comment? It's going to be fairly obvious if there
8 are major problems. The other problems that you are looking
9 at--cataract--are going to take a long time. We have this
10 with a lot of devices. Don't think it's just the ophthalmic
11 panel that grapples with it. The issue is at what time
12 period would it be reasonable to look at these devices and
13 say, yes, we're happy to take the risk that they're going to
14 be in for a very long time.

15 I think asking a company to go three years might
16 be too long if, in fact, as you say, at one year, everything
17 looks pristine. If it doesn't look pristine, it's going to
18 be hard even at three years to come in and say we're coming.
19 If you have a lot of complications at one year, three years
20 isn't going to help you very much. So I know how you think,
21 as clinicians, and I know how conservative people want to be
22 with new things, but you have to look at the other side;
23 that it might be unreasonable to ask them to go three years.

24 DR. McCULLEY: But, Ralph, are you not arguing
25 against all of the discussions we had before relative to

1 endothelial cell count and cataract formation?

2 DR. ROSENTHAL: I am.

3 DR. McCULLEY: So you are saying that all of those
4 discussions you think were--

5 DR. ROSENTHAL: No. I'm not just saying--

6 DR. McCULLEY: --not valid.

7 DR. FERRIS: You have a post-marketing option.

8 DR. ROSENTHAL: That's what I was getting at. You
9 have a post-marketing option.

10 DR. McCULLEY: So all of our discussions about
11 progressive endothelial cell loss, about cataracts that we
12 had before, we had no point in having.

13 DR. ROSENTHAL: Oh, absolutely not because we got
14 the sense of what the panel felt. Obviously, now we're
15 coming to the crux of it because, I mean, the duration of
16 the study is related to the worry about the long-term
17 complications. I'm just raising these issues from another
18 perspective. To be honest--

19 DR. McCULLEY: I wish you'd brought that up when
20 we were discussing those specific things or maybe the
21 context needs to be different or I'm not sure. Because we
22 clearly had our discussions relative to endothelial cell
23 loss and relative to cataract formation--

24 DR. ROSENTHAL: You did.

25 DR. McCULLEY: --that pushed us toward a

1 recommendation for three years' of data, and that's why I
2 said, as I did, as an aside at those points, that that is
3 suggesting that that would be part of a PMA submission, and
4 then it was stated we'll talk about that later. So I'm
5 still trying to reconcile in my mind.

6 DR. ROSENTHAL: You have a right to say what you
7 want. I'm just trying to tell you that if you ask for
8 three-year data, you are imposing an enormous burden on the
9 company--

10 DR. McCULLEY: On examers, we requested two-year
11 data.

12 DR. ROSENTHAL: Okay.

13 DR. MACSAI: And got three.

14 DR. ROSENTHAL: But what did we get?

15 DR. MACSAI: Some of the patients got three.

16 DR. ROSENTHAL: What was approved?

17 DR. MACSAI: It was two when it came before the
18 panel, the first two lasers.

19 DR. McCULLEY: It was two years. We requested
20 two-year data on the initial examiner submissions. What we're
21 saying with the intraocular implanted device, it brings in
22 another dimension and level of potential complication that's
23 intraocular that we're significantly concerned about; i.e.,
24 cataract formation, endothelial cell loss that we know is
25 going to occur, we presume is going to occur at some higher

1 rate than normal, and we don't know what it is. For that
2 reason, we want to see three-year data.

3 DR. ROSENTHAL: But Dr. Ferris said if it doesn't
4 occur, can they come in and--

5 DR. McCULLEY: That's what I said, three years,
6 unless it looks like--

7 DR. ROSENTHAL: --you're going to say you've got
8 to look two more years. It's not fair to them.

9 DR. McCULLEY: We're saying that we would expect
10 three-year, unless they have overriding or compelling
11 evidence that the concern that we have has been removed,
12 which could be done for endothelial loss. I don't think it
13 can be done for cataracts because of the three-year magic
14 number that Walter alluded to.

15 Marcia was up next.

16 DR. YAROSS: Marcia Yaross. I guess the question
17 is whether or not the issues where the panel wants to see
18 three-year follow-up can be addressed through substudies,
19 where either those substudies can be started very early and
20 then have more data by the time you have one-year on the
21 entire cohort or entire group, or, alternatively, if those
22 can be continued following the PMA. If everything is
23 looking good, you submit and continue that follow-up for a
24 longer period of time on those groups. I think those are
25 alternatives.

1 DR. McCULLEY: Yes. We talked about substudy for
2 endothelial cell count. The numbers didn't seem to lend
3 themselves so well to substudies with cataract formation, as
4 best I remember.

5 Marian?

6 DR. MACSAI: Ralph, when you talk about other
7 devices and other panels, I think we have to remember this
8 isn't a cardiac valve. This isn't a hip replacement.

9 DR. McCULLEY: Speak into the mike.

10 DR. MACSAI: We're not treating something that
11 there is no other alternative for. I mean, spectacles, and
12 contact lenses, and surface laser surgery are currently safe
13 and approved. There are other approved modalities. Why do
14 we have to hurry? I guess I don't understand that. It's
15 not like people are dying or walking around crippled.

16 DR. McCULLEY: The hurry, I think, Marian, is on
17 the commerce side. It's the expense to the company and the
18 reality of doing a study that's affordable to bring a
19 product to the market--my impression.

20 Woody?

21 DR. VAN METER: Woody Van Meter. The reason that
22 I was comfortable with three-year data is because
23 cataractogenesis and endothelial cell loss are fairly
24 difficult to determine in the clinical situation. And in
25 the absence of doing specialized testing for nuclear

1 cataract formation, assuming we had one that were cheap and
2 easy to do, and assuming we had some way to measure a few
3 cells picked off here and there from the endothelium, which
4 we don't, the reason we've got to wait three years is
5 because we're not good enough to determine small losses in
6 either one of those two areas. You might be able to find it
7 after three years, whereas, you wouldn't find it after one
8 year. I'm not sure that it's fair to say just because
9 everything is fine at one year, that it's going to be fine
10 at three years.

