

1 disease--that it may be possible. So, I just  
2 wanted to add that clarification that I think I  
3 agree with what most of the panel said but I am  
4 still believing we would need for some of the  
5 safety outcomes these controls.

6 DR. WEISS: I am going to have one comment  
7 from Dr. Maguire and then I am going to ask if the  
8 agency needs anything more from us on this  
9 question, just because we have eight of these to  
10 get through. Dr. Maguire?

11 DR. MAGUIRE: I have a question for the  
12 agency. Does FDA separate groups for presbyopic  
13 correction if it is reasonable to expect that one  
14 of those groups is more likely to have problems  
15 with safety and efficacy, specifically the high  
16 myope group? That would be a reason to separate  
17 them out. Is that correct?

18 DR. EYDELMAN: In any refractive  
19 indication we usually break it up into the ranges  
20 of refractive error. For example, for LASIK we  
21 broke it up to 7 and above 7, and emmetropia would  
22 probably be analyzed separately. So, yes, the data  
23 would come in and then we would ask for internal  
24 stratification of the data according to refractive  
25 indication.

1 DR. MAGUIRE: But you would still run the  
2 study as a whole? In other words, you wouldn't  
3 place more stringent control requirements on  
4 patients with high degrees of myopia than the  
5 people with the other indications that led Dr. Lane  
6 to say they shouldn't be included at all in our  
7 discussion here.

8 DR. EYDELMAN: Well, it is certainly up to  
9 the sponsor to design what kind of trial they want  
10 to do and what inclusion criteria they want to  
11 expand their design to. We would certainly take  
12 your recommendations from today and try to give  
13 guidance to the sponsor accordingly.

14 DR. WEISS: Dr. Rosenthal?

15 DR. ROSENTHAL: I know what Dr. Maguire is  
16 getting at, and I think if there is a marked  
17 discrepancy between two populations in the study  
18 one would probably ask to look at both of them  
19 together and then separately.

20 DR. WEISS: Dr. Smith has a quick  
21 question.

22 DR. SMITH: I just wanted to clarify an  
23 issue. In the first question here we are talking  
24 about clear lens extraction in the correction of  
25 presbyopia.

1 DR. WEISS: Yes.

2 DR. SMITH: Some of those patients may be  
3 myopic, hyperopic. We are not talking about their  
4 lens extraction for the treatment of high myopia.

5 DR. WEISS: We have not gone to question  
6 two, that is right.

7 DR. SMITH: But this is clear lens  
8 extraction and the indication is presbyopia. So,  
9 that doesn't cover 25 year-olds who are minus 20.

10 DR. WEISS: You are a hundred percent  
11 right.

12 DR. SMITH: So, I think that myopes are  
13 complicating our discussion.

14 DR. WEISS: Well, you might have a 50  
15 year-old who is minus 20 and presbyopic.

16 DR. SMITH: Right.

17 DR. WEISS: We are going to then narrow  
18 things down as we go on, hopefully, but right now,  
19 from what I understand, most of the panel wants  
20 controls. Most of the panel is talking about  
21 active controls. Some of the panel is talking  
22 about historical controls for safety and active  
23 controls for efficacy, and some of the panel is  
24 talking about randomization. I would sort of like  
25 to cut things off at this point because we have

1 eight questions and we have sort of gone over on  
2 this one. Does the agency need anything else from  
3 us on that particular question?

4 DR. EYDELMAN: No, thank you.

5 DR. WEISS: Fine.

6 DR. BRUCKER: Jayne--

7 DR. WEISS: Sorry--

8 DR. BRUCKER: No, no, can you answer a  
9 question about something. Can somebody just tell  
10 me in a sentence about the range of accommodation  
11 of these multifocal intraocular lenses?

12 DR. WEISS: It is not relevant to this  
13 question. We are going to get there but basically  
14 I want to go in order. I mean, I can tell you the  
15 crystal lens labeling I think was 1 diopter. Dr.  
16 Brucker, from the PMA that was presented to the  
17 panel for the crystal lens, which is the  
18 accommodatve IOL that has been FDA approved, the  
19 labeling gave approximately 1 diopter of  
20 accommodation, for your information.

21 So, question number two, should the  
22 clinical study inclusion/exclusion criteria limit  
23 subject enrollment based on the criteria listed  
24 below? So, now what we are going to do is try to  
25 address in a succinct fashion each of the criteria

1 listed and their ranges.

2           The first one is refractive error/axial  
3 length. What would be the range that you would  
4 want for hyperopia? Do you want to include  
5 emmetropia and what is the range for myopia? Why  
6 don't we start with emmetropia? Do you think that  
7 a clear lens extraction trial for the correction of  
8 presbyopia should include emmetropes? Dr. Brucker,  
9 why don't you start on your end? Should we be  
10 putting plano people in here who need 2 diopters  
11 for their reading? Should they have clear lens  
12 extraction?

13           DR. BRUCKER: Yes.

14           DR. WEISS: Yes. Dr. Ferris?

15           DR. FERRIS: I apologize for this but I  
16 think it is going to take forever if we go through  
17 all of these. I think that what ought to be  
18 included is what is likely to be included in  
19 practice. So, if people are going in practice to  
20 include myopia, it needs to be in there. If they  
21 are going to include hyperopia, it needs to be in  
22 there. Are there extreme levels where you would  
23 want to exclude them? Yes, and I think that is the  
24 grey zone and we have to talk about that.

25           DR. WEISS: Actually, I think your point

1 is well taken. When we are going around, I am  
2 going to change sort of the question to you. Why  
3 don't you give me the refractive range that you  
4 would like? You don't have to say from this range  
5 to this range; you can stop around emmetropia or  
6 low myopia or low amounts of hyperopia if you would  
7 like. Some might want it to be only on the whole  
8 range. One example would be from plus 10 to minus  
9 20. Another example would be that you might think  
10 it would be indicated from plus 6 to plus 10 and  
11 from minus 6 to minus 20 and not have the low  
12 myopes, the low hyperopes and the emmetropes. We  
13 can go about it that way. I think that is sort of  
14 addressing what you are saying. I understand there  
15 is a grey zone but where would you put the  
16 limitations?

17 DR. FERRIS: Right, so "I'll see you and  
18 raise you one."

19 [Laughter]

20 I think that I would exclude extreme  
21 hyperopia and extreme myopia but I would leave the  
22 definitions of that probably to the company, but I  
23 would want to include certainly to minus 10 and  
24 probably to plus 5, and I would be flexible on more  
25 and less--well, I am not sure I would be too

1 flexible on less. Where I am going to raise one is  
2 I think for moderate myopia, let's say over minus  
3 4, I would like to power the study high enough so  
4 that you could say something specifically about  
5 myopia separately from emmetropia and hyperopia.

6 DR. WEISS: Well, I am going to ask for  
7 either abstentions or numbers because I think what  
8 the FDA really wants from us is numbers. That is  
9 why they are coming to us. From what I understand,  
10 you are saying from minus 4 to minus 10 in terms of  
11 the myopic range.

12 DR. FERRIS: I would like to power it so I  
13 could look at least at that range separately, and I  
14 would include, and I think this is totally  
15 arbitrary, but plus 5 to minus 14.

16 DR. WEISS: So, you are saying plus 5 to  
17 minus 14 and you would be including emmetropes.

18 DR. FERRIS: Absolutely.

19 DR. WEISS: So, you would be including  
20 plus 1's and minus 1's in that.

21 DR. FERRIS: Well, this is all about  
22 presbyopia, isn't it? Ask Dr. Brucker whether he  
23 is happy with his presbyopia.

24 DR. WEISS: Dr. Brucker, we won't to ask  
25 if you are happy with your presbyopia, but plus 5

1 to minus 14--

2 DR. BRUCKER: I am not happy with my  
3 presbyopia--

4 DR. WEISS: Okay, it is an aside and it  
5 will be on transcript for evermore. But what are  
6 your numbers, again? Plus 5 to minus 14 including  
7 those with your refractive error?

8 DR. BRUCKER: Yes, I would just say that  
9 you might want to look statistically. I wouldn't  
10 hold it exactly to where that minus 14 is if the  
11 numbers are so small that it isn't worth it. You  
12 must be minus 12 or minus 15, somewhere in that  
13 range is okay because the numbers get so small that  
14 it doesn't matter anyway. In other words, I think  
15 a minus 20 myope should be excluded but whether it  
16 be minus 12 or minus 14 from the standpoint of the  
17 FDA or the sponsor really doesn't matter to me. Do  
18 you understand?

19 DR. WEISS: Dr. Eydelman?

20 DR. EYDELMAN: No, I don't because what we  
21 are talking about is inclusion criteria--

22 DR. BRUCKER: Correct.

23 DR. EYDELMAN: --we are not talking about  
24 determination of sample size. Right now we are  
25 just trying to figure out for whom the risk/benefit

1 is such that it warrants inclusion.

2 DR. BRUCKER: Make is simple, make it  
3 minus 14.

4 DR. WEISS: Dr. Bradley?

5 DR. BRADLEY: You are not going to like  
6 me. It seems that you are asking us the wrong  
7 question, if you don't mind me asserting that. You  
8 are asking us to identify a refractive range and  
9 age range for which the risk/benefit is acceptable.  
10 It seems to me the question should be what is the  
11 risk/benefit that is acceptable and then we will  
12 determine the refractive range. We have not  
13 identified the risk/benefit that we find  
14 acceptable.

15 DR. EYDELMAN: Unfortunately, from the  
16 design of the study we will first have to decide  
17 who we study before we give you the answer.

18 DR. BRADLEY: Well, I think the  
19 presentation this morning was trying to educate us  
20 on the risks, in particular retinal detachment,  
21 associated with lens extraction. If we have a  
22 sense of what that risk is and we can say what is  
23 an acceptable risk--is it 1 percent? Is it 0.1  
24 percent? Once we have that acceptable risk, then  
25 the data will tell you what the acceptable

1 refractive range is; what the acceptable age range  
2 is. For us to do that in our head and come up with  
3 an acceptable refractive range and acceptable age  
4 range, quite frankly, is impossible. Therefore, I  
5 abstain.

6 DR. WEISS: Okay, so we have an  
7 abstention. See, I do like you, Dr. Bradley. Dr.  
8 McMahan?

9 DR. MCMAHON: All presbyopia short of  
10 nanophthalmos, up to minus 10.

11 DR. WEISS: Can you repeat that? For  
12 hyperopia you don't want those who are  
13 nanophthalmic?

14 DR. MCMAHON: Correct.

15 DR. WEISS: That is good.

16 DR. MCMAHON: Basically, that is about  
17 plus 8.

18 DR. WEISS: So, you would extend the level  
19 of hyperopia to just short of someone who has  
20 something pathologic and is going to get a  
21 devastating complication. And for myopia?

22 DR. MCMAHON: Minus 10.

23 DR. WEISS: Minus 10, and you would also  
24 include emmetropes?

25 DR. MCMAHON: Yes.

1 DR. WEISS: Uncharacteristically, I will  
2 abstain. Dr. Grimmitt?

3 DR. GRIMMETT: I am less concerned about  
4 the range of hyperopia, albeit from a cataract  
5 surgeon's perspective it is difficult. You don't  
6 have enough interior chamber depth to do the  
7 surgery in high hyperopes through the shallow ACs.  
8 But I am in agreement with Dr. McMahon's comment  
9 that short of nanophthalmos I am not really too  
10 concerned about the level of hyperopia.

11 Myopia, I am a little cautious here due to  
12 the fact that these are performed on younger age  
13 patients and we saw this morning that high myopes  
14 have an increasing rate of retinal detachment that  
15 looked almost like an exponential function the  
16 longer you followed them out. I am up to minus 8  
17 on the myopia.

18 DR. WEISS: And you would also include  
19 emmetropes?

20 DR. GRIMMETT: True.

21 DR. WEISS: I would ask the panel one  
22 question, if you have someone who is, let's say,  
23 plano and they have a decent chance of having the  
24 glare and halos and they are going to achieve a J3  
25 or J5 with the risk of lens extraction, do you want

1 to include emmetropes? I am going to continue  
2 along and I know you have a comment on that, Dr.  
3 Bressler, but we will start with Dr. Mathers and  
4 continue along. Dr. Mathers?

5 DR. MATHERS: Well, I think it is a real  
6 ethical question about what we are recommending  
7 because as a scientist and a physician I would  
8 really like to know this data but I am very  
9 concerned about the relative risk of doing these  
10 clear lens extractions on relatively young people,  
11 particularly in their 40s or maybe even younger. I  
12 think that is going to get more difficult in the  
13 hyperopic group that are going to be pushing to  
14 have their surgery earlier.

15 But because this is being done now, I  
16 think it is imperative that we really find out, and  
17 I think that actually it is worth the risk of  
18 having a couple of hundred people be in this group  
19 to get us information even if there is an ethical  
20 question. I think we will solve the larger ethical  
21 question. And, I think there will be people who  
22 are willing to undergo that risk, a few people, and  
23 it won't take that many. But I think that we  
24 should be careful about extending the age range  
25 down too far. I can't tell you exactly what this

1 is but I am sure that we need the information in  
2 the younger age group but I would just be cautious  
3 about extending it down so I would go for hyperopic  
4 patients fairly high up to about a minus 10, minus  
5 12.

6 DR. ROSENTHAL: Could I just comment on  
7 something? DR. WEISS: Dr.  
8 Rosenthal?

9 DR. ROSENTHAL: The patients can't be too  
10 young because they are going to have to have some  
11 accommodative loss, which is number C). So, I  
12 don't think a 20 year-old myope with minus 20 is  
13 going to fit into that inclusion criteria.

