

1 presented and discussed and labeled as such, but all  
2 of the analyses on which the claims are being made  
3 were those prospectively laid out in the protocol.

4 The next slide shows the completion of our  
5 conclusions regarding adherence to the protocol.  
6 There were three protocol specified cohorts for study  
7 in this trial. The first was an attempt to identify  
8 what might be called the intention to treat, that is,  
9 all patients treated on the study and categorized in  
10 the treatment group to which they were assigned. This  
11 is a respectable analytic strategy.

12 There was superimposed on the intention to  
13 treat cohort the additional requirement that worst  
14 score imputation be used to replace missing values for  
15 those patients who did not have second look data.

16 These two notions are independent and  
17 separate, that first being intention to treat and the  
18 second being a method for imputing missing data. Dr.  
19 Rubin will have more to say about that in a moment.

20 The second analysis that was specified in  
21 the protocol was to analyze those patients who had  
22 complete data at second look laparoscopy. This is

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1 called the evaluable patient analysis, and you've  
2 heard many of the results based on that protocol  
3 prespecified invalid analysis.

4 Here was a third analysis specified in the  
5 protocol. You heard that if patients are excluded  
6 based on reasons unrelated to the device that there's  
7 essential balance in the two treatment groups, making  
8 that analysis essentially consistent with the second  
9 one, and so statistics on that have not been  
10 presented.

11 All of those analyses, however, are  
12 prespecified, and we've reviewed the findings from all  
13 of them.

14 The third issue is on the next slide and  
15 deals with pooling of data. There is going to be some  
16 contention about this issue, but I want to provide you  
17 with my reasoning supporting by my colleagues about  
18 the rationale for using data from all the sites.

19 First of all, this was a common protocol.  
20 It was written and conducted as such. The inclusion  
21 and exclusion criteria were identical at all sites in  
22 both continents as you would expect from a multi-

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1 center study. The procedures used in the trial in  
2 evaluation were identical in the U.S. and Europe.

3 As I mentioned earlier, in addition, the  
4 randomization was blocked and stratified, which is  
5 really the strongest justification for pooling because  
6 the estimates of treatment effect from each of the  
7 centers regardless of where they are from provide  
8 unbiased estimates of the treatment effect.

9 The basic issue in deciding whether or not  
10 the data from the two continents should be pooled has  
11 to do with evidence of a common treatment effect. We  
12 like to pool when there's evidence that the treatment  
13 effect might be the same across the pooling units, and  
14 the protocol attempted to lay out some criteria under  
15 which we could reassure ourselves that there was, in  
16 fact, a common treatment effect across continents.

17 Those criteria are listed on the next  
18 slide, and quite honestly if I had written this  
19 section of the protocol, I don't think I would have  
20 written it this way, but nevertheless, I think these  
21 criteria are substantially in the ballpark and  
22 appropriate for the purpose.

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1           The first criteria and probably the most  
2 meaningful one is that there should be no significant  
3 interaction between the treatment effect and the  
4 continent, indicating that there is a common treatment  
5 effect or no evidence that there is a difference in  
6 the treatment effect.

7           Secondly, we would be reassured if there  
8 are similar statistically as well as qualitatively  
9 demographic in pretreatment or baseline variables.  
10 The protocol states that lack of similarity might be  
11 a basis, but it's not required to be a basis for  
12 precluding the combining of the data from the two  
13 comments.

14           And then thirdly, the similarity on second  
15 look adhesion scores was just to be something that  
16 would provide reassurance that combining the data from  
17 the comments would be appropriate.

18           In fact, if we look at these criteria,  
19 there is no interaction between continent and  
20 treatment once you account for adhesiolysis category.  
21 The failure to account for adhesiolysis category is  
22 the sources of the differences in interpretation on

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1 this issue.

2 If you fail to account for it, it appears  
3 that there is quantitative interaction between  
4 treatment and continent, and I'm choosing my words  
5 very carefully here, quantitative meaning that the  
6 treatment effect is in the same direction on both  
7 continents, but has different magnitude.

8 However, the fact that the interaction is  
9 substantially in the same direction after accounting  
10 for adhesiolysis means that there is sense in talking  
11 about an overall treatment effect even though there  
12 are slightly different magnitudes on the two  
13 continents.

14 More appropriately, however, the proper  
15 thing to do is to account for the effect of  
16 adhesiolysis, and when you do that, you see that the  
17 apparent interaction between treatment and continent  
18 is, in fact, not an interaction at all. It is the  
19 effect of the uncontrolled predictor variable,  
20 adhesiolysis, which is different in the two continents  
21 as a matter of patient characteristics and medical  
22 care practices.

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1           So, in fact, properly accounting for that  
2 factor shows that the treatment effect is common and  
3 satisfies the first pooling requirement.

4           Next, there are some differences in  
5 baseline variables, as you might expect, given the  
6 different demographics of the two continents.  
7 However, it's our opinion that these are  
8 inconsequential and are not an impediment to combining  
9 the data because none of these factors modify the  
10 effect of treatment, as I've just indicated in the  
11 reasoning about continent.

12           And in the case of differences in baseline  
13 factors, there are sound statistical procedures  
14 available for accounting for those differences and  
15 preserving lack of bias and precision in the overall  
16 estimate of the treatment effect.

17           And then finally, the data support that  
18 second look adhesion scores between the U.S. and  
19 Europe are similar, again, after accounting for the  
20 predictor factor, adhesiolysis. Thus, we have  
21 satisfied all of the three requirements laid out in  
22 the protocol for pooling of the data.

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1 DR. COLTON: Let me deal with the issue  
2 number one -- next slide, please -- which is  
3 statistical power.

4 First of all, statistical power is a  
5 probability statement about a hypothetical treatment  
6 effect. In the pivotal trial, the observation of  
7 statistically significant differences between  
8 treatment and control for any endpoint is unaffected  
9 by the original power calculation in the study  
10 protocol.

11 The sample size in the pivotal trial was  
12 determined based on differences in the primary  
13 outcome, mAFS scores, as observed in a pilot study.  
14 The original power calculations were based on standard  
15 methods, and this key information gleaned from the  
16 pilot study.

17 Had there been a more precise estimate of  
18 the true standard deviation of the primary outcome,  
19 one probably would have planned a smaller trial. When  
20 the trial was complete, the difference in scores, in  
21 mAFS scores in the study, that is, the evaluable  
22 population, was smaller, namely, a one unit change

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1 than that anticipated when the study was designed  
2 based on the pilot study results, a 2.1 unit change.

3 However, it's important to note the  
4 standard deviation was also smaller, 1.5 for INTERGEL  
5 and 2.2 for control compared to the standard deviation  
6 of five, which was the basis for the sample size  
7 calculation.

8 Hence, in the actual pivotal trial there  
9 is greater precision of estimation than had been  
10 originally anticipated.

11 And another important point we feel is  
12 that there's no rationale to question the validity of  
13 a trial because the treatment effect and/or the  
14 variance observed are smaller than that hypothesized  
15 before the trial began. This trial assessed the  
16 incremental benefit provided by an adjunctive  
17 treatment and found that it was statistically  
18 significant.

19 It would have been preferable, of course,  
20 to have had a more precise measurement of the outcome  
21 of interest with less variation than a large effect  
22 with more variation.

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1 Now, comments on the medical importance of  
2 this statistically significant results is clearly in  
3 the bailiwick of the judgment of clinical experts, and  
4 you're already heard the consensus panel on the  
5 clinical significance of the statistically significant  
6 findings.

7 Don.

8 DR. RUBIN: I'm Donald Rubin, and I, too,  
9 have no financial interest in LifeCore, although I,  
10 too, am assured that I'm not working for free.

11 I'm going to be talking about two closely  
12 related issues. They're incomplete ascertainment and  
13 ITT analysis, intention to treat analysis.

14 With respect to incomplete ascertainment,  
15 16 of the 281 randomized and treated patients did not  
16 complete the study. That's less than six percent did  
17 not have second look data.

18 You already saw this in Dr. Johns'  
19 presentation and saw that most of the reasons for not  
20 having second look data are unrelated to the  
21 treatment.

22 The findings reported by the sponsor are

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1 based on the evaluable population, which includes the  
2 265 patients, and this is not uncommon in such trials.

3 Now, in support of these evaluable  
4 population results which you have seen, these are  
5 analyses based on these 265 with second look data,  
6 there were four separate sensitivity analyses that  
7 were performed and submitted by the sponsor in support  
8 of the analysis of the evaluable population.

9 And these sensitivity analyses were based  
10 on various imputation methods for those people without  
11 second look data. The robustness and propriety of the  
12 evaluable population results as submitted by the  
13 sponsor were supported by these four sensitivity  
14 analyses.

15 Moreover, the propriety and robustness of  
16 the evaluable population analyses were supported by  
17 independent intention to treat analyses that we  
18 created based on scientifically imputed data.

19 Now, I'd like to talk about intention to  
20 treat analysis, and I'm going to spend a few slides on  
21 this because you'll see this phrase "intention to  
22 treat analysis" repeatedly, I believe, in the

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1 subsequent FDA presentation, and I think it requires  
2 some clarification.

3 The ITT population includes all those  
4 randomized and treated, including the 16 patients  
5 without second look data. So the intention to treat  
6 population is size 281.

7 Now, I think we're all sympathetic to the  
8 use of this population and understand the reasons for  
9 its use in many trials, and including this trial.

10 However, it is impossible to conduct an  
11 ITT analysis without imputation. In this case there  
12 are 16 people without second look data, and if you can  
13 conduct an analysis on all 281, you have to do some  
14 kind of imputation, either explicit or implicit, of  
15 this missing second look data for these 16.

16 What the FDA did and what the sponsor  
17 agreed to do as a sensitivity analysis was input the  
18 worst possible score. So it's worst possible score  
19 imputation. This is not an ITT analysis, but it's an  
20 analysis on the ITT population after imputing the  
21 worst possible score to that population.

22 But you'll see the phrase repeatedly "ITT

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1 analysis," and I want to be sure that we're clear  
2 about that.

3 It is our view that this imputation method  
4 is neither mainstream nor scientifically defensible in  
5 this trial. There are trials where it may be  
6 defensible, and perhaps I'll say something about that  
7 later during questions and answers, but we do not  
8 believe it's defensible nor scientifically reasonable  
9 in this trial.

10 As an example of that, there is a woman  
11 who refused second look data, second look examination  
12 because she was pregnant, and yet she was imputed to  
13 have the worst possible adhesion score on all  
14 outcomes. And I don't believe that's considered  
15 scientifically reasonable at all.

16 Now, we also connected our own independent  
17 analysis that I designed of the ITT population based  
18 on what I regard as scientific imputations. In this  
19 technology I was blinded to the results. I had no  
20 idea which treatment group was being imputed. I had  
21 no idea what effect it would have on the final  
22 analyses. There were no outcome, no second look data

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1 available at all in doing that, and I can describe  
2 that more in detail later if anybody is particularly  
3 interested in that.