11 DR. McCULLEY: I think we've made our points, and
12 we're back on something that we spent a very long time on
13 before. I think that if you have a specific request for
14 Clarification, we can do that, otherwise we're going to be
15 repeating ourselves.

16 MS. LOCHNER: I just have one clarification. It
17 seemed like the discussion was focused on intraocular. Do
18 you have any special--is it the same recommendation for
19 corneal?

20 DR. McCULLEY: The duration of study for
21 intracorneal devices, and you are right, it was focused. We
22 came down before on a new technology principle being applied
23 broadly. Walter did say in his first comment, when I then
24 tried to bring it up again and why Ming voted against the--
25 it was 14 to 1 voted against--is that intracorneal

1 implantable device would not necessarily seem to be the same
2 as an intraocular implantable device. He then explained why
3 he voted against it later, but I think it is somewhat
4 different. But the group, 14 to 1, felt like it should not
5 be treated differently in our previous discussion.

6 Does the group want to change, or soften, or
7 redirect, amend that in some way? Dr. Matoba?

8 DR. MATOBA: Alice Matoba. My understanding was
9 that that discussion would just pertain to the sample size,
10 not necessarily the length of follow-up.

11 DR. BULLIMORE: This is Dr. Bullimore. That's
12 absolutely correct, and I would certainly entertain shorter
13 follow-ups with devices where we, based on our professional
14 perspective, perceive a lot of risk of complications and
15 less safety issues.

16 DR. McCULLEY: Good. Thanks for that
17 clarification. You are right.

18 So would the panel want to recommend a shorter
19 duration follow-up for intracorneal implantable devices and,
20 if so, what? Woody?

21 DR. VAN METER: I agree that it should be shorter
22 because we're less worried about the endothelium and the
23 cataractogenesis, and I think that we used two years for the
24 examer laser for the earlier data, and I think two years is
25 reasonable for this.

1 DR. McCULLEY: Is there agreement, disagreement?

2 [No response.]

3 DR. McCULLEY: Two years on intracorneal.

4 MS. BOULWARE: There could be concerns about
5 progressive cell loss in a corneal implant. It's a constant
6 pressure on the endothelium, I mean, depending on--

7 DR. McCULLEY: We don't deny it. That's why we
8 want to see endothelial cell counts and data, but we feel
9 that the relative concern about that would give us a degree
10 of comfort with two years' data. We're not saying we don't
11 want the data.

12 MS. BOULWARE: So two years for PMA submission,
13 but then three years of total follow-up or two years of
14 total follow-up?

15 DR. FERRIS: Two-year follow-up on intracorneal
16 implantable devices, three-year follow-up on intraocular
17 implantable devices. Rick?

18 DR. FERRIS: Mr. Chairman, I think you were trying
19 to get at this issue, and I will try to rephrase it. Do you
20 need two-year follow-up on the full cohort of 500 or 550
21 enrolled or do you need one-year follow-up on all 550 and
22 two-year follow-up on at least some proportion of the
23 overall group? And, again, it would seem to me that from
24 the point of view of whoever is bringing this to panel, that
25 there could be circumstances where the subset that have

1 gotten to two years are large enough and the data are good
2 enough looking that that would be sufficient, that you don't
3 have to wait until the last enrolled patient got to two
4 years before you would submit.

5 DR. McCULLEY: That was certainly true for
6 endothelial cell count.

7 DR. BRADLEY: Mr. Chair, could you speak into the
8 mike, please.

9 DR. McCULLEY: That was certainly true for
10 endothelial cell count. Ming?

11 DR. WANG: Ming Wang. Sorry for my ignorance. A
12 question for Dr. Rosenthal and FDA. Is there a safe check
13 if a company comes back one year after IDE the results so
14 terrible and they still elect to proceed, is there a safe
15 check FDA can terminate that?

16 DR. McCULLEY: Yes.

17 DR. ROSENTHAL: They report periodically through
18 the whole study, not, you know, and all of the adverse
19 events are recorded. So we are aware of what's going on,
20 and we can step in.

21 DR. McCULLEY: We're on page 11 of 17. Are we
22 through with page 11?

23 MS. BOULWARE: Yes. The next issue is bilateral
24 implantation. Our concerns have been that the long-term
25 effects may be unknown at the time that both eyes are

1 exposed to any device. So we've encouraged the enrollment
2 of contact-lens-tolerant subjects, especially in the early
3 phases, to avoid anisometropia and recommended a strong
4 informed consent document with an addendum that addresses
5 bilateral implantation.

6 Our proposal is for no bilaterals in Phase 1,
7 because we have no safety data available. In Phase 2, once
8 we've received a report on 50 subjects with six months of
9 follow-up, we would allow bilateral implantation with a
10 waiting period of somewhere between three and six months.
11 We would like your comments on this proposal.

12 DR. McCULLEY: Comments? Seem reasonable, and
13 what our recommendation would be, I suppose, would come down
14 to, once you've established it, assuming you've established
15 reasonable safety on the first eye, should the second eye
16 wait three or six months, and I guess it would depend on
17 what the data looked like and what the time lines looked
18 like.

19 MS. BOULWARE: I also want to emphasize that we do
20 entertain protocol waivers for subjects who, for one reason
21 or another, the investigator feels it's very important to
22 have the second eye done.

