

1 so much statistical significance when I'm dealing with  
2 three versus 17, and then when I split it up such as  
3 you're doing, which I think is perfectly appropriate  
4 and correct, it's even less compelling.

5 And I think the sponsor or somebody should  
6 try to fill us in on that.

7 DR. GORDON: Judy Gordon.

8 I think the sponsor mentioned that there  
9 seems to be and I similarly was left with the  
10 impression of small numbers relative to the shift  
11 scores, and I think the shift scores serve at least in  
12 part to address some of the issues you're describing  
13 in terms of surgical factors.

14 But they didn't have a chance to present  
15 it. I don't know if everyone is interested in seeing  
16 it, but it was suggested that there was a larger  
17 effect than maybe we're left with the impression that  
18 there is. So if others are interested, maybe this is  
19 a good time for the sponsor to show this.

20 DR. SHIRK: But my question is if we're  
21 looking at shift scores or basically looking at a very  
22 small population, and is that population we're looking

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1 at specifically empowered to do or meet the question  
2 that we're asking.

3 CHAIRMAN RAMSEY: Any comments? Do you  
4 want to have some response?

5 Steve.

6 DR. PIANTADOSI: Well, let me try to  
7 provide a sensible answer. I think it's a fair  
8 question. There's a lot of factors flying around  
9 here, and you asked the question how can we cope with  
10 those and account for and sort out those factors in  
11 dissecting out the treatment effect, and the answer is  
12 a word. It's very simple. And the answer is  
13 randomization.

14 That's why we do randomized studies, so  
15 that we don't have to make an explicit model based,  
16 quantitative accounting of all the factors that we  
17 think are affecting the outcome.

18 It's a fair point that maybe not all the  
19 patients stand to benefit from a given intervention.  
20 That's true of every clinical trial that's ever been  
21 done. It's particularly true in my home base, which  
22 are cancer studies, where it seems quite evident that

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1 when you apply a treatment it's not necessarily the  
2 case that everybody benefits a little bit or a known  
3 amount. Some people seem to benefit a lot; others  
4 don't, but that kind of finding, since we can't tell  
5 ahead of time who is going to benefit and who isn't  
6 going to benefit, that's why we use the rigorous  
7 methods for reduction of bias, estimation of the  
8 treatment effect, and that's why we use a larger  
9 study, so that we get enough of the kind of patients  
10 who are going to experience a benefit to detect.

11 There is nothing about the fact that a  
12 relatively small fraction of patients appeared to  
13 benefit, that invalidates the methodology of the trial  
14 or the result that you're seeing. This is part and  
15 parcel for why we do randomized trials.

16 DR. D'AGOSTINO: Well, you say, well,  
17 maybe there's some subjectivity in rating the lesions  
18 or adhesions.

19 DR. PIANTADOSI: There is.

20 DR. D'AGOSTINO: You know, then if you  
21 have three versus 17, if maybe the 17 wasn't really  
22 17, but it was 14, and then maybe the baseline is nine

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1 versus 17; well, maybe if it was nine versus nine, you  
2 know, there's be something different.

3 So the --

4 DR. PIANTADOSI: Yes, if the data were  
5 different, the result would be different, but they're  
6 not. And, yes, there's subjectivity. That's why we  
7 have a control group.

8 And we can change the data and say  
9 hypothetically we would come to a different conclusion  
10 if the data were different, but we have a large,  
11 rigorously done trial. There's masking to remove the  
12 influence of the subjectivity. There's randomization,  
13 and the outcome is the outcome.

14 DR. RUBIN: I'd like to amplify that if I  
15 may. I'd like to amplify that.

16 Steve's point on the importance of the  
17 randomization really is critical here, and I'm sure  
18 many of you realize this, but if you have a randomized  
19 trial and you have some noisy data, there's a noisy  
20 baseline assessment perhaps and noisy second look  
21 assessment, that noise can only contribute to smaller  
22 estimated effects of treatment versus control, can

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1 contribute only to less significant effects of  
2 treatment versus control.

3 It can't create a significant difference.  
4 The assessments were blinded. No one knew whether  
5 people were taking INTERGEL or Ringer's solution. If  
6 you had found nonsignificance, you could say, "Well,  
7 that's because there was a lot of noise in the data.  
8 There was a lot of uncertainty in how you record this  
9 subjectivity and how you record this."

10 But once you find significance, once you  
11 find real effects that are consistent, that noise  
12 can't explain them away.

13 I've been a situation where we have an  
14 endpoint. It doesn't turn out to be good. We say,  
15 "Gee, look at the data." And you say, you know,  
16 "Maybe compliance is what's going on," and you get the  
17 data and you analyze it for compliance, and, boy,  
18 compliance was it.

19 And you analyze and no matter how you  
20 analyze it from that point on, compliance is it.

21 You run another study and compliance shows  
22 nothing, but severity does, and no matter how you

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1 analyze it, severity does.

2 And so we have this sort of shifting of  
3 endpoints and what have you with some of these  
4 numbers. So it's not as -- you know, in a nice world  
5 what you're saying would be very comforting, but I  
6 think that there's one study here. It's not going to  
7 be replicated. It can't be, \$25 million or something  
8 like that, and so there's a lot of -- and the numbers  
9 are small, and so I think, you know, pushing to think  
10 these things out and just to say randomization handles  
11 it, it's a little discomfoting for me.

12 DR. RUBIN: I agree with that, but I think  
13 that the characterization that there was a shifting of  
14 endpoints, looking around for the correct endpoints  
15 really isn't an accurate characterization.

16 DR. D'AGOSTINO: This is what I was trying  
17 to get at.

18 DR. RUBIN: Yes.

19 DR. D'AGOSTINO: When was it unclearly?

20 DR. RUBIN: I understand that. I think  
21 Karen may be more appropriate than I in describing the  
22 pathway that took place, but in my understanding, all

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1 of these endpoints were either specified in the  
2 initial protocol as approved by FDA or requested by  
3 FDA, and there weren't lots of them. There were just  
4 ones to clarify the conclusions. They weren't  
5 shifting around looking for significance. I think  
6 there always was significance, and there was just  
7 repeated significance with these different outcomes.

8 DR. BECKER: I'd just like to add that the  
9 original primary endpoint for the pivotal trial, which  
10 is the mean of the adhesion scores evaluated at the 24  
11 anatomical sites was also statistically significant.

12 CHAIRMAN RAMSEY: Let me get the FDA. Do  
13 you guys want to chime in on this discussion?

14 DR. WITTEN: Well, I just want to clarify  
15 about the deficiency letter or deficiency letters in  
16 general, which is sometimes when we're looking at a  
17 trial and in discussion with the sponsor, they  
18 indicate some other information that might shed some  
19 light on the benefit of their product. We will ask  
20 for that analysis in a deficiency letter.

21 And then, of course, we would want to look  
22 at the results as we did here.

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1 CHAIRMAN RAMSEY: Okay. Go ahead.

2 DR. KIM THORNTON: One of the questions we  
3 were asked to look at regarding the statistical  
4 significance, there seems to be a difference in terms  
5 of the intention to treat analysis in terms of how the  
6 decision is made as to use the worst case scenario in  
7 both the INTERGEL and control groups versus a more  
8 conservative estimate, and how do you rectify that  
9 because obviously you're coming up with a completely  
10 different conclusion.

11 CHAIRMAN RAMSEY: Go ahead if you'd like  
12 to respond first.

13 DR. WITTEN: The question that you're  
14 being asked, the first of those questions -- I mean,  
15 I'm sorry I don't have the right wording -- is whether  
16 or not the statistically significant results that were  
17 provided show clinical significance or something like  
18 that.

19 And so I think one question is if you --  
20 and that question is if you take the analysis that's  
21 under discussion provided by the sponsor, and you  
22 accept that analysis taking into account how it was

1 performed and what the study was and how it was  
2 designed.

3 Is there clinical significance of those  
4 results?

5 DR. PIANTADOSI: Could I provide a  
6 supplemental answer to Dr. Thornton's question?

7 The reason way in which that decision is  
8 made or how you evaluate evidence is to essentially do  
9 a sensitivity analysis. You try several different  
10 things, and you ask yourself are the results under  
11 different sets of assumptions and different procedures  
12 consistent with one another.

13 If I do the evaluable cohort analysis, if  
14 I do an all patients analysis with the worst possible  
15 score imputed, do they look the same?

16 If I use other methods for imputation, if  
17 I make other assumptions about how to replace those  
18 missing data points, what consistency do I see across  
19 all of those analyses?

20 And actually what we've seen is a  
21 considerable degree of consistency. The one analysis  
22 that appears inconsistent with the other set is the

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1 one that makes the most possible conservative  
2 assumption, and that is the one that seems to generate  
3 the heat or the nonsignificant findings in the  
4 questions.

5 But the general answer to the question is  
6 let me try several different things and see if the  
7 finding holds up under any possible set of  
8 assumptions.

9 CHAIRMAN RAMSEY: Go ahead.

10 Actually since the FDA -- since that was  
11 a main issue, go ahead and address that, and then  
12 we'll hear your question.

13 MR. KOTZ: Yes. There are, you know, a  
14 lot of different ways to look at the data, and that's  
15 not the only way. The way the FDA looked at the data  
16 is not the only way to show nonstatistical  
17 significance. I'm just trying to show you that there  
18 are many ways. If you take the data and you look at  
19 all of the evaluable patients in the U.S., only  
20 evaluable patients, and if you weren't lost to follow-  
21 up, if you look at that data set, no statistical  
22 difference in the secondary endpoints.

1                   So, you know, there is a question of, you  
2 know, it just has to do with how you -- it does have  
3 to do with how you look at the data and what the  
4 statistical analysis is, and you know, they think one  
5 way and we think the other.

6                   So I don't know if we're ever going to,  
7 you know, totally resolve that issue.

8                   CHAIRMAN RAMSEY: Let me have you ask your  
9 question now.

10                  DR. SHIRK: Well, I guess I'm going to  
11 come back to the original question that I asked, and  
12 that's basically the study design from the original  
13 PMA and ask each of the groups to say obviously what  
14 was there, was that a statistically fair model to look  
15 at, given the situation, and if not, why not? Okay?