4 But the important thing is that we had no  
5 idea, any of us, in what effect it would have on the  
6 resultant analysis.

7 Also, the method was entirely  
8 nonparametric. No model was used. It was based on  
9 matching the important baseline variables. They were  
10 the center, the randomization center, and baseline  
11 adhesion scores, and that's how the imputations were  
12 done.

13 It was independent in treatment group and  
14 continent. In other words, each treatment group and  
15 continent, those four categories, Treatment A, B,  
16 continent, Europe-U.S., were completely independently  
17 imputed. So there was no contamination of continent  
18 results or treatment results across treatment groups  
19 or across continents.

20 Moreover, the imputation incorporates  
21 uncertainty of the imputed values in order to allow  
22 for valid inferences. In other words, more than one

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1 imputed value was created, and the analyses of these  
2 multiply imputed data sets was combined according to  
3 standard combining rules.

4 The results of this independent analysis  
5 were as follows. INTERGEL was superior to lactated  
6 Ringer's solution for all subjects, regardless of the  
7 baseline adhesion rate. The relative risk, again, was  
8 greater than five, very significant results in support  
9 of the evaluable population results.

10 The superiority of INTERGEL over lactated  
11 Ringers was even true in the U.S. alone and even in  
12 the U.S. alone for those patients with no baseline  
13 adhesiolysis. So that the superiority of INTERGEL  
14 over lactated Ringers was clear even if you exclude  
15 the European centers and even if you exclude in the  
16 U.S. those with baseline adhesiolysis.

17 Moreover, the variability of the outcome,  
18 the variability of the primary outcomes was typically  
19 substantially less with INTERGEL than with control.  
20 That is, there was a difference in level of effect  
21 that was in favor of INTERGEL, and moreover, the  
22 variability of the second look variables was less,

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1 substantially less in many cases when using INTERGEL  
2 than when using control, indicating that surgically  
3 clinically you'd have more predictable, good outcomes  
4 with INTERGEL than with control.

5 In conclusion of this part on intention to  
6 treat analysis, these results based on the scientific  
7 imputed population strongly support the findings that  
8 have been reported on the evaluable population.

9 DR. COLTON: We have two more slides and  
10 which I will do.

11 First, where do we stand? Now, here's our  
12 conclusions. First, the pivotal trial results are  
13 appropriate and reliable. That is, we find them  
14 statistically valid. A statistically significant  
15 difference in AFS scores has been demonstrated with a  
16 high degree of certainty, very respectable p value,  
17 for INTERGEL conferred a fivefold lower risk of  
18 moderate to severe adhesions, and the results are  
19 supported by statistically significant secondary  
20 variables.

21 These results are consistent -- you've  
22 heard this already -- with pilot study and with animal

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1 studies that have been conducted. They are supported  
2 by four separate imputation analyses that the sponsor  
3 conducted. They are supported by additional  
4 independently conducted intention to treat analyses  
5 based upon scientifically imputed second look data.

6 And finally, last slide, please.

7 We find the data analyses presented by the  
8 sponsor are robust and they're adequate to support  
9 conclusions regarding clinical significance by  
10 appropriately qualified clinical experts.

11 One final word, also my personal view is  
12 I really feel to me at my age and stage of career  
13 development this has been a great learning experience  
14 for me, and one of the things, it's been really a  
15 wonderful experience to work with colleagues as  
16 talented and creative as Dr. Piantadosi and Dr. Rubin,  
17 and really apart from getting compensated for my time,  
18 I've really enjoyed working with these two colleagues  
19 on this.

20 I think this concludes the LifeCore  
21 presentation.

22 CHAIRMAN RAMSEY: Thanks.

1 Just a comment that you may not be working  
2 for free, but I'm nearly working for free.

3 (Laughter.)

4 DR. COLTON: We know.

5 CHAIRMAN RAMSEY: We are close to break.  
6 I do want to allow a couple of moments for the panel  
7 to ask questions of those who did presentations for  
8 LifeCore this morning.

9 Yes.

10 DR. D'AGOSTINO: Yes. I enjoyed the  
11 presentations. Quite impressive.

12 When I look at the data, and tell me why  
13 I'm wrong, you keep saying fivefold increase and what  
14 have you, but it's like three versus 17. You did  
15 imputation for the missing data, but what if the 17  
16 was 14? What would the significance be? How stable  
17 are even the evaluable patients? How stable are these  
18 analyses?

19 Do you follow my questions?

20 DR. RUBIN: I sort of do. We did not do  
21 an analysis where we actually changed the observed  
22 values of the data to see what would happen if actual

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1 observed second look data were something else. We  
2 always left those the same.

3 But when we did both the sensitivity  
4 analysis that were performed and submitted by the  
5 sponsor and our analyses where we did the scientific  
6 imputations, those imputations were changed. They  
7 were basically, including the sponsor's sensitivity  
8 analysis, they were all over the map to cover what we  
9 regard as anything reasonable that could --

10 DR. D'AGOSTINO: And was --

11 DR. RUBIN: -- the extremes.

12 DR. D'AGOSTINO: -- the test an exact test  
13 or was it the asymptotic version of the test? Because  
14 there must be zeros all over the place in these tables  
15 that are being pooled.

16 DR. RUBIN: That's correct, but, in fact,  
17 the tests were not done by a natural permutation test  
18 or randomization test. But if you look at the  
19 occurrence of zeros, the data are more benign than a  
20 binomial with the probability of .8.

21 And so these are more robust than the  
22 usual Wilcoxon tests, Mann-Whitney-Hume tests, T

1 tests, would be completely supported by the underlying  
2 randomization based analysis that would be permutation  
3 tests.

4 DR. D'AGOSTINO: Jim, what I'm trying to  
5 get at is just how robust are even the evaluable. I  
6 mean there's five and so forth. I'm jumping into the  
7 middle.

8 thank you.

9 CHAIRMAN RAMSEY: Yes.

10 DR. SHIRK: Dr. Shirk.

11 I've got a question for the statisticians.  
12 The initial PMA obviously was -- the statistics for  
13 the initial PMA was set up on an intent to treat, and  
14 I think that that would have -- if you look at the  
15 initial PMA, there would have been 303 or 304 patients  
16 that were evaluable.

17 There was obviously a calculated dropout  
18 rate in this so that the statistical model that they  
19 set up initially obviously was based on a 20 percent  
20 dropout rate for the INTERGEL group and also a ten  
21 percent, I think, dropout rate for the control group.

22 So that, you know, how does this analysis

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1 and the endpoints and your analysis of the endpoints  
2 change between the two things since obviously the  
3 endpoint agreed on was based on a much higher dropout  
4 rate and obviously applying worst case scenario to  
5 those patients who dropped out?

6 DR. BECKER: Dr. Piantadosi.

7 DR. PIANTADOSI: Yes. Thanks.

8 If I understand your question, the short  
9 answer is that only good things happen when the  
10 dropout rate and missing data rate is lower than that  
11 which you planned for in the trial. So ordinarily I  
12 would not expect that the findings would be incorrect,  
13 so to speak, because I had less of a dropout rate than  
14 what I planned for in the protocol.

15 The usual effect of dropouts, treatment  
16 crossovers and other kinds of imperfections in the  
17 data is to create a situation where the treatment  
18 effect is smaller and closer to the null value than it  
19 might otherwise be.

20 The additional precision, the addition  
21 observation generated by observations that you have  
22 but didn't expect to have improve the inference. So

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1 I think the fact that the trial as conducted did not  
2 quite measure up to the way that it was planned in the  
3 sense that the treatment effect was smaller, the  
4 variability in the treatment effect was smaller, and  
5 the compliance to the plans of the protocol was higher  
6 than that originally planned is actually a strength of  
7 the trial, not a weakness.

8 CHAIRMAN RAMSEY: Did you have a question?

9 DR. KIM THORNTON: I have one question.

10 CHAIRMAN RAMSEY: Okay. Go ahead.

11 DR. KIM THORNTON: This is for Dr.  
12 Piantadosi.

13 You had mentioned that you might have  
14 developed criteria for pooling of data that would have  
15 been different than what was included in this  
16 protocol. What might you have done differently?

17 DR. PIANTADOSI: Well, I think that the  
18 criteria laid out sort of captured the general sense  
19 of what provides reassurance that data are poolable,  
20 but I probably would have written the criteria a  
21 little more sharply and a little more clearly.

22 The main issue for me is whether or not

1 you can generate evidence for or against a common  
2 treatment effect across the units that you want to  
3 pool. Now, what's very common and known when we  
4 design multi-center clinical trials is that we're  
5 going to see a fair amount of heterogeneity among the  
6 treatment centers that participate in the trial if we  
7 look at each center at the treatment effect or  
8 treatment difference that's provided by each center.

9 And sometimes that heterogeneity, if you  
10 look at it within each center, can be rather startling  
11 and bewildering, but because each of the estimates is  
12 guaranteed by the procedures, the randomization and  
13 the methodology of the trial to be free of bias, then  
14 we can pool those and average them and provide an  
15 overall treatment effect.

16 So ordinarily when we look around among  
17 centers to see whether there's heterogeneity in the  
18 treatment effect, sometimes we see it; sometimes we  
19 don't. And the real issue is: is there heterogeneity  
20 of such a large degree that you would disbelieve that  
21 you're really seeing the same treatment effect in the  
22 U.S. and Europe or in Center A and Center B.

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1                   And I think that can be stated more  
2 clearly than it was in the protocol, but I'm not  
3 trying to object to the way the protocol was written  
4 or the way those analyses were carried out. I'm  
5 simply telling the panel that when one evaluates the  
6 use of those criteria in the protocol, it's important  
7 to consider this predictor variable, adhesiolysis,  
8 because failure to account for it properly will make  
9 it look as though there's an interaction when, in  
10 fact, there is not.

11                   CHAIRMAN RAMSEY: I'm going to take a  
12 chair privilege to cut us off. We are going to have  
13 a chance to ask the panel questions in the afternoon,  
14 ask LifeCore questions, and I'd like us to take a ten  
15 minute biology break here, and then we'll move on.

16                   (Whereupon, the foregoing matter went off  
17 the record at 10:21 a.m. and went back on  
18 the record at 10:44 a.m.)

19                   CHAIRMAN RAMSEY: We're going to get  
20 started in just a minute. The FDA person is coming  
21 back to start with their presentation.

22                   I realize at the start that I didn't state

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1 for you my background. So I thought I'd just take 30  
2 seconds to do that.

3 My background is that I'm, in addition to  
4 being an Associate Professor at Fred Hutchinson Cancer  
5 Center in the University of Washington, my background  
6 is I'm a general internist. I practice at the  
7 University of Washington, and I have expertise in  
8 health economics and evidence based medicine. So that  
9 should make everyone hate me.

10 (Laughter.)

11 CHAIRMAN RAMSEY: No, but those are my  
12 areas of expertise, and I just wanted to make sure  
13 everyone knew my background.

14 It should be just a moment and then --  
15 okay. Here she comes. So we're now going to start  
16 with the FDA presentation.