23 DR. McCULLEY: Speak into the mike, Arthur.

24 DR. BRADLEY: I'm not quite sure whether to make
25 this comment or not. But it seems to me a little bit odd,

1 we've just sort of imposed a three-year follow-up before
2 we're allowed to go on and do other eyes, and now we're
3 saying you can go on and do the other eye after three
4 months. I'm not quite sure how those two are reconcilable.

5 DR. McCULLEY: That's a very interesting
6 philosophical point. But from a reality standpoint, in many
7 of these people, we are creating significant anisometropia.
8 So it's a practical consideration weighed against
9 philosophical idealism or philosophical sense.

10 DR. McCULLEY: Rick?

11 DR. FERRIS: And just to follow-up, as we heard,
12 these aren't bunnies. They are free-living human beings,
13 and they can go to Europe and get this done or they can go
14 elsewhere to get it done, and I'm not sure that--it seems to
15 me that the point of the informed consent being well-written
16 and clear, that there is a clear risk that you're taking if
17 you have this other eye done before it's approved is a
18 critical feature, both for doing it here and for then going
19 elsewhere to get it done.

20 DR. BRADLEY: Just to follow-up on that. Is it
21 possible then to put in the document that the patient is
22 going to sign-off on that we are requiring a three-year
23 follow-up in order to ascertain safety and that they are, in
24 effect, going ahead with less than "three years' follow-up,
25 so there is some uncertainty about the long-term safety, and

1 they have to acknowledge that risk?

2 DR. McCULLEY: Good point.

3 MS. BOULWARE: Yes. We generally have something
4 in the informed consent that states what the length of
5 follow-up is because they have to agree to come back for all
6 of those visits. But that's a good point.

7 DR. McCULLEY: A very good point. I think we have
8 addressed this issue effectively now. We can move to the
9 next.

10 DR. ROSENTHAL: Could I just tell Dr. Bradley
11 that, in fact, much of this pressure comes from the patients
12 themselves.

13 DR. McCULLEY: Move on, please.

14 DR. ROSENTHAL: With a sample of one.

15 DR. McCULLEY: Move on, please.

16 MS. BOULWARE: Once we've had bilateral
17 implantation, the question comes up as to whether to include
18 the bilateral eyes in the cohort evaluation. We have
19 generally recommended that only the first eyes be included
20 in the cohort because, in many instances, the data are not
21 poolable. If the results from the first eye are used to
22 determine a more accurate treatment for the second eye, then
23 those data are not poolable, and so we have only included
24 the first eyes in the cohort. Should we change this
25 approach?

1 And this also kind of gets back to the question on
2 sample size. I wanted to clarify whether we were talking
3 subject or eyes.

4 DR. McCULLEY: Eyes.

5 MS. BOULWARE: I think eyes.

6 DR. McCULLEY: We were talking eyes. What about
7 this, Mike?

8 DR. BELIN: I think, for the initial time we see a
9 new technology, they should not be poolable because one of
10 our major concerns is safety. And we use an example like
11 uveitis, we would have patients who may or may not be
12 susceptible to uveitis, and if we have to pick, we just cut
13 our patient population in half, and I don't think we should
14 do that until we have a good, safe safety handle on the
15 procedure.

16 DR. McCULLEY: Differing opinion to that?

17 DR. WANG: Ming Wang. I think you should
18 distinguish what characteristics. If it's safety issue, the
19 second eye can be. But if it's IOL calculation, as you say,
20 it could be biased with initial study. If it's safety,
21 there's no reason not to include the second eye.

22 DR. McCULLEY: I think there's disagreement to
23 that.

24 MS. LOCHNER: Just as a point of clarification, we
25 always still review the second eye data. It's included in

1 the safety analysis throughout the IDE, and when the panel
2 reviews it, it's just reported separately. And for the
3 purposes of sort of obtaining the sample size, it's not
4 counted. We don't--that data is never just not reported or
5 whatever. We still consider it in our safety analysis.

6 DR. McCULLEY: Rick?

7 DR. FERRIS: Rick Ferris. In addition to the bias
8 that you talk about here, eyes tend to be correlated in
9 virtually everything, and so they are not independent units.
10 At least statistically they can't be viewed as independent
11 units. Now I am a little confused as to whether this 550
12 was units, statistical units or whether it was eyes, and
13 there is a considerable difference.

14 DR. McCULLEY: Well, but if we don't include
15 second eyes as part of the cohort, then the unit is the
16 first eye.

17 DR. FERRIS: Of course.

18 DR. McCULLEY: And I think that's what we're
19 saying.

20 DR. FERRIS: So it's 550 people, and it may be 700
21 or 800 or up to 1,100 eyes that you'll get information on.
22 But in terms of all of the statistical analyses, it'll be
23 the first eye as the--

24 DR. McCULLEY: First eye, right. That's what I
25 hear the panel saying. Agreement?

1 DR. FERRIS: I feel very strongly that that's the
2 way it ought to be.

3 DR. McCULLEY: Okay. Well, I think that you
4 represent the majority.

5 Any further comment on this?

6 [No response.]

7 DR. McCULLEY: Now, once again, we are at a point,
8 this time no testimonials, no admonitions, anyone who has a
9 comment that they would like to make on the section we have
10 just discussed. There will be an opportunity for a third at
11 the end to comment on what we have discussed then, with the
12 reminder that we started the session, both yesterday and
13 today, with open public hearings, where you were invited to
14 speak about what you wished to.

15 We now are down to business. If you would like to
16 contribute to our business, I would invite you to the podium
17 for your comments.

18 **PUBLIC COMMENT**

19 SHIRLEY MCGARVEY: I'm Shirley McGarvey, and I am
20 an independent consultant to several companies developing
21 products for refractive error correction. I have a few
22 comments with respect to both the phase-in and the number of
23 concurrent studies.