14 DR. MATHERS: But a 30 year-old with a  
15 plus 5 would be knocking on your door.

16 DR. WEISS: Not necessarily, and I think  
17 we are going to get to that because we have  
18 criteria for degree of accommodative loss. Your  
19 level for hyperopia was--a number?

20 DR. MATHERS: Seven.

21 DR. WEISS: Seven. Dr. Ho?

22 DR. HO: I think Dr. Smith addressed this  
23 issue earlier where things start to begin to get a  
24 little less than grey. But to answer this  
25 question, I think, first of all, the notion of

1 active and separate historical controls is  
2 appealing and is a little different than what I  
3 described earlier. I think with respect to a range  
4 of accommodative refractive error I would be  
5 comfortable with anything that is non-pathologic on  
6 the hyperopic side. I am a little more protective  
7 on the myopic side, for this study design that you  
8 are describing, to minus 6.

9 DR. WEISS: Give me a number for  
10 hyperopia, if you would.

11 DR. HO: Plus 8.

12 DR. WEISS: Dr. Smith?

13 DR. SMITH: Plus 8 to minus 10, including  
14 emmetropes.

15 DR. WEISS: Dr. Bressler?

16 DR. BRESSLER: I am going to give you a  
17 number but you may not like it. I agree that we  
18 need to find out what is going on in the majority  
19 of the population that this may be appealing to,  
20 and I would like to say there is good data on what  
21 the refractive errors are, for example, in the  
22 United States and I would go with 95 percent of  
23 what the refractive errors are out there and  
24 exclude the extremes on either end. We can look up  
25 that number. I don't have it with me but the 95

1 percent is the number I want to use and I don't  
2 know if it is minus 8, minus 5, minus 6.

3           Then, I would add to the FDA's advice that  
4 there be a corollary to whatever this number range  
5 becomes to add to it something that many have  
6 alluded to, and that is if there are pathologic  
7 features that are normally associated with those  
8 extremes. So, we have people who are minus 3 every  
9 now and then but, because of the way their cornea  
10 and lens are, they are actually myopic and you can  
11 see the myopic changes. The same is true with the  
12 hyperopes. So, as you have your inclusion criteria  
13 for this, add something that includes those sorts  
14 of pathologic appearances.

15           DR. WEISS: And I think that would address  
16 2 E) on this list for are there any other criteria.  
17 Thank you. Dr. Brown?

18           DR. BROWN: My concern is that regardless  
19 of how restrictive we make the study, the procedure  
20 will be done on anyone essentially and that is my  
21 concern. So, I don't want to be too restrictive  
22 and I would go along with Neil's recommendation of  
23 a 95 percent interval in the population, and I also  
24 think it will provide important data. The rate may  
25 be lower than we are expecting in that minus 6 to

1 minus 10. So, I think that I would go that way and  
2 be more inclusive for this study.

3 DR. WEISS: Dr. Stark?

4 DR. STARK: It was interesting to me that  
5 Dr. Lane's presentation from the company would  
6 restrict it to low myopes and low hyperopes just  
7 for presbyopia, and it would exclude all the  
8 pathologic cases. That may get them through  
9 earlier or sooner with less complications. But  
10 once it is approved, then it is going to be  
11 promoted as lens removal or lens exchange. So, I  
12 think we should have the range that will show us  
13 what the moderately high hyperopes and myopes do  
14 and if there are any potential complications. For  
15 example, myopes have larger eyes. A 4 mm optic in  
16 that myopic eye, that larger eye, larger pupil  
17 sometimes, may cause significant problems with  
18 nighttime vision. So, I would say in the range of  
19 a minimum of plus 6 to 10-12.

20 But also, we need to correlate that with  
21 axial length. I think Neil addressed the issue.  
22 Some of these people have a very flat cornea but an  
23 extremely long eye and are lower myopes but, in  
24 fact, they may have a 28 mm axial length. So, we  
25 may want to tie into this refractive range a

1 certain axial length. Certainly, an axial length  
2 of less than 18 is a nanophthalmic eye and it would  
3 depend on the cornea what the refractive error was.  
4 An axial length greater than 28 mm or 29 mm is one  
5 that is subject to a lot more potential for  
6 problems. So, we need to put that in with the  
7 refractive error.

8 DR. WEISS: Dr. Eydelman actually has  
9 included that in this portion of the questions.  
10 So, as long as you are bringing it up, Dr. Stark,  
11 do you want to exclude patients with an axial  
12 length greater than 28 or 29 and less than 18?

13 DR. STARK: Well, I would tend to include  
14 them but you may find your analysis of retinal  
15 complications in the high myopic population is more  
16 related not exactly to what the preoperative myopia  
17 was but what the preoperative axial length was.  
18 That is the important information for them, and  
19 also in the controls we would have to do axial  
20 length measurements.

21 DR. WEISS: You want axial length to be  
22 known in addition to the level of myopia or  
23 hyperopia but you would not be excluding people on  
24 axial length by itself.

25 DR. STARK: Well, I certainly would

1 exclude the hyperopes less than 18.

2 DR. WEISS: So, less than 18 would be the  
3 exclusionary criteria.

4 DR. STARK: And maybe less than 20. But  
5 we would have to correlate that with the  
6 refraction.

7 DR. WEISS: Would you have an upper limit  
8 of axial length for the high myopes or not?

9 DR. STARK: Probably 28.

10 DR. WEISS: So, 18 to 28 would be the  
11 range that you would want to be including in the  
12 study. Dr. Maguire?

13 DR. MAGUIRE: I agree with everything that  
14 has been said from the standpoint that we know  
15 there is a slippery slope on increased  
16 complications when you get to the very high myopes  
17 and the very high hyperopes. I have the same  
18 distaste for the idea of operating on emmetropes to  
19 correct presbyopia given the obvious public health  
20 issues that are here. But, you know, we have  
21 crossed the Rubicon already so we have to do this.

22 I also have a question for FDA. It seemed  
23 to me that at the last ocular lens panel discussion  
24 we had for guidance in the past, we were informed  
25 that there were monofocal IOL studies for low

1 myopia going on already. Isn't that correct? Down  
2 to like minus 2 or something?

3 DR. ROSENTHAL: Phakic IOL.

4 DR. MAGUIRE: Oh, that as phakic IOLs.

5 Still, a phakic IOL is down to minus 3. So, we  
6 have crossed the Rubicon. We just have to get the  
7 information so we can not be in the type of problem  
8 we are now where we don't have information and FDA  
9 can't say anything.

10 DR. WEISS: Dr. Ferris?

11 DR. FERRIS: I just want to make a quick  
12 comment, and I rarely disagree with Dr. Bressler  
13 but the thing I worry about here is that we are  
14 dancing around what I think is the crux of this  
15 issue and that is informed consent. I think that  
16 we all have different risk/benefit internal ratios  
17 and the Hamlets shouldn't tell the Admiral  
18 Farraguts what to do, but I worry that if there is  
19 a special group that is at extra risk of having  
20 this done and is at extra risk of having  
21 complications, we need to have something to tell  
22 them about that extra risk because they are going  
23 to be told about the extra benefits--

24 DR. WEISS: I mean, we can just sort of  
25 add that to e) here, that those people who are at

1 more risk, they should have a little more detailed  
2 informed consent.

3 DR. WILLIAMS:

4 DR. EYDELMAN: That would be routine under  
5 the IDE procedures.

6 DR. WEISS: Dr. Rosenthal?

7 DR. ROSENTHAL: No, I don't think that is  
8 what Dr. Ferris is getting at. He was getting at  
9 to include people at the extremes so that you can  
10 provide--

11 DR. FERRIS: Yes, if you don't have them  
12 you can't tell them what their extra risk is, and  
13 if you tell them what the risk in the study  
14 is--here is this minus 15 and you tell them we did  
15 this study and there wasn't any problem, that may  
16 be the wrong thing to tell them. That is why I  
17 said you need to power it enough so that you have  
18 some reasonably high myopes because they are at  
19 extra risk. Unless you are going to say absolutely  
20 never are you going to do this in high myopes, and  
21 we already know that is stupid because it is  
22 happening right now.

23 DR. WEISS: Just to play devil's advocate,  
24 I would say why limit it to minus 14?

25 DR. FERRIS: I wouldn't limit it at all.

1 But probably the truth is--what Neil was getting at  
2 I think, once you get above minus 14, and I don't  
3 know where the number is, you are going to have so  
4 few of them that you are not going to be able to  
5 really give good risk estimates. You are just not  
6 going to have them.

7 DR. WEISS: We need to sort of end this  
8 portion of it because we are really taking too  
9 long. From what I have heard from panel members,  
10 the high amount of hyperopia that has been  
11 suggested is to go up to plus 8, and it sort of  
12 varied between plus 5 and plus 8 but everyone has  
13 had the same sentiment that we want to avoid any  
14 patients who might have any indication that they  
15 could have nanophthalmos.

16 There has been consensus essentially on  
17 doing the emmetropes, the low myopes and the low  
18 hyperopes. There has not been anyone who has been  
19 against that. Then, in terms of the higher level  
20 of myopia, it had been expressed between minus 6  
21 and minus 14 by various members of the panel but  
22 now I am hearing, Dr. Ferris, that you might go  
23 even higher if those people could be recruited  
24 because even if they had a higher adverse reaction  
25 that is something you would want to get into the

1 literature.

2 DR. FERRIS: Sure, and if I was advising  
3 the company I would tell them don't put those minus  
4 20s in here. So, I am advising the FDA that I  
5 would like to see all the data I can have but I can  
6 understand, if I was doing this study, I would like  
7 to say, you know, these people are at special risk  
8 and I am going to tell them they are at special  
9 risk and I don't even want to include them in the  
10 study.

11 DR. WEISS: Dr. Brucker?

12 DR. BRUCKER: Yes, my point when I was cut  
13 off which you now have accepted, which I do not  
14 appreciate, is the fact that if you go from a minus  
15 14 to a minus, let's say, 28 and let's say you have  
16 2 patients in every half step category, you may  
17 wind up having 20 or 30 patients in this range of  
18 minus 14 to minus 28 and not be able to analyze  
19 them because they are spread out so thin and that  
20 is such a rare population of patients.

21 My inference to you was look at the  
22 general population--Neil was saying 95  
23 percent--take a look at the general population.  
24 Don't get yourself screwed up by having one patient  
25 in each of these half diopter refractions and not

1 be able to analyze them. Power adequately so that  
2 you have all of the bases covered, but make sure  
3 that you don't get yourself tilted on this last  
4 five percent, as Neil was saying, so you that can't  
5 answer any questions. That was my inference.

6 DR. WEISS: In addition to what I was just  
7 mentioning in terms of the range, there were two  
8 members of the panel who would prefer to look at  
9 the 95 percent. Do you have any idea what we would  
10 be talking about with a 95 percent refractive  
11 range?

12 DR. EYDELMAN: It would be much lower. It  
13 is definitely under 7 because we looked at it--

14 DR. WEISS: Myopia?

15 DR. EYDELMAN: Myopia. I don't have the  
16 numbers in front of me but I would venture to say  
17 somewhere around 4 or 5 diopters. I mean, it is  
18 pretty low.

19 DR. WEISS: Then, Dr. Bressler, if it only  
20 went up to minus 4 or minus 5 would you change your  
21 mind on wanting 95 percent? Of course, many of the  
22 patients who are going to want this are those with  
23 higher amounts of myopia and we won't have the  
24 information, which is sort of what Dr. Ferris was  
25 alluding to.

1 DR. BRESSLER: Yes, a little bit but not  
2 completely to what Rick said. So, you know, maybe  
3 go to 97.5 percent. But I am concerned about  
4 having any studies done on minus 15 or minus 20 or  
5 minus 24 at this time even to get the information  
6 because I think I already know the information,  
7 that there is a much, much higher risk of retinal  
8 detachment that far outweighs any immediate benefit  
9 I can see in terms of their gaining no reading  
10 glasses for presbyopia. We are talking about  
11 presbyopia, not their refractive error for  
12 distance. So, I am not ready to open the flood  
13 gates to it. I want enough of the minus 4's, 5's,  
14 6's, 7's, 8's because they will be different  
15 perhaps from the minus 2's.

16 DR. WEISS: We will have one comment from  
17 Dr. Ferris, and then we are just going to sort of  
18 briefly go through the axial length because I think  
19 this is just basically a personal viewpoint which  
20 you can agree to disagree in terms of whether you  
21 want to have the data to document the higher risk,  
22 or whether your concern is with the individual  
23 patient and you don't want them being the one to  
24 get the retinal detachment and prove what you  
25 suspect might be occurring in any case. Dr.

1 Ferris?

2 DR. FERRIS: Just a quick comment, and  
3 that is that although I understood this comment  
4 about staging this and we will do the safe ones  
5 first and then we will do the risky ones next, I  
6 think the reality is that we have one shot at this,  
7 that there is not going to be the second study and  
8 maybe you can do post-marketing studies but I would  
9 like to review the history of how effective those  
10 are. So, I think there is probably one shot at  
11 getting this information.

12 DR. WEISS: Dr. Stark had suggested an  
13 axial length range inclusion from approximately 18  
14 or 20 to 28 or 29. Would anyone from the panel  
15 disagree with that?

16 DR. STARK: I would probably go to 20; 18  
17 really--

18 DR. WEISS: Is pushing it. So, we will  
19 change that from 20 to 28, 29. Dr. Grimmer?

20 DR. GRIMMETT: What is the old rule, 3  
21 diopters per millimeter, or something like that,  
22 different from 24 mm as average? I am a little  
23 worried about the upper range. Probably around 27  
24 or so, which would be about minus 9 I guess if you  
25 use the average rule of thumb, and then I would

1 probably do the same on the plus side, something  
2 like that.