16                  DR. RUBIN: Maybe you could clarify that  
17 a little bit. When you say was that a fair model to  
18 look at, are you talking about the pilot study  
19 outcomes as a model for designing the --

20                  DR. SHIRK: Right. Using the pilot model  
21 and the spread that they wanted between the adhesion  
22 scores, and it seems to me like what we're arguing

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1 basically, the FDA is arguing that we set up this  
2 model, and obviously it didn't meet the model.

3 Now, you're saying, well, vote with the  
4 model. You know, we want to know whether it's  
5 statistically significant or not, and we're going to  
6 use whatever statistical analysis that we've got to  
7 get there.

8 And I think that, you know, my question  
9 basically is using the initial data that was presented  
10 and the way the study was set up and the way the  
11 statistical analysis was set up, was that a fair  
12 model. So --

13 DR. RUBIN: I think I understand.

14 DR. SHIRK: -- the noise is out of it.  
15 Okay?

16 DR. RUBIN: I think I understand the  
17 question and reorient me if I don't.

18 The pilot study in my opinion is  
19 completely irrelevant to understanding the results of  
20 this trial. We could have designed this trial,  
21 conducted this trial and analyzed this trial whether  
22 the pilot study was ever done or not. It is

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1 completely irrelevant.

2 The fact that we use pilot data and  
3 apparently the pilot data that were obtained were  
4 within the scope of variation of what was observed,  
5 but they were not a perfect match to what was  
6 subsequently observed in the trial. It's irrelevant.

7 The point is that the randomized study was  
8 rigorously done. There are no methodologic flaws in  
9 that study, and it demonstrates a particular result.

10 The fact that that result either  
11 incorporates heterogeneity within the study centers or  
12 is slightly quantitatively inconsistent with some  
13 earlier smaller pilot study in no way changes the  
14 inference from the randomized trial. It's completely  
15 and totally irrelevant.

16 This is a point that the FDA has missed.  
17 They're reasoning incorrectly about this. The fact  
18 that the power calculation was done, the variance  
19 estimate was taken from the pilot trial in no way  
20 changes the inference from the randomized trial.

21 DR. RUBIN: Just to reinforce that -- am  
22 I allowed to reinforce or may I just reinforce that?

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1 I've been doing statistics for many, many  
2 years, and I'm traditionally trained. My advisor was  
3 Wayne Cochran, and the statistics here are fine, and  
4 the results in the pivotal trial are not affected by  
5 the results in the pilot study.

6 CHAIRMAN RAMSEY: Let's give the FDA a  
7 chance to discuss the issue.

8 DR. HORBOWYJ: I think one of our main  
9 issues, and looking at the pilot study as well as the  
10 pivotal study, is looking at it clinically and looking  
11 at clinical significance in addition to statistical  
12 significance because we are approving this for  
13 patients, and it's really whether or not something is  
14 statistically significant -- our most important part  
15 is whether it's clinically significant.

16 And in that point I think it is relevant  
17 somewhat to look at the pilot study where a small  
18 number of patients were treated and a certain result  
19 came up, and then at the pivotal study as well where  
20 a large number of patients were treated and the number  
21 of patients who are perceived to have had a benefit  
22 are of an order of magnitude that almost approximates

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1 that of the pilot study.

2 CHAIRMAN RAMSEY: So in other words, I  
3 want to make sure the panel is clear on this. I think  
4 the issue is whether the study was designed to detect  
5 a certain level of difference between treatment and  
6 control and what was found was about half of what it  
7 was originally designed, but it was still found to be  
8 statistically significant if you include Europe and  
9 the U.S.

10 DR. HORBOWYJ: And the first question  
11 asked: is it clinically significant? Are the results  
12 of this study clinically significant?

13 CHAIRMAN RAMSEY: And that's really the  
14 first question we've been asked to focus on.

15 DR. HORBOWYJ: That's really the first  
16 question, right. So if you have a change, a mAFS  
17 score of one and a change of adhesion incidence of  
18 one, is that clinically significant?

19 CHAIRMAN RAMSEY: Okay. So Dr. Carlson  
20 would like to ask a question.

21 DR. CARLSON: So first I'm going to try to  
22 clarify something for myself, and anybody please chime

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1 in and correct me if I'm off base.

2 Whether it's relevant or not, a lot of the  
3 discussion has had to do with this pilot study and the  
4 basis for which the study was designed and the  
5 expected results based on that pilot study. The  
6 prediction was that there would be a certain numerical  
7 difference. In fact, there wasn't. There was a lower  
8 incidence of these adhesions even in the control group  
9 such that it was almost impossible to demonstrate that  
10 degree of a numerical difference.

11 So the question then comes down to is the  
12 percentage difference that we're seeing clinically  
13 relevant because the numerical difference is not  
14 nearly what was expected when the study was designed.

15 Is that a fair way of assessing this, FDA?  
16 And then I'll --

17 DR. HORBOWYJ: I think that when you --  
18 and this is my personal opinion as an FDA personnel --  
19 that when you look at percentages, you do have to look  
20 at the same time at the numbers because you can have  
21 a change from two to one and it's 50 percent, or you  
22 can have a change, you know of much greater magnitude,

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1 and it somewhat has a different significance.

2 DR. CARLSON: But you have to look at the  
3 opportunity for improvement as well, correct?

4 DR. HORBOWYJ: So I think you have to look  
5 at everything, and see really what is significant.

6 DR. CARLSON: Okay.

7 DR. HORBOWYJ: I don't think it's  
8 appropriate to just choose one.

9 CHAIRMAN RAMSEY: Okay. Do you want to  
10 have a quick response?

11 DR. PIANTADOSI: Yeah, just a quick  
12 response.

13 And I agree that whether or not a  
14 treatment effect of a given magnitude is clinically  
15 significant or not is the fundamental question.  
16 However, that information or the answer to that  
17 question is not contained in the hypothetical that was  
18 constructed prior to the start of the trial.

19 Nobody in this room has done more power  
20 calculations than I have. I do them by the hour,  
21 and --

22 (Laughter.)

1 DR. PIANTADOSI: Okay, Ralph. I take that  
2 back.

3 And all I can tell you is that these are  
4 hypothetical constructs whether they are based on real  
5 pilot data or whether they're based on the literature  
6 or whether they're based on the gestalt of the  
7 investigator.

8 And that's fine as a way to tell yourself  
9 how big the study should be. Once the data are in  
10 hand, the hypothetical that you engaged in to pick the  
11 sample size is meaningless.

12 DR. CARLSON: I understand.

13 CHAIRMAN RAMSEY: Go ahead, Hector.

14 DR. GONZALEZ: My question doesn't have  
15 much to do with the study and so on because there's a  
16 voluminous amount of information, but in reading the  
17 materials one of the things that I picked up, and I  
18 think probably the sponsor might be able to help me  
19 with that question because they're the ones that  
20 raised it in one of their letters, but in the letter  
21 of January 4th, you know, that Dr. Becker sent to Les  
22 Weinstein, on page 3 at the top of it there's a

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1 statement that says that CDRH approved compassionate  
2 use of INTERGEL in two patients and then on three  
3 others on an emergency basis.

4 What was the outcome of those patients  
5 clinically?

6 DR. BECKER: Gere, would that be a  
7 question for you? Doug?

8 DR. JOHNS: The five patients in question,  
9 if you will, four of those patients had small bowel  
10 obstruction and were having surgery to clear the  
11 adhesions associated with that bowel obstruction. The  
12 fifth patient was a chronic pain patient. All five  
13 patients had surgery. All five patients received  
14 INTERGEL. All fine patients are doing fine, no second  
15 surgeries required.

16 CHAIRMAN RAMSEY: Dr. D'Agostino.

17 DR. D'AGOSTINO: Just in terms of the  
18 pilot study to hopefully put it to bed, I mean, I  
19 agree 100 percent with what was said that you need  
20 something to generate numbers, but once you have the  
21 data, don't go back to that. It's a story that's not  
22 interesting anymore.

1                   And so I think if I'm following where  
2 we're heading, though the question starts off saying  
3 statistical significance, I think that I'm comfortable  
4 that there is statistical significance, and then  
5 question then for me becomes when I look at the data  
6 I'm basically looking at three versus 17.

7                   The sponsor tells us this is a fivefold  
8 difference when you do the appropriate adjustments,  
9 but I still see three versus 17, and is that  
10 clinically relevant?

11                   I'd love to give an answer to that.

12                   CHAIRMAN RAMSEY: Let's actually have some  
13 medical --

14                   DR. MASTROIANNI: But isn't that why we do  
15 statistical analysis? Because numbers are small, and  
16 it extrapolates the numbers to make clinical sense?

17                   I mean, any study then is flawed because  
18 how many patients is enough to show effectiveness?  
19 Yes, 100 percent is okay, but is 50 percent okay? And  
20 is that repeatable?

21                   So I think that we have to take the  
22 statistical analysis of the information, and if it is

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1 statistically significant, then it does make a  
2 difference, and it is clinically relevant.

3 DR. D'AGOSTINO: In a number of other  
4 fields we worry about that question, and we say that  
5 the study should run until we get enough events so  
6 that we don't end up with 20 events. We end up with  
7 500 events, and then we split it up and see treatment  
8 versus control and so forth.

9 DR. MASTROIANNI: I mean, sure.

10 DR. D'AGOSTINO: So, you know, it's a real  
11 question.

12 DR. DeCHERNEY: Well, that's not  
13 necessarily true through. I mean, there are many --

14 DR. D'AGOSTINO: No. I say this is the  
15 issue.

16 DR. DeCHERNEY: You can always do a  
17 limited number of patients in any given study.

18 DR. D'AGOSTINO: Exactly, and that's the  
19 issue. Do we think the three and 17 has supplied  
20 enough information because of all of the statistical  
21 safeguards, the design of the study or do we want  
22 something else?

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1 CHAIRMAN RAMSEY: Go ahead.