24 The point I tried to make this morning is that
25 study design should really be determined by the key issues

1 that are associated with the modality of correction. And
2 phase-in, which is determined by the size in the phase and
3 the timing prior to it being able to expand, I don't think
4 should be fixed for all modalities equally. It should be
5 determined by all available information on that modality,
6 irrespective of the source of that information because, even
7 now, many of the new technologies have quite a lot of
8 international clinical data available prior to being
9 initiated as studies into studies in this country.

10 This is consistent with some work the FDA has more
11 globally underway in a session they are holding with HEMA
12 later, sometime early in November, related to Bazian
13 statistics, wherein, they're looking at external sources of
14 information that could be brought to bear on the safety and
15 efficacy questions, so that smaller studies might be
16 possible in order for the collective body to come to a
17 decision on the merits of the product.

18 And so I would just argue that, again, instead of
19 setting phases that are hard and fast with specific numbers
20 and specific time frames, that each modality has its own
21 characteristics that should drive those dimensions.

22 With respect to the number of concurrent studies,
23 it would seem reasonable that some of these issues, taking
24 from international data, as well as the domestic studies,
25 wherein, you're getting some of the data by the time you are

1 going to Phase 3 and allow it to do that expansion, that the
2 other indications for use for the other ranges of refraction
3 should be possible to be initiated at that point into Phase
4 2 studies, possibly. Because many of the safety issues can
5 be addressed irrespective of the range of correction because
6 some of those safety issues are common to the modality and
7 not unique to the range.

8 Thank you very much.

9 DR. McCULLEY: Thank you. Next?

10 BARBARA FANT: Barbara Fant, independent
11 consultant.

12 I think in terms of the adverse events when we're
13 looking at long-term formation of cataracts, I think you
14 have to differentiate between the types of cataracts that
15 you're looking at and also the mechanism of action for those
16 cataracts. Is it cataract formation due to persistent
17 touch? Is it cataract formation because of changes in
18 aqueous flow, so there's not nutrients getting to the
19 cataract? Are there other problems with aqueous flow that
20 may be causing long-term changes with intraocular pressure?
21 Are you looking at cataracts that are due to trauma induced
22 during the surgery?

23 If you look at traumatic cataracts versus those
24 that are caused long-term, I think that it's very different
25 in terms of when they occur, how they occur, and they can be

1 characterized. I think, in order to look at duration of
2 study and long-term adverse events, I think you have to
3 identify what the long-term adverse events are and what the
4 proposed mechanism of action is for those adverse events.
5 Otherwise you could take this on further, I think as Dr.
6 Rosenthal said, is that, "Okay, we haven't seen it at one
7 year. Now, let's try two years, let's try five years, or
8 let's try ten years to see if this is going to occur." So I
9 think you have to look at the source of the potential
10 adverse event and when it's likely to occur.

11 As far as lengthening the term, the duration of
12 the study, if you lengthen it out to two years or three
13 years versus one year, you're also lengthening out or you're
14 increasing the likelihood that those patients are going to
15 drop out of your study. So you're making it increasingly
16 harder to get 90 percent follow-up at three years than you
17 do 90 percent at one year.

18 So, again, if you're going to recommend a three-
19 year follow-up study, I think you have to look again at what
20 percentage of case report forms or what percentage of
21 follow-up that you're willing to accept, and are you looking
22 at only safety data in terms of follow-up or are you looking
23 at efficacy data in terms of follow-up? Because the
24 efficacy data likely is not going to change. The safety
25 data may possibly change if you see something long-term. So

1 I think those are two different issues that you're looking
2 at in terms of duration.

3 And then, thirdly, I'd like to say also with
4 international data, many of these modalities are coming
5 through, where they've been used in Europe, other countries,
6 and such. So we do have some historical data on these.
7 When you're looking at, again, long-term adverse event
8 profiles, if you're looking at cataracts, whatever it may
9 be, is that there may be other data available that can sort
10 of drive the discussion or drive the review.

11 If you have a modality that's been used in Europe
12 for five or ten years and you don't see cataracts forming in
13 five or ten years in that particular set of information, I
14 don't think there's anything to say that would lead you to
15 suspect that patient's in the U.S. are more prone to a
16 cataract forming in that patient in some other part of the
17 world. So you do have, I think, historical data that can
18 help you look at adverse events and how long a duration of
19 that study would be.

20 So I think, again, it depends somewhat on the
21 individual device and what additional information is
22 available to support the safety and efficacy of that device.

23 DR. McCULLEY: Thank you. George, limit it to
24 five minutes.

25 GEORGE WARING: George Waring. Addressing the

1 issue of the duration of studies, I would like to make a
2 case that intraocular lenses are not really new devices.
3 These are new applications of a totally known and totally
4 accepted type of device; in contrast, for example, to examer
5 lasers, when we began those studies through the FDA, where
6 examer laser treatment of the cornea was a new device that
7 had no track record in human use.

8 Therefore, I would think that evaluating phakic
9 intraocular lenses is something that could be done closer to
10 a one-year time frame than a two- or three-year time frame
11 because we know about the basic overall biology and overall
12 safety of this kind of device.

13 In terms of eye enrollment, I would make a plea in
14 a Phase 2 trial to be able to continue to enroll the second
15 half of those eyes if we accept 100, while we're waiting for
16 the follow-up on the first half of the eyes. So that we
17 don't hit a lag phase in there, where we have to stop
18 enrolling patients and sit and wait, but the manufacturer,
19 the clinics, the patients who want the surgery, can be
20 enrolled sequentially and done.

21 In terms of follow-up, I would emphasize what
22 others have said. This is not the ARAD study. These are
23 not cataract patients. They don't have diabetic
24 retinopathy. These are mobile myopes who have lifestyles
25 just like yours and mine, and if we impose on them

1 restrictions of too long a follow-up, for example, for the
2 second eye, they will simply go out of the country. I've
3 had many of my patients go to Canada, for example, for
4 treatments that they couldn't get here. I think that is not
5 good for clinical practice or for the development of
6 technology.