3 DR. WEISS: Is that enough information for  
4 the agency on that one?

5 DR. EYDELMAN: Yes, thank you.

6 DR. WEISS: We are running late already.  
7 It is early but we are running late. So, we are  
8 going to go to b) and see how quickly that goes.  
9 We are going to break for lunch in a little bit but  
10 we are going to delay that just a tad.

11 Patient age, does anyone from the panel  
12 want to suggest a range? By the way, we don't have  
13 to limit any of these criteria so you could say you  
14 don't want to limit patient age but these are  
15 things that, if you do want to limit them, what  
16 would you like the range to be? And, if you don't  
17 want to limit them, we will hear from you. I am  
18 not going to go around on this one. I am just  
19 going to ask someone from the panel to propose if  
20 they want to limit age, and if they do, what they  
21 want to limit it to. Dr. Ferris?

22 DR. FERRIS: For me, I would go to C). If  
23 we are talking about presbyopia I don't care how  
24 old they are.

25 DR. BRESSLER: I concur. I don't want age

1 discrimination. It really depends on how the  
2 person presents. You could have a 35 year-old who  
3 happens to have what we are thinking of as the 50  
4 year-old eye.

5 DR. WEISS: So, would anyone from the  
6 panel disagree with that? Dr. Mathers?

7 DR. MATHERS: But I thought that the issue  
8 of changing the vitreous face and retinal  
9 detachment predisposition increases as you come  
10 into the younger age group. So, I think age, in  
11 and of itself, is a relevant factor and if we are  
12 not careful we are going to be operating on mid-30s  
13 and the retinal detachment rate may be much  
14 different than in the 50 or 60 year-old group.

15 DR. WEISS: And you might operate on a  
16 mid-30s and that might be the one with the minus 15  
17 or minus 12 or minus 10.

18 DR. MATHERS: Right. So, I would be more  
19 in favor of limiting it to, say, 45; maybe 40 but  
20 not less than that.

21 DR. WEISS: Is there any disagreement with  
22 that? Does anyone have a problem with limiting?  
23 Would you want to suggest 40 or 45?

24 DR. MATHERS: Well, ethically? We might  
25 as well get the data; let's go to 40.

1 DR. WEISS: So, we have a suggestion of a  
2 lower age limit of 40. Does anyone disagree with  
3 that?

4 DR. MCMAHON: I do.

5 DR. WEISS: Dr. McMahon?

6 DR. MCMAHON: The median age of patients  
7 coming in with enough symptomatic complaints for  
8 presbyopic correction is 44 so I would set the  
9 limit at 45. That way you would have reasonable  
10 certainty the patient has presbyopic symptoms.

11 DR. WEISS: Does anyone have any strong  
12 feeling that it should be less than 45? Dr.  
13 Mathers?

14 DR. MATHERS: The hyperopic group is going  
15 to be extremely, say, attractive for this procedure  
16 and we are not going to know how they are going to  
17 do. They are going to want this at 40 and I think  
18 we should find out because we have a chance here  
19 to find out. If we don't go to 40 now we are not  
20 going to go.

21 DR. WEISS: Dr. McMahon, does that change  
22 your opinion or no?

23 DR. MCMAHON: Dr. Mathers has a very good  
24 point and I balance that median age for presbyopic  
25 symptoms keeping in mind that presbyopes, many of

1 which go around uncorrected if they are relatively  
2 low presbyopes, come in with their symptoms  
3 earlier. At the same time, you raise the issue  
4 with regard to vitreous face issues and so forth,  
5 so I would still argue for 45.

6 DR. WEISS: Do you need anything more?  
7 No? That is fine. Dare we go to degree of  
8 accommodative loss? I see glucose levels dropping  
9 as I bring that one up, and preoperative  
10 endothelial cell count, after the last two panel  
11 meetings, my glucose level with drop on that one  
12 too. So, it is 12:10. We are going to be back  
13 here in one hours. Dr. Ferris?

14 DR. FERRIS: I am curious. Are we not  
15 looking at degree of accommodative loss because we  
16 can't measure it?

17 DR. WEISS: No, no, no. That was just a  
18 slight bit of poor humor. I assume that is going  
19 to take us more than three minutes to get through,  
20 unless anyone has the answer. Seeing no answer, we  
21 will break for lunch.

22 [Whereupon, at 12:10 p.m., the proceedings  
23 were recessed for lunch, to resume at 1:10 p.m.]

1                   A F T E R N O O N   P R O C E E D I N G S

2                   DR. WEISS: We are now going to continue  
3 with panel deliberations. We are going to be  
4 changing the format somewhat in terms of trying to  
5 pare things down to get through these questions at  
6 a more rapid pace. So, I am not going to be going  
7 around polling anyone anymore. We are just going  
8 to basically throw the question out. If someone  
9 has a relevant comment, and I emphasize relevant,  
10 then please address it. We will be getting  
11 basically to all of the important questions but it  
12 serves the agency's purposes much better if we  
13 discuss the issue at hand when the issue at hand is  
14 in front of us.

15                   So, we are going to now go on to 2 c),  
16 degree of accommodative loss. Does anyone on the  
17 panel have a comment as to whether the clinical  
18 study inclusion/exclusion criteria should limit  
19 subject enrollment on degree of accommodative loss  
20 and, if you think it should limit it on degree of  
21 accommodative loss, based on what type of  
22 measurement of accommodative loss? Does anyone  
23 have a comment directed to this? Dr. Bradley?

24                   DR. BRADLEY: It seems to me that if the  
25 device that is to be studied has the potential to

1 provide a large degree of either accommodation or  
2 what has been characterized as  
3 pseudo-accommodation, which means without actual  
4 power change effective near vision is provided,  
5 then I would think the inclusion criteria would  
6 stretch to earlier ages and higher levels of  
7 residual accommodation. If the device only has a  
8 very limited accommodative range or limited amount  
9 of pseudo-accommodation, it would seem reasonable  
10 to limit the device to those who have only small  
11 amounts of residual accommodation.

12 DR. WEISS: Was that a definite maybe?

13 DR. BRADLEY: It means you can't have a  
14 single answer for every product. I mean, one  
15 answer doesn't fit all. It depends on how  
16 effective the product is going to be. The idea is  
17 if you have a lens that can produce half a diopter  
18 of accommodation it doesn't make a lot of sense to  
19 remove natural lenses that have 2 diopters of  
20 residual accommodation and replace it with a half  
21 diopter accommodating lens. Whereas, if the new  
22 lens has 4 diopters of accommodation, it makes a  
23 lot of sense to take out the 2 diopter residual  
24 accommodative natural lens and replace it with an  
25 IOL that gives 4 diopters. Does that make sense?

1 DR. WEISS: Is that good enough for the  
2 agency? Do you need more discussion on that? Dr.  
3 Eydelman?

4 DR. EYDELMAN: Yes, multifocal IOLs don't  
5 particularly have an accommodative range; they have  
6 a near visual acuity correction in a certain  
7 percentage of patients. None of the standards or  
8 guidances particularly cull out the accommodative  
9 loss prior to MIOL enrollment because obviously, we  
10 are treating cataracts. So, that would not  
11 necessarily be applicable for MIOL replacement.

12 DR. WEISS: Dr. Bradley?

13 DR. BRADLEY: Yes, that brings us to the  
14 pseudo-accommodation issue. I think it would seem  
15 reasonable to me for the sponsor to have to  
16 convince the FDA. If they want to expand the range  
17 of patients to include those with larger amounts of  
18 residual accommodation, they would have to present  
19 the FDA with some sort of argument that these  
20 patients would actually benefit by this new lens.  
21 Does that make sense? For example, if you have a  
22 patient with 2 diopters of residual accommodation,  
23 arguably they can focus at 50 cm perfectly well.  
24 It seems to me the sponsor would have to convince  
25 the FDA to include those patients by suggesting

1 that with the new lens they would be able to see at  
2 closer distances than 50 cm, more than they would  
3 with their original lens.

4 DR. WEISS: Dr. Brucker?

5 DR. BRUCKER: The issue was brought up by  
6 Walter or Dr. Mathers. If you have a patient who  
7 is going to be in the younger age group and is a  
8 hyperope and they still have some accommodative  
9 power left, they may be able to see J1 at 14 in.  
10 That is wonderful. But if they have lost  
11 everything else they are going to be coming around  
12 and saying, "wait, I used to be able to see  
13 everything on the table in front of me. I couldn't  
14 see up close but I could see everything on the  
15 table," and now you have taken their lens out. So,  
16 the question that he is raising is if you don't  
17 have an accommodative range, it is fine, take the  
18 lens out; put an IOL in their eye and it is not a  
19 problem. But if a patient has 2 diopters of  
20 accommodation left in their eye and they are 38  
21 years of age or 41 years of age, is it appropriate  
22 to sacrifice that accommodative power because you  
23 are going to give them 14 in of no glasses up  
24 front? It may not be. And, that needs to be  
25 considered in the indications, the labeling, etc.

1 There may not be enough risk/benefit; there may not  
2 be a ratio that is worthwhile. If you still have  
3 all that accommodation the risks aren't worth it.  
4 If you are 55 or 60 years of age and, sure, you  
5 can't see anything on the table in front of you,  
6 put the IOL in their eye.

7 DR. WEISS: Dr. Mathers?

8 DR. MATHERS: Regardless of what the  
9 accommodation is at the time of surgery, in a  
10 fairly short period of time they are going to lose  
11 a lot of that accommodation anyway. It may be that  
12 the efficacy is actually going to be better in  
13 hyperopes who still have accommodative levels  
14 intact because their ciliary body still acts better  
15 than for someone who has lost it and it would be  
16 interesting to find that out. So, I don't think  
17 that we should limit the entrance criteria but we  
18 should put in a reasonable effort in measuring  
19 afterwards to find out how efficacious it is in  
20 which group and for how long.

21 DR. ROSENTHAL: Excuse me--

22 DR. WEISS: Dr. Rosenthal?

23 DR. ROSENTHAL: It is rather difficult.  
24 They are going to have near visual acuity that can  
25 be measured. They are going to require plus 2 to

1 read J1 or plus 1.5 to read J1. Maybe we should  
2 take it from that viewpoint rather than from  
3 accommodative loss. What should we be including in  
4 the study? Shall we allow the sponsor to operate  
5 and implant a lens in someone who can read J2 with  
6 a plus 0.50?

7 DR. WEISS: Dr. Ferris?

8 DR. FERRIS: Well, one might ask how dumb  
9 the company is going to be to include those  
10 patients because, at the end of the day, they are  
11 going to have a lot more risk with including them.  
12 So, surely you would want to include people who are  
13 having trouble if your outcome is going to be that  
14 you have to show improvement.

15 DR. ROSENTHAL: What is trouble?

16 DR. FERRIS: Well, I agree with what I  
17 think you were saying, that you would like to say  
18 that they can read at some level and the world is  
19 grey. My world is grey and you can pick the level  
20 but I would think that these are people that can't  
21 read J2. I don't care what you pick but you had  
22 better be able to show that you have at least done  
23 them a favor by doing this surgery which is surely  
24 putting them at risk.

25 DR. WEISS: Dr. Maguire?

1           DR. MAGUIRE: I think this morning Dr.  
2 Mathers said that we only get one shot at this and  
3 we should have our age limit relatively low because  
4 of that. He picked 40. He picked that because he  
5 wants to get at a critical safety issue, which is  
6 retinal detachment in young patients. I think we  
7 should just leave the degree of accommodative loss  
8 alone and cast a wide net because one of the  
9 outcomes might be that people with relatively  
10 minimal loss have decreased quality of life after  
11 the lens and that is something we need to know, if  
12 that stratifies by age. So, I don't think there  
13 should be an exclusion criteria based on degree of  
14 accommodative loss.

15           DR. WEISS: I would voice the opposite  
16 opinion because this is for correction specifically  
17 of presbyopia. I think we get to a slipperier  
18 slope if we have no criteria for accommodative  
19 loss. I would like to see that someone, indeed,  
20 required a plus 1.50 for near or plus 2 for near.  
21 Otherwise, why is this lens being used for  
22 presbyopia? Dr. Maguire?

23           DR. MAGUIRE: I respect that outcome but I  
24 would also respectfully submit that you are  
25 thinking in terms of simple spherocylindrical

1 optics and a lot of these lenses that we are going  
2 to see are going to give people simultaneously good  
3 distance and near vision because they work on the  
4 concept of increasing depth of field, and any lens  
5 that gives you vision through increasing depth of  
6 field pays the price of optical degradation to do  
7 it. We know that already because of the subjective  
8 complaints of these people. They all complain of  
9 halos. We know the optics are not that good but  
10 they form a positive opinion despite that in about  
11 92-95 percent of the patients. So, I think you  
12 just have to let that go. I think you have to go  
13 with the low age group and not bring accommodation  
14 into it because we are on a lot of different  
15 simultaneous slipper slopes that counteract. I  
16 think we get one shot and we have to look at that.

17 DR. WEISS: Any other opinions on this  
18 issue? Dr. Ferris, Dr. Bradley and then I am going  
19 to ask you if you have enough information on this.  
20 Dr. Ferris?

21 DR. FERRIS: I actually think we are going  
22 to have to get to this when we start talking about  
23 efficacy and how we are going to measure it. That  
24 is going to determine what level of accommodative  
25 loss or what reading level you have because if you

1 are at the ceiling you are never going to be able  
2 to show improvement, if you understand what I mean  
3 by that. So, some of these other things that are  
4 down the road may come back to this.