2 DR. SHIRK: But that was my question. I  
3 mean, basically we're looking at 20 percent of the  
4 study, you know. Forget those patients. I mean,  
5 obviously that becomes a much smaller group than the  
6 200 you were talking about before. Okay?

7 I mean, are we to make our decision on  
8 essentially 40 patients? I mean, that's --

9 DR. DeCHERNEY: Well, because that's why  
10 you take the events and you apply statistical analysis  
11 to it.

12 DR. SHIRK: What can you say on 40  
13 patients? Do you know what I mean?

14 CHAIRMAN RAMSEY: Go ahead. Please talk  
15 to the microphone.

16 DR. HORBOWYJ: When looking at three and  
17 17, I would just like to remind you also that there  
18 was a difference of eight patients at baseline. So I  
19 think that is something to be taken into account.  
20 There were eight more patients in the control group  
21 who started out in that group. So then the difference  
22 really is 6.5 or six patients. I'm sorry.

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1 CHAIRMAN RAMSEY: You know, it seems --

2 DR. BECKER: That's inaccurate.

3 CHAIRMAN RAMSEY: Okay.

4 DR. BECKER: Or we're misunderstanding Dr.  
5 Horbowyj's slide.

6 CHAIRMAN RAMSEY: Does the panel want to  
7 have clarification on that issue?

8 DR. SHIRK: Yes, I would like to see.

9 CHAIRMAN RAMSEY: Okay. Let's let  
10 LifeCore present, and then I'd like FDA to comment on  
11 whether they agree with the accuracy. So go ahead.

12 DR. BECKER: Okay. I think there is a  
13 misunderstanding about the shift tables, and they are  
14 difficult to grasp when you only get to see it for 15  
15 seconds. And patients benefitted both ways, in both  
16 directions.

17 So actually Doug Johns can put that slide  
18 up again and explain the shift tables again, and then  
19 we would like to comment on FDA's analysis of that  
20 data because some calculations were done that it looks  
21 as if the second look scores were adjusted at baseline  
22 twice.

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1 DR. FARO: Can I add something?

2 CHAIRMAN RAMSEY: Okay. Quickly, while  
3 we're putting things up.

4 DR. FARO: While we're setting up the  
5 overhead.

6 The comment about making an inference on  
7 a small number of patients in a study make me think of  
8 I was chair of the Data Monitoring Committee for the  
9 breast cancer prevention trial, which involved 13,000  
10 women, and the decision, the ultimate conclusion that  
11 Tamoxifen prevents breast cancer is based on only a  
12 few hundred women who have breast cancer.

13 So this notion that a small proportion --

14 DR. D'AGOSTINO: But if you got 13,000  
15 people in this study, you would have a lot of events.

16 DR. FARO: Oh, right, yes.

17 DR. D'AGOSTINO: You know, so it gets  
18 circular.

19 DR. FARO: Oh, no. It's just the idea.

20 DR. D'AGOSTINO: Here we only have 400  
21 people in the study.

22 CHAIRMAN RAMSEY: Okay. Well, let's go

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1 ahead and have you present. Well, go ahead.

2 DR. JOHNS: Okay. If you focus on, first  
3 of all, the number of patients, and we'll use the  
4 binary analysis because it's simpler. It puts it in  
5 two categories. So patients with minimal and mild  
6 adhesions at baseline.

7 Look first at row one in the INTERGEL  
8 group. There were 122 of these patients. One hundred  
9 and nineteen of that 122 remained in the minimal  
10 category. Three became moderate and severe.

11 In contrast, there's 117 patients in the  
12 minimal and mild category in the control population.  
13 Of those, ten became moderate and severe.

14 Now, if you look at the moderate and  
15 severe patients at baseline, yes, there's fewer  
16 patients there to begin with. There were nine in the  
17 INTERGEL group, all nine of which improved. There  
18 were 17 in the control group. Slightly more than half  
19 improved.

20 At the end of the day, if you define  
21 moderate and severe adhesions as a treatment failure,  
22 and we'll have to ask the clinicians if they agree

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1 with that, and I think you've heard that, you've got  
2 a 13 percent failure rate in your treatment -- excuse  
3 me -- in your control population, and you can  
4 influence that to the level of two percent by use of  
5 INTERGEL.

6 Now, over half of those treatment failures  
7 in the control population came from patients who did  
8 not have a problem with adhesions at baseline. So  
9 it's those 117 patients from which the failures came  
10 from that constitute the majority in the control  
11 population.

12 CHAIRMAN RAMSEY: What I'd like to do,  
13 and, panel, you can disagree with me on this and I  
14 will retract, but one problem we're having, I think,  
15 is the two parties are presenting two different tables  
16 with slightly different analysis of the same data set,  
17 and it would be useful to me, and you can tell me no,  
18 but to have FDA comment on this table relative to what  
19 they presented to us to tell us whether they agree or  
20 disagree with what was just said.

21 And if you'd like to also present your  
22 table, sort of this summary argument and contrast it

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1 to it, I think that also would be helpful to us.

2 DR. HORBOWYJ: My table goes with  
3 sponsor's table, which is Table 3.1, which was given  
4 to the panel in like review.

5 CHAIRMAN RAMSEY: Can you give us a moment  
6 to find that table?

7 DR. HORBOWYJ: Yes.

8 PARTICIPANT: Dr. Horbowyj, was it in your  
9 presentation packet?

10 DR. HORBOWYJ: In my presentation packet,  
11 which you now have, of the overheads with notes on  
12 page 32 is the information that I presented this  
13 morning.

14 MR. WEINSTEIN: The new overheads are  
15 overheads that were in the panel pack.

16 CHAIRMAN RAMSEY: The ones that we  
17 just --

18 DR. HORBOWYJ: They were the overheads  
19 that were handed out just now.

20 CHAIRMAN RAMSEY: You know, did we  
21 actually get -- I don't think we got the -- no, we  
22 didn't get the slides that you --

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1 DR. HORBOWYJ: Apparently some people did.

2 CHAIRMAN RAMSEY: Get that, yes. Okay.

3 I hear what -- okay. Go ahead.

4 DR. HORBOWYJ: In any case, as the sponsor  
5 just said, it's somewhat difficult for me to read from  
6 here, but there are nine patients out of 131 in the  
7 INTERGEL group who had moderate to severe adhesions at  
8 baseline and 17 in the control group out of 134, when  
9 then nine minus 17 is eight, and that is where my  
10 comment as to the difference of eight comes from.

11 DR. CARLSON: You're saying at baseline  
12 there's a difference of eight patients --

13 DR. HORBOWYJ: Right.

14 DR. CARLSON: -- in terms of who had this  
15 particular severity of adhesions.

16 DR. HORBOWYJ: Right. Eight more control  
17 patients had moderate to severe adhesions at baseline  
18 compared to cohort of INTERGEL.

19 DR. CARLSON: Is that a significant  
20 difference?

21 DR. HORBOWYJ: I don't know.

22 DR. RUBIN: Well, it certainly shouldn't

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1 be because that's randomized. It's just noise.  
2 You're looking at noise.

3 CHAIRMAN RAMSEY: No, I think the issue is  
4 though the --

5 DR. HORBOWYJ: I'm looking at the  
6 magnitude of the numbers.

7 DR. D'AGOSTINO: The magnitude. I don't  
8 think -- the statistical significance argument, I  
9 guess, is over, and now the question is: is there  
10 enough in the numbers to make us happy that there's  
11 something clinically going on?

12 DR. HORBOWYJ: Right. And so at the end,  
13 at second look in the evaluable population as the  
14 sponsor presents -- and I agree. I'm not trying to be  
15 at all critical. I'm just presenting the information  
16 as it was presented to us -- and as you have said,  
17 there were three INTERGEL patients and 17 control  
18 patients who had moderate to severe adhesions, a  
19 difference of 14, and the only thing that I'm saying  
20 is that at baseline, the difference was that eight  
21 more patients had moderate to severe adhesions in the  
22 control group, and at second look there were 14.

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1           But then you're comparing eight and 14,  
2           and if we're saying that the groups were comparable  
3           and eight was not important statistically, was it  
4           clinically significant?

5           And then if we're saying 14 now is  
6           statistically significant, well, clinically is it  
7           significant?

8           I'm just asking to look at the whole  
9           picture at the beginning and at the end.

10           And so then that difference, eight and 14,  
11           is six.

12           DR. DeCHERNEY: If there's an absolute  
13           difference in the numbers and it's statistically  
14           significant, which means you're magnifying the numbers  
15           in some mathematical way, that makes it clinically  
16           significant.

17           DR. CHIACCHIERINI: Yes. I'm Richard  
18           Chiacchierini. I am Senior Vice President for  
19           Statistics for C.L. McIntosh. I'm a consultant to  
20           LifeCore. I have no financial interest in the company  
21           other than my fee for service basis, and I have been  
22           assisting LifeCore since January of 2000.

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1 I also might add that I was the former  
2 Director of the Division of Biostatistics at CDRH and  
3 FDA for 12 years.

4 The way that the FDA has evaluated that  
5 data is totally incorrect, and the reason it's totally  
6 incorrect is because the net change from beginning the  
7 study to the end of the study is irrelevant because  
8 every patient had an opportunity to experience  
9 adhesions. So the fact that those nine didn't develop  
10 adhesions doesn't mean we should subtract them from  
11 the 17 who developed them.

12 And so that total difference, the fact  
13 that everyone independently had an opportunity to  
14 develop an adhesion, means that every patient who  
15 entered the trial had a risk, a potential risk of  
16 developing adhesions, and so making the difference of  
17 the before and after numbers is irrelevant.

18 DR. D'AGOSTINO: I get a lot of comfort in  
19 these discussions because it's nice to know that  
20 statistical significance is equivalent to clinical  
21 significance. That's what we oftentimes end these  
22 discussions with.

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1 DR. FARO: Only if they move together.

2 DR. D'AGOSTINO: We have statistical  
3 significance. What you just said makes perfect sense  
4 for the statistics argument. The numerical is what is  
5 bothering some people.