7 In terms of the second eye, for phakic intraocular
8 lenses, the data from the first eye are not used to plan the
9 implantation of the second eye most of the time. So I would
10 argue that these are, in, fact independent, that the first
11 and second eye can be pooled into your cohort of 500 eyes,
12 and that they are not dependent on each other, even though I
13 understand what Dr. Farris said in terms of biological
14 response and the two eyes being linked. I think with these
15 artificial devices, it's somewhat different.

16 Finally, in terms of follow-up for post-market
17 surveillance, could not the FDA gain its two- or three-year
18 data, as Dr. Rosenthal pointed out, in a post-market
19 surveillance at two or three years and, yet, allow these
20 products to come to PMA application of possible approval
21 based on one-year data if the data are good and if they
22 justify that and still protect patients in terms of longer
23 term follow-up and possible recall if there are long-term
24 problems identified.

25 Thank you.

1 DR. McCULLEY: Thank you, George. Don?

2 DON SANDERS: Don Sanders. I just wanted to
3 reinforce one of the points. I agree with George on
4 virtually all of his points, but on the issue of using
5 fellow eyes, I think that, first of all, with this type of
6 technology, I think you could probably prove efficacy with
7 10 to 15 patients, and I think the issue is safety. And if
8 we're looking at incidence of adverse reaction rates, and
9 we're using, for instance, a group of myopes, I think it is
10 possible to do a poolability analysis for the first and
11 second eye and see if they are poolable with regard to
12 safety issues. They have been used, I am aware of them
13 being used in some of the PRK studies, where fellow eyes and
14 the primary eyes were pooled for safety analysis and then
15 the primary eye was used for efficacy and stability.

16 Thank you.

17 DR. McCULLEY: Thank you. I don't think we want
18 to try to debate the issues that have been brought up,
19 unless the FDA feels like they need clarification.

20 Dr. Bradley?

21 DR. BRADLEY: Just a suggestion to the FDA,
22 stimulated by Dr. Waring's comments, really, and some of the
23 others. It seems to me that if we have data from
24 implantation of phakic IOLs, whether they be from Europe or
25 from the U.S., we may have within that data set some

1 indication of the chance that cataract will develop if it
2 has not developed after one year. I am wondering what that
3 value is. If there is no cataract developed after one year,
4 what's the chance that it's going to develop by Year 3?
5 That's the specific question.

6 DR. McCULLEY: That was what Walter was addressing
7 before, and he was using the example of vitrectomy. Since
8 he's not here, and we've lost our once-maligned
9 vitreoretinal surgeon, Rick?

10 DR. FERRIS: Well, now, wait a second.

11 DR. McCULLEY: He was the maligned one. You're
12 the unmaligned one.

13 DR. FERRIS: For example, with vitrectomy, some 50
14 percent develop nuclear change within one year. So it may
15 well be that these changes could develop quickly or it may
16 well be that they develop slowly and chronically and without
17 data you cannot tell.

18 I was going to make a somewhat different comment
19 with regard to pooling the data. I think there are times
20 where you can pool the data. However, you have to take into
21 account the correlation of eyes because two eyes are not the
22 same as two different people. For example, even with
23 complications, if there is an--I don't know that it would
24 happen with implanted devices--but idiosyncratic responses
25 are person-based, not necessarily eye-based.

1 If there is a bias of implantation, if something
2 bad happened in the first eye, I can only guess what might
3 happen with the other eye. I would guess they didn't get
4 one of these things. So it points out why you can't--your
5 enumerator is going to be affected if there is a bias about
6 getting it in the second eye, and also the rate is going to
7 be affected by correlation between eyes.

8 So, by all means, I think it's useful to look at
9 all of the eyes. I was only interested in whether there
10 were going to be--I didn't want it to be confusing to
11 anybody about what the number of individuals in the study
12 was.

13 DR. McCULLEY: Donna?

14 MS. LOCHNER: I would just like to make a comment
15 about phase-in. First of all, it was our intention that
16 Phase 2 enrollment, which is 100 subjects, would continue--
17 these 100 subjects would continue to be enrolled, but that
18 we would have to wait until 50 of them got out to form four
19 before expansion to three. So it wasn't our intention that
20 they had to stop.

21 The second point I wanted to make is that we do
22 try to be flexible on phase-in, taking into account a
23 company's outside-of-the-U.S. experience. The problem that
24 we oftentimes run into is a company will have experience of
25 using a device for several years internationally. They

1 aren't able to produce very good data about how that device
2 performed internationally. So we're weighing sort of a
3 feeling that, well, maybe we would have heard about problems
4 against actually having data to base that on. We tend to
5 err conservatively with that if we don't have the data to
6 know whether or not some of the basic safety issues have
7 been addressed.

8 So I just wanted to make that point. I think that
9 if the panel feels that just the fact that there has been
10 international experience, whether it's very good data to put
11 on the table or not, we need to factor that in. It's very
12 hard for us to factor that in when there is no good data on
13 the table, just the statement by the company that's been
14 used for several years in Europe or South America or
15 whatever.

16 DR. McCULLEY: I think you have to have data, but
17 if data is available, then take it into consideration.

18 MS. LOCHNER: Right. That's what we tried to do.

19 DR. McCULLEY: We'll move on to your next point,
20 subject evaluations all subjects.

21 MS. BOULWARE: The subject evaluations that we are
22 asking sponsors to collect the data on the screen and the
23 next, not all of these are performed at every exam. Just to
24 give you a list, you will see the subject questionnaire that
25 was discussed earlier. We definitely want reports of visual

1 symptoms. I think we will include the three questionnaires
2 that Dr. Rosenthal had discussed earlier, we will certainly
3 be pretty strong on that point to address some of the
4 panel's concerns.