5 DR. WEISS: So, you would like to show  
6 some degree of accommodative loss preoperatively.

7 DR. FERRIS: If you are testing presbyopia  
8 I would like to show that you have done something  
9 about it, yes.

10 DR. WEISS: Dr. Bradley?

11 DR. BRADLEY: It is worth reminding  
12 ourselves that presbyopia is really two different  
13 creatures. In some sense we stop presbyopia in  
14 young adulthood but we only turn up at the clinic  
15 when we can no longer read. Accommodation is  
16 declining throughout our life. In some ways this  
17 study will be self-selecting. I mean, patients who  
18 are manifesting problems with their presbyopia, and  
19 it may be that they are down to 2 diopters of  
20 accommodation; it may be that they are 1 diopter  
21 hyperope and they are down to 3 diopters of  
22 accommodation. So, that may vary. The actual  
23 amount of accommodation may vary at the time the  
24 patient presents with problems with presbyopia.  
25 So, in some ways you might must let the patient

1 self-select this. They are seeing their clinician  
2 because they have a problem with presbyopia. Maybe  
3 that is the patient base you should use.

4 DR. WEISS: It appears that we have no  
5 consensus on this one. Is that sufficient for the  
6 agency?

7 DR. EYDELMAN: I guess it will have to do.

8 DR. ROSENTHAL: Actually, we have a  
9 consensus--

10 DR. WEISS: We have a consensus of one.  
11 Dr. Rosenthal?

12 DR. ROSENTHAL: --that is that if they  
13 have to have reading glasses for what we would  
14 consider a reasonable amount of dioptric power and  
15 the lens can achieve a better dioptric power at  
16 near, then I think it is reasonable. But I don't  
17 want to give someone who has plus 2.5 to read The  
18 Wall Street Journal--you know, I think that is  
19 putting people maybe at undue risk but I think we  
20 have a sense where we can go with that.

21 DR. WEISS: Dr. Stark?

22 DR. STARK: Well, you need to leave a  
23 little of your accommodative power in reserve so I  
24 would say that the need for reading glasses or  
25 bifocals and no more than 3 diopters of

1 accommodative reserve, and it could be no more than  
2 2 diopters or no more than 4, but if you say 4  
3 diopters, then in general people can get by with  
4 that and read. So, they are not just doing clear  
5 lens extraction and then throwing in a bifocal with  
6 it; it is for presbyopia.

7 DR. WEISS: Dr. Mathers, and then I think  
8 we will be concluding this.

9 DR. MATHERS: This is very much a moving  
10 target. It is a dynamic process when you are  
11 talking about what someone's accommodation is in  
12 January, the same year in December it is going to  
13 be less. In two years, by the end of the study, in  
14 two or three years, it is definitely going to be  
15 less. So, I don't think it is critical how you get  
16 in because we are all going to be there anyway and  
17 we need to spread a broad net.

18 DR. WEISS: Well, at least in my opinion,  
19 I am in agreement with Walter and Ralph, that we  
20 should have some documentation of some degree of  
21 accommodative loss in terms of needing a bifocal or  
22 accommodative reserve so you have something to  
23 compare it to as far as the success of this  
24 procedure. But we have, obviously, a mixture of  
25 opinions up here. So, if that is fine with the

1 agency we can go on. Is that okay?

2 DR. EYDELMAN: I just wanted to say  
3 something about clarification regarding what Dr.  
4 Ferris said. Obviously, when you are discussing  
5 efficacy criteria you will have to take that into  
6 consideration but normally the way we do the  
7 studies, it is not each individual subject's  
8 improvement.

9 DR. WEISS: Dr. Ferris?

10 DR. FERRIS: If you enroll people who  
11 don't need anything to read J1 how are you going to  
12 show that this treatment was effective? You can't  
13 show improvement if you have no place to go. It  
14 would be incredibly dumb for a company to do that  
15 because they are going to have some proportion of  
16 patients who didn't improve. Well, they didn't  
17 improve because they couldn't improve. Maybe they  
18 did improve. Maybe they could read J0.5 but we  
19 don't even have that. So, it would be silly to put  
20 people into a trial if the outcome--for example in  
21 some trial if 3 lines visual gain, it would be dumb  
22 to put 20/20 people in because they are not going  
23 to get 3 lines visual gain no matter how good your  
24 treatment is, or let's say 20/15. That was my  
25 point about the ceiling, that usually your

1 eligibility criteria are such that if your outcome  
2 is a certain level of visual improvement and that  
3 is at least possible to attain, otherwise you have  
4 a bunch of people who are going to be negative even  
5 if you conceivably help them.

6 DR. EYDELMAN: So, if I can just  
7 paraphrase what you are saying, you recommended in  
8 lieu of degree of accommodative loss an appropriate  
9 inclusion/exclusion criteria is uncorrected near  
10 VA.

11 DR. FERRIS: Well, the reason I said  
12 outcome variable is that it depends on what outcome  
13 variable you are going to choose. That is going to  
14 drive the eligibility criteria. So, if you choose  
15 an outcome variable that says you improve by a  
16 certain amount of accommodative amplitude, maybe it  
17 is the accommodative amplitude that drives it. If  
18 it is that you can read at a certain level, like  
19 J1, then you probably want to have people that  
20 can't read J1 at the start.

21 DR. WEISS: Dr. Rosenthal, did you have a  
22 comment?

23 DR. ROSENTHAL: No.

24 DR. WEISS: No? Malvina, you are fine?  
25 Okay. So, we are going to go on to a less

1 controversial point, preoperative endothelial cell  
2 count. Any thoughts on preoperative endothelial  
3 cell count? Should that be inclusion/exclusion  
4 criteria? Dr. Mathers?

5 DR. MATHERS: I think it should be an  
6 exclusion criterion because we do not want to do 40  
7 year-olds with an 1,800 cell count.

8 DR. WEISS: So, have an age-related  
9 minimum before you could enter the patient in this  
10 study. Am I paraphrasing your correctly? Dr.  
11 Grimmatt?

12 DR. GRIMMETT: I would be in favor of just  
13 what we discussed at the last couple of meetings of  
14 having a sliding scale, similar to what the FDA  
15 proposed based on projections into the future so  
16 you would have enough cells when you are older.  
17 So, the younger you are, you need a higher cell  
18 count. So, I would be in favor of exactly the  
19 sliding scale that we did before.

20 DR. WEISS: I would add something to that.  
21 I don't believe the sliding scale could be the same  
22 as the one for phakic IOL because you have more  
23 trauma induced by the cataract surgery on top of  
24 the IOL implantation, I would think. Or not?

25 DR. EYDELMAN: Well, the sliding scale is

1 obviously going to depend on what your endpoints  
2 are, but I think you can discuss that in  
3 relationship--

4 DR. WEISS: Okay. So, I think there is  
5 some thought about having that as an inclusion  
6 criteria, with the FDA coming up with endothelial  
7 cell counts per age. Any other factors that should  
8 be inclusion or exclusion criteria? It was  
9 mentioned by Dr. Bressler before that patients with  
10 pathologic changes, that should be included as  
11 exclusion criteria as far as hyperopia/myopia. Dr.  
12 Stark?

13 DR. STARK: Corneal astigmatism should be  
14 considered, otherwise the patients are going to  
15 wind up with multiple surgical procedures which may  
16 complicate the issue.

17 DR. WEISS: So, you would like to have  
18 astigmatism up to X amount?

19 DR. STARK: Yes.

20 DR. WEISS: Up to 7.5?

21 DR. STARK: I would say probably 1.5  
22 because you will correct 0.75 of a diopter with a  
23 corneal incision for the IOL.

24 DR. WEISS: Okay. Anyone else with? Dr.  
25 McMahan?

1 DR. MCMAHON: Presuming that visual acuity  
2 distance and near is going to be part of this. I  
3 think there needs to be a minimum level of visual  
4 acuity and the standards that are being applied for  
5 distance acuity probably are fine. There aren't  
6 really good standards for near acuity. We have had  
7 one trial that we have seen that I have some  
8 questions about that I raised at the last panel  
9 meeting in terms of what those standards should be.  
10 For example, preop best corrected visual acuity,  
11 and for the one trial that I am familiar with there  
12 was a certain percentage J3 or better enrolled.  
13 Right?

14 DR. ROSENTHAL: What about distance visual  
15 acuity, Dr. McMahon?

16 DR. MCMAHON: Personally, I would like to  
17 see 20/25 or better.

18 DR. WEISS: Best corrected? So, basically  
19 I think you are saying that these people should  
20 have excellent best corrected visual acuity and  
21 they shouldn't be having other pathology going on,  
22 otherwise they should not be included in the study.  
23 Does anyone disagree with that?

24 DR. BRESSLER: Only a comment, going on  
25 the same theme of this morning, you know, wanting

1 to find out how this is going to happen in moderate  
2 myopia, minus 8 and minus 10, there are a lot of  
3 people out there with 20/32 vision from some slight  
4 degenerative changes that may be suffering from  
5 their presbyopia and I am not exactly clear why we  
6 want this excellent sort of vision.

7 DR. WEISS: Dr. Mathers?

8 DR. MATHERS: You might stratify to be  
9 slightly more liberal for the high myopes, I would  
10 think, say 20/30 or something. If you do 20/80 you  
11 are not going to learn as much but you could make  
12 it softer for the higher myopes.

13 DR. BRESSLER: Then I am more comfortable  
14 with even 20/40-ish where you can see if there are  
15 changes.

16 DR. WEISS: Dr. McMahon?

17 DR. MCMAHON: Since the general consensus  
18 was that there were active controls, you want to  
19 have decent enough vision so that you can tell  
20 differences between the groups. If you use either  
21 historical controls or preoperative controls, then  
22 I think you can have a lot more slip in terms of  
23 entrance visual acuity to get to where you want to  
24 go.

25 DR. BRESSLER: My last question is in

1 terms of diabetic retinopathy, and that is although  
2 it is rare, there is documentation of an atypical  
3 edema that develops when you have diabetic  
4 retinopathy, and it is probably true when you have  
5 other vascular abnormalities, like having had a  
6 vein occlusion, and should those be included in the  
7 mix? Presumably they would be randomly assigned to  
8 both sides, but is the risk worthwhile where you  
9 have a known event that can affect them and they  
10 haven't lost vision from their cataract yet?

11 DR. WEISS: Dr. Ferris?

12 DR. FERRIS: I think diabetic retinopathy  
13 is actually a point that should be carefully  
14 addressed because there is published data showing  
15 that this is a group having particular problems  
16 with accommodative amplitude, particularly those  
17 that have relatively severe diabetic retinopathy.  
18 So, it is a group at risk but they also are  
19 particularly at risk from a surgery. So, I think  
20 some discussion, maybe not here but some careful  
21 discussion about whether you are or are not going  
22 to include them--and if you are to include them,  
23 then I think you need to include enough so that you  
24 can actually say something about them.

25 DR. WEISS: I assume the company in that

1 case is going to want to exclude those patients  
2 because they are not going to improve their data.

3 Dr. Eydelman, did you have any comment on that?

4 DR. EYDELMAN: Basically the same thing.  
5 For device investigation they exclude all ocular  
6 pathology.

7 DR. WEISS: Walter, did you have a  
8 comment?

9 DR. STARK: No, that was the comment I was  
10 going to make.

11 DR. WEISS: Any other comments on this?  
12 If the agency is satisfied with the answers to  
13 question 2 we will go to question 3. What should  
14 be the primary safety endpoint for the study,  
15 retinal detachment rates, endothelial cell loss, or  
16 any other primary safety endpoint? Dr. Bressler?

17 DR. BRESSLER: When someone has vision  
18 loss so they are having cataract surgery to correct  
19 that, all of the litany of side effects that could  
20 occur that were given in that FDA grid are at low  
21 enough rates that people are willing to undergo  
22 that. But I wonder if you have to have some sort  
23 of cumulative morbid event as your safety? If you  
24 just said retinal detachment then, that alone may  
25 not change. But if you said retinal detachment or

1 cystoid edema or endophthalmitis or features that  
2 affect visual acuity, since you are starting  
3 presumably with an otherwise normal eye except for  
4 the presbyopia, it seems that this is a little  
5 different safety question than just safety for  
6 cataract surgery when there is vision loss from the  
7 cataract.

8 DR. WEISS: You are saying sort of  
9 cumulative--

10 DR. BRESSLER: Events that affect visual  
11 acuity in some way.

12 DR. WEISS: Dr. Ferris?

13 DR. FERRIS: Just in general I object to  
14 the term primary safety endpoint because if any  
15 serious endpoint was reached, I think it would then  
16 become a primary one. If there was lots of  
17 endothelial cell loss, I don't care whether there  
18 was retinal detachment or not, that may be primary.  
19 If there is lots of retinal detachment it may not  
20 matter how much endothelial cell loss there is.  
21 So, I have sort of a general problem with picking  
22 one outcome. I know why the agency does that for  
23 statistical reasons, but for the harm side I think  
24 you are looking at all of them, and maybe the major  
25 reason for even doing this study is that you want

1 to inform patients as to what the risk is so you  
2 want to measure all of these risks. Because any  
3 risk that you think is clinically important we  
4 should be measuring and we should be informing the  
5 patients about, and I don't know which one is  
6 primary; they are all primary in my view.

7 DR. WEISS: Would that be satisfactory?

8 DR. EYDELMAN: No.

9 DR. WEISS: No?

10 DR. EYDELMAN: Because--

11 DR. WEISS: Go ahead.

12 DR. FERRIS: For LASIK, didn't we have a  
13 grid that you had to meet certain criteria for  
14 multiple negative outcomes, that you couldn't have  
15 worse than this for several different bad outcomes?