17 DR. KRAUS: I'm six, three. I'm used to  
18 lifting mics.

19 I'd like to start this morning by saying  
20 good morning and welcome and thank you all for coming.  
21 I'd like to thank the Chairman and members of the  
22 panel. Mr. Weinstein has done a great job of

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1 organizing everything.

2           Representatives of LifeCore Biomedical,  
3 Dr. Feigal, members of FDA, and especially members of  
4 the public for showing such an interest in this  
5 regulatory process.

6           My name is David Kraus, and I am a  
7 reviewer in the Office of Device Evaluation, Division  
8 of General Restorative and Neurological Devices at the  
9 Center for Devices and Radiological Health. I'm a  
10 cell biologist by training and lead reviewer for the  
11 INTERGEL adhesion prevention solution PMA, which is  
12 being discussed here today.

13           Next slide, please.

14           I'd like to introduce the folks who did  
15 the reviewing and helped me immensely and actually did  
16 most of the work. Dr. Lisa Harvey reviewed the animal  
17 infection data. Dr. Roxy Horbowyj reviewed the  
18 clinical data as the lead clinical reviewer. Dr.  
19 David Kaplan was our manufacturing reviewer. Dr.  
20 Richard Kotz was our statistics reviewer.

21           I, as well as being the lead reviewer, did  
22 the preclinical toxicology, and Dr. Diane Mitchell

1 was our OB-GYN clinical consultant.

2 Next slide, please.

3 Today you will be hearing a presentation  
4 on how the FDA review team interprets the data  
5 presented in the INTERGEL adhesion prevention solution  
6 PMA and the amendments which followed. I will be  
7 giving you a brief overview and an introduction.

8 Dr. Horbowyj will give a review of the  
9 pilot and clinical studies performed in support of  
10 approval of the PMA, and then she will be followed by  
11 Dr. Kotz, who will discuss the agency statistical  
12 analysis of the clinical data presented in the PMA.

13 I'd like to emphasize that the agency's  
14 presentation will focus solely on the clinical data  
15 and the statistical analyses that are presented in the  
16 PMA. At this time we do not feel that there are any  
17 preclinical issues that need to be discussed any  
18 further at this meeting.

19 Next slide, please.

20 This slide shows the indication for use  
21 proposed by LifeCore Biomedical in the original PMA  
22 submission, and I'm not going to read it. It's in

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1 your handouts.

2 Slide 5, please.

3 The following is the indication for use as  
4 proposed in the subsequent amendment, which followed  
5 the not approvable recommendation from the panel at  
6 the January 12, 2000 General and Plastic Surgery  
7 Devices Panel meeting. This was submitted in the  
8 amendment which was discussed previously by the  
9 sponsor, which was presented to the agency in June of  
10 2000.

11 Again, it's been read, and I'm not going  
12 to read it again.

13 Can I have the next slide, please?

14 As you have already listened to the  
15 sponsor's presentation and interpretation of the study  
16 results and you're now prepared to hear the FDA  
17 presentation, please keep the following question in  
18 mind. During this afternoon's discussion period,  
19 you'll be asked to comment on this question.

20 The question is: does the PMA as actually  
21 was read by Dr. Ramsey this morning -- and I won't  
22 read it again.

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1 I'd like to now introduce our clinical  
2 reviewer, Dr. Roxy Horbowyj.

3 DR. HORBOWYJ: Good morning. My name is  
4 Roxy Horbowyj. I'm a general and critical care  
5 surgeon and a clinical reviewer for this submission.

6 I will present the FDA clinical  
7 perspective of INTERGEL use in patients undergoing  
8 clean, open, gynecologic procedures for pain,  
9 infertility, or irregular bleeding.

10 Next slide, please.

11 I will briefly present background on  
12 adhesions and adhesion evaluation, as well as a  
13 summary of private study data and highlights of a  
14 pivotal study which apply to the currently proposed  
15 indications for use.

16 Adhesions -- next slide, please -- form as  
17 a protective response to localize a peritoneal insult.  
18 Most commonly adhesions are due to trauma, foreign  
19 bodies, or infection. Adhesions may cause or minimize  
20 morbidity.

21 For example, adhesions may prevent  
22 volvulus or contain a bowel leak. Adhesions, however,

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1 may also cause pain, bowel obstruction, and female  
2 infertility.

3 Adhesions may be characterized by their  
4 rotation, whether the adhesion occurs at a surgical  
5 site known as the direct adhesion or a remote site  
6 known as an indirect adhesion; by occurrence, that is,  
7 whether the adhesion is new, known as de novo, or  
8 previously lysed, that is, reformed.

9 Adhesions may also be characterized by  
10 their extent over which they cover in a particular  
11 anatomic site, and by severity, how difficult the  
12 adhesion is to lyse, how vascularized the adhesion is.

13 At this time there is no consensus as to  
14 how to best predict which peritoneal cavity adhesions  
15 or which adhesion characteristics specifically will  
16 cause or minimize morbidity.

17 Next slide, please.

18 Adhesion evaluation consensus on how best  
19 to correlate adhesion characteristics with clinical  
20 outcome has not been reached. To evaluate adhesions,  
21 the American Fertility Society has published a method  
22 of adnexal evaluation which included an adhesion

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1 scoring method called the American fertility society  
2 score, the AFS score.

3 For the INTERGEL pivotal study, the  
4 sponsor developed several scores to evaluate adhesions  
5 based on the AFS score, two scores specifically were  
6 the modified AFS score and a retrospected AFS score.

7 The AFS in INTERGEL clinical study scores  
8 differ in the number of anatomic sites evaluated,  
9 method of anatomic site evaluation, and method of  
10 determining the final score per patient.

11 Now I will go over the scores.

12 Next slide, please.

13 The AFS score was developed for evaluating  
14 adnexal adhesions in an effort to address the need for  
15 a standardized classification scheme for adhesions  
16 expected to be associated with infertility. In  
17 determining an AFS score for a patient, four anatomic  
18 sites are evaluated per patient: the right ovary, the  
19 right tube, the left ovary and the left tube.

20 The scores per side are summed. The final  
21 AFS score per patient is the score of the side with  
22 the lowest summed score. The higher score

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1 representing the side with the higher adhesion burden  
2 is dropped.

3 Next slide, please.

4 An AFS score, as published by the American  
5 Fertility Society, is based on the incident, extent,  
6 and severity of an adhesion at an anatomic site. A  
7 score of zero, one, two, four, eight or 16 is assigned  
8 to a tube or ovary depending on the severity of the  
9 adhesion, which may be mild or severe and the extent  
10 of the adhesion, which may be localized, moderate, or  
11 extensive.

12 The final AFS score range is zero to 32 as  
13 the tube and ovary per side are summed, and the higher  
14 score is dropped.

15 Next slide, please.

16 The published literature and its  
17 interpretation of the American Fertility Society  
18 scores are often limited by small sample sizes that  
19 are reported and by the use of variations of the  
20 published score. For example, different anatomic  
21 sites may be evaluated. Some studies report use of  
22 the score applied only to the fallopian tube, and

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1 sometimes different score assignments are used, a  
2 range of zero to 20 instead of zero to 32. So a  
3 direct comparison is difficult.

4 Interobserver reproducibility at the level  
5 of 0.7 has been reported as observed in less than one  
6 third of surgeon pairs studied, and the published  
7 reference is on the slide there.

8 Next slide.

9 The modified American Fertility Society  
10 score developed by the sponsor to evaluate adhesions  
11 throughout the peritoneal cavity used 24 prespecified  
12 anatomic sites. At each site the incidence, extent,  
13 and severity are evaluated according to the published  
14 AFS scoring scheme, except in the case of four sites:  
15 the small bowel, the omentum and the left and right  
16 colon, which were to be assigned an extent score of  
17 moderate for any adhesion noted at these sites.

18 The final modified AFS score, mAFS score,  
19 per patient is the average of 24 site scores. No  
20 scores are dropped, and then AFS score range is zero  
21 to 16.

22 When attempting to interpret a single mAF

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1 score per patient, it's notable that a single mAF  
2 score per patient in a graph of mAFS versus number of  
3 sites with adhesion may refer to a broad range of  
4 adhesions.

5 I'm sorry I don't have a pointer, but I  
6 think it may be useful to -- in looking at this chart,  
7 for example, if a patient has one adhesion, our colors  
8 have been changed here. So I will go through this  
9 more slowly.

10 If a patient has mAFS score, which is on  
11 the vertical axis, of one, and if you follow across,  
12 you can see that you can have a range of the number of  
13 adhesions with this one score.

14 So the consequences and potentials of  
15 evaluating just a single score alone may be varied  
16 because of the associated, potentially different  
17 number of adhesions that may be associated with a  
18 single score.

19 While I have this up, let me also --  
20 you've now heard extensively about the study design  
21 very well put forth by the sponsor and their outcomes  
22 as well. But in the pivotal study, patients who were

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1 enrolled and inclusion/exclusion criteria was that  
2 patients were to have fewer than 12 adhesions.

3 So in this area of potential scores and  
4 adhesions that is possible with the scoring system,  
5 this is the area that was studied, and as the sponsor  
6 has said, it was less than one -- there was less than  
7 one change in number of sites of adhesions comparing  
8 INTERGEL and control and a change in approximately one  
9 in mAFS score.

10 So essentially the changes that were  
11 experienced in the study were about the size of one of  
12 these blocks.

13 Next slide, please.

14 Going back to the retrospective American  
15 Fertility score now, the mAFS score was designed  
16 prospectively for this study, but retrospective to the  
17 pivotal study to provide a score that addresses  
18 adnexal adhesions alone, in other words, an analogue  
19 to the AFS score, the sponsor calculated adhesion  
20 scores for each ovary, tube from the mAFS scores.

21 This required the use of ten mAFS score  
22 sites as in the mAFS score system. Each ovary was

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1 evaluated as three anatomic sites, and each tube was  
2 evaluated at two anatomic sites.

3 The extent per ovary or tube was  
4 calculated using the average of the extent to numeric  
5 values from all sites making up a tube or ovary. The  
6 severity per tube or ovary was assigned as the maximum  
7 severity of contributing sites.

8 The calculated extent and the assigned  
9 severity scores determined the overall tube or ovary  
10 adhesion score. The ovary and tube scores per side  
11 were summed, and the lower sum score became the rAFS  
12 score as was done with the published score.

13 The final retrospective AFS score range  
14 then was zero to 32, as is found in the published  
15 score.

16 Next slide, please.

17 The retrospective AFS score was also  
18 stratified in several ways, which are listed here.  
19 The retrospective AFS score had these strata as the  
20 basis for the current claims.

21 Next slide, please.

22 Overall, considering the modified AFS

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1 score and the retrospective AFS score, there are  
2 several limitations to score interpretation. For  
3 example, as I've tried to demonstrate with the graph,  
4 the mAFS score overlaps confounds interpretation of a  
5 single score alone. The correlation of clinical  
6 outcome with an mAFS score or change in the mAFS score  
7 is not known. The correlation between the standard or  
8 force site AFS score and the retrospective ten site  
9 AFS score is not know, and the correlation of clinical  
10 outcome with any AFS score stratification has not been  
11 established.