5 These are additional evaluations, dilated fundus,
6 pachymetry was mentioned, topography, keratometry.

7 DR. McCULLEY: So what you're asking us to comment
8 on is, is this sufficiently inclusive? Is it too inclusive?
9 And you're not specifically asking us to comment on the
10 intervals or the times, the forms on which the individual
11 tests are performed.

12 MS. BOULWARE: That's correct.

13 DR. McCULLEY: So if we limit ourself to that,
14 Mike?

15 DR. BELIN: A real quick comment. UCVA distance
16 and you have BSCVA distance. I would just add distance in
17 there, also BSCVA, since some of these procedures at least
18 we are losing accommodation, and we should not assume that
19 we have not lost their speculative corrected near visual
20 acuity.

21 DR. McCULLEY: I had that and the only other thing
22 is on your dilated exam, it's dilated lens and fundus exam.

23 Dr. Matoba?

24 DR. MATOBA: It's a question. Is best corrected
25 visual acuity just with spectacle or contact lens or

1 whichever is better?

2 DR. McCULLEY: It's BS, best spectacle. For these
3 purposes, it's spectacle.

4 DR. MATOBA: Sometimes, with the higher myopes,
5 especially, there is a difference between contact lens
6 visual acuity and spectacle. And if the contact lens
7 modality is available to that patient and, in fact, he's
8 using it--

9 DR. McCULLEY: That's a point, but it always has
10 been best spectacle, and then we've used contact lenses
11 post-op for contact lens refraction for best possible
12 correction to try to differentiate between irregular
13 astigmatism and other. So that's where we've used contact
14 lens--or requesting contact lens corrections. Other than
15 that, it's been best spectacle. But you make a valid point,
16 there is a real difference between the two.

17 I saw hands over here. Dr. Grimmett?

18 DR. GRIMMETT: Michael Grimmett. You said it, but
19 I was going to make the point that, of course, contact
20 lenses in a patient who has had an implantable corneal
21 device can obviously mask irregular astigmatism, something
22 you'd want to know by the spectacle.

23 DR. McCULLEY: Right. And we've taken--that's in
24 there.

25 Dr. Higginbotham?

1 DR. HIGGINBOTHAM: Just a quick note. I'm sure
2 some of this will be customized for any AC-implanted lenses.
3 Certainly, I would suggest a gonioscopic examination,
4 perhaps, the first six months, baseline. That may be a one-
5 year, but just to cover that because that's not going to
6 necessarily end up causing any IOP elevation if there's
7 minimal change.

8 DR. McCULLEY: The other would be evidence of iris
9 transillumination defects with a lens that might chafe.

10 Rick?

11 DR. FERRIS: Rick Ferris. As you said, I think it
12 should be dilated lens exam, but I would suggest that we
13 add, based on clinical standards or some such thing, that it
14 isn't just the routine clinical lens exam. It has to be a
15 lens exam that's using some sort of standard definitions.
16 Otherwise I think the data is almost totally useless.

17 DR. McCULLEY: That I agree. Good to restate. I
18 think that we meant to make that as the standard for all of
19 the exams with the intraocular implantable devices.

20 Dr. Bradley?

21 DR. BRADLEY: Just a question. Why are you
22 measuring mesopic pupil size?

23 MS. BOULWARE: Especially for those devices where
24 optic diameter may be a concern to see, in those patients
25 who have an optic diameter, then their mesopic conditions

1 would be larger than or equal to or larger than the optic.
2 For future labeling purposes, it may be that you need to
3 either contraindicate a device for patients with a mesopic
4 pupil size above a certain size or to add a warning for
5 those patients that they may have increased difficulties.

6 DR. BRADLEY: I would just add a couple of
7 comments then. Under levels lower than mesopic, the pupil
8 might dilate further, particularly when driving at night,
9 and from my own experience, with very dark irises, it's
10 rather quite difficult to measure pupil diameter under low-
11 light conditions, and you might have to struggle with those
12 data.

13 DR. McCULLEY: Okay. Next point?

14 MS. BOULWARE: You've seen these. We've talked
15 about cell counts, we've talked about corneal sensitivity.
16 That's done. Is there anything else that you want to
17 recommend that we do, either on all subjects or as a
18 substudy? There are a couple that are thrown up here for
19 your consideration.

20 DR. McCULLEY: I would almost think, on corneal
21 implantable devices, that corneal sensation would not be a
22 bad idea. Easy enough to do pre- and post-op.

23 Eve?

24 DR. HIGGINBOTHAM: I would just like to enter a
25 strong veto for visual fields.

1 DR. McCULLEY: Okay.

2 MS. BOULWARE: Consider it gone.

3 DR. McCULLEY: Dr. Grimmett?

4 DR. GRIMMETT: Regarding corneal sensation,
5 wouldn't you then have to specify a device, an esthesiometer
6 or whatever way you are going to do it? I'm not even sure
7 if you were to specify that, that it's reliable enough to
8 make a difference.

9 DR. McCULLEY: Oh, I think so. Having done some
10 trials with esthesiometers, they are a very worthwhile
11 device. I think it would be important to specify how it
12 would be done, though.

13 DR. YAROSS: Marcia Yaross. Based on the
14 experience that we've had with glare testing under the
15 mesopic conditions, we find that that's typically not
16 predictive of the patient experience, and so I would
17 question whether or not that adds significant useful
18 information beyond the subjective questionnaire information.

19 DR. McCULLEY: Any other comments? Gary?

20 DR. RUBIN: Gary Rubin. I agree that in many
21 cases the measurement of glare sensitivity is not predictive
22 of subjective responses, but it may be predictive of
23 performance; for example, driving at night performance
24 rather than what people complain of. I think there's a
25 reasonable expectation that glare testing is of some value

1 in predicting how people are actually able to behave in
2 their daily activities.