6 DR. CHIACCHIERINI: But I'd like to add --  
7 this is Dr. Chiacchierini again -- Dr. D'Agostino, in  
8 the June 2nd amendment, in response to the failed to  
9 follow up in the 16 patients, a number of sensitivity  
10 analyses were done which did exactly what you  
11 suggested in a sense that the first of which was a  
12 true intent to treat analysis, a rather conservative  
13 intent to treat analysis in which randomly the success  
14 rate for the control group was imputed to anybody who  
15 didn't have a second look, and it's conservative  
16 because the success rate for the treated group was  
17 higher.

18 When we did that, we did that 1,000 times  
19 to see what the frequency of times that we would  
20 observe a nonsignificant result, and the results are  
21 as follows.

22 The median p value for those 1,000

1 imputations was .006, and the upper 95 percent  
2 confidence interval was .0 -- .03. What that implies  
3 is nearly the entire population was below .05, and so  
4 no matter which way we slice the three and the 17 and  
5 change those numbers, we're still going to be  
6 statistically significant the vast proportion of the  
7 time.

8 DR. D'AGOSTINO: That was the question I  
9 was asking earlier today when I said what if it was  
10 14, three and 14. I was not under the impression that  
11 you did a sensitivity analysis that really addressed  
12 that. I was under the impression that you did a  
13 sensitivity analysis in terms of different imputation  
14 schemes.

15 DR. CHIACCHIERINI: You are correct, but  
16 the opportunity was for all of those 16 patients to  
17 have shifted those numbers, and those numbers in some  
18 instances did come closer together, but out of the  
19 1,000 imputations, the number of circumstances which  
20 resulted in imputations that resulted in non-  
21 statistical significance was a handful.

22 DR. D'AGOSTINO: I don't think there's a

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1 problem with the statistical significance.

2 CHAIRMAN RAMSEY: It seems to me, just to  
3 use an evidence based medicine term that I'm familiar  
4 with, is that what we're arguing with here is relative  
5 risk reduction versus absolute risk reduction as a  
6 result of the treatment, and I think we're clear on  
7 the relative risk reduction that's been presented, and  
8 I think we all understand.

9 Has anyone computed an absolute risk  
10 reduction? And then the corollary of that would be  
11 the number needed to treat.

12 The reason I'm asking that is that it  
13 might clarify for the panel what level of difference  
14 we're talking about here.

15 DR. CHIACCHIERINI: In the revised  
16 analysis in June 2000, there was an analysis that was  
17 done that used the Cochran-Mantel-Haenszel adjustment  
18 procedure that proceeded to compute an odds ratio or  
19 in this case a relative risk. The relative risk is a  
20 relative computation of risk of the ratio of the  
21 control group to the treated group. That relative  
22 risk was a fivefold reduction. The relative risk was

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1 .19.

2 And whether we adjust it for continent,  
3 whether we adjust it for adhesiolysis or whether we  
4 left it unadjusted, the relative risk from that  
5 analysis was a fivefold reduction from .19 to .18.

6 CHAIRMAN RAMSEY: Again, I think we  
7 understand that the relative risk is great, but the  
8 absolute risk, I think, is what we've been asking, the  
9 panel has been asking about, and I don't --

10 DR. BECKER: Would you like to hear from  
11 Dr. Gere diZerega, who --

12 CHAIRMAN RAMSEY: I'm sorry. We can't  
13 hear you.

14 DR. BECKER: I'm sorry. If you would like  
15 to hear from Dr. Gere diZerega, who designed the  
16 clinical trial, he is available.

17 DR. DeCHERNEY: In terms of absolute risk,  
18 those are absent changes that take place, and they're  
19 not in terms of relative risk.

20 CHAIRMAN RAMSEY: All right. Well, let me  
21 ask the panel. We focused on Question 1 which you  
22 could find here, which is whether the statistically

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1 significant differences between INTERGEL solution and  
2 control can be considered to be clinically  
3 significant.

4 If you don't have more questions on that  
5 issue, I want to move on to the second issue the  
6 second issue.

7 Is there someone you'd like to comment?  
8 No?

9 DR. BECKER: I'm sorry. I thought that  
10 there was still the opportunity to ask FDA to comment  
11 on clinical significance, and I thought that we  
12 were -- you were asking us to do the same.

13 CHAIRMAN RAMSEY: Let me ask the panel.  
14 Would you like to hear this individual? I'm sorry?

15 DR. KIM THORNTON: I don't have any  
16 reservation in hearing his comment.

17 CHAIRMAN RAMSEY: Okay. Why don't you go  
18 ahead.

19 DR. diZEREGA: My name is Gere diZerega.  
20 I'm a Professor of OB-GYN at the University of  
21 Southern California. I've been involved with this  
22 clinical trial since 1995.

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1           It was at my hospital. Prior to 1995 we  
2 performed the pilot clinical trial which generated so  
3 much discussion.

4           I've been a consultant to the sponsor  
5 since the initiation of the clinical study.

6           And what I would like to do is directly  
7 comment on what I think is a very important part of  
8 the clinical significance, and I think one of the  
9 reasons that the shift table is informative to me as  
10 a clinician in talking to other clinicians, nothing  
11 about statistics, and what I'd like to draw your  
12 attention to is the far right-hand side of this slide.

13           If you notice, from the standpoint of view  
14 of someone who does reproductive surgery, what I want  
15 to do is make patients better and reduce failures. As  
16 Dr. Mastroianni, who was one of the authors of the AFS  
17 system, reported to us earlier, patients who received  
18 moderate to severe scores are failures from the  
19 standpoint of view of the likelihood of reproducing.

20           This is a fairly routine result in this  
21 kind of patient population. If there were fewer  
22 myelomectomies, as Dr. Shirk has suggested, this

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1 number would even be higher.

2 So the 13 percent failures with this kind  
3 of a mixed population is what we would expect, and  
4 I've been involved with these types of clinical trials  
5 since 1980, with the first clinical trial for adhesion  
6 prevention. This is an expected result.

7 What is special and unique here to me as  
8 a health care provider is the two percent. This is  
9 the reduction that I focus on as someone taking care  
10 of women. I can reduce that failure rate, that 13  
11 percent, down to two percent with the use of this  
12 device, which certainly we found to be very safe in  
13 our clinical participation.

14 CHAIRMAN RAMSEY: Before we move on to the  
15 second question of safety, let me ask the FDA if they  
16 want to make any closing comments on this particular  
17 issue. No?

18 DR. HORBOWYJ: No.

19 CHAIRMAN RAMSEY: Okay. So let's move on  
20 to the second question, which is really safety. Do  
21 the benefits of the product outweigh the potential  
22 risks, including any risk of infection?

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1                   And I'll open it to the panel for  
2 questions.

3                   DR. CARLSON: I have a couple of questions  
4 regarding the infection risk, which has been discussed  
5 ad nauseam, so I will try to make them brief. We've  
6 heard there are a lot of ways to look at the  
7 infections or the possible infections or the probable  
8 infections, and the numbers we've heard from the  
9 experts from the company are that there were three in  
10 the control group and three in the treatment group.

11                   FDA tells us that there were possibly six  
12 in the treatment group and three in the control group.

13                   Are those two numbers fundamentally  
14 different? Are they statistically significant?

15                   And I'd be interested in both clinical and  
16 statistical feedback from any of our colleagues here.

17                   DR. SHIRK: I don't think they're  
18 statistically significant.

19                   DR. RUBIN: No, they're not.

20                   DR. SHIRK: Thank you.

21                   (Laughter.)

22                   DR. SHIRK: That took care of that. What

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1 was the second part of it? That's it?

2 DR. CARLSON: Well, if they're not  
3 statistically significantly different, they're not  
4 likely to be clinically significantly different.

5 DR. SHIRK: Absolutely.

6 CHAIRMAN RAMSEY: I guess I'd like to know  
7 what the p value is from both the FDA on their  
8 calculations and from LifeCore on the infection rate.

9 DR. SHIRK: On the six versus three?

10 CHAIRMAN RAMSEY: In the tables, I think  
11 you're referring to p equals not significant, but the  
12 actual number isn't given. I mean, is it .06? Is it  
13 .5?

14 DR. BECKER: I can find it.

15 DR. FARO: I think the important point to  
16 understand in this type of surgery, to begin with, is  
17 a very low risk operation with regard to infectious  
18 potential. Most pelvic infections that occur in  
19 female patients undergoing pelvic surgery occur in  
20 those women where the vagina is opened to the  
21 peritoneal cavity because the microbes involved are  
22 usually endogenous microbes from the patient. It's

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1 not from the environment.

2 So I think that's why we're seeing a low  
3 number of infections, to begin with, and this material  
4 doesn't seem to be conducive to enhancing growth of  
5 bacteria, as was demonstrated in the rat study, which  
6 I think is an excellent study to look at for infection  
7 potential.

8 DR. CHIACCHIERINI: Mr. Chairman, we have  
9 the p values.

10 CHAIRMAN RAMSEY: Okay.

11 DR. CHIACCHIERINI: For the crude analysis  
12 of the ten versus four, a chi square with each  
13 correction gave a p value of .19. Had we used a  
14 Fisher's exact test, the p value would even be higher  
15 because it's a less sensitive test.

16 For the FDA's numbers of six and three,  
17 the p there is .5 using the same test.

18 CHAIRMAN RAMSEY: Okay.

19 DR. CHIACCHIERINI: Point, five.

20 CHAIRMAN RAMSEY: Yeah. Other questions  
21 from the panel or discussion? Sure, go ahead.

22 DR. SHIRK: I had one question, and that

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1 has to do with the statement of use and what we're  
2 really voting. That's basically to LifeCore basically  
3 how -- you know, since it's a labeling issue -- what  
4 patients would qualify for use of this, you know,  
5 device. Are we talking about only those patients who  
6 either have severe or moderate adhesions at the time  
7 of surgical findings or undergoing of a procedure like  
8 myomectomy? Are you talking about general use for  
9 everybody who has gynecologic surgery for, you know,  
10 for essentially reproductive stuff?