16 DR. EYDELMAN: Yes, you are correct. What  
17 we are talking about is different ways of  
18 constructing clinical study designs. Primary  
19 safety endpoint is the terminology used under ISO  
20 for clinical trial design and that is why it  
21 appears here. The way it is usually done is you  
22 determine the one that, as you mentioned, you base  
23 your cohort size and that is why this question is  
24 before the sample size and duration determination.  
25 So, here we are not asking you which is the only

1 safety endpoint you will be collecting. We are  
2 definitely going to be collecting information on  
3 all of them. What we are asking you is which one  
4 is important enough to drive the statistics, which  
5 one should we base the sample size on, and that is  
6 why the answer I got so far doesn't really address  
7 that.

8 DR. WEISS: We have quite a few comments  
9 on this. Dr. Maguire, Dr. Mathers, then Dr. Brown,  
10 then Dr. Bressler. DR. MAGUIRE: I think one  
11 endpoint should be the incidence of secondary  
12 intraocular surgical procedures. Is that yes or  
13 no? Does that sound like a not good idea to you,  
14 Dr. Eydelman?

15 DR. EYDELMAN: No, I think perhaps panel  
16 members are getting confused between question 3 A)  
17 and the following question where different adverse  
18 event rates for which we should be collecting  
19 information are being addressed.

20 DR. MAGUIRE: Okay.

21 DR. EYDELMAN: I just wanted to make sure  
22 that people are clear on that.

23 DR. WEISS: You stated it already, but if  
24 you could stated it again for the panel, what is  
25 meant by the word primary safety endpoint?

1 DR. BRUCKER: Wouldn't it be the lowest of  
2 the incidence rates so that the lower rate would be  
3 the retinal detachment which we would expect to be  
4 lowest?

5 MR. CALOGERO: I guess it is using a  
6 combination of the lowest rate plus, additionally,  
7 your minimal detectable difference--

8 MS. THORNTON: Don, I am sorry, they are  
9 telling me they can't hear you.

10 MR. CALOGERO: Don Calogero, FDA. We are  
11 using this in an attempt to determine the sample  
12 size here. So, we have all these adverse events  
13 here. Some of them are at very low rates, as you  
14 know. But you can't simply pick the one with the  
15 lowest rate because that particular event might  
16 allow a much larger minimum to detect the  
17 difference. So, it really has to be what you want  
18 to drive the precision of your study, what  
19 endpoint, what is the most important one to drive  
20 the sample size. We need that information, that  
21 feedback to be able to determine the sample size  
22 for the study.

23 DR. WEISS: So, let me ask you a question.  
24 Dr. Bressler was suggesting to, let's say, select a  
25 certain number of lines of lost vision from a

1 variety of causes. Would that be able to drive the  
2 study or no? Did I understand you correctly?

3 DR. BRESSLER: Well, it was a list of  
4 events that either affect visual acuity or have the  
5 potential to, and those could be defined, but my  
6 concern was exactly what you were bringing up in  
7 the trial design, that is, if you make it, for  
8 example, retinal detachment and you are doing  
9 people less than 8 diopters or less than 6  
10 diopters, whatever you choose, I can tell you right  
11 now you are not going to be able to detect  
12 difference, not that there is one but the event  
13 rate is so low you won't be able to detect a safety  
14 problem. But if you say to the patient after the  
15 fact, well, what is my risk of something going  
16 wrong--they are not asking what is my risk of  
17 retinal detachment and macular edema and  
18 ophthalmitis and needing another intraocular  
19 surgery, etc. If those could be defined, I was  
20 just expressing a possible opinion of using that as  
21 your primary safety endpoint, and then it doesn't  
22 have to be that large a study. You are not going  
23 into 10,000, you know you are at 1,000, 400 or  
24 whatever.

25 DR. WEISS: Is that potentially possible

1 or no?

2 MR. CALOGERO: It would be an unusual  
3 study design. Suppose that results in a sample  
4 size of 75. For that particular outcome you can  
5 detect a difference between the two groups but it  
6 may tell you absolutely nothing about much more  
7 specific ones, say the retinal detachment rate when  
8 it is small. Even if you use the historical  
9 control, essentially close to 0.1 percent, 0.3  
10 percent, your minimal detectable difference with  
11 that sample size may turn out to be 5. So, for  
12 that adverse event you can only say with any  
13 confidence that it is somewhere below 5 percent if  
14 you don't see it in the study. If it is above 5,  
15 then it is different than that.

16 Later on in this presentation we look at  
17 actually slides that go into what you can detect,  
18 the sample sizes, so even for the low adverse event  
19 rates for retinal detachment if your minimal  
20 difference is large enough--it reaches a point, of  
21 course, where the study size does become  
22 reasonable. So there are two things you have to  
23 weigh there. It is unfortunate this whole  
24 discussion is sort of like a circle; you have to  
25 look at all these factors simultaneously.

1 DR. BRESSLER: I do understand that is why  
2 I am concerned because I think, if I were testing  
3 this, I too would probably design a trial where I  
4 am only going to include people where the event  
5 rate of that retinal detachment is down to 0.1  
6 percent, or something, by saying no one over minus  
7 6 diopters or something. As a patient, we want to  
8 know what is our risk of these other events.

9 DR. BRUCKER: And the other--

10 DR. WEISS: Dr. Brucker, we are going to  
11 go with Dr. Mathers, Dr. Brown and then we will be  
12 coming back to you. Was there anything else you  
13 wanted to say on that point? No? Dr. Mathers?

14 DR. MATHERS: I think there are really  
15 only two options, either it is the retinal  
16 detachment rate or it is the endothelial cell  
17 count. The endothelial cell count is going to be a  
18 much softer endpoint that occurs way late in the  
19 game. It is not going to be useful to do that if  
20 you are talking about a study that is only three  
21 years long, or whatever, and retinal detachment is  
22 a reasonable thing to look at. From the examples  
23 that you gave us here, you can design a study that  
24 has a reasonable power for a fair sized population  
25 and I think that is what you should do.

1 DR. WEISS: Dr. Brown?

2 DR. BROWN: I basically concur with that.

3 In terms of what we are trying to do as a primary  
4 safety endpoint, and as everyone has said there  
5 will be secondary endpoints that will also be  
6 looked at, but in terms of the primary safety  
7 endpoint, the numbers that you presented in your  
8 grid don't seem extreme and I think that that  
9 should be in part because of the implication of it  
10 and in terms of later loss of function and because  
11 of the lack of data that we don't have in some  
12 these areas of refractive error, I think that that  
13 should be the primary safety endpoint.

14 DR. WEISS: Dr. Brucker?

15 DR. BRUCKER: What was the safety endpoint  
16 used for the original approval of the IOL?

17 DR. EYDELMAN: Endophthalmitis, rate of  
18 endophthalmitis for the monofocal IOL.

19 DR. BRUCKER: So, the rate of  
20 endophthalmitis in this study would probably be  
21 higher than the projected rate of retinal  
22 detachment in this study. So, would it be  
23 reasonable to then look at endophthalmitis as a  
24 primary safety endpoint?

25 DR. EYDELMAN: Probably not because--

1 DR. BRUCKER: Could you put that up again?

2 Or, it is not worth it I guess.

3 DR. EYDELMAN: I just want to make one  
4 point, what I stated before, most likely we would  
5 entertain clear lens IOLs for clear lens extraction  
6 after the establishment of the safety and efficacy  
7 in the cataractous population. So, what we are  
8 trying to say is that if a sponsor established that  
9 their MIOL is safe after cataract extraction, then  
10 it is hard to say that when you take the same exact  
11 material and the same exact MIOL and the only  
12 difference for the population is that the rate of  
13 endophthalmitis is going to be different. So, we  
14 want to try to avoid the situation where a sponsor  
15 comes in and claims there are no additional safety  
16 endpoints to establish.

17 DR. WEISS: From what I hear from the  
18 panel in terms of what primary safety endpoints you  
19 can actually use, it seems like retinal detachment  
20 is the one that was most frequently mentioned by  
21 the members of the panel. If that is sufficient  
22 for you--

23 DR. BRESSLER: Can I make one other  
24 comment?

25 DR. WEISS: Yes, Dr. Bressler?

1 DR. BRESSLER: I just want to point out  
2 that we have on the grid this 0.5 percent of  
3 retinal detachment but it has been pointed out by  
4 Dr. Lane, and it is true I think if you look in the  
5 literature, that if we exclude a certain degree of  
6 myopia it could be as low as 0.1 percent. So, you  
7 have to take a 0.1 percent level and put that into  
8 the mix as well.

9 DR. WEISS: Okay, I see agreement by the  
10 agency. We will go on to part B)--Malvina?

11 DR. EYDELMAN: I am sorry, since you  
12 agreed on minimal endothelial cell density as preop  
13 criteria, perhaps you could look at the table on  
14 your left to give us some guidance as to what cell  
15 density at age 75 you recommend and then we can  
16 calculate back as to the inclusion criteria.

17 DR. WEISS: This is sort of an additional  
18 thing while we are on this topic. Any comments  
19 from the panel as far as whether you want 1,000,  
20 1,200, 1,400 or 1,500 cells left at age 75?

21 DR. EYDELMAN: Thank you.

22 DR. WEISS: Walter?

23 DR. STARK: I am going to pass.

24 DR. WEISS: Pass? Bill?

25 DR. MATHERS: I think 75 shouldn't be

1 considered the end of life for these people. They  
2 probably have 20 more years to go. We should go to  
3 the higher count, 1,500.

4 DR. WEISS: So, 1,500. Dr. Grimmer?

5 DR. GRIMMETT: I concur with 1,500.

6 DR. WEISS: Dr. Brucker?

7 DR. BRUCKER: What was used in the prior  
8 studies of the anterior chamber IOLs?

9 DR. EYDELMAN: We weren't that advanced  
10 then.

11 DR. BRUCKER: So, we have no information  
12 from prior studies.

13 DR. WEISS: Seeing no other comments, the  
14 only two comments voiced have been for the higher  
15 levels of 1,500. Now we will go on to part B) of  
16 question 3. What should be the acceptable adverse  
17 event rate associated with the safety endpoint,  
18 which I think we have defined here as being retinal  
19 detachment rate? Dr. Bressler has mentioned that  
20 it would be more towards the 0.1 because certain  
21 degrees of myopia might be excluded. Dr. Ho?

22 DR. HO: I agree in general with Neil's  
23 comments but we have to be a little bit careful  
24 because those comments are based on cataract  
25 surgery in older patients and age is a relevant

1 risk factor here. Let's say the average age for a  
2 cataract patient might have been 65 years, we are  
3 talking now about somewhere between 50 and 55 years  
4 or 40 and 50 years, and you could be surprised with  
5 a little bit of a difference there.

6 DR. WEISS: Dr. Bressler?

7 DR. BRESSLER: The younger ones though may  
8 have had the higher rate if you controlled again  
9 for their refractive error. So, we do see younger  
10 people who are higher myopes come in with their  
11 posterior capsular opacity, etc. I think that was  
12 again referring to Dr. Lane's presentation, saying  
13 that if we exclude some of these we are really  
14 going to have a lower event rate.

15 DR. WEISS: Dr. Ferris?

16 DR. FERRIS: So, the corollary to that is  
17 that if you are going to set a retinal detachment  
18 rate you may want to set a different rate for  
19 non-myopes and myopes because the underlying rate  
20 is going to be different.

21 DR. WEISS: So, it sounds like we have to  
22 set it for the high myopes, lower myopes and  
23 hyperopes, or low myopes and hyperopes versus  
24 higher myopes?

25 DR. FERRIS: Yes, just the two.

1 DR. WEISS: And do you want to suggest  
2 what rates you would want for those, what numbers?  
3 Dr. Brown?

4 DR. BROWN: I have spent some time  
5 thinking about that beforehand and the 0.3 percent  
6 per year, from reviewing the data, seemed to be  
7 reasonable for the myopic population. We wouldn't  
8 want to go beyond that. But the other thing that  
9 this does imply if we separate, which I think we  
10 should do, is that we are going to have to make  
11 sure that the sponsor stratifies the population.  
12 We need strict requirements, we need this many  
13 patients within this refractive range and this many  
14 patients within this refractive range for it all to  
15 play out.

16 DR. WEISS: I think that is a good  
17 suggestion so you won't be in a situation where you  
18 have minus 15's and we don't have enough data. Is  
19 that sufficient information for the agency? Well,  
20 since they are discussing it, it sounds like not.  
21 So, anyone else have any comments on this  
22 particular issue? Dr. Brucker, do you have any  
23 comments on the retinal detachment rate?

24 DR. BRUCKER: Dr. Ferris just said that we  
25 had said that a couple of hours ago. I think that

1 is the proper way to stratify it. I think that is  
2 correct.

3 DR. EYDELMAN: Perhaps as we go to 4 A)  
4 that will be clarified a little.

5 DR. WEISS: So, what is missing for you,  
6 Malvina? What haven't you gotten from the answer  
7 from the panel on this one?

8 DR. EYDELMAN: The number.

9 DR. WEISS: So basically, bottom line, you  
10 want a number from us as far as what we are looking  
11 for the high myope rate versus the rest of the  
12 population.

13 DR. EYDELMAN: What would be acceptable.  
14 I think perhaps looking at the table on the left in  
15 conjunction with question 4 A)--again we are in  
16 this circular logic but I think what we are looking  
17 at is the maximal allowable retinal detachment rate  
18 that you would find acceptable. That drives the  
19 sample sizes so if you now start breaking it out  
20 into different subgroups, then we would have to  
21 have that number of subjects for each indication.

22 DR. WEISS: Basically, if the panel is  
23 willing to agree to a higher percentage, then the  
24 study enrollment goes down.

25 DR. EYDELMAN: Yes. Again, you can do it

1 by sub-indications or as a group.

2 DR. WEISS: Dr. Ferris?

3 DR. FERRIS: Did I miss in a previous  
4 slide that for that endothelial cell count that we  
5 were already over 1,000?