12 And now I will address the INTERGEL  
13 clinical studies.

14 Next slide, please.

15 INTERGEL, as you have heard, is a 0.5  
16 percent ferric hyaluronate gel. It's an aqueous  
17 solution of sodium hyaluronate ionically cross-linked  
18 with ferric chloride.

19 Next slide, please.

20 The objectives of the projects that if we  
21 were to assess the methodology of use and to make a  
22 preliminary assessment of the safety of 300 cc's of

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1 INTERGEL compared to 300 cc's of lactated Ringer's  
2 solution in patients undergoing peritoneal cavity  
3 surgery by laparotomy, and with second looks  
4 laparoscopy.

5 Objectives of the pivotal study were to  
6 assess the safety and effectiveness of INTERGEL  
7 compared to lactated Ringer's solution in the same  
8 volumes and improve any or reducing adhesions in  
9 patients undergoing peritoneal cavity surgery.

10 The pivotal study design was based on  
11 product study outcome.

12 Next slide, please.

13 The pilot study was a prospective,  
14 randomized, single center, single investigator study  
15 of 21 patients undergoing laparotomy for infertility  
16 with six to 12 week follow-up for second look  
17 laparoscopy.

18 Three hundred cc's of INTERGEL or lactated  
19 Ringers were left in the peritoneal cavity at the end  
20 of surgery. The adhesion incidence, extent and  
21 severity were evaluated, evaluated 18 prespecified  
22 anatomic sites at baseline and at second look, and a

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1 modified AFS score was calculated retrospectively.

2 At second look differences between  
3 INTERGEL and control were 4.65 for the mean AFS score,  
4 4.91 for the mean adhesion incidence.

5 At second look adjusted for baseline,  
6 differences between INTERGEL and control were 4.12  
7 mean AFS score and 4.13 mean adhesion incidence. The  
8 difference between INTERGEL and control in the mean  
9 modified AFS score at second look adjusted for  
10 baseline, which was 4.12, was the basis for the  
11 pivotal study design.

12 Infection in the pilot study occurred in  
13 one out of 11 INTERGEL patients and zero out of ten  
14 control patients.

15 Next slide, please.

16 The pivotal study was a prospective,  
17 multi-center study to be undertaken at 12 U.S. and six  
18 European centers. The study was to enroll otherwise  
19 healthy 18 to 45 year old females with pain, bleeding,  
20 or infertility and adhesions at up to 11 of 24  
21 prespecified anatomic sites.

22 Randomization to INTERGEL or control

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1 occurred preoperatively, that is, before all inclusion  
2 and exclusion criteria were evaluated.

3 The dose of 300 cc's per patient was not  
4 adjusted for patient weight. Follow-up was to occur  
5 at seven days postop. for laboratory evaluations and  
6 at six to 12 weeks for second look laparoscopy. A  
7 third party masked device application or evaluation  
8 was proposed.

9 Next slide, please.

10 Pivotal study endpoints were for safety  
11 and for effectiveness. Safety was evaluated by  
12 adverse events. Effectiveness was evaluated by  
13 primary and secondary endpoints as the sponsor has  
14 reported also.

15 The primary endpoint was the modified  
16 American fertility score based on 24 sites. Secondary  
17 endpoints included the proportion of adhesions:  
18 adhesion incidence, yes or no; adhesion extent, which  
19 was evaluated at zero, one, two, or three; and  
20 adhesion severity, which was evaluated as zero, one or  
21 three.

22 Next slide, please.

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1 From pilot study data, the evaluable  
2 pivotal study cohort was expected to demonstrate a  
3 difference between INTERGEL control group mean AFS  
4 score of 4.1. This was the second look mean AFS --  
5 mean mAFS score adjusted for baseline. Assumptions in  
6 the design of the pivotal study were that loss to  
7 follow-up would be 20 percent in the INTERGEL group  
8 and ten percent in the control group.

9 The sponsor also proposed a loss to  
10 follow-up patients would be assigned a mAFS score of  
11 16, and it was planned that an intent to treat  
12 analysis was being performed with these assumptions.

13 Therefore, based on these assumptions,  
14 differences between INTERGEL and control mean AFS  
15 score, mean mAFS score adjusted for baseline decreased  
16 from 4.1 to 2.1.

17 The sample size to detect a difference of  
18 2.1 in the mean mAFS score was then 180 patients.  
19 This was with a standard deviation of 5.0 for both  
20 groups and assuming the ITT analysis, a power of 80  
21 percent and a significance level of 0.05.

22 Next slide, please.

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1           The study was designed to evaluate 180  
2 patients. Two hundred and eighty-one patients,  
3 however, were enrolled, 200 in the U.S. and 81 in  
4 Europe. Two hundred and sixty-five patients were  
5 evaluable, 188 in the U.S. and 77 in Europe.

6           A comparable number of patients enrolled  
7 into the INTERGEL and control groups in each  
8 continent. A comparable loss to follow-up occurred in  
9 each continent. However, only about half of the loss  
10 to follow-up that was expected and accounted for in  
11 study design occurred. The actual overall evaluable  
12 population was 85 patients larger than the  
13 prospectively calculated sample size.

14           Hence, the calculated sample size of N  
15 equals 180 was higher than necessary to detect a  
16 difference of 2.1, the mean mAFS score, with a  
17 standard deviation of 5.0 for both groups, which had  
18 been reduced from 4.1 by adjustment for expected loss  
19 to follow-up and planned intent to treat analysis.

20           Next slide, please.

21           It is notable that at baseline INTERGEL  
22 and control cohorts were clinically comparable within

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1 each continent. Comparing U.S. and Europe, cohorts  
2 were clinically comparable for distribution of age,  
3 weight, inclusion and exclusion criteria.

4 Comparing the U.S. and Europe, however,  
5 the cohorts were not clinically comparable for  
6 distribution of race, baseline adhesion incidence,  
7 mAFS score, or AFS scores. Procedure type also varied  
8 as the sponsor has demonstrated to you today.

9 Therefore, the U.S. and European cohorts  
10 were not considered combinable clinically or by  
11 prospective combinability criteria, which FDA  
12 statistician Richard Kotz will discuss.

13 Next slide, please.

14 Specifically differences in race between  
15 the U.S. and Europe were demonstrated here on this  
16 slide. Approximately 40 to 50 percent of the U.S.  
17 population was Caucasian, while approximately 80 to 90  
18 percent of the European population was Caucasian.

19 Next slide, please.

20 This slide demonstrates differences  
21 between the European and the U.S. populations for mean  
22 adhesion evaluation at baseline. The incidence of

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1 adhesions in the U.S. patient cohorts was 2.49 and  
2 2.27 for INTERGEL and control, respectively, while the  
3 incidence of adhesions in Europe was 6 and 6.4 for  
4 INTERGEL and control, respectively.

5 This similar trend and difference was  
6 noted for other adhesion evaluation parameters as  
7 well.

8 Next slide, please.

9 There were also differences in the number  
10 of percentages of patients who underwent adhesiolysis  
11 in Europe compared to the U.S. Approximately 40  
12 percent of patients in the U.S. underwent adhesiolysis  
13 where up to 78 percent of patients in Europe underwent  
14 adhesiolysis.

15 As a result, 60 percent or so patients in  
16 the U.S. had non-adhesiolysis associated procedures;  
17 whereas in Europe only 22 to 30 percent of patients  
18 had non-adhesiolysis associated procedures.

19 Next slide.

20 The current indications for use that the  
21 sponsor has proposed is that the INTERGEL solution is  
22 a single use intraperitoneal instillate indicated to

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1 reduce the likelihood of developing moderate or severe  
2 postoperative adnexal adhesions in patients undergoing  
3 adhesiolysis or myomectomy during conservative  
4 gynecologic pelvic surgery by laparotomy, when used as  
5 an adjunct to good surgical technique.

6 INTERGEL solution was also shown to reduce  
7 adhesion formation to sites in addition to the adnexal  
8 and adhesion formation at surgical sites including the  
9 anterior abdominal wall.

10 I will go over the pivotal study data that  
11 is suggested to support these claims in terms of the  
12 retrospective scores and stratifications as provided  
13 by the sponsor and in terms of the combined U.S. and  
14 European evaluable patient population as this is the  
15 basis in which the sponsor proposes these claims.

16 Next slide, please.

17 As to the aspect of the claim referring to  
18 the likelihood of developing moderate or severe  
19 postoperative adnexal adhesions, that is, in the  
20 strata retrospective AFS score equal to 11 to 32, it  
21 is notable that at baseline the number of patients  
22 with moderate to severe adhesions was nine out of 131

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1 patients in the INTERGEL group and 17 out of 134  
2 patients in control. This is a difference of eight  
3 patients 5.8 percent. It's shown here on the first  
4 slide, first line.

5 For these patients with moderate to severe  
6 adhesions at baseline, at second look there were nine  
7 fewer patients with moderate to severe postoperative  
8 adhesions in the INTERGEL group and ten fewer patients  
9 in the control group, nine and ten.

10 This is a comparable number of patients,  
11 fewer patients in the moderate to severe adhesion  
12 group at second look.

13 The sponsor notes that this is 100 percent  
14 reduction in INTERGEL patients from nine to zero and  
15 a 59 percent reduction in control patients.

16 However, as the sample size of this  
17 subgroup of patients with moderate to severe adhesions  
18 is small, nine and 17 out of 265 total, it is not  
19 possible to know if the effect of the INTERGEL group  
20 is limited by the number of patients in the subgroup  
21 by device effect, by chance, or by other factors, such  
22 as surgical technique.

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1           The sponsor also notes that the difference  
2           in the number and percentage of patients with moderate  
3           or severe adhesions is three out of 131 compared to 17  
4           out of 134, a difference of 14 patients, which is  
5           10.3.

6           This difference, however, does not account  
7           for the differences between INTERGEL control at  
8           baseline. Accounting for baseline, the difference  
9           between INTERGEL and control in the number of patients  
10          with moderate or severe postoperative adhesions is  
11          six, or 4.5 percent.

12          Next slide, please.

13          Referring to patients undergoing  
14          adhesiolysis or myomectomy during conservative  
15          gynecologic pelvic surgery by laparotomy, for this  
16          analysis the retrospective AFS score was stratified  
17          into two groups, zero to ten and 11 to 32.

18          The shift analysis was performed for  
19          procedure subgroups, myomectomy, no myomectomy,  
20          adhesiolysis, non-adhesiolysis, tubal procedures,  
21          ovarian procedures and endometrial ablation.

22          Nominal statistical significance of p less

1 than 0.05 is reported for the myomectomy and  
2 adhesiolysis subgroups only. It is notable, however,  
3 that most patients were part of more than one  
4 subgroup.

5 Next slide, please.

6 As to the aspect of the claim referring to  
7 adhesion reformation to sites in addition to the  
8 adnexa on the prospective scale, in terms of incidence  
9 the difference between INTERGEL and control is 0.94.  
10 This difference is less than one adhesion.