11 I mean, obviously you could open end this  
12 thing and infer that basically if it works for  
13 moderate and severe adhesions, it works for mild  
14 adhesions. So let's give it to 100 percent of the  
15 patients. Okay?

16 So I guess my question would be basically  
17 from a marketing standpoint and from a labeling  
18 standpoint, what are the indications for use?

19 DR. DeCHERNEY: I can answer that.  
20 Certainly anyone whose potential reproduction, you  
21 know, from a gynecologic standpoint is an issue.  
22 Myomectomies, if they're done in patients that want

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1 further reproduction, and there's kind of a trend in  
2 America now to do myomectomies on 44 year olds, which  
3 perhaps is passing; those patients I don't think would  
4 be candidates, but certainly the 34 year old who has  
5 a myomectomy.

6 Tubal surgery patients; lysis of adhesion  
7 patients, and the only group that I would add are  
8 women that have ovarian surgery, ovarian cysts removed  
9 early on in their life, also to preserve reproduction,  
10 and if you look at the INTERCEED studies, it's one of  
11 the most effective areas, is the use of wrapping the  
12 ovary and preventing adhesions since those patients  
13 have up to 40 percent chance of forming periovarian  
14 adhesions.

15 So that's pretty much the group that I  
16 would reserve use of this agent for.

17 DR. SHIRK: But that almost encompasses  
18 everybody we operate on in the 35 to 20 year old  
19 range, who wants to preserve fertility.

20 DR. DeCHERNEY: Well, that's true, but the  
21 majority of the three million cases, certainly 60  
22 percent of them are hysterectomies, and if you went

1 further on and had cancer surgery, the majority of the  
2 three million cases are not patients that are  
3 requiring future fertility.

4 DR. SHIRK: The question was just so the  
5 panel understood what the indications for use were  
6 going to be. Do you know what I mean?

7 DR. GORDON: Maybe I could add to that.  
8 I mean, the indication for use statement is very clear  
9 or the proposed indication for use statement, and so  
10 I think what you're talking about is what is the real  
11 clinical usage going to be.

12 But I think in our assessment we need to  
13 limit that judgment to what the sponsor has proposed.  
14 I mean, obviously it may or may not lend itself to  
15 other applications, but there won't be an opportunity  
16 to market other applications. Other studies would  
17 have to be done to support that.

18 So I think we're getting a little bit off  
19 target there.

20 DR. SHIRK: I don't know if we're getting  
21 off target because labeling and use become a major  
22 issue in the question. Do you know what I mean? In

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1 any panel meeting for, you know -- that you look at a  
2 PMA, you obviously look at the labeling issue.

3 So I think it's something that, you know,  
4 as a panel we have to address. I mean, it's something  
5 -- I mean, are we totally overlooking those issues?  
6 And since we basically are serving two functions  
7 today, basically just dissolving a dispute obviously,  
8 but secondly, looking at a brand new essentially PMA.  
9 Okay?

10 I mean, so it's no different than bringing  
11 a new PMA. A PMA obviously, since the indications  
12 have changed, you've not gone through the same process  
13 that we would go through if the general surgery  
14 plastics people would go through it or the OB-GYN  
15 panel goes through it. I mean, a lot of those issues  
16 are basically issues that the panel goes through.

17 And I don't think that as a panel we need  
18 to totally circumvent those issues. Do you know what  
19 I mean? Because we obviously have two jobs here, I  
20 think, you know, one, just dissolving the dispute on  
21 safety and effectiveness, and two, then basically  
22 looking at the device in total as basically okaying an

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1 entire PMA.

2 CHAIRMAN RAMSEY: Okay. You're free to  
3 respond if you'd like.

4 DR. GORDON: No, no. I agree, and I guess  
5 then the issue is: is this indication for use  
6 statement appropriate or should it be modified?

7 CHAIRMAN RAMSEY: Does anybody have any  
8 comments on changing the indication for use statement  
9 or the appropriateness of it?

10 (No response.)

11 CHAIRMAN RAMSEY: Okay. Let me open it up  
12 to just general questions or comments among ourselves  
13 about any aspect of what we've heard today unless you  
14 have another question you'd like to focus or comment  
15 on, point two, the safety issue. Any general  
16 questions or comments for ourselves or for FDA or the  
17 sponsor group?

18 DR. D'AGOSTINO: Can I go back to one? As  
19 the statistician on the panel, I laid out quite  
20 nicely, I think, or quite clearly hopefully what I  
21 think about the statistics. I'd love to hear what the  
22 panel members think about the clinical significance.

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1                   We've asked a lot of questions. Are we  
2 moving quickly to that discussion?

3                   CHAIRMAN RAMSEY: Well, let me just say as  
4 a procedural note that we are going to -- I'm going to  
5 close this off momentarily and we're going to have an  
6 open hearing again, and then we will move on to the  
7 voting procedures.

8                   DR. SHIRK: Yeah, from a clinical  
9 standpoint, I think, you know, again, I've got some  
10 questions as to how great the clinical value is. I  
11 don't think that there's any question that there's  
12 probably some clinical value in this thing, and it's  
13 statistically significant.

14                   But as to is this magic stuff where you  
15 throw it in the belly and all the adhesions float  
16 away? I don't think that's true. Okay?

17                   DR. DeCHERNEY: But that's nobody's  
18 contention.

19                   DR. SHIRK: No, and so that the public --  
20 but you know, it's only going to be physicians who use  
21 it and tell patients, "I put this stuff in and now all  
22 the adhesions we took down shouldn't come back." I

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1 mean, I don't think that's going to happen.

2 Obviously like in the other adhesive  
3 device that we use, there's going to be some  
4 improvement, but it's certainly, you know, not a magic  
5 cure for adhesions, and so I think, I mean, from a  
6 clinician's standpoint that's the way I look at it.

7 Like, yeah, there's an advantage, but how  
8 great an advantage, I think, is still yet to be  
9 demonstrated, and that will come from other studies.

10 DR. GONZALEZ: If I could just follow up  
11 on that because in one of the reports I was reading,  
12 there was a question. I don't know if it was FDA that  
13 raised it. It must have been FDA. I found it very  
14 fascinating because it said, "Well, does the INTERGEL  
15 prevent adhesions or does it delay the formation of  
16 them?"

17 And I can't remember who raised that. I  
18 want to say it was an FDA report, and so that question  
19 is really almost tangential to your issue as to  
20 whether long term, you know, what does it do one way  
21 or the other.

22 DR. KIM THORNTON: Well, personally, I

1 think that if you have an agent that could have any  
2 clinical effect on reducing adhesions and you can show  
3 some sort of significance both statistically and  
4 clinically, then it may be of benefit to patients that  
5 are going to be using it.

6 I think that you need to make sure that  
7 from a labeling perspective, if -- I mean, you know,  
8 we can certainly set up guidelines where we can be  
9 restrictive, given to the population it's been studied  
10 in. Other studies will expand those indications if  
11 appropriate and if, you know, they demonstrate that  
12 it's clinically significant in other areas.

13 DR. DeCHERNEY: Actually Dr. diZerega's  
14 work and others have shown that the adhesions are  
15 practically formed within 48 to 72 hours. So if it  
16 deters adhesion formation immediately, it probably is  
17 a longstanding effect.

18 CHAIRMAN RAMSEY: Is there any more  
19 discussion among the panel about the two subquestions  
20 we have here or anything else before I move on to the  
21 public hearing?

22 It seems that the winds of time have

1 changed and now we're doing well.

2 (Laughter.)

3 CHAIRMAN RAMSEY: But I don't want to cut  
4 us off if there's more discussion to be had.

5 Shall I reread the question? Okay. Let  
6 me reread the main question again for the panel  
7 because this is, in essence, what we're voting for.

8 Does the PMA, as amended, provide  
9 reasonable assurance of the safety and effectiveness  
10 of INTERGEL for its intended use as an intraperitoneal  
11 instillate for reduction of adhesion formation  
12 following gynecologic pelvic surgery?

13 Let me close with that question the  
14 section of panel discussion and now move on to the  
15 second open public meeting, and at this session  
16 interested persons can have an opportunity to address  
17 issues specific to the matter before the committee.

18 As we've been doing all day today, I would  
19 ask people addressing the panel to come forward and  
20 speak clearly into the microphone and also to state  
21 whether they have any involvement, including, but not  
22 limited to, financial interest in any medical device

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1 company, including LifeCore or any of its competitors,  
2 and also please state the nature of your interest,  
3 such as, for example, whether the company has paid you  
4 for your time or travel to appear here today.

5 MR. WEINSTEIN: Now, one person did  
6 respect to speak in the afternoon. It's Ms.  
7 Weatherman. Is she here?

8 CHAIRMAN RAMSEY: Let me just have a show  
9 of hands for all those who would like to comment. One  
10 other person.

11 Okay. There was an individual who  
12 presented this morning who wanted to show a video, Dr.  
13 Thornton. He's not here? Oh, there he is. Okay.

14 How long is your video?

15 DR. MELVIN THORNTON: About three and a  
16 half minutes.

17 CHAIRMAN RAMSEY: Okay. Very good. Go  
18 ahead.

19 MS. WEATHERMAN: Good afternoon. My name  
20 is Bess Weatherman. I'm a partner at Warburg Pincus,  
21 which is a venture capital firm based in New York, and  
22 I'm also the Vice Chair of the National Venture

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1 Capital Association Medical Industry Group.

2 Neither Warburg Pincus nor myself  
3 personally nor any of our portfolio companies, to my  
4 knowledge, have any stock ownership in the sponsor or  
5 are receiving any remuneration whatsoever for speaking  
6 here today.

7 Warburg Pincus is the largest independent  
8 venture capital firm in the world with assets under  
9 management of ten billion, and I'm the partner  
10 responsible for investing a portion of those assets in  
11 medical device companies.

12 The National Venture Capital Association  
13 is the largest venture capital association in the  
14 world and represents approximately 450 of the largest  
15 venture capital firms in the U.S., the collected  
16 assets under management of over 300 billion, and  
17 annual venture investments of over 50 billion.