3 DR. McCULLEY: Art?

4 DR. BRADLEY: Again, I think it's extremely
5 important to have a very clear understanding of why a
6 particular test, such as glare testing, is being used. It's
7 not just to expand the total number of tests we're going to
8 do, hopefully, we'll catch something, type of attitude.
9 This is an optical device that we're inserting, and if we
10 have any belief that, based on theory or medical expertise,
11 that we believe there will be some potential scatter source
12 within the eye, then I think it is incumbent upon us to do a
13 test to evaluate that, and one of the tests that are
14 available to us is, in fact, to look at glare, vision under
15 glare conditions.

16 It has the added advantage that this is exactly
17 the situation that we all face during night driving and, in
18 fact, we have lots of experience with corneal surgery to
19 indicate this is, in fact, a problem that people have
20 suffered from in the past.

21 So if we believe that the procedure might produce
22 a scatter source within the eye, then I think we need a test
23 of that, and this is one.

24 DR. McCULLEY: Dr. Bullimore?

25 DR. BULLIMORE: Just to add to that very quickly,

1 we are, with some of these new technologies, we're adding to
2 additional refractive devices to the eye more sources of
3 reflection, scatter, and I think at this stage it's prudent
4 to take some additional visual measures.

5 DR. McCULLEY: Art?

6 DR. BRADLEY: It's not prudent to take additional
7 visual measures. It is prudent specifically to include a
8 test that would pick up scatter and reflections from these
9 surfaces. It doesn't have to be a visual test.

10 DR. McCULLEY: I agree.

11 DR. BULLIMORE: I agree, Arthur.

12 DR. McCULLEY: You got him. Okay, Dr. Grimmett?

13 DR. GRIMMETT: Michael Grimmett. I agree, in
14 substance, with Dr. Bradley that contrast sensitivity offers
15 the ability to measure a different way of visual
16 performance. Just as a question, is it specified with what
17 type of test that these patients are going to be tested
18 with? Because there can be high variability, as we all
19 know, depending on the exact testing equipment that is used.

20 MS. BOULWARE: We cannot recommend a specific
21 test. We can ask for a class of test that tests varying
22 spatial frequencies. We can ask for a minimum number of
23 spatial frequencies to be asked, and that does limit the
24 number of tests out there that would provide that
25 information. But we, as an agency, cannot appear to be

1 endorsing a particular test.

2 MS. LOCHNER: We can, however, discourage one that
3 we know is an invalidated or gives poor results, and we can
4 ask the company to sort of justify use of a test that we
5 know is unreliable. In some of the earlier, I don't even
6 know if they are around any more, but some of the earlier
7 tests were notoriously unreliable.

8 DR. GRIMMETT: Right. I know there's some ongoing
9 work by Dr. R. Ginsberg in the West--

10 MS. LOCHNER: Right.

11 DR. GRIMMETT: --with its functional driving
12 simulator and, certainly, those type of modalities.

13 MS. LOCHNER: And we also look closely at the
14 glare source and levels.

15 DR. BRADLEY: Just a point of clarification. I
16 wasn't advocating contrasensitivity testing. I was
17 advocating visual glare testing that can be done with a
18 contrasensitivity test, a visual acuity test, a driving
19 simulator test. There are many ways you could test it, but
20 the important ingredient is that you have a glare source
21 present while testing. That's what I was advocating.

22 DR. McCULLEY: Eve?

23 DR. HIGGINBOTHAM: It doesn't seem like there's
24 much enthusiasm for contrast sensitivity. So I'd like to
25 offer the possibility of not emphasizing that as a mandatory

1 measurement.

2 DR. RUBIN: I'd like to endorse it, and we can get
3 into a discussion why, if you would like to.

4 DR. McCULLEY: Endorse contrast sensitivity?

5 DR. RUBIN: Yes.

6 DR. McCULLEY: If we get into this, then we're
7 never going to get anywhere.

8 DR. HIGGINBOTHAM: I'll withdraw my--

9 DR. McCULLEY: Just leave it in. Leave it in. I
10 think it has the potential. We've yet to see it's greatest
11 potential realized, but this is a discussion that would be
12 extremely frustrating.

13 MS. LOCHNER: This would be very hard, I think,
14 within the branch itself to convince us it's not needed
15 because of experience we've seen that isn't public. I would
16 have to say we would have to be very convinced.

17 DR. McCULLEY: Can we just leave it at that then?

18 DR. HIGGINBOTHAM: Yes.

19 DR. McCULLEY: Can we go to the next point?

20 MS. BOULWARE: Very quickly. We have laid out the
21 time frames that we are proposing for subject evaluations.
22 For corneal implants, these time frames are the same as
23 those recommended for the laser. Guidance?

24 DR. McCULLEY: Any reason to deviate?

25 DR. HIGGINBOTHAM: No.

1 DR. McCULLEY: Next point?

2 MS. BOULWARE: For the chamber implants, these
3 time frames are from the draft IOL, aphakic IOL guidance.
4 Any comments?

5 [No response.]

6 MS. BOULWARE: Seeing none, our last issue is the
7 inclusion of other procedures within an IDE study. We have
8 strongly recommended that other procedures not be included
9 during the pivotal study to avoid the introduction of
10 confounding variables and have asked that the
11 inclusion/exclusion criteria be written accordingly.

12 However, if sponsors wish to have a separate protocol to
13 look at some of these issues, they certainly can do that.

14 Do you have any comments on this issue?

15 DR. McCULLEY: It seems perfectly reasonable. No
16 disagreement.

17 MS. BOULWARE: Last, but certainly not least, I'd
18 like to thank the panel very much for their time and their
19 recommendations. If you have any other recommendations,
20 we'd certainly be willing to hear them at this time, and we
21 will, as soon as we get this out in a draft, you will get a
22 copy. We really appreciate the time that you have spent
23 today.