11 In terms of proportion of sites with  
12 reformed adhesions, the difference between INTERGEL  
13 control is 0.2, which the sponsor notes is 31 percent  
14 reduction in reformed adhesions.

15 As to the extent and severity of reformed  
16 adhesions, the difference between INTERGEL and control  
17 is 0.5 and 0.53, respectively. This difference in  
18 extent and severity represents less than one category  
19 of change for extent and severity as these parameters  
20 were graded in the trial.

21 Next slide, please.

22 As to the aspect of the claim referring to

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1 adhesion formation at surgical sites on the  
2 prospective scales, in terms of incidence the  
3 difference between INTERGEL and control is 0.69  
4 adhesions. This difference represents less than one  
5 adhesion per patient.

6 In terms of proportion of sites with  
7 reformed adhesions, the difference between INTERGEL  
8 and control is 0.11, which the sponsor notes is a 23  
9 percent reduction in reformed adhesions.

10 As to the extent and severity of reformed  
11 adhesions, the difference between INTERGEL and control  
12 is 0.33 and 0.36, respectively. This difference of  
13 0.33 in extent and 0.36 in severity represents a less  
14 than one category change for extent and for severity  
15 as these parameters were evaluated in this trial.

16 Next slide, please.

17 A notable adverse event is infection, and  
18 infection is notable here as infection is known to  
19 cause adhesions. The study population in this trial  
20 included only clean, nonmalignant cases in 18 to 45  
21 year old, otherwise healthy and immune competent  
22 patients.

1 Patients who are at lowest risk for  
2 infection as clean, contaminated, contaminated and  
3 dirty cases were excluded interoperatively, and no  
4 malignant cases were enrolled.

5 Please note that the numbers that I'm  
6 reporting and have reported are as presented to FDA in  
7 our submissions.

8 The incidence of infection was reported to  
9 be 7.0 percent in INTERGEL treated patients and 2.9  
10 percent for control overall. In terms of possibly  
11 related infection as per investigator and the  
12 sponsor's independent assessors, the incident of  
13 infection possibly related to the device used was 4.2  
14 percent in INTERGEL treated patients and 2.2 percent  
15 in control, a difference of two.

16 These are all listed on this slide, but  
17 I'm not really sure how well it's projecting for  
18 everyone to see.

19 So assessed by the independent assessor  
20 and investigator, this is the overall infection rates  
21 of 4.2, six patients, and three patients for control  
22 overall.

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1           The incidence of infection possibly  
2 related to the device use in U.S. INTERGEL patients  
3 was 4.9 percent, five patients, compared to two  
4 percent, two patients, in U.S. in control, a  
5 difference of 2.9 percent.

6           I have a listing of the patients and will  
7 gladly read off the diagnoses that were assigned and  
8 considered to be related to device use by the  
9 investigator and independent assessor, which I believe  
10 was Dr. Sever.

11           Continuing on this slide, the European  
12 incidence of infection was the same for INTERGEL and  
13 control cohorts.

14           Next slide, please.

15           In summary, device use was studied in  
16 18.45 year old women with low baseline adhesion burden  
17 and otherwise good health undergoing clean, noncancer  
18 gynecologic procedures. Baseline evaluation  
19 differences between continent and treatment groups are  
20 greater than differences within a continent per  
21 treatment group for variables such as race, adhesion  
22 evaluation, and procedure type.

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1 Revised indications for use are based on  
2 evaluable patients from the U.S. and Europe, the U.S.  
3 constituting or contributing 188 patients, Europe  
4 contributing 81.

5 The revised indications for use claims are  
6 based on binary stratification of retrospective AFS  
7 scores and shift analysis of seven procedure  
8 subgroups. The nominal statistical significance, p  
9 less than 0.5, noted for the myomectomy and  
10 adhesiolysis subgroups only.

11 Next slide, please.

12 Moderate to severe adhesions with respect  
13 to this, nine fewer INTERGEL and ten fewer control  
14 patients with moderate to severe adhesions at baseline  
15 had moderate to severe adhesions at second look.

16 Accounting for baseline, six, or 4.5  
17 percent fewer INTERGEL patients, had moderate to  
18 severe adhesions at second look compared to control.

19 Reformed and surgical site adhesions at  
20 second look from this aspect, the incidence  
21 demonstrated a difference between INTERGEL and control  
22 that is less than one occasion, and from the aspect of

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1 extent and severity, the differences between INTERGEL  
2 and control were less than one category of change.

3 As far as infection rate, as possibly  
4 related to device use per investigator and independent  
5 assessor, 4.9 percent U.S. INTERGEL treated patients  
6 compared to 2.0 percent U.S. control patients were  
7 rated this way, and 2.5 percent of patients in the  
8 European cohorts both in INTERGEL and control were  
9 assessed to be possibly related to device use per the  
10 investigator and independent assessor.

11 Next slide, please.

12 Thank you.

13 I will now present our statistician,  
14 Richard Kotz, to present the statistical perspective.

15 MR. KOTZ: Thank you, Dr. Horbowyj.

16 I'm Richard Kotz. I'm a statistician at  
17 the FDA and will be presenting the statistical review  
18 of the INTERGEL adhesion barrier. I have been  
19 statistical reviewer for this product since the  
20 development of the pivotal study protocol.

21 I will first present the sponsor's study  
22 protocol and the results of their study, specifically

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1 the proposed sample size and analysis plan specified  
2 in the protocol. I will then show that it's  
3 inappropriate to pool the U.S. and European subjects,  
4 and that there is no difference between INTERGEL and  
5 the control when data is analyzed in the manner  
6 described in the protocol.

7 In the second part of my talk, I will  
8 discuss the sponsor's revised claim and show that the  
9 secondary endpoints, reformed and surgical site  
10 adhesions, and the retrospective defined endpoint AFS  
11 score do not demonstrate the superiority of INTERGEL  
12 over the controls.

13 Next slide.

14 The sample size was based on results from  
15 the sponsor's 20 subject pilot study. They observed  
16 a difference in modified AFS score of four between the  
17 two treatments. INTERGEL had a modified AFS score of  
18 1.7 and a standard deviation of 1.4, and the control  
19 had a score of 5.7 with a standard deviation of 2.8.  
20 These were at second look.

21 This is the designated primary endpoint,  
22 modified AFS score as the designated primary endpoint

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1 in this study.

2 Much focus was also placed on the  
3 secondary endpoint, incidence of adhesions in which  
4 there was a difference of 4.9 at second look, 6.1 for  
5 INTERGEL and 11.0 for the control.

6 The sponsor expected a loss to follow-up  
7 of 20 percent for INTERGEL and ten percent for the  
8 control groups. Though we generally require an intent  
9 to treat study design for pivotal studies, the sponsor  
10 chose to assign the worst modified AFS score of 16 to  
11 those patients.

12 Furthermore, it should be noted that it is  
13 not the worst case analysis. The worst case analysis  
14 involved treating all of the INTERGEL loss to follow-  
15 up patients as failures and the control loss to  
16 follow-up patients as successes.

17 Note that by the design of the study with  
18 an unequal rate of patients lost to follow-up and  
19 assigning them the worst score, the sponsor has  
20 reduced the difference to be detected between the two  
21 treatment groups from 4.1 to 2.1. This treatment of  
22 loss to follow-up patients also increased the standard

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1 deviation to 5.0. This is important in the  
2 calculation of the sample size.

3 They calculated the sample size necessary  
4 to test for a difference of 2.1 with a standard  
5 deviation of 5.0 and a power of 80 percent for a two-  
6 sided test of five percent to be 90 subjects per arm.

7 To analyze the data, they plan to use an  
8 intent to treat analysis to assign the worst scores to  
9 subjects lost to follow-up. They also proposed using  
10 non-parametric statistics since the modified AFS  
11 scores were skewed to the right.

12 The sponsor planned to include 200  
13 subjects in this study. Since they were conducting a  
14 concurrent European trial of 80 subjects, they would  
15 use only U.S. subjects unless they found that the U.S.  
16 and European subjects could be combined.

17 If combinable, they would stop the U.S.  
18 study at 120 subjects and combine them with the 80  
19 European subjects to obtain the desired 200 subjects.

20 If not combinable, they would continue  
21 enrolling U.S. subjects until they had 200 and only  
22 use the U.S. subjects in their statistical analyses

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1 for effectiveness.

2 In their protocol, they specified three  
3 conditions which must be satisfied in order for it to  
4 be acceptable to combine patients across continents.  
5 You've already seen these, but, again, first, the  
6 baseline demographic pretreatment variables, including  
7 adhesion scores should be similar.

8 Second, there should be no significant  
9 interaction between continent and treatment effect.

10 And, thirdly, second scores should be  
11 similar.

12 In the following slides, I will  
13 demonstrate that the first two conditions do not hold  
14 and that, therefore, the U.S. patient group is the  
15 appropriate data set for statistical analysis.

16 I want you to first note that I changed  
17 this slide slightly from that in the slide you  
18 received for last week to make it easier to read. All  
19 of the numbers are the same. I just changed the order  
20 for ease of interpreting the results.

21 I'm not very good with these pointers, but  
22 I will give it a shot.

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1 Note that the sample size is approximately  
2 100 each treatment group in the U.S. and 40 per group  
3 in Europe.

4 (Pause in proceedings.)

5 MR. KOTZ: Okay. Thank you. We'll keep  
6 on going. Okay. Thank you.

7 First note -- oh, wait. Let's first look  
8 at the modified AFS score. Note that differences  
9 between continents for both groups are statistically  
10 significant -- forget that -- are statistically  
11 significant, and note that the baseline in Europe is  
12 about two to three times greater than in the U.S. So  
13 baseline in Europe is twice as large. In Europe it's  
14 twice as large as that in the U.S. for the INTERGEL  
15 patients, and the same is true for the control  
16 patients.

17 For the incidence of adhesions, the  
18 differences are also highly statistically  
19 significantly different, less than .001, for both  
20 treatment groups, and the baseline in Europe is also  
21 two to three times greater than that in the U.S., six  
22 versus 2.49, the INTERGEL patients, 6.4 versus 2.3 for

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1 the control group, control patients.

2 Next slide.

3 This second condition is that there should  
4 be no interaction between continent and the effect for  
5 each of the treatments, INTERGEL and the control. We  
6 must measure this as a change from baseline since it  
7 has been established that the baseline across  
8 treatments -- across continents are so very different.

9 This interaction is evaluated in the next  
10 four slides for each combination of treatment,  
11 INTERGEL and control, and for each endpoint, modified  
12 AFS and incidence.

13 Next slide.

14 First, let us look at the change in the  
15 modified AF score from baseline to second look across  
16 continents for the INTERGEL patients. Note that in  
17 the U.S. the second look is three and a half times  
18 greater than the baseline, 2.74 versus .78. In Europe  
19 it is only about 40 percent greater, 2.2 versus 1.6.