18 The NVCA, the National Venture Capital  
19 Association, members who actively invest in drugs,  
20 medical devices, and biotechnology have invested over  
21 six billion in these areas in the last year alone and  
22 over 40 billion over the last ten years.

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1 We are the largest single source of  
2 development capital in the United States for  
3 biotechnology and medical devices. At any given time,  
4 the venture capital industry is responsible for the  
5 management of over 400 medical device and  
6 biotechnology companies, and over the past 20 years  
7 have founded more than 3,000 such companies.

8 In turn, these companies were responsible  
9 for developing or introducing virtually all of the  
10 drugs derived from biotechnology, and most of the  
11 groundbreaking new medical devices introduced during  
12 the past 20 years to the benefit of millions of  
13 patients in the United States and around the world.

14 I have followed the INTERGEL dispute over  
15 the last year and appreciate the opportunity to offer  
16 my views.

17 First, the venture capital community's  
18 willingness to fund medical device and drug  
19 development ventures depends critically, if not  
20 primarily, on consistency and predictability in the  
21 regulatory process. Regulatory decisions that are  
22 unpredictable or surprising add substantial additional

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1 risk to our investments, which are already extremely  
2 risky.

3 An increase in this level of risk reduced  
4 the flow of investments into this area. A significant  
5 operating assumption of those of us who invest in  
6 medical technology has been that statistically  
7 significant results of blinded, multi-center,  
8 randomized, placebo controlled trials was the  
9 regulatory gold standard and supported the strongest  
10 assumption of approvability in the absence of  
11 extraordinarily persuasive evidence of lack of  
12 efficacy or clear safety problems.

13 In the past, the clear legislative and  
14 regulatory policy has always been to approve such  
15 technology and let the medical community decide, the  
16 physicians, whether or not its ultimate fate, whether  
17 to use the device, therefore insuring a strong flow of  
18 new venture technology to the U.S. public.

19 The position of the FDA in this dispute  
20 represents a marked departure from this policy. By  
21 rejecting the successful results of a level one  
22 clinical trial without the clear, contrary, scientific

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1 evidence historically required to do so, the FDA is  
2 setting a very negative precedent.

3 In the past, similar adverse changes in  
4 regulatory practice have caused substantial reductions  
5 in investment in new mechanical technology and,  
6 therefore, their proliferation for the patients who  
7 need them.

8 Another important issue today is the  
9 effectiveness, fairness, and independence of this  
10 dispute resolution process. The establishment of the  
11 medical device dispute resolution panel was a long  
12 sought goal of the medical venture capital community,  
13 which was fully achieved in the FDA Reform Act passed  
14 in 1997.

15 While it is obvious that such a forum must  
16 exist in the interest of basic fairness and due  
17 process, how it is actually implemented and whether  
18 its judgments are perceived as reasonable and  
19 independent will be the acid test of whether it  
20 fulfills its charter.

21 These panels must be more than mere  
22 advisory panels whose role is largely controlled by

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1 the FDA. They must fulfill their clear legislative  
2 mandate and independently decide whether the probable  
3 benefit to health outweighs the probable risk for a  
4 subject device or drug.

5 Therefore, the independence of your  
6 decision here today and the procedures you follow will  
7 be widely examined and may significantly affect the  
8 continued development of many new medical devices.

9 Thank you.

10 CHAIRMAN RAMSEY: Thanks for your comment.

11 Can we have the next presenter, please?

12 DR. MARTENS: Hello. My name is Mark  
13 Martens. I'm Chairman of OB-GYN at Franklin Square  
14 Hospital Center and Director of Women and Children's  
15 Services for MedStar in Baltimore.

16 I wasn't planning on speaking today. So  
17 I hope I don't --

18 CHAIRMAN RAMSEY: Please state  
19 affiliations.

20 DR. MARTENS: Oh, yeah. I feel  
21 embarrassed after the last presentation. I bought 100  
22 shares of stock three or four years ago before I even

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1 heard about INTERGEL.

2 I drove myself down here. I paid my hotel  
3 bill a little while ago. I didn't receive any money  
4 for the consultant meeting they had before, and in the  
5 last FDA presentation, as promised I donated my fee to  
6 an education company in Minnesota.

7 So I'm here as a patient advocate, and I  
8 hope the comments of the first physicians who were up  
9 here, whom I've never met before, aren't forgotten.

10 As Chairman, and some of my colleagues on  
11 the panel know, as Chairman, especially as previous  
12 Director of Gynecology, they think that we're magical  
13 surgeons. So I get the most difficult cases. They  
14 come to me. They're always adhesion cases. They're  
15 always chronic pelvic pain, and no one wants to do  
16 anything because the patients -- you know when you  
17 operate on them and do adhesiolysis that the adhesions  
18 are going to come up unless you have something.

19 I've also done 125 studies. I believe I  
20 was told I was the largest enroller on the last  
21 product that was approved by the FDA, and I didn't  
22 come here for that product. I'm here today because if

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1 you're going to use this pilot study, I've enrolled  
2 more patients in double blind, randomized trials for  
3 adhesiolysis than in that pilot study, and I saw a  
4 clinical difference with this product.

5 I currently -- the reason I'm here is as  
6 a patient advocate. What I currently do is I tell my  
7 patients that the best way to have this problem  
8 treated, severe adhesions and prevention of adhesions,  
9 is to go to Canada. I do that right now.

10 And if they can't afford to go to Canada,  
11 I get compassionate use, and I've done that. I feel  
12 that strongly about this.

13 Unfortunately, compassionate use may not  
14 be available much longer as mentioned with the  
15 previous conversation, and I'm now setting up a  
16 hierarchy, and I'm doing it, not you all, but I'm  
17 setting up a hierarchy where rich patients get care  
18 and poor patients don't.

19 I'm sorry to get a little sappy, but you  
20 know, I graduated from George Washington University 20  
21 years ago, and we sat through the Hippocratic oath and  
22 I didn't take it seriously. I'm taking it seriously

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1 now.

2 Patients who have it don't have a life.  
3 They have pain. They have hysterectomies when they're  
4 20 years old, and we need to do something about it.  
5 So I take this very seriously.

6 Now, clinical data, let me get focused  
7 again. I don't want to do harm to patients. So I  
8 will not operate on a patient if I'm going to tell  
9 them, "Adhesions may come back. You may have problems  
10 again," and so that's a problem, but I do sometimes.

11 The clinical data here I think is very  
12 strong. I thought it was all solved, that I wasn't  
13 going to get up and talk because I thought clinical  
14 significance is as plain as English. It seems like  
15 statistics is multi-lingual, and we didn't get very  
16 clear today.

17 But I'm trained to clinically evaluate  
18 patients and publications. I've written over 100  
19 publications. I'm on the editorial board.

20 This paper, these data have been published  
21 twice in peer reviewed journals. So I think the data  
22 are strong.

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1           As a clinical investigator, again, I've  
2           seen these trials over and over again. Dr. Shirk,  
3           these are very difficult studies to do. I hate doing  
4           these studies because I'm telling patients that I'm  
5           going to do a second surgery on them. The only way I  
6           can get it through my mind is to say that there's good  
7           data saying that if you want a baby and you have  
8           adhesions, lysing of adhesions at a second look  
9           improves your outcome, and that barely gets me by my  
10          ethics to say, "Do these studies."

11                    You can't do these studies any better than  
12           this study was done, and my patients who felt better,  
13           I didn't do a second look on if they didn't want to  
14           because their pain was gone, and I didn't want to  
15           subject them to that pain.

16                    These patients are given a score in the  
17           ITT that says they did horribly, and it's costing them  
18           and it's cost against the product. The whole idea  
19           that we're trying to get these patients pregnant, the  
20           only reason I do these studies is because they way  
21           they want to get pregnant. Having their pregnancy in  
22           the trial would cost against the product. So this ITT

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1 analysis really disturbed me.

2 And, again, six out of the seven patients  
3 didn't have a second look were in the treatment group.  
4 So I mean, I think that proves something to me.

5 So ethics, the ethics and the clinical  
6 values, its clinical efficacy, hopefully with  
7 statistical efficacy, the clinical efficacy is what  
8 doctors do to patients, and what I do because I've  
9 seen this product; I've used this product; because  
10 I've seen patients like this, but unfortunately I'm  
11 forced to set up pelvic pain centers. A pelvic pain  
12 center is about as profitable, as happy for the  
13 medical staff as PMS centers. I mean, they're  
14 difficult patients. We don't have cures for them.

15 But if you take the worst case scenario  
16 where someone said a change in the baseline score from  
17 2.-something down to something and it was .19 or two;  
18 if you take ten percent out of 400,000 patients that  
19 are being operated on every year, two million that  
20 have these type of surgeries, I'll take that ten  
21 percent any time.

22 So I think there's a lot of clinical

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1 significance to that, and I know you, too, in your  
2 practices see patients like this.

3 So basically the concerns about infection,  
4 I think, have been addressed. I would be vigilant  
5 about infections. I think labeling should address the  
6 possibility of infections, but the numbers weren't  
7 significant. I hope significance is important.

8 So thank you for allowing me to speak at  
9 this meeting today.

10 CHAIRMAN RAMSEY: Thank you. Thank you.

11 Well, I understand there's one -- yes?  
12 Okay, great. So you are going to present a video,  
13 yes?

14 DR. MELVIN THORNTON: Yes. First off,  
15 thank you for the second opportunity. My video wasn't  
16 working earlier.

17 But what I wanted to do is there's a lot  
18 of talk about statistical significance. We talk about  
19 is it clinically significant, and what I'd like to do  
20 is to show you what moderate-severe adhesions are in  
21 patients who are just presenting for complaint of  
22 infertility, and their only history is significant for

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1 prior surgery.

2 So may I have the first slide?

3 What you're going to see here, this is a  
4 young woman who presented to our hospital. Her chief  
5 complaint was infertility. She had a history of  
6 ovarian surgery. She had a cyst removed, and what you  
7 can see here is a lot of adhesions between the bowel  
8 and the anterior abdominal wall, and this pointer is  
9 not working, but that is her right ovary where she had  
10 her surgery from.