6 DR. WEISS: Well, I think these are two  
7 separate pieces of data.

8 DR. FERRIS: Well, no, they are not. If  
9 you have a 1,000 then you have enough to look at  
10 retinal detachment.

11 DR. EYDELMAN: No.

12 DR. FERRIS: What do you mean, no?

13 DR. EYDELMAN: No, because you have  
14 determined that you want the retinal detachment  
15 rate to be the primary endpoint and the endothelial  
16 cell was as an inclusion criteria. In other words,  
17 all we said was we are going to calculate back and  
18 figure out what minimal endothelial cell loss the  
19 subject would need in order to end up with that.

20 DR. WEISS: We are not determining  
21 enrollment based on that graph even though they had  
22 information on enrollment based on that graph. Is  
23 that correct?

24 DR. BRUCKER: The graph says 113 patients  
25 and 1,500 cells. It doesn't as go as high. If we

1 used 0.3 here we would need 321 patients. I think  
2 that is the question he was asking. It is not over  
3 1,000.

4 MR. CALOGERO: It depends on the duration  
5 of the study. For the one-year study it is over  
6 1,000.

7 DR. FERRIS: Then I agree with what you  
8 said. That is why I said I wasn't sure what  
9 whizzed by--

10 DR. EYDELMAN: We are going to see it  
11 again in a minute.

12 DR. WEISS: So, Dr. Ferris, you are okay  
13 and, Dr. Brucker, you are okay?

14 DR. FERRIS: I am okay, except I am  
15 totally lost. We haven't come up anywhere  
16 near--and the reason we haven't is that it is a  
17 complex issue and we don't have all the numbers in  
18 front of us. I am glad you have these numbers  
19 because that is what we need to drive this because  
20 we say they are all important and we want to make  
21 sure that we pick one of the important ones, sort  
22 of the least common denominator here. So, you have  
23 to look at them all in combination and that is why  
24 we are struggle. That is why I struggle because I  
25 thought what whizzed by was 1,500. Well, if it

1 1,500 we are done. But if it is 100 we are nowhere  
2 near done.

3 DR. WEISS: Unfortunately, you are not  
4 done yet.

5 DR. FERRIS: Right. My view is that if  
6 retinal detachment is the driving one, then we need  
7 to look at two groups. We need to look at the high  
8 myopes and in each of those groups you have to have  
9 adequate samples.

10 DR. WEISS: Yes, basically I think I just  
11 hear consensus on that. I think what Malvina  
12 wanted is, okay, we agree that there have to be two  
13 different groups but it would be helpful to her if  
14 we gave some number for these two different groups.  
15 Dr. Mathers had a comment. Was it addressing that,  
16 Bill?

17 DR. MATHERS: Yes. Are we assuming that  
18 for the non-high myopes the normal retinal  
19 detachment rate is about 0.01?

20 DR. EYDELMAN: Yes.

21 DR. MATHERS: So, 0.1 would be ten times  
22 higher?

23 DR. EYDELMAN: Yes.

24 DR. MATHERS: And 0.1 would be a pretty  
25 high number and it is already ten times higher.

1 So, 0.3, 30 times higher than the normal rate is  
2 too high, right?

3 DR. BRUCKER: But that is exactly the  
4 reason--

5 DR. WEISS: Dr. Brucker, could you hold  
6 it? Have you finished?

7 DR. MATHERS: So, I would go down on the  
8 left side of the chart.

9 DR. WEISS: So, you want to go to what  
10 number?

11 DR. MATHERS: 321, three years and the  
12 lowest number there, the lowest allowable  
13 detachment rate.

14 DR. WEISS: That is not the lowest  
15 allowable detachment rate. Malvina?

16 DR. EYDELMAN: That would allow you to  
17 detect maximum of 0.3 percent annual loss in a  
18 three-year study.

19 DR. FERRIS: So, that is one retinal  
20 detachment.

21 DR. HILMANTEL: Can I say something here?

22 DR. WEISS: Yes.

23 DR. HILMANTEL: These numbers are  
24 calculated--I am sorry, I am Gene Hilmantel--these  
25 numbers are calculated to try to get the minimum

1 size that let's you detect that rate, but there is  
2 a caveat here. For most of these, especially with  
3 the lower rates, the study would only pass the  
4 endpoint if you got zero retinal detachments. So,  
5 if you want to have a study that would permit one  
6 or more retinal detachments and still pass the  
7 criterion, you have to have a larger sample size  
8 than in the chart here.

9 DR. WEISS: Basically practically, the  
10 smallest percentage we could define in this, let's  
11 say for the non-high myopes would be 0.3 percent?

12 DR. HILMANTEL: That is correct.

13 DR. WEISS: So, the 0.1 percent which was  
14 brought out by more than one person is not  
15 something you would be considering. The least rate  
16 that we could consider as the panel is 0.3 percent.  
17 So, let's just address that.

18 DR. HILMANTEL: I mean, you can consider  
19 whatever you want to--

20 DR. WEISS: But it wouldn't be practical.

21 DR. HILMANTEL: --but the smaller it is,  
22 the larger is the sample size.

23 DR. WEISS: Okay, so if it is not  
24 practical, we can deal with that.

25 DR. ROSENTHAL: It is not that it is not

1 practical, if you feel that a retinal detachment  
2 rate of one percent is acceptable, then it is  
3 acceptable. If you feel that it is not acceptable  
4 and 0.3 is acceptable, that is what is acceptable.  
5 So, we need to know what you feel is an acceptable  
6 retinal detachment rate.

7 DR. WEISS: Well, what was brought out  
8 previously was 0.1 percent.

9 DR. ROSENTHAL: That makes the study  
10 enormous.

11 DR. BRESSLER: And that is why I wasn't  
12 voting for retinal detachment being a primary  
13 safety endpoint because it is going to be  
14 impossible to do.

15 DR. WEISS: Dr. Ferris had a comment and  
16 then Dr. Brucker. Dr. Eydelman?

17 DR. EYDELMAN: I just wanted to point out  
18 that our cumulative RD rate from the FDA grid is  
19 0.3 percent so the chances are you are not going to  
20 be way--

21 DR. WEISS: Way far off from that. We are  
22 going to have Dr. Ferris, Dr. Brucker and then Dr.  
23 Ho. Dr. Ferris?

24 DR. FERRIS: I guess I am a little  
25 confused now with the maximum allowable retinal

1 detachment rate. If your expected number is one  
2 detachment and you get one detachment, you have no  
3 idea what the rate is. If these 321 people bought  
4 lottery tickets and somebody one, the rate of  
5 lottery ticket winning would not be 0.3 percent.  
6 We need at least a couple of events to be able to  
7 say anything about retinal detachment. I also  
8 agree with what Neil was saying, that is, it may be  
9 unreasonable to power a study to get an accurate  
10 assessment of retinal detachment rate. So, somehow  
11 there has to be a balance between reason and what  
12 you would like.

13 DR. WEISS: Dr. Brucker?

14 DR. HILMANTEL: Can I say something?

15 DR. WEISS: Yes.

16 DR. HILMANTEL: Gene Hilmantel again. In  
17 this type of pre-approval study, you are absolutely  
18 correct, the only thing you can demonstrate really  
19 with any confidence is that the rate is less than a  
20 certain maximum allowable rate that we would  
21 select. To really get a handle on the rate you  
22 need many more patient years and that can probably  
23 only be addressed in a post-approval type of study.

24 DR. WEISS: Dr. Brucker?

25 DR. BRUCKER: Yes, I think that the

1 problem is that when you talk about the rates and  
2 you have 0.3 most people might say that is fine for  
3 the entire cohort. But now you are talking about  
4 splitting them up, and if you start to split them  
5 up and you only have one rate we are not saying  
6 that you are going to look at them all with the  
7 same end rate. So, if you wanted to go down to 0.1  
8 you would be at 1,000 patients or whatever it is,  
9 it is too many. So, you are going to have to go  
10 back and recalculate. You are asking us for a  
11 number and that is not what we are offering you.  
12 We are telling you as doctors and surgeons that  
13 that rate is going to be extremely, extremely low  
14 and we don't expect that. This is an acceptable  
15 rate if you take a look at the whole cohort. One  
16 percent is unacceptable. If now your rate, as Rick  
17 was saying, is zero in the series of patients that  
18 are done that are medium myope and emmetrope you  
19 will have no retinal detachments, in other words,  
20 and you got one or two in the other group, the high  
21 myopes, that is going to be all right but you are  
22 going to be analyzing them separately. So, you  
23 can't keep asking us what is the number; what is  
24 the number if you are going to analyze two groups  
25 separately. Do you understand what I am saying?

1 DR. WEISS: But can't you just give two  
2 numbers?

3 DR. HILMANTEL: You can give us guidance  
4 if you want.

5 DR. BRUCKER: The point is that the 0.1  
6 for the emmetropic patient would give you 1,000  
7 patients which is unacceptable. If you go up to  
8 one percent in the high myope, that also is too  
9 high. So, you are going to have to look at the  
10 aggregate number; 0.1 percent is too high and 0.1  
11 gives you 1,000 patients. We can't design a study  
12 based upon that. Now, if you wanted to ask  
13 everybody in this room whether they think it has to  
14 be less than one percent retinal detachment rate  
15 regardless of the group of patients being looked  
16 at. Does that make sense?

17 DR. WEISS: Dr. Eydelman?

18 DR. EYDELMAN: It makes sense but I am  
19 just trying to get further guidance. I mean, what  
20 we are saying is that you have a different maximum  
21 allowable rate depending on the population.

22 DR. BRUCKER: Right.

23 DR. EYDELMAN: That is fine. What we are  
24 asking you is tell us, please, what the two  
25 populations are and what would be the maximum

1 allowable rate for each of the populations. Then  
2 we can go ahead and design a study around it.

3 DR. BRUCKER: So, Neil and myself would  
4 respond to you by saying that had you made a  
5 table--and these tables are wonderful; I  
6 congratulate both of you for doing this--had you  
7 made a table, one of them being from emmetropia to,  
8 let's say, minus 6 and the second table from minus  
9 6 to minus 16 you probably would have had two  
10 numbers because the literature that you have  
11 described gives you different retinal detachment  
12 rates. But you didn't give us that; you are only  
13 giving us one aggregate and we can't give you an  
14 answer because we don't know the number.

15 DR. WEISS: Dr. Ho?

16 DR. HO: I was going to echo Sandy's  
17 comments precisely. I think that if you look at  
18 the literature you presented, there is one study of  
19 52 myopes where the retinal detachment rate was an  
20 astounding 2 percent at 4 years and then up to 8  
21 percent at 7 years. This conversation is beyond my  
22 comfort level to start with for clear lens  
23 extraction for presbyopia. I am way on the left  
24 over here and way down in numbers of years. I  
25 understand the limitations. I think this is a very

1 significant public health issue. I think there  
2 could be many thousands, millions of patients that  
3 could be--seduced is maybe not the right word but  
4 that would be enticed by advertisements of throwing  
5 your glasses away. I think we need to be more  
6 careful here. If you ask me for numbers I would  
7 say for the general group 0.3 is probably okay; for  
8 the myopes, you know, something a little bit higher  
9 but not too much higher.

10 DR. WEISS: I understand what Dr. Eydelman  
11 is asking us for and I understand the sentiments on  
12 the panel but I still think we can get more in the  
13 direction of what you are saying, not an exact  
14 number but I would assume that everyone here would  
15 agree that you wouldn't want to be higher than one  
16 percent for the high myopes. Would anyone disagree  
17 with that? Would anyone want to have a higher  
18 percent than one percent RD rate for the higher  
19 myopes? So, one percent would be the maximum for  
20 the high myopes.

21 DR. HILMANTEL: Can I just clarify?

22 DR. WEISS: Yes.

23 DR. HILMANTEL: That wasn't the rate per  
24 year. So, if it is one percent per year over ten  
25 years it would be ten percent.

1 DR. WEISS: Dr. Bradley?

2 DR. BRADLEY: I think starting with Dr.  
3 Lane's presentation this morning and everything I  
4 have heard from our esteemed surgeons here, the  
5 impression I get is that the lens extraction  
6 procedure is now so safe that with reasonable  
7 numbers you are not going to be able to evaluate  
8 whether a particular clear lens extraction product  
9 or lens that is going to be put in is going to  
10 elevate the hazard by any reasonable amount. You  
11 are simply not going to be able to evaluate that  
12 because the procedure itself is so safe. All you  
13 can do with these numbers is essentially screen for  
14 a disaster; you cannot evaluate whether there is a  
15 reasonable increase in hazard because the procedure  
16 itself is so safe. It can only be done post-market  
17 with large sample sizes. But I believe these  
18 numbers seem reasonable as a screen for a disaster  
19 basically and I think what the people around the  
20 table are saying is that the number of 0.3 percent  
21 sounds about reasonable.

22 DR. WEISS: The agency will speak,  
23 obviously, but I am going to think that Dr.  
24 Bradley's comments should probably be the bottom  
25 line here, that most people have voiced 0.3 percent

1 so why don't we leave it at 0.3 percent and you can  
2 see that there is a lot of discussion and  
3 discomfort on this issue? Do you have any comments  
4 on this?

5 DR. HILMANTEL: Yes, my only comment that  
6 one of the questions we are asking you in essence  
7 is, is this something that we should look at in a  
8 pre-approval study, given that all we can do is  
9 establish that the rate is less than a certain  
10 amount?