20 When we look at the graft, we see  
21 substantial interaction between the change from  
22 baseline in the U.S. and Europe. That is illustrated

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1 by the fact that the lines are not parallel. Rather,  
2 they intersect.

3 The difference between continents in  
4 change from baseline is even more pronounced for the  
5 control patients. In the U.S., the second look is  
6 more than four times greater than the baseline, 2.8  
7 versus .68. In Europe it is only 25 percent greater.

8 When we look at the graph, again, we see  
9 substantial interaction between the change from  
10 baseline in the U.S. and Europe.

11 Now, let us turn to the same comparisons  
12 for incidence of adhesions. Again, we see for  
13 INTERGEL the increase over baseline was greater than  
14 threefold, .68 to 2.83, while less than 25 percent in  
15 Europe, and again, our graph shows substantial  
16 interaction, the continent and change from baseline.

17 Next slide.

18 And finally for the control we see a three  
19 and a half fold increase over baseline in incidence of  
20 adhesions for U.S. patients, while for Europe, the  
21 increase over baseline is only 30 percent, for three  
22 and a half-fold, jumps from 2.27 in the baseline; at

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1 second look in Europe, 6.4 to 8.2. That increase  
2 represents 30 percent. And, again, there is evidence  
3 of interaction.

4 Next slide.

5 In summary, the baseline values are highly  
6 statistically significantly. In fact, we have seen  
7 that the modified AFS score and number of adhesions  
8 are consistently two to three times greater in the  
9 European patients. The U.S. and European patients are  
10 very different with respect to baseline values.

11 We also saw substantial interaction  
12 between change from baseline and continent. At second  
13 look, the U.S. patients scored three to four times  
14 greater than baseline for both modified AFS and  
15 incidence of adhesions while the European patients  
16 show only a modest 25 percent to 40 percent increase  
17 in their scores.

18 Thus, the U.S. and European patients  
19 appear to respond very differently to effects of  
20 treatment. Therefore, it is clearly not appropriate  
21 to pool the U.S. and European patient data, and thus,  
22 the U.S. data is the appropriate data set to evaluate

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1 the device effectiveness.

2 Next slide. Now let us turn to the issue of  
3 comparing the effect of INTERGEL on adhesion formation  
4 to that of the control, lactated Ringers, for both the  
5 primary endpoint, modified AFS, and the secondary  
6 endpoint, incidence of adhesions.

7 We will use the statistical analysis plans  
8 specified in the protocol. That is an intent to treat  
9 analysis of the 200 U.S. patients.

10 Next slide, please.

11 First, let us look at the results for the  
12 modified AFS score. Both baseline and second look  
13 scores are provided. It is clear that there's very  
14 little difference between INTERGEL and the control for  
15 both baseline and second look scores, .78 -- .68 at  
16 baseline and approximately 2.74 to 2.83 at second  
17 look.

18 The magnitude of the difference at second  
19 look is only .1 in modified AFS score, and the  
20 difference is non-significant using Wilcoxon test. We  
21 see the difference in change from baseline was only  
22 about .2, 1.96 for the INTERGEL to 2.15 for the

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1 control.

2 Next slide.

3 Now let us look at the results for  
4 incidence of adhesions. Again, notice that there is  
5 very little difference between INTERGEL and the  
6 control for both baseline and second look. In fact,  
7 the magnitude of the difference is the same at  
8 baseline and second look, that is, .2 adhesions, and  
9 if you notice there's no change from baseline for the  
10 two -- in score for change in baseline in the two  
11 groups.

12 All differences were not significant using  
13 the Wilcoxon test.

14 Next slide, please.

15 Therefore, when using the analysis plan  
16 specified in the protocol, that is, an intent to treat  
17 analysis of the 200 U.S. patients, we found that there  
18 was no statistically significant difference between  
19 INTERGEL and the control for the modified AFS score  
20 and no statistically significant difference between  
21 INTERGEL and the control in the incidence of  
22 adhesions.

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1 In fact, the observed difference of .1 for  
2 the modified AFS score was much smaller than the 2.1  
3 difference that this intent to treat study was  
4 designed to detect.

5 Thus, it has been demonstrated that the  
6 data are not combinable across continents, and  
7 therefore, the complement of 200 U.S. patients is the  
8 appropriate one to analyze and has been demonstrated  
9 there is not a statistically significant difference  
10 between INTERGEL patients and control patients with  
11 respect to either modified AFS or incidence of  
12 adhesions at second look.

13 Next slide.

14 Now I would like to discuss problems with  
15 the sponsor's analysis of all of the patients. If you  
16 recall, the pilot study had a difference of 4.1 in the  
17 modified AFS score between INTERGEL and control at  
18 second look.

19 After this study was adjusted for an  
20 unequal loss to follow-up and the worst scores were  
21 given to patients lost to follow-up in both groups,  
22 the sponsor calculated that the difference in modified

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1 AFS score that they wanted to detect was now 2.1 and  
2 that the standard deviation would increase to 5.0.

3 As already mentioned, the resulting sample  
4 size necessary to detect this difference at 2.1 with  
5 80 percent power based on this intent to treat  
6 analysis was 90 patients per treatment arm.

7 The sponsor's approach was to analyze the  
8 primary and secondary endpoints using the combined  
9 U.S. and European evaluable patients, ignoring loss to  
10 follow-up. This results in a study in which the  
11 clinical and statistical significance are no longer  
12 aligned.

13 In fact, the post hoc analysis plan now,  
14 the sponsor's post hoc analysis plan now has 80  
15 percent power to detect a difference of only 0.75  
16 instead of the 2.1.

17 Thus, using this approach can lead to  
18 analyses of the data that can result in misleading p  
19 values.

20 Next slide.

21 Now we will go on to Part 2 of my  
22 presentation. After the conclusion of the previous

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1 panel meeting, the sponsor submitted an amendment with  
2 a revised indication for use. The first part of the  
3 revised claim addresses adnexal adhesions.

4 To support a claim of effectiveness with  
5 respect to adnexal adhesions, the sponsor uses the AFS  
6 score as opposed to the modified AFS score.

7 The second part of the revised claim  
8 addresses pelvic and abdominal adhesion reformation,  
9 and the sponsor uses selected secondary endpoints  
10 performed on surgical site adhesions in an attempt to  
11 support this claim.

12 Next slide.

13 Let us first look at the second part of  
14 this revised claim. The sponsor uses the results for  
15 the secondary endpoints, reformed adhesions and  
16 surgical site adhesions, to support this part of the  
17 claim. Note that these two endpoints are subsets of  
18 the secondary endpoint incidence of adhesions. The  
19 sponsor claimed he found significant differences for  
20 these two endpoints, but only after departing from the  
21 original analysis plan using the combined U.S. and  
22 European evaluable patient group, excluding patients

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1 lost to follow-up.

2 The problem with this analysis plan is  
3 that it gives misleading p values for the reasons just  
4 discussed.

5 We should also note that since the sponsor  
6 failed to detect differences in total incidence of  
7 adhesions, the analysis of selected subsets of this  
8 endpoint can only be considered exploratory.

9 Next slide.

10 This slide presents averages for reform  
11 and surgical site adhesions for the U.S. intent to  
12 treat patient group. Also note that I have included  
13 results for de novo adhesions as well for purposes of  
14 completeness.

15 All of these form overlapping subsets of  
16 the total incidence of adhesions. Average incidence  
17 of baseline adhesions are also presented for purposes  
18 of comparison.

19 Now, let us look at the table for these  
20 endpoints. I think it is clear from this table that  
21 there's very little difference between the two  
22 products for any of the three endpoints listed above,

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1 reformed, surgical site, de novo adhesions. In fact,  
2 none of them even come close to approaching  
3 statistical significance.

4 Next slide.

5 In summary, not only were there no  
6 statistical differences between groups for the  
7 modified AFS and incidence of adhesions, but there  
8 were no statistical difference in any of the selected  
9 endpoints, reform, de novo, or surgical site  
10 adhesions, when analyzing the data as proposed in the  
11 study protocol.

12 Next slide.

13 Next we will review the data supporting  
14 the part of the revised claim dealing with adnexal  
15 adhesions. To evaluate this, the sponsor used an AFS  
16 score. Note that this score was specified, defined,  
17 and calculated after the study was completed. then  
18 exploratory or after the fact analyses were performed  
19 on the data.

20 The problem with exploratory analyses on  
21 post hoc endpoints is that if you look hard enough you  
22 can eventually find one with a small p value. That

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1 is, you will eventually find a difference that appears  
2 to be statistically significantly different.

3 Note that these types of analysis are best  
4 suited for exploring new hypotheses that can be tested  
5 in a new study. In the sponsor's last commitment,  
6 they presented the data for the AFS score stratified  
7 across three subgroups, though they have also  
8 previously presented the data partitioned in two,  
9 four, and five subgroups as well.

10 Because FDA didn't have sufficiently  
11 detailed data, we can only present an intent to treat  
12 table for the U.S. patients' data partitioned over two  
13 subgroups. This data is presented in the next slide.

14 Now let us look at the AFS data. Now in  
15 this table that the number of patients with the  
16 baseline status specified in the left is in the  
17 denominator. The number of patients, those patients  
18 having moderate or severe AFS scores at second look in  
19 the numerator, and I will illustrate this with the  
20 data in the first cell, that being this one.

21 Of the 79 patients with minimal and mild  
22 AFS score at baseline, 12 developed moderate or severe

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1 AFS scores at second look or we can take the next  
2 cell. There's five INTERGEL patients with minimal or  
3 mild -- I mean with moderate or severe adhesion score,  
4 AFS scores at baseline. Zero developed moderate or  
5 severe scores at second look.

6 As we can see from this table, there's no  
7 difference between INTERGEL and the control for the  
8 minimal-mild group, and we can reach no conclusion for  
9 the moderate or severe group as the sample sizes are  
10 so small.

11 In fact, there are only five INTERGEL  
12 patients with moderate-severe condition at baseline in  
13 the U.S.

14 Next slide. Oh, no, that slide.

15 In summary, when using the analysis plan  
16 specified in the protocol, the results show no  
17 difference between treatment groups for any of the  
18 subgroups, that is, post hoc endpoint.

19 In contrast, the sponsor's analysis used  
20 the smallest subgroup of patients with moderate and  
21 severe adhesions to derive their analysis, combined  
22 U.S. and European patients. But note that this

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1 subgroup accounts for less than ten percent of the  
2 patients in the study and includes on five U.S.  
3 INTERGEL patients.

4 Next slide.

5 Assess en route (phonetic).

6 (Laughter.)

7 MR. KOTZ: In summary, the sponsor has  
8 bought the design and intent to treat study to  
9 evaluate 180 to 200 patients, including an expected 20  
10 percent INTERGEL and ten percent control loss to  
11 follow-up. The specified sample size was reached with  
12 200 U.S. patients.