11 That is moderate to severe adhesions. If  
12 you can give me a reduction, if you can give me,  
13 although out of my patients only two percent of those  
14 will have that, I'll take that any day. Okay?

15 But 13 percent of the patients it has been  
16 shown will have these moderate-severe adhesions. If  
17 you can reduce it down to two percent, like I say,  
18 I'll take it any day.

19 Next slide.

20 And this is another common surgery that  
21 women undergo. This is a myomectomy, and what you're  
22 seeing here with the myomectomy, once again, you're

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1 going to see bowel attached to anterior abdominal  
2 wall, and right here, inside of the adhesion, severe  
3 adhesions here, is her right ovary and her right  
4 fallopian tube.

5 Once again, her chief complaint was  
6 infertility. Her only history was a previous  
7 myomectomy. This is what we're talking about when we  
8 talk about clinically significant or when we take  
9 patients from the moderate to severe category down to  
10 the mild to minimum. To me that is very clinically  
11 significant, and it's what our goal of being a  
12 physician is, is to take care of our patients.

13 Thank you.

14 CHAIRMAN RAMSEY: Thank you.

15 Again, we are well ahead of time, and what  
16 I think I'm going to do is have us take a ten minute  
17 break. I would like the panel to collect their  
18 thoughts. We won't be talking among ourselves, but  
19 just for a moment to collect their thoughts before we  
20 come back and vote.

21 Okay. So, please, ten minutes only. Come  
22 back at 2:30.

1 (Whereupon, the foregoing matter went off  
2 the record at 2:19 p.m. and went back on  
3 the record at 2:31 p.m.)

4 CHAIRMAN RAMSEY: Those of us who live on  
5 the left coast have long plane rides that we're hoping  
6 to catch.

7 During the break I was informed that a  
8 member of the public who did raise her hand and wished  
9 to speak, we just didn't see her. So --

10 MR. WEINSTEIN: I think it's Augusta  
11 Sisler.

12 CHAIRMAN RAMSEY: Yes. So I'd like to  
13 give her a moment before we move on to the  
14 deliberation and vote.

15 And please state your name and your  
16 interest.

17 MS. SISLER: Hi. My name is Augusta  
18 Sisler. I'm a volunteer with the International  
19 (inaudible) Society.

20 I'm also a patient who has had five  
21 surgeries for adhesions, and I haven't worked in a  
22 couple of years due to it. And I'm here to promote

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1 awareness of this issue or issues.

2 So if you have any questions to ask me,  
3 how it feels, I can tell you for a fact.

4 The doctor that just got up recently, I  
5 could hardly -- as he was talking, I could hardly hold  
6 the tears back because I know what he feels, the way  
7 he feels for his patients.

8 This affects thousands of people. It's  
9 not only men -- I mean lots of women. When the  
10 adhesions hit your bowel or, you know, the small bowel  
11 and your reproductive system and you can't eat because  
12 of the adhesions are restricting and pulling, there's  
13 got to be something out there.

14 I'm not here to support, you know, any of  
15 the groups. I'm just here for patient awareness, and  
16 I'll tell you it's really scary when you can't work.  
17 You can't eat.

18 And I applaud all of you doctors out there  
19 that are helping us, and I hope that the government  
20 will also help. So let's get to work.

21 Thank you.

22 CHAIRMAN RAMSEY: One question. Thank you

1 for commenting.

2 (Applause.)

3 CHAIRMAN RAMSEY: I'm sorry to ask you  
4 this, but it's just for a point of record, whether you  
5 have any financial interest in the company or --

6 MS. SISLER: No.

7 CHAIRMAN RAMSEY: -- were paid to come  
8 here by any --

9 MS. SISLER: No, sir.

10 CHAIRMAN RAMSEY: Okay.

11 MS. SISLER: Nope, I have never been paid  
12 to do anything and am just here to promote a witness.

13 CHAIRMAN RAMSEY: Thank you for your  
14 comments. We appreciate them.

15 MS. SISLER: Thank you.

16 CHAIRMAN RAMSEY: Okay. I am now going to  
17 close the public hearing and move on to the panel  
18 deliberations and vote portion of the meeting.

19 I'm going to begin by asking any panel  
20 members have any comments or summary statements they  
21 would like to make before we move on to the next part.

22 (No response.)

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1 CHAIRMAN RAMSEY: No. Okay. In that case  
2 I'm going to turn it over to Les who's going to -- I'm  
3 sorry. Back up.

4 I want to give the sponsor and the FDA a  
5 chance to have a closing argument, and we'll begin  
6 with FDA.

7 DR. WITTEN: We don't have any additional  
8 comments.

9 CHAIRMAN RAMSEY: No additional comments.  
10 Okay.

11 Would the sponsor like to have any closing  
12 comments?

13 DR. BECKER: Yes, just briefly to say that  
14 we are gratified with the fair forum and the  
15 conclusions regarding the statistical significance of  
16 the study. We feel that the testimony you've heard is  
17 quite compelling that the product is safe and that the  
18 benefits outweigh the risks.

19 CHAIRMAN RAMSEY: Okay. Well, I'll turn  
20 it over to Les Weinstein who will give us the options  
21 for voting.

22 MR. WEINSTEIN: These are the panel voting

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1 options.

2 Medical device premarket approval  
3 application, PMA, must stand on its own merits, and  
4 the panel's recommendation must be supported by safety  
5 and effectiveness data in the application or by  
6 applicable publicly available information.

7 Safety is defined in the federal Food,  
8 Drug, and Cosmetic Act as reasonable assurance based  
9 on valid scientific evidence that the probable  
10 benefits to health on the conditions of intended use  
11 outweigh any probable risks.

12 Effectiveness is defined as reasonable  
13 assurance that in a significant portion of the  
14 population the use of the device for its intended uses  
15 and conditions of use when labeled will provide  
16 clinically significant results.

17 The panel's recommendation options for the  
18 vote are as follows:

19 One, approval. There are no conditions  
20 attached.

21 Two, approvable with conditions. The  
22 panel may recommend that the PMA be found approvable

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1 subject to specified conditions. Prior to voting each  
2 of the conditions should be discussed and voted on by  
3 the panel.

4 Three, not approvable. The panel may  
5 recommend that the PMA is not approvable if the data  
6 do not provide reasonable assurance that the device is  
7 safe or, if a reasonable assurance has not been given,  
8 that the device is effective under the conditions of  
9 use prescribed, recommended or suggested in the  
10 proposed labeling.

11 Following the voting, the Chair will ask  
12 each panel member to present a brief statement  
13 outlining the reasons for his or her vote.

14 This statement that I just ready, by the  
15 way, panel, is in the information that I gave to you  
16 last night. So you do have a copy of it for your  
17 reference.

18 CHAIRMAN RAMSEY: Okay. Now we will vote  
19 on a recommendation to FDA's Director of the Center of  
20 the Devices and Radiological Health as to how the  
21 scientific dispute regarding the approvability of this  
22 PMA should be resolved.

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1           The recommendation, as Mr. Weinstein said,  
2 was approval, approvable with conditions, or not  
3 approvable. Would one of the panel members like to  
4 make a motion?

5           Someone has to.

6           DR. D'AGOSTINO: I move for approval.

7           CHAIRMAN RAMSEY: Do we have a second to  
8 that motion?

9           DR. KIM THORNTON: I'll second that.

10          CHAIRMAN RAMSEY: In that case, I'm going  
11 to go and ask each voting member to make their  
12 individual vote --

13          MR. WEINSTEIN: Excuse me. You need to  
14 discuss the motion first, right?

15          CHAIRMAN RAMSEY: We need to discuss?

16          PARTICIPANTS: Yes.

17          CHAIRMAN RAMSEY: Okay. I'm sorry.  
18 Procedural mistake. We'll move on to discussion of  
19 the motion from the panel.

20          Do you have a comment?

21          DR. GONZALEZ: Well, I don't know if it's  
22 a comment or if it's a condition or how maybe the

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1 panel can help me with it, but in sifting through all  
2 the information there were two things that concerned  
3 me. And I'm speaking now as a consumer  
4 representative.

5 And one, you know, how to do with that  
6 question I raised earlier about the prevention versus  
7 the delay of adhesions. So somewhere that troubled me  
8 about whether we should have some condition, some  
9 caveat that could be worked out between the sponsor  
10 and the agency to ferret that information out as a  
11 possibility.

12 The other part is the infectious issue,  
13 and for that part, I had the question about the option  
14 of either tracking the possibility of infection in  
15 those cases or something of that type. As I say,  
16 those are just the two larger issues. I really don't  
17 know how to couch them in terms of a final  
18 recommendation, however. Maybe the panel can help me  
19 with that.

20 CHAIRMAN RAMSEY: Are you suggesting that  
21 we attach conditions to --

22 DR. GONZALEZ: That's basically what I'm

1 trying to do, I think.

2 CHAIRMAN RAMSEY: Okay.

3 DR. GORDON: Could I ask a question? Is  
4 the condition that you want definition or separation  
5 of the data sets? Because I think that if you look at  
6 the indication for use, it's quite clear in saying  
7 reduce the likelihood of developing moderate or  
8 severe, which was reflected in the shift data, and  
9 reduce adhesion reformation.

10 I'm wondering if you want additional  
11 clarity around that or I think it will be helpful to  
12 FDA and the sponsor if we can be more specific in  
13 what's needed because to put a condition on a  
14 recommendation, I think we need to give some specific  
15 -- I think we need better clarity around what you  
16 would like that condition to be.

17 CHAIRMAN RAMSEY: I have a procedural  
18 question here. Dr. Gonzalez is not a voting member.

19 DR. GONZALEZ: No.

20 CHAIRMAN RAMSEY: And I'll go around and  
21 ask whether someone would entertain a motion to  
22 approve with conditions. Do I need to ask a voting

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1 member whether they would?