11 DR. WEISS: Dr. Maguire?

12 DR. MAGUIRE: I am going to look at it  
13 from a patient standpoint. You can look at it two  
14 ways, you can say a low incidence of retinal  
15 detachment or you can say my risk of retinal  
16 detachment is five or ten times higher over X  
17 period of time if I have this done than if I don't  
18 have this done. That is how patients think about  
19 it. Okay? And, we are talking about incidences 10  
20 or 30 times higher and barely being able to detect  
21 it. I also understand that if we did a study to be  
22 able to detect something 3 or 5 or 10 times higher  
23 than expected, it would be too many patients.

24 So, what that tells me is that the public  
25 health effects of clear lens extraction and retinal

1 detachment are not going to be elucidated by any  
2 pre-approval study by the FDA. It is not going to  
3 happen. So, there is a potentially serious public  
4 health effect if clear lens extraction in  
5 pseudophakic IOLs that will remain after this study  
6 goes. It will have to be addressed elsewhere.

7 We had absolutely no analysis from Dr.  
8 Lane on how he came to the conclusion of retinal  
9 detachment when the confounding factors were  
10 removed. I am not at all sure if he included YAG  
11 laser capsulotomy in that or not. If that was an  
12 issue, obviously that can be up in the 30 and 50  
13 percent.

14 DR. WEISS: Because of interest in time  
15 and we have five more questions to get through and  
16 less than an hour to do it in--I still hear the  
17 sentiment from the panel that that should be  
18 included. The number is controversial but 0.3  
19 percent has been mentioned more than once. If that  
20 is satisfactory for you we will go on to question  
21 4.

22 DR. EYDELMAN: And I understood 3 is  
23 pre-PMA because the question was twofold,  
24 percentage and the number of years before the PMA.  
25 I saw a couple of people pointing to number 321

1 which implies 3 years.

2 DR. WEISS: In 4 (A, are we not going to  
3 get to the duration of the study?

4 DR. EYDELMAN: No.

5 DR. WEISS: Because in 3 I didn't think  
6 the amount of time for the study was being  
7 addressed, unless you want us to address it now.  
8 It just said adverse event rate.

9 DR. EYDELMAN: No, we were discussing 4  
10 (A.

11 DR. WEISS: No, we haven't gone to 4 (A  
12 yet or, if we did, I didn't know it. Maybe I  
13 missed it. So, you want us to get involved in the  
14 duration of the study.

15 DR. EYDELMAN: It was a conjoined effort.

16 DR. WEISS: Is there consensus that it  
17 should be three years? Dr. Ferris?

18 DR. FERRIS: I would say three years is a  
19 good minimum length for the study, and I was going  
20 to make a suggestion with regard to a slightly  
21 different approach to sample size, and that is that  
22 I think people would like to know if there is a one  
23 percent risk, and I think you could power the  
24 studies so that you would have enough power to give  
25 a reasonable estimate of the absolute risk.

1           There are two issues here. One is the  
2 relative risk and one is the absolute risk. The  
3 absolute risk is almost uninterpretable by patients  
4 because one percent, a tenth of a percent or a  
5 millionth of a percent--they think it is very low.  
6 So, it seems like you need some sort of confidence  
7 as to what the actual rate is so you can say it is  
8 one percent but that is ten times higher than what  
9 you would have if you don't have this procedure. I  
10 think you need both numbers, and you need enough  
11 cases to have some confidence about what that  
12 number is. The 321--I am glad someone else pointed  
13 out that I don't read the graphs very carefully  
14 because it is per year so that is actually three  
15 cases. I think you can do the math; the agency can  
16 do the math to get some sort of reasonable  
17 confidence because I think the most important thing  
18 we are going to do is to be able to tell these  
19 patients what their risk is and you need enough  
20 patients to be able to tell them what the risk is,  
21 and then the Admiral Farraguts can go ahead and the  
22 Hamlets can think about that and not do it, but at  
23 least they would have something to base their  
24 determination on.

25           DR. WEISS: Dr. Stark?

1           DR. STARK: But if we are going to have  
2 two groups, the mid-myopes and the high myopes,  
3 then we are talking about twice that number. Could  
4 we compromise and say 0.3 for the lower myopes and  
5 hyperopes and 0.5 for the others? That would give  
6 a total of a little over 500 patients, which is  
7 what the cohorts have been in the past.

8           DR. WEISS: Dr. Ferris?

9           DR. FERRIS: I am sorry, I did the math  
10 for the non-myopes. The math for the myopes is  
11 going to be a smaller number because you are going  
12 to have more events. So, you would need maybe a  
13 third of the number or less because their rate is  
14 something like one percent per year so you are  
15 going to need a much smaller number.

16           DR. WEISS: That is a good point, Walter.  
17 Three years is what we are talking about, it seems.  
18 Dr. Bressler?

19           DR. BRESSLER: I just want to make a  
20 discussion point about potentially considering two  
21 years. Most of the literature, to my knowledge,  
22 suggests that complications that happen after  
23 cataract surgery happen within a year's time. So,  
24 by going to two years we will catch them, if there  
25 were some additional problems going on. But it

1 gets more and more expensive and less likely to get  
2 follow-up as you try and get these people out to  
3 three years. So, I am not sure we need that third  
4 year.

5 I will point out that in the clear lens  
6 extraction minimum data that FDA presented this  
7 morning, which was very helpful, that 8 percent  
8 rate was because there were some detachments  
9 happening at three, four and five years after the  
10 cataract surgery and these were high myopes. So,  
11 it is not clear in my mind if that is just  
12 detachments that were going to occur due to the  
13 pathologic myopia anyway. We just don't have any  
14 strong data to suggest that there is an increased  
15 retinal detachment rate beyond the one to two  
16 years. So, I am just suggesting that you could  
17 consider two years.

18 DR. WEISS: Just for members of the panel,  
19 for those who were at the last two meetings, we  
20 always get involved in these difficulties with  
21 endothelial cell loss. That probably won't be an  
22 issue here because it is a standard operation, but  
23 the less number of years of data you have, the more  
24 difficult it is to try to figure out what is going  
25 on.

1 DR. BRESSLER: I was only talking about  
2 retinal detachment.

3 DR. WEISS: You know, that is something  
4 the panel can discuss.

5 DR. BLUSTEIN: Could I say something?

6 DR. WEISS: Yes.

7 DR. BLUSTEIN: This is Joe Blustein from  
8 the FDA. The relative risk for retinal detachment  
9 is greatest within the first year. It is about  
10 10-20 times greater having cataract surgery than  
11 not, but it still continues out and after 4 years  
12 it is still 6 to 7 to 10 times greater than not  
13 having surgery. So, the risk of retinal detachment  
14 persists even beyond that first, second and third  
15 year.

16 DR. WEISS: Dr. Ho?

17 DR. HO: I would echo those comments that  
18 were just made. I think I would be comfortable  
19 with a shorter follow-up for those patients that  
20 are less at risk, that is, those that are low  
21 myopes, emmetropes or hyperopes that we have  
22 included. But I would like to see longer studies,  
23 particularly considering some of the literature  
24 that is out there for the higher myopes.

25 The other issue is that the cataract

1 surgery results are for a group of patients that  
2 are older. This is clearly a different set of  
3 patients and if you are younger and you are more  
4 myopic I am not as comfortable with two years. I  
5 think I would be reasonably comfortable with two  
6 years for the non-highly myopic group.

7 DR. WEISS: Dr. McMahon?

8 DR. MCMAHON: I would like to support Dr.  
9 Bressler's view. At several of these types of  
10 meetings where we have tried to look at these  
11 shallow slope differences, we are always left with  
12 a quandary and I think we have an opportunity here,  
13 since the majority of the retinal detachment risk  
14 associated with the surgery is in the first year or  
15 so, of shortening the Phase III trial. But then I  
16 would like to argue for a detailed post-market  
17 study for a much longer period of time to pick up  
18 those sorts of things. That is exactly where that  
19 prospective case control kind of thing can come  
20 into play that I mentioned earlier.

21 DR. BLUSTEIN: In the large cohort studies  
22 about 40 percent of the retinal detachments  
23 occurred within the first year, and then 60 percent  
24 occurred within years two to three or four and that  
25 was the length of those cohort studies. That is

1 just information.

2 DR. WEISS: What I am beginning to hear is  
3 sort of a trend, especially in view of the primary  
4 safety endpoint of retinal detachment, that a  
5 two-year study with post-market follow-up would be  
6 sufficient. Does anyone have any disagreement with  
7 that? Dr. Mathers?

8 DR. MATHERS: There would be an advantage  
9 in endothelial cell count to look at a three-year  
10 point, and I am going to predict that 40 years  
11 after the operation the endothelial cell count is  
12 going to be the more important number than the  
13 retinal detachment rate. So, I would argue for  
14 three.

15 DR. WEISS: But would you be averse to  
16 having that post-market?

17 DR. MATHERS: That is fine.

18 DR. WEISS: Because we could still include  
19 that in post-market. Dr. Ferris?

20 DR. FERRIS: Just one last comment,  
21 although I agree with you that the endothelial cell  
22 count is going to be important, remember that the  
23 retinal detachment rate, as was pointed out,  
24 doesn't stop. So, when you multiply 25 years, 30  
25 or 40 years times that, that is going to be a

1 pretty ugly number too.

2 DR. WEISS: Dr. Stark?

3 DR. STARK: I think in the original study,  
4 the standard study, I would like to see a little  
5 longer than three years to ensure that we are not  
6 opening Pandora's Box here. There has not been a  
7 lot of clear lens extraction in 40 year-old normal  
8 people. But with the tight vitreum- retinal  
9 adhesion in those patients the fact that we are  
10 going to be jarring that, maybe separating it and  
11 causing some retinal detachments we may see an  
12 unusually high number of retinal detachments in  
13 these people and thinking, well, no, they were just  
14 supposed to be the myopes that got the retinal  
15 detachments.

16 So, I am a little concerned about it. You  
17 know, when you see the cataract patients you look  
18 at them and, as a clinician, most of the myopes and  
19 the young cataracts will have vitreous detachment  
20 already and that may be contributory to the cause  
21 of the cataract. There may be an association. So,  
22 this may be an entirely different group of people  
23 that have a very tight vitreum-retinal adhesion.  
24 So, I would rather see the three years. What I  
25 would to ensure though is that we get that

1 post-approval follow-up on those patients in high  
2 numbers because I think if something still can be  
3 done, or at least the public education, if four and  
4 five years out--Joseph Colin criticized the Italian  
5 group for saying that there was a high rate of  
6 retinal detachments in these patients at four years  
7 because he only had two percent, but then it went  
8 to eight percent at eight years. So, I think we  
9 just want to make sure we are not missing a big  
10 problem.

11 DR. WEISS: So, agency, I think you can  
12 hear the mixture of opinions, somewhere between two  
13 and three years and I think the points you raised  
14 here are important ones about the vitreous and  
15 younger patients.

16 We are going to go on to B), do you  
17 believe a post-market study is indicated? I am  
18 going to answer that. The impression I get from  
19 the panel is that most people are talking about a  
20 post-market study. If so, what is an appropriate  
21 type of study, sample size and length of follow-up  
22 for such a study? That is all going to get  
23 answered in about the next four minutes. Anyone  
24 have a quick answer for that one? Walter?

25 DR. STARK: If you are just looking at

1 retinal detachment events you should be able to  
2 pick that up and visual acuity and YAG laser  
3 capsulotomy probably. So, I would say five years.

4 DR. BRESSLER: I would echo that--

5 DR. WEISS: Dr. Bressler?

6 DR. BRESSLER: I am sorry, yes, as you go  
7 beyond five years in this age group, they start  
8 moving around and you can't even follow them and I  
9 don't think you will have data to interpret as  
10 well, so to be reasonable with what is expected and  
11 what we are looking for, I think five years is a  
12 good number.

13 DR. WEISS: Dr. Blustein?

14 DR. BLUSTEIN: I think you need to be  
15 aware that a post-market study doesn't necessarily  
16 mean following the same cohort that was in the PMA.  
17 It can be following a new cohort once this lens is  
18 out in the market or a sample of that cohort and it  
19 can be followed for five years or longer to see  
20 what complication rates are.

21 DR. WEISS: So, Dr. Start and Dr.  
22 Bressler, when you were speaking about five years  
23 did you mean the same cohort?

24 DR. BRESSLER: Not necessarily.

25 DR. WEISS: Not necessarily? And would

1 you want a new cohort followed for a five-year  
2 period of time or would you like to follow the same  
3 cohort?

4 DR. EYDELMAN: Well, it depends on the N.

5 DR. BRESSLER: Right. You would probably  
6 have to add to that cohort because, right, you  
7 wouldn't have enough.

8 DR. WEISS: Dr. Blustein?

9 DR. BLUSTEIN: Comments that have kind of  
10 come to the panel in the past about this is in the  
11 hands of the best surgery on a group, and it is a  
12 whole different issue once it gets out there into  
13 the market. I think that you have to take that  
14 into account too, that retinal detachment rates,  
15 complication rates may be very low in this cohort  
16 but once it is out in the market it might be a  
17 different issue.

18 DR. WEISS: So, you are bringing up the  
19 point that it might be beneficial to have a new  
20 cohort and you would want to know from us how many  
21 years and what is the sample size. Is that  
22 correct?

23 DR. BLUSTEIN: Correct.

24 DR. WEISS: Dr. Rosenthal?

25 DR. ROSENTHAL: I just wanted to comment

1 that it is fairly obvious that there are two  
2 approaches you can take, both of which you have  
3 mentioned. You either follow the existing cohort  
4 out to whatever time you feel appropriate or you  
5 set up another type of study. Now, the other study  
6 can't be as intense as the existing study. I think  
7 this panel has been told several times that there  
8 are other ways of doing post-market studies. For  
9 example, with the 30-day contact lens there was a  
10 very large number of patients being enrolled for a  
11 reasonable--I forget what the time frame is, in  
12 which only major events are being reported. It  
13 seems to me a similar type of post-market study  
14 could be arranged here where you enroll so many  
15 patients and you look for major events. We are not  
16 interested in visual acuity; we are interested in  
17 whether or not they have had a retinal detachment  
18 or whatever else you are interested in.