13 Since the U.S. and European data were  
14 clearly shown to be not combinable, the U.S. patient  
15 group comprises the appropriate patient group to  
16 analyze, clearly showing that using the analysis plan  
17 specified in the protocol, that is, an intent to treat  
18 analysis of the 200 U.S. patients, that there was no  
19 difference between INTERGEL and control for modified  
20 AFS score, the number of adhesions, reform and  
21 surgical site adhesions and AFS status. Thus, the  
22 product did not demonstrate superiority over the

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1 control for the primary endpoint or for any of the  
2 secondary endpoints the study was designed to  
3 evaluate.

4 Thank you.

5 CHAIRMAN RAMSEY: We're running well  
6 behind, and we have agreed to give LifeCore a chance  
7 to rebut, but I would like to ask the panel if they  
8 have any brief clarifying questions regarding the  
9 presentation for FDA.

10 Go ahead.

11 DR. D'AGOSTINO: Richard, are you saying  
12 that it's inappropriate to pool because the protocol  
13 said that the rates have to be the same in the U.S.  
14 and Europe?

15 Where I'm going is that if the subjects  
16 are randomized within centers and within countries  
17 within centers, what difference does it make if the  
18 rates are higher in Europe versus U.S. on baseline?

19 MR. KOTZ: Well, not only are they higher  
20 on baseline, but we saw the treatment effect very  
21 different as well. The effect of treatment seemed to  
22 be very different, too.

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1 It just makes it very difficult to  
2 (pause) --

3 DR. D'AGOSTINO: I don't want to take too  
4 much time. We can get into this, but I think this is  
5 a point that we want to get back to.

6 CHAIRMAN RAMSEY: A quick one hopefully?

7 DR. SHIRK: Yes. I guess I'd ask Richard  
8 obviously the same question that I asked the  
9 statisticians from LifeCore. I guess your opinion is  
10 that by not following the intent to treat protocol,  
11 that you significantly skewed the data towards success  
12 rather than failure. Is that sort of what you're  
13 saying, or that you've got a smaller --

14 MR. KOTZ: Yes. Well, they affect the p  
15 values of the statistical test, the statistical test  
16 using an evaluable analysis on the intent to treat  
17 study design.

18 Does that address your question, Dr.  
19 Shirk?

20 DR. GORDON: I have one comment here.

21 CHAIRMAN RAMSEY: Okay.

22 DR. GORDON: Just quickly, I guess just a

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1 general concern relative to how protocols go through  
2 the IDE PMA process. It was of concern to me in  
3 reviewing the information that the protocol -- and you  
4 know, there were copies of the statistical plan  
5 throughout these documents -- clearly identified three  
6 types of analyses, and yet FDA has identified the  
7 intent to treat as the only one the sponsor agreed to  
8 present and hasn't presented anything else, and that  
9 isn't clear to me from the documents.

10 So I'm assuming that the protocol implies  
11 that --

12 MR. KOTZ: For effectiveness, for  
13 statistical effectiveness the intent to treat analysis  
14 was the one that was specified. Yes, they specified  
15 several analysis plans, but we requested an intent to  
16 treat analysis plan for demonstration of  
17 effectiveness.

18 DR. GORDON: But it also shows or  
19 identifies an efficacy for efficacy purposes an  
20 evaluable -- I'm just making the point again relative  
21 to this process.

22 MR. KOTZ: Yes. If the panel is

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1 interested, I have all that data that I presented for  
2 the evaluable patients in the U.S., and I can present  
3 that to you, and you can evaluate the differences.

4 I don't think it's appropriate to  
5 statistically evaluate that data, but you can -- I'm  
6 perfectly happy to put that up.

7 CHAIRMAN RAMSEY: Let's -- okay. Go ahead  
8 and make one response if you'd like. I'm sorry. I  
9 don't know your name.

10 DR. WITTEN: Excuse me. This is Dr.  
11 Witten from FDA.

12 I just want to clarify in response to your  
13 question that the clinical perspective that was  
14 provided by Dr. Horbowj was based on the same data  
15 set used by the sponsor, which was the evaluable data  
16 set of the combined cohort.

17 CHAIRMAN RAMSEY: We will have time for  
18 questions after this session, and we are running late.  
19 So I would like to give the sponsor their designated  
20 time for rebuttal. They get extra credit if they can  
21 do it in less than 15 minutes.

22 (Laughter.)

1 DR. BECKER: Thank you.

2 I would like to clarify a couple of things  
3 for the record, and then we have a statistical  
4 comments by Dr. Piantadosi and clinical comments by  
5 Dr. DeCherney.

6 First of all, I'm very concerned about the  
7 discussions regarding the analysis plans specified in  
8 the protocol. Everybody has a copy of the protocol in  
9 your panel pack. If you'll refer to the protocol on  
10 page 28, it clearly identifies three evaluable cohorts  
11 for the efficacy analysis.

12 It does not state that the worst case  
13 imputation, the so-called intent to treat, is the  
14 primary analysis of the study. So on page 28 of the  
15 protocol, you'll find that there's three cohorts  
16 described, and all of those analyses were done by the  
17 sponsor.

18 Secondly, on page 31 you will see a  
19 special paragraph inserted into the protocol, and it  
20 reads, "As requested by FDA, a worst case imputation  
21 will be used to deal with missing data on patients at  
22 second look."

1           In 1995, I know it's hard for everybody to  
2 remember, and people, you know, who were there maybe  
3 aren't there anymore, but at the time that was  
4 considered to be by FDA -- that was presented as a  
5 requirement for clearance of the IDE, and the sponsor  
6 was told, "Put it in there and then do other  
7 appropriate analyses when you get the data per  
8 standard statistical practice."

9           So the sponsor did not choose to do this  
10 worst case analysis that I think everybody here agrees  
11 is unscientific and not sound.

12           Finally, before I turn this over to Dr.  
13 Piantadosi, I want to address another apparent  
14 misconception that will help us maybe bridge this  
15 disconnect today between our two views of this data  
16 and the submission under consideration.

17           We've heard the word "retrospective" many,  
18 many, many times, and I think that it's important to  
19 recognize, first of all, that as we have also said  
20 many times all of these analyses were prospectively  
21 defined in the protocol.

22           But FDA did, in fact, not just ask for,

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1 but required these AFS scores. On December 7th, 1999,  
2 during the course of the review of this PMA, FDA  
3 issued a major deficiency letter, and if you've never  
4 had a major deficiency letter sent to you, let me tell  
5 you what it is.

6 It's a letter in which FDA informs the  
7 sponsor that the review of the PMA cannot continue  
8 unless additional information is provided, and in  
9 order to complete the review you are given a list of  
10 analyses, studies, whatever that need to be done.

11 And in this major deficiency letter of  
12 December 7th, 1999, Item No. 8 says, "Please provide  
13 shift tables for standard AFS scores. The tables  
14 should be presented for the change in baseline after  
15 surgery standard AFS score and the unadjusted second  
16 look standard AFS score. The shift tables should show  
17 the shifts of patients from the minimum-mild disease  
18 group into the moderate-severe disease group and vice  
19 versa. In addition, the tables should be for all  
20 patients, patients with no adhesiolysis and patients  
21 with adhesiolysis."

22 So I want to clarify for the record that

1 this information was required by FDA.

2 Finally, I hope that after lunch you might  
3 give us an opportunity to explain why there seems to  
4 be a misunderstanding about the shift tables and this  
5 perception that only a few patients benefitted, when  
6 in fact all subgroups of patients benefitted in this  
7 trial.

8 Dr. Piantadosi.

9 DR. PIANTADOSI: Thank you.

10 I'd like to address a couple of points  
11 focused on the statistical review that I think are in  
12 error, and much of the difference that you've heard  
13 between the sponsor presentation and the FDA  
14 conclusions are a consequence of that error.

15 I'm going to focus on the issue of pooling  
16 because you've heard several different things about  
17 pooling, and I'd like to really clear that up.

18 The short answer to Dr. D'Agostino's  
19 question about why either baseline differences or  
20 treatment differences between continents should be  
21 consequential is that they are inconsequential. As I  
22 indicated in my remarks earlier, the issue is whether

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1 or not there is a common treatment effect across  
2 continents.

3 The information that the FDA has showed  
4 you regarding this point actually doesn't bear on the  
5 point. If I could show the first transparency, this  
6 is a reproduction of the slides that the FDA has used  
7 to argue that there are differences between the United  
8 States and Europe that render the data not poolable.

9 This is incorrect. Look at the first  
10 chart in the upper right-hand corner. What you see  
11 there is crossing lines within the INTERGEL group.  
12 You cannot learn about treatment by continent  
13 interactions by looking only within one of the  
14 treatment groups, and what you see here is actually  
15 very similar effects during the trial within the  
16 INTERGEL group.

17 And similarly, in the control group you  
18 cannot learn about interaction between treatment  
19 effect and continent by looking within the control  
20 group, and the whole series of such analyses presented  
21 by the FDA in support of their point that the data are  
22 not combinable are incorrect.

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1           The issue is whether the differences  
2 between these two control groups is a function of  
3 continent or not, and in that regard, this notion,  
4 this footnote which is mentioned on the table is a  
5 very telling footnote, and the FDA knows, for example,  
6 that they have to put that footnote there because if  
7 you remove this condition, that is, if you look within  
8 adhesiolysis category, you will see that the data are,  
9 in fact, combinable.

10           The second transparency I'm going to show  
11 demonstrates this. What you're going to see on this  
12 transparency is the results of the study and the  
13 baseline. Let's look over on the left first.

14           In U.S. and Europe, broken down by  
15 patients in the two adhesiolysis categories, look at  
16 the baseline and look at the treatment effects. They  
17 are similar in the U.S. and Europe in both  
18 adhesiolysis groups.

19           What the FDA has done in arguing against  
20 poolability is to combine the adhesiolysis groups,  
21 which you can see are different. They're different as  
22 a matter of characteristic of the patient and medical

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1 practice on the two continents. They have combined  
2 those two groups and then said that U.S. and Europe  
3 are not combinable on that basis.

4 In fact, the U.S. and Europe are similar  
5 and are combinable. That does satisfy the criteria in  
6 the protocol once you account for adhesiolysis.

7 Furthermore, if you look over here and  
8 pool across adhesiolysis, so this part of the analysis  
9 is analogous to, but not identical to what the FDA has  
10 done. You can see that actually there's a fairly  
11 strong similarity with the exception of the baseline  
12 scores in the U.S. and Europe.

13 Now, why doesn't this look more like the  
14 FDA analysis? It's because this has been based on  
15 scores for the evaluable patient population.

16 So what happens is if you make the two  
17 mistakes that the FDA has made, if you fail to account  
18 for adhesiolysis and you use the worst case  
19 imputation, then this picture looks like you should  
20 not be combining U.S. and Europe.

21 But if you read the protocol carefully,  
22 you'll actually realize that the criterion for

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1 poolability that I'm referring to here refers to the  
2 evaluable patient population.

3 So, in fact, this is the correct way to  
4 decide whether or not the data are poolable across  
5 U.S. and Europe. They are. One needs to simply  
6 account for the adhesiolysis variable and then you see  
7 the homogeneity of treatment effect, and you see the  
8 absence of treatment by continent interaction. All  
9 three of the criteria listed in the protocol are  
10 satisfied and the data are poolable.