2 DR. SHIRK: Nancy, do you want to weigh  
3 in?

4 CHAIRMAN RAMSEY: Right now there's a  
5 motion on the floor.

6 DR. GONZALEZ: You have a main motion, and  
7 I'm just raising the question. I was talking, you  
8 know, about those two issues.

9 DR. GORDON: And I'm asking for additional  
10 clarification before you go to add a condition,  
11 meaning what exactly is the condition.

12 CHAIRMAN RAMSEY: I think what we need to  
13 do is to vote, and then if it is not voted as  
14 approved, as the motion stands, then we will go back  
15 and see if there is a motion for approvable with  
16 conditions and then discuss that. Is that acceptable?

17 Because we have a motion that we have to  
18 resolve with a vote right now.

19 DR. CARLSON: On the other hand, the  
20 implication of his point might affect the vote. So  
21 personally I would like to hear if he has anything  
22 more to say about the conditions because it affects

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1 the current vote, not because --

2 CHAIRMAN RAMSEY: And that's fine, and if  
3 you have more comments you'd like to make along the  
4 line --

5 DR. GONZALEZ: The only other piece I  
6 would add, and I don't know how to phrase it except  
7 that I made the comment earlier. I said that maybe we  
8 could have something that one of the conditions would  
9 be that the panel recommends with the approval part  
10 that the agency and the sponsor may develop protocols  
11 to track the delay and the prevention of adhesions and  
12 the instances of infection.

13 CHAIRMAN RAMSEY: Okay. Let me move on  
14 and vote on the original motion, and if it is not  
15 approved as the motion is stated, then we'll go back  
16 to that.

17 So I'm just going to go around the room  
18 starting with Dr. Thornton to ask to vote on the  
19 motion for approvable. In favor or opposed?

20 DR. KIM THORNTON: In favor.

21 CHAIRMAN RAMSEY: Okay. Dr. Shirk?

22 DR. SHIRK: Yes.

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1 CHAIRMAN RAMSEY: Dr. Carlson?

2 DR. CARLSON: Approve.

3 DR. D'AGOSTINO: Yes.

4 CHAIRMAN RAMSEY: Dr. D'Agostino.

5 So we have a quorum.

6 (Applause.)

7 CHAIRMAN RAMSEY: We have a majority. So  
8 we have a unanimous vote in favor of approval, and the  
9 next step in the procedure is to ask each voting  
10 member to give a reason for their voting for approval.

11 So, again, I'll start with Dr. Thornton.

12 DR. KIM THORNTON: I think in answer to  
13 the questions that were posed, first, it's my opinion  
14 that in terms of demonstrating statistical  
15 significance in the study that the sponsor did that,  
16 and that the statistical significance was also  
17 indicative of clinical significance.

18 The safety data with regards to infection,  
19 I think it was clear that there wasn't an increased  
20 incidence in infection in the study group as compared  
21 to the control group. So as a result of that I think  
22 that the data that was presented here answered the

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1 questions that were posed and warranted approval.

2 CHAIRMAN RAMSEY: Okay. Dr. Shirk.

3 DR. SHIRK: Well, I guess I voted yes  
4 because I think it was statistically significant, I  
5 thought. How clinically significant it is, I think,  
6 is still in question, and the magnitude of the  
7 clinical significance, but certain clinical  
8 significance follows statistical significance.

9 I do think it's safe. I think the study  
10 could have been much more well managed from the  
11 beginning. It was obviously confused by both a pilot  
12 study and also by the fact that you had multiple  
13 parameters involved with this, and I think that's  
14 created some fairly marked confusion on the review of  
15 this process.

16 CHAIRMAN RAMSEY: Dr. Carlson.

17 DR. CARLSON: I'll be frank and brief in  
18 that coming into this based on the data I had up till  
19 this morning I was not inclined to approve even with  
20 conditions. I would congratulate the FDA and the  
21 sponsor on their very excellent and clear  
22 presentations.

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1 I had specific questions each of which  
2 were answered to my satisfaction regarding the  
3 endpoint, which I think was agreed to prior to the  
4 study and which, though not perfect and though  
5 intermediate, appears to be the best available  
6 endpoint we have now.

7 The combinability I had questions about,  
8 and I was satisfied with the answer there. The risk  
9 for infection was answered appropriately, and in  
10 regards to the analysis, I thank all of the  
11 statisticians, particularly Dr. D'Agostino, regarding  
12 the, quote, unquote, retrospective analysis and the,  
13 quote, unquote, subgroup analysis.

14 That left clinical significance, and  
15 although the absolute numbers aren't as great as I  
16 think anyone other than maybe the sponsor's  
17 competitors would like to see, I think we're facing a  
18 situation in medicine today where we've made  
19 tremendous strides in the past century, and the  
20 strides that we make are going to be incremental. It  
21 makes it much more difficult to assess what's  
22 effective and what's not, and I congratulate everybody

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1 on their analysis.

2 DR. D'AGOSTINO: I also want to thank the  
3 sponsor and the FDA for the thought process and the  
4 time they spent and the wonderful presentations they  
5 made.

6 I was quite a virgin, you know, to the  
7 particular problem and read through the materials, and  
8 the discussion and the transcript of the previous  
9 meeting left me completely confounded in terms of how  
10 I should go, but I think as we saw materials develop,  
11 sent to us, and then the sponsor's material, the FDA's  
12 material, and the unfolding today, I think what we  
13 have is a very powerful study. Forget the expense of  
14 it. That's probably not what we should be worrying  
15 about, but a multi-national study that really did have  
16 to me a lot of consistency.

17 And I understand where the FDA's  
18 objections came from, but I think that they were  
19 addressed quite correctly and substantially by the  
20 sponsor, and I think the data from a statistics point  
21 of view, given all of the rigor, the imputation  
22 methods and so forth, that there's a lot of robustness

1 there, and we can feel very comfortable about it.

2 With the clinical significance, as I said,  
3 I've lived through more and more of these situations  
4 where statistical significance becomes equivalent to  
5 clinical significance because we don't seem to want to  
6 bite the bullet on that, but even though the numbers  
7 are small, I mean, this was a pool of subjects that  
8 was evidently quite hard to deal with and so forth,  
9 and there is substantialness to this.

10 And I was playing some of the games and I  
11 was asking what if that 17 became 15 and so forth, and  
12 even doing some approximate analysis. They would have  
13 to come down pretty far before you'd lose the  
14 significance.

15 So I hope the sponsor doesn't have on  
16 television after the Claritin ads that there's a  
17 fivefold improvement.

18 (Laughter.)

19 DR. D'AGOSTINO: But there is an  
20 improvement, which I buy and really believe in.

21 CHAIRMAN RAMSEY: Okay. Now, the voting  
22 members have had a chance to have their say, but we

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1 also would like the consumer and industry  
2 representatives, if they are so inclined, to comment.  
3 So, Dr. Gordon, would you like to comment first?

4 DR. GORDON: I would like to comment  
5 because I think these forums are so important. I've  
6 spent most of my professional career because I believe  
7 in this process, the regulatory review and the quality  
8 of that review, and I've had consistently good  
9 experiences with this, and again, I commend everyone's  
10 effort in seeking a balanced approach.

11 But I'm really encouraged that this forum  
12 has played out the way it has because I think it could  
13 be an excellent resource for companies, although  
14 certainly one of last resort because there are many  
15 opportunities for interaction within the agency before  
16 one undertakes something that's this resource  
17 intensive.

18 But I think that this has been a really,  
19 really thoughtful forum, and everyone had really great  
20 comments. And I think if companies are considering  
21 it, then it's certainly worth undertaking.

22 CHAIRMAN RAMSEY: Thank you.

1 And Dr. Gonzalez.

2 DR. GONZALEZ: From a personal  
3 perspective, one of the things that I always enjoy  
4 about coming to these meetings is that, you know, we  
5 have always had hard working folks on whatever side of  
6 the table they are, whatever side of the aisle they  
7 are, whatever you want to call it, and that that hard  
8 work is only, you know, reflected in making -- in my  
9 case as a panel member, making me a much better  
10 person, a much more knowledgeable individual with some  
11 of the issues that come forth.

12 So we also get a tremendous amount of  
13 education, plus in addition to the hard work we put  
14 in.

15 So second, I do want to congratulate both  
16 FDA and the sponsoring agency for their hard work in  
17 making this presentation on both sides of the fence.

18 CHAIRMAN RAMSEY: Okay. I have some  
19 privilege as Chairman to make a closing comment, and  
20 I've strived mightily not to show any partiality to  
21 one party or the other, and I'm going to continue to  
22 do that in the closing comments, but just one comment

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1 on this panel and the process.

2 It is, I think, a panel that will be used  
3 as last resort, and I also should comment that this is  
4 merely a recommendation to the Director, not a binding  
5 rule, but I do hope that the Director will take the  
6 strength of the consensus very seriously in their  
7 decision ultimately on this device.

8 As I said, I think one of the most  
9 important parts of this panel is to have impartiality  
10 and to give both sides a chance to present their  
11 views, and I hope both parties feel that they had an  
12 adequate chance to represent their views and be heard.

13 If that's not the case, I personally would  
14 like to hear those opinions.

15 So let me just move on and close and say  
16 that this concludes the Medical Devices Dispute  
17 Resolutions Panel review of scientific issues in  
18 dispute between LifeCore Biomedical, Incorporated, and  
19 FDA regarding PMA 990015 as amended for INTERGEL  
20 adhesion gel prevention solution.

21 On behalf of the panel or on behalf of the  
22 FDA I'd like to thank the panelists, and I would also

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1 like to thank the sponsor and the FDA for what I know  
2 was a tremendous amount of effort on their behalf to  
3 come to this meeting.

4 We're now adjourned.

5 (Whereupon, at 2:54 p.m., the meeting was  
6 concluded.)

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CERTIFICATE

This is to certify that the foregoing transcript  
in the matter of: MEETING

Before: MEDICAL DEVICES DISPUTE  
RESOLUTION PANEL

Date: THURSDAY, SEPTEMBER 6, 2001

Place: GAITHERSBURG, MARYLAND

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.

*Laurie Rosbach*

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