24 DR. McCULLEY: Any other comments, except on
25 contrast sensitivity?

1 [Laughter.]

2 DR. McCULLEY: Sally?

3 MS. THORNTON: I'd just like to make a few closing
4 comments and ask the public to stay tuned to our Web site.
5 We'll be putting up shortly, probably first two weeks of
6 November, our plans for the January time that we have
7 tentatively set aside, and I would also like to thank our
8 panel for a lot of very hard and very substantive work that
9 they've done today and yesterday.

10 Thank you.

11 DR. HIGGINBOTHAM: I'd like to thank Dr. McCulley
12 for leading such a wonderful session and keeping us out of
13 conflict.

14 DR. McCULLEY: I haven't adjourned yet. Thank
15 you.

16 [Laughter.]

17 DR. ROSENTHAL: Before you end, Sally, can you
18 clarify whether or not we need to have another time for
19 public comment based on the last part?

20 MS. THORNTON: Dr. McCulley and I were just
21 discussing it. I think he is planning to do that.

22 DR. McCULLEY: It's there and we announced it was
23 going to be there. But with the same admonition as before,
24 the floor is open, the podium is open, if you wish to make a
25 comment relative to the last section that we have just

1 discussed. It is not a time for open public hearing
2 surrogate. So if anyone has comments related to the last
3 section that we discussed, please feel free to come to the
4 podium, and I didn't mean to pick on George a minute ago
5 when I said five minutes. It's just I realized I hadn't
6 said it, and George only spoke for three. He was real good.
7 But five-minute limit.

8 **PUBLIC COMMENT**

9 DR. MAXWELL: I'm Andrew Maxwell in private
10 practice in Fresno and function as a medical monitor for
11 ophthalmic devices for Alcon Laboratories.

12 I just had a question back on contrast
13 sensitivity, not to debate it, but to ask FDA if they can
14 tell us what maybe are acceptable; is contrast acuity as
15 opposed--you know, letters, as opposed to sign wave.
16 Because it's easier to do some of those tests, particularly
17 with glare and mesopic conditions.

18 MS. LOCHNER: We generally have accepted the
19 acuity letter charts. Where we have problems is if it is
20 only at one spatial frequency.

21 DR. MAXWELL: But if you have multiple
22 frequencies--

23 MS. LOCHNER: But if there's multiple frequencies,
24 we do.

25 DR. ANDREW MAXWELL: And then a second comment, to

1 go back to not doing second procedures during a pivotal time
2 period, do you have a definition as to what that means?

3 MS. BOULWARE: It wasn't a pivotal time frame. It
4 was the pivotal study. So your main safety and
5 effectiveness study that you are using to support approval,
6 it's not appropriate, for example, to allow patients to have
7 an astigmatic treatment if you are only treating sphere or
8 to treat an overcorrection as a planned part of your study.
9 If you would like to look at other corrections, for example,
10 for astigmatism on top of your spherical correction, you can
11 certainly set up a protocol to do that. But the main study
12 we would like to keep scientifically clean, so to speak.

13 DR. MAXWELL: And I certainly understand that.
14 But I would also present to you the patient or the argument
15 who maybe had a 12 diopter phakic lens, and they may be
16 three diopters undercorrected, and they are very unhappy.
17 Then am I going to go back and exchange the lens, which
18 maybe has greater risk than doing a PRK on top of that? Or
19 they have significant residual astigmatism, am I going to be
20 bound to wait for three years before I might do something to
21 help the patient?

22 MS. BOULWARE: I think if you have a patient that
23 is tremendously unhappy and wants the device removed, then
24 certainly you are ethically bound to do that. We are
25 talking about a planned--planning that 200 of your 500

1 patients would be allowed to go out and have some other
2 procedure done after your initial procedure. I mean, you
3 are going to really screw up all of your data analysis.
4 That's what this was really meant to address, not the
5 patient who is very unhappy and wants it removed.

6 MS. LOCHNER: Or you want to do a PRK, not remove
7 the device, but do a PRK on top of it.

8 I think we could handle this on case-by-case
9 basis, and we keep them, obviously, to a minimum. But I
10 think the issue was just keeping the original data set very
11 pristine in terms of introducing other confounding
12 variables. But I think on a case-by-case basis, we would
13 entertain that.

14 DR. ROSENTHAL: May I make a comment? These are
15 clinical trials, and patients have to accept the fact that
16 they are being enrolled in clinical trials, and clinical
17 trials have certain parameters which have to be adhered to.
18 If you're running a clinical trial for cancer chemotherapy,
19 and you happen to be a control, for a while you don't get
20 the drug. It's just until they break the code or--

21 These are clinical trials, and we try to make the
22 result from the clinical trial as clear as possible to
23 support the safety and efficacy issues, and that is what
24 that issue is about.

25 DR. McCULLEY: Are there any other comments?

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[No response.]

DR. McCULLEY: I'd like to thank the panel. I hope I've not been too severe at times. We had a lot to get through, and this ended up being, I think, a challenging day, and I appreciate all of your cooperation.

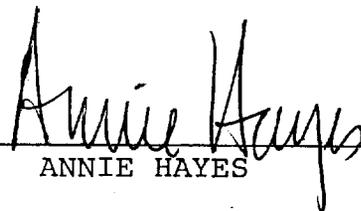
Hearing no objections, we will adjourn the meeting.

[Whereupon, at 3:40 p.m., the proceedings were adjourned.]

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C E R T I F I C A T E

I, ANNIE HAYES the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.


ANNIE HAYES