19 So, you can approach it either way and we  
20 need the panel's input on which way do they think  
21 is the best way to approach it.

22 DR. WEISS: Dr. Blustein, Dr. Mathers,  
23 then Dr. Stark and Dr. Ho.

24 DR. BLUSTEIN: You don't have to be  
25 specific about length of time to follow and sample

1 size. That can all be handled through the agency.  
2 We just need to know the events of concern that the  
3 panel wants to address.

4 DR. WEISS: I think the one event of  
5 concern that everyone is bringing up is retinal  
6 detachment. Dr. Maguire?

7 DR. MAGUIRE: The one event that  
8 definitely would need a separate population is  
9 removal of the lens or other secondary intraocular  
10 procedures down the line. I think it is very wise  
11 to look at what we have learned from cataract  
12 extraction with presbyopic correcting lenses in  
13 cataractous patients. One thing we found with the  
14 Array lens is that even though in the initial  
15 cohort there was a sizeable class that were unhappy  
16 with their procedure. They didn't elect to have  
17 them removed when it went into general circulation.  
18 About that same percentage that were unhappy now  
19 decided to have their lens implant removed, five or  
20 seven percent. So, I think absolutely we need  
21 that.

22 The other thing is that we need to have a  
23 fairly long period of follow-up because we don't  
24 know if the accommodative efficacy will remain  
25 stable and if the degree of optical degradation in

1 some of these lenses will remain tolerable after  
2 the initial period of euphoria.

3 DR. WEISS: Dr. Mathers

4 DR. MATHERS: I agree with those comments  
5 and also you are going to need to measure  
6 endothelial cell count and the longer duration you  
7 have the better because you are trying to draw an  
8 extrapolation over 40 years, and you simply can't  
9 do that on a three-year time point. I think that  
10 is going to be important.

11 DR. WEISS: The other thing that I would  
12 mention, which was mentioned by a panel member  
13 before, is YAG capsulotomy. I think you mentioned  
14 that, Leo. Dr. Ho?

15 DR. HO: They covered it.

16 DR. WEISS: Dr. Stark?

17 DR. STARK: I was just going to say that  
18 YAG laser capsulotomy increases the risk of retinal  
19 detachment by about three times. So, we have to  
20 know that number and it might be nice to know that  
21 number out to five years so I would think that if  
22 you could follow a subset of the original cohort.

23 Also, the other thing that would be nice  
24 to know, and maybe by ultrasound to obtain it, is  
25 what is the status of the vitreum before these

1 surgical procedures and what happens afterwards.

2 DR. WEISS: I think the endpoints we are  
3 talking about are retinal detachment, secondary  
4 intraocular lens procedures, YAG capsulotomy.  
5 Anything else you need to know from us on this  
6 question? Dr. Brucker?

7 DR. BRUCKER: I guess once it goes out  
8 into the public for a new cohort, you may look at  
9 retinal detachments but you may have a lot of  
10 broken capsules by other surgeons. So, it might e  
11 worthwhile to make sure that you have  
12 intraoperative complications so that you know how  
13 to interpret the retinal detachments.

14 DR. WEISS: Yes, I think that is an  
15 excellent point because your rate of RD goes up by  
16 five percent or something. Are you okay, agency,  
17 on question number 4? If so, we will move to  
18 question number 5.

19 DR. EYDELMAN: So, there was basically no  
20 consensus on the sample size or follow-up?  
21 Correct?

22 DR. WEISS: What I understood the last  
23 comment to be is you didn't need the sample size  
24 from us but the follow-up, from what I was hearing  
25 here, was about five years.

1 DR. EYDELMAN: We don't need the sample  
2 size if we have a rate.

3 DR. WEISS: A rate of what? Retinal  
4 detachments?

5 DR. EYDELMAN: That we are trying to  
6 detect. It is one or the other.

7 DR. WEISS: Would anyone be averse to  
8 suggesting the same rate that we had for the study?  
9 Would there be any objection to that?

10 DR. MAGUIRE: I think it should be lower.  
11 I think we should think in terms of relative risk  
12 of retinal detachment and other things happening  
13 compared to baseline.

14 DR. WEISS: The problem that Dr. Brucker  
15 introduced is that the level of surgery may go down  
16 so to expect the complication rate to go down might  
17 not be practical. Dr. Bressler?

18 DR. BRESSLER: But I think we want to  
19 inform the public what is their minimal risk that  
20 we are reasonably sure that they are taking on from  
21 this post-marketing survey. Because we can't do  
22 that from the original trial that is planned. From  
23 the original trial we can say, let's say for the  
24 non-high myope, okay, your risk is no greater than  
25 30 times, you know, retinal detachment. To me,

1 that is all that we can get out of that original  
2 trial but that is not acceptable for the safety of  
3 the tens of millions that this could apply to.

4 DR. WEISS: So, do you have a percentage?  
5 Would you want to go back to the 0.1 percent?

6 DR. BRESSLER: I would actually go even  
7 lower, 0.05 and say, well, your risk is not greater  
8 than times what your retinal detachment rate is.

9 DR. WEISS: Dr. Maguire was agreeing on  
10 that. Is that acceptable to the agency, just to  
11 say 0.05 percent retinal detachment rate with  
12 five-year follow-up? Dr. Stark?

13 DR. STARK: How many patients would you  
14 need?

15 DR. WEISS: Well, I think what they were  
16 saying is that the amount of patients would be  
17 driven by the percentage of the primary safety  
18 endpoint. Is that correct?

19 DR. EYDELMAN: Right. What we are saying  
20 is there are two ways you can do it. You can  
21 either tell us the sample size, we think if 2,000  
22 eyes are followed for 5 years it will give us  
23 enough information. Or, you can tell us the rate  
24 that you want us to figure out--

25 DR. WEISS: So, Dr. Bressler and Dr.

1 Maguire who were agreeing, would you prefer to go  
2 with a percentage or would you prefer to define a  
3 sample size?

4 DR. BRESSLER: I like 0.05 and following  
5 out to five years. My guess is that it will end up  
6 being about 2,000 people followed in this  
7 post-marketing survey.

8 DR. WEISS: Dr. Stark, were you in  
9 agreement with that way of going about it?

10 DR. STARK: Yes.

11 DR. WEISS: Dr. Brucker?

12 DR. BRUCKER: Just to clarify, are you  
13 saying that you think that it is worthwhile in a  
14 post-marketing surveillance to follow these  
15 patients at a more stringent level? You are saying  
16 0.5?

17 DR. BRESSLER: No, 0.05. I am just  
18 looking for retinal detachment, and 0.05 is five  
19 times what their expected retinal detachment rate  
20 is if they had not had the surgery. So, we can  
21 tell them you are not taking a risk any greater  
22 than five times the risk. Is that what a  
23 reasonable person might want to know in doing this?

24 DR. WEISS: Dr. Ho, yours will be the last  
25 comment on this particular thing because we are

1 running late.

2 DR. HO: I think the public needs to know.  
3 I think we will have incomplete information on  
4 informed consent which, in my opinion, is really  
5 why we are here and it is still a "buyer be aware"  
6 situation. But I think the public looks at the  
7 absolute rates more than they do the relative  
8 rates. Is my chance of infection 1/100? Okay, I  
9 will make my judgment. Five times 1/10,000 is less  
10 meaningful obviously. So, I would be comfortable  
11 for a large number of patients over five years and  
12 I would be comfortable with, let's say, 2,000  
13 patients over five years.

14 DR. WEISS: I think we are all saying the  
15 same thing so we can move on. We are talking about  
16 0.05 percent or the rate or approximately 2,000  
17 patients and they may be coinciding. You are not  
18 fine with that?

19 DR. EYDELMAN: No, I am fine with that. I  
20 have just been told that 2,000 will not do it.

21 DR. WEISS: How many will do it?

22 DR. EYDELMAN: We don't have the numbers  
23 but from what I hear they will be much higher.

24 DR. WEISS: Dr. Stark?

25 DR. STARK: I was just going to ask is

1 that too onerous for the companies? They will say,  
2 well, fine, we will just to continue to use it  
3 off-label. You need to get a little input from the  
4 companies about what they would think they could  
5 possibly do; 2,000 people followed for five years  
6 is a lot of patients.

7 MR. MCCARLEY: And it is times two because  
8 you divided that into two groups.

9 DR. WEISS: So, we would have to have  
10 4,000 patients--

11 MR. MCCARLEY: More than 4,000.

12 DR. WEISS: Basically, by creating a 0.05  
13 percent that is still too onerous. That is what  
14 you are saying.

15 DR. EYDELMAN: Well, it is definitely your  
16 recommendation whether it is too onerous or not.  
17 But we are saying it is going to be a very large  
18 sample size.

19 DR. BRESSLER: Although the market may be  
20 tens of millions of people.

21 DR. WEISS: Dr. Ho, and this will be the  
22 second last comment for Dr. Ho.

23 DR. HO: I would strongly echo Neil's  
24 sentiments there, the market could be much more  
25 significant and we need to do that. I will give

1 you an example, we had a new treatment for patients  
2 with macular degeneration. We followed over 4,000  
3 patients for a shorter time period but, again, you  
4 need that N to get the numbers.

5 DR. WEISS: So, there is consensus. I  
6 will leave it at that. Question 5, acceptable  
7 adverse event rates for posterior chamber IOLs at  
8 one year following cataract extraction are listed  
9 in the FDA grid. A), are these rates applicable  
10 for correction of presbyopia in non-cataractous  
11 eyes via clear lens extraction at one year postop?  
12 So, do you want to use the same rates in clear lens  
13 extraction as are listed on the FDA grid? Dr.  
14 Stark is nodding yes. Dr. Maguire is nodding no.

15 DR. STARK: I wasn't nodding.

16 DR. WEISS: You weren't nodding?

17 DR. STARK: You were trying to speed this  
18 along!

19 DR. WEISS: Dr. Maguire?

20 DR. MAGUIRE: I am not saying what number  
21 it should be but if you are looking in terms of  
22 public health effects, people that have serious  
23 persistent problems starting at a younger age has a  
24 much bigger impact, especially in a working  
25 population. So, I think we should be more

1 stringent.

2 DR. STARK: I agree, and the  
3 cumulative--cumulative, not transient--cumulative  
4 macular edema of three percent is too high to be  
5 acceptable for clear lens extraction.

6 DR. WEISS: I would also agree. You  
7 always have to weigh risk/benefit and even though  
8 people find such difficulties with presbyopia, I  
9 still think the benefit is less than if you had a  
10 visually significant cataract so we have to look at  
11 the risk a little differently. Is there a  
12 consensus that the grid should not be the same as  
13 what is applicable for cataractous eyes? If there  
14 is consensus, do you need anything else from us on  
15 A)? Please don't tell us you need percentages in  
16 each category. He who hesitates is lost, Malvina,  
17 so we can move on to number B).

18 DR. EYDELMAN: Well, number B) asks for  
19 percentages.

20 DR. WEISS: Oh, I see. Should acceptable  
21 adverse event rates be adjusted for study duration?  
22 If yes, how? These were for one year, correct?

23 DR. EYDELMAN: Correct.

24 DR. WEISS: Now we have three years in  
25 non-cataractous eyes. Does anyone think the

1 study--well, obviously we all do. So, now you need  
2 to tell us numbers?

3 DR. EYDELMAN: Hopefully. I mean, you can  
4 pick one or two categories.

5 DR. WEISS: Dr. Ho and then Dr. Grimmitt.

6 DR. HO: Keeping in mind what we are  
7 trying to do here, risk/benefit presbyopia versus  
8 loss of vision from a cataract, I would almost look  
9 at these numbers and say, you know, ratchet me down  
10 one log unit down the board and I would almost find  
11 that acceptable I think.

12 DR. GRIMMETT: I agree with Dr. Stark that  
13 the cumulative macular edema at three percent seems  
14 high. I think that is too high to be acceptable in  
15 clear lens extraction.

16 As I mentioned earlier, the cumulative  
17 hyphema rate--I was astounded to see that it is  
18 listed at 2.2 percent, quite frankly, because just  
19 thinking about my practice I just don't see  
20 hyphemas after cataract surgery certainly with  
21 modern phaco. That is why I was wondering if that  
22 was driven by old extra-cap or some other type of  
23 surgery. Does anybody else here see hyphemas after  
24 cataract surgery? So, I think for that rate to be  
25 an acceptable rate and just let it ride, I think

1 that should be exceedingly low, hyphema after clear  
2 lens extraction. I can't remember one in ten  
3 years.

4 DR. STARK: And it will be because  
5 probably many of these were limbic incisions,  
6 scleral incisions and that is why there was a  
7 little circulating hyphema. But now, with clear  
8 corneal incisions it would be less than one  
9 percent.

10 DR. WEISS: Dr. Eydelman, you were saying  
11 this was from the '80s to the early '90s, this  
12 grid?

13 MR. CALOGERO: '87 to '96.

14 DR. WEISS: We do have something more  
15 recent than this or no?

16 DR. EYDELMAN: We have a draft of  
17 something that is more recent but it hasn't been  
18 vetted.

19 DR. WEISS: Do you need more from us on  
20 this? Dr. Rosenthal?

21 DR. ROSENTHAL: This, to me, is one of the  
22 bigger issues. You are subjecting patients to  
23 surgery with a cataract. These are the rates which  
24 have become acceptable to get a new lens on the  
25 market. Now, are you going to ratchet them all