11 Finally, I'd like to address one point.  
12 I know Dr. Rubin and Dr. Colton are to have something  
13 to say. The notion of what is a subset analysis, and  
14 this has also been implicitly incorrectly defined by  
15 the statistical reviewer at FDA.

16 A subset analysis normally refers to a  
17 subset of patients on the clinical trial, and why we  
18 worry about subset analyses are that we're afraid  
19 somebody is going to fish around in the data until  
20 they find a smaller set of patients than those  
21 randomized in the trial that demonstrates the kind of  
22 treatment effect that they would like to use to their

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1 advantage.

2 That is not what's been done here, and  
3 referring to these analyses as a subset analysis is  
4 incorrect. What has been done here is that the  
5 outcome which was prospectively collected has been  
6 used, but not all of the points on the outcome have  
7 been used.

8 This is not a subset analysis. It's the  
9 same issue as if I do a study with survival as an  
10 outcome, and I also measure time to disease  
11 progression or response rate in a cancer trial, and I  
12 may not use all of those outcomes or I may use an  
13 outcome censored by one rather than another. That is  
14 not a subset analysis, provided I conduct it on all of  
15 the patients on the trial, which is what has been done  
16 here.

17 So referring to this as a subset analysis  
18 in an attempt to remove and denigrate its pedigree is  
19 incorrect, and I want to be very sure that the panel  
20 understands that this is not that type of subset  
21 analysis.

22 Thank you.

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1 Dr. Rubin

2 DR. RUBIN: Although I'll focus my  
3 comments on the imputation and the ITT analysis, I did  
4 want to make one comment that Dr. Colton addressed  
5 earlier.

6 This issue of the pilot study and the  
7 difference between a pilot study and the pivotal  
8 study, we have a pilot study of 21 subjects, and you  
9 have a pivotal study of 281, and the fact that there  
10 are some differences there are supposed to somehow  
11 impugn the p values and the analyses of the  
12 unbiasedness of the randomized pivotal trial of 281  
13 subjects is really absurd. They don't affect the p  
14 values. They don't affect the obtained data. They  
15 just don't.

16 The pivotal trial is more than ten times  
17 as large. It's not at all a surprise that the results  
18 in the pivotal trial are somewhat different than the  
19 results in the pilot study, and in fact, I think if  
20 you did statistical tests, did some back of the  
21 envelope ones, they're not even significantly  
22 different between the pivotal trial and the pilot

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1 because the pilot is so small and it has such large  
2 variability relative to pivotal trial.

3 Ted may want to add to that later.

4 With respect to the ITT population and the  
5 ITT analysis, as I suggested earlier this morning, you  
6 would see lots of transparencies with ITT analysis on  
7 it, as if that meant that that was the ITT analysis.

8 I want to emphasize again ITT refers to  
9 the intention to treat population because all of those  
10 patients who were randomized and treated, there were  
11 281 patients randomized and treated. There were 16  
12 without second look data, and in order to do an ITT  
13 analysis on that population, you must somehow impute  
14 either explicitly or implicitly.

15 Now, the analysis, the imputation analysis  
16 that the FDA proposed and carried out was based on the  
17 worth possible value being imputed from each woman  
18 without a second look. The worst possible value of  
19 AFS, the worst possible value of modified AFS; so even  
20 a woman who was pregnant at the time for second look  
21 who refused second look because she was pregnant, she  
22 was imputed to have the worst possible values of

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1 adhesions.

2 I don't think that's reasonable. I don't  
3 think it's scientific at all.

4 The fact that FDA can come up with an even  
5 less scientific and even less reasonable method of  
6 imputation, that is, everybody who was exposed to  
7 INTERGEL gets the worst possible value and everybody  
8 who was exposed to Ringers gets the best possible  
9 value, the fact that that's even a less scientific and  
10 less reasonable analysis doesn't justify the analysis  
11 that they did as being reason nor scientific. It's  
12 just not.

13 This idea that the results are only shown  
14 for a small subpopulation in the U.S., I do have some  
15 transparencies that were based on the scientific  
16 imputation that we did do that was blinded, again, to  
17 outcome, blinded to results, and maybe it's  
18 appropriate. I just put up one transparency which  
19 shows result of those analyses in the U.S.

20 So this is only in the U.S. It does not  
21 even include the European patients, and it only is  
22 looking at those patients in the U.S. with no baseline

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1 adhesiolysis, and as noted by other people, in the  
2 U.S. more than half the patients had no baseline  
3 adhesiolysis.

4 And you'll see that in this subgroup that  
5 there are 63 INTERGEL, 59 controls, and with respect  
6 to all the outcomes, they're in the favorable  
7 direction, and for the modified AFS, which is the  
8 primary endpoint, both adjusted and unadjusted,  
9 adjusted for baseline adhesions, the results are  
10 significant, well beyond the traditional .05 level.

11 So if you want to take away some P values  
12 that you think are scientifically founded, there they  
13 are, and they're strongly in favor of INTERGEL over  
14 control.

15 Thank you.

16 DR. COLTON: I just want to add a few  
17 words with regard to the issue of statistical power,  
18 and in fact, actually in some of the correspondence  
19 from the FDA, there was a term used of a study being  
20 overpowered, and Dr. Kotz referred to misleading p  
21 values.

22 And first of all, if one believes in p

1 values, and not all statisticians believe in p values,  
2 but I think certainly the FDA is among those who  
3 worship at the shrine of the p value --

4 (Laughter.)

5 DR. COLTON: -- the p value is, the power  
6 of the study, as I said, is a hypothetical statement.  
7 I think we've shown with reasonable back-up and  
8 evidence that the continental and the U.S. sites can  
9 be combined. There's no reason not to combine them.

10 Even though the study may have been  
11 designed to have a sample size of 180, here are the  
12 data. Here are the total data we have. Here's what  
13 we calculate, and putting it in terms of a p value,  
14 here is the p value.

15 It's not misleading. This is the  
16 statistical significance. Whether that p value, for  
17 whatever difference was found, is clinically  
18 meaningful, I think we've already said that that is  
19 really an issue that is to the clinical expertise.

20 But to me what has been done in this  
21 study, here are all of the data we have. We've  
22 analyzed all the data. We've stratified. We've

1 looked at the continent versus the U.S.

2 When we look at all of the data together  
3 and we make reasonable assumptions about the missing  
4 data, these are the p values that we come up with, and  
5 I don't think they can be in any way said as being  
6 misleading or being overpowered. This is what we  
7 found, and the issue is: is this clinically important?

8 Okay. I just have three points. Number  
9 one, the fact that adhesions are not predictive of  
10 morbidity, I don't think that's true. As far as  
11 infertility is concerned, there are a fair number of  
12 prospective studies looking at the surgical approach  
13 where infertility is corrected because the only pick-  
14 up mechanism is altered.

15 Now, as far as the AFS score versus the  
16 modified AFS score, essentially the -- and you heard  
17 that this was required -- the AFS score is really a  
18 carve-out of the modified AFS score. all of the data  
19 points that are necessarily to calculate out the AFS  
20 score are present in the modified AFS score as  
21 designed in the study.

22 So although the score is retrospectively

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1 calculated, it's based on prospective data.

2 Now, the criticism that neither of these  
3 scores are perfect and predict outcome, I think that  
4 that's fair. There are no studies documenting that  
5 the AFS score predicts outcome, and basically what  
6 it's evolved to us just an observational score. There  
7 has to be some way to observe adhesion formation and  
8 adhesion reformation, and the AFS score just  
9 quantitates that.

10 Now, just looking at outcome, Dr. Horbowyj  
11 talked about the incidence and did quote the figures  
12 of a 31 percent decrease in reformation and a 23  
13 percent decrease in surgical site adhesions, and as  
14 far as a clinical standpoint, that's impressive and  
15 comparable at least to other adjuncts of therapies  
16 that are available.

17 DR. FARO: In regards to their analysis on  
18 infection, it would be helpful for me to understand  
19 what criteria Dr. Horbowyj used if she reviewed these  
20 clinical records in deciding which patients actually  
21 met criteria for infectious postoperative morbidity.

22 In reviewing it on a limited case basis,

1 the wound infection rates, if we just focus on that,  
2 was comparable, two patients in each group. I don't  
3 think that Ringer's lactate or lactated Ringers or  
4 INTERGEL contributed to wound infection in either  
5 case. I think the low rate of wound infection is  
6 acceptable in gynecologic abdominal surgery that we  
7 saw here.

8 If we look at a patient classified as  
9 having bladder pain and then classified as infected,  
10 it's rather difficult to determine a diagnosis of  
11 infection in this patient. Many patients who have  
12 Foley catheters inserted will have bladder pain  
13 postoperatively. They will have bladder spasm  
14 secondary to the indwelling catheter.

15 So we have a discrepancy here, but the  
16 bottom line is this compound in no way supported  
17 infection in the animal studies. There was no  
18 statistical difference between the two groups, and I  
19 would expect if this compound had a basis for inciting  
20 infection in the pelvic cavity or in the abdominal  
21 cavity, we would have seen a significant number of  
22 patients who developed a paralytic ileus following

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1 surgery, and this was not the case.

2 And these dissections that are done in  
3 this type of surgery often involve adhesions between  
4 the adnexa, the uterus and the bowel.

5 So I think this is, in my opinion, very  
6 safe agent with regard to infectious morbidity and the  
7 potential risk for infectious morbidity.

8 CHAIRMAN RAMSEY: Okay. We are 40 minutes  
9 behind schedule. Yeah, I think we're going to cut  
10 lunch to 45 minutes. That will be the penalty for  
11 over-going, and let us convene back at five minutes to  
12 one.

13 (Whereupon, at 12:11 p.m., the meeting was  
14 recessed for lunch, to reconvene at 12:55 p.m., the  
15 same day.)  
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## A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:00 p.m.)

CHAIRMAN RAMSEY: Welcome back. The meeting will reconvene with a panel discussion portion of our meeting.

Although this portion is open to the public, we ask the public attendees not participate except at the specific request of the panel. Okay?

As I stated at the beginning of today's meeting, the panel is charged to answer the following question and to make a recommendation to the center director as to how this dispute should be resolved, and I'm going to read the question and try to be accurate this time.

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

And in answering that question, we have two specific questions to address. One is whether the statistically significant differences between INTERGEL

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1 solution and control can be considered clinically  
2 significant, and second, whether the benefits of the  
3 product outweigh the potential risks, including any  
4 risk of infection.

5 And I think a couple of procedural things  
6 before I get started. Someone left a key that was  
7 found on the floor, and if this is anyone's we'll  
8 leave it out front for you to get.

9 And so let me go on. So what we're going  
10 to do now is the panel is going to discuss among  
11 itself and ask questions of the sponsor or the FDA.

12 One thing for the panel. Dr. Piantadosi  
13 has to leave at 1:30 to teach a class, and so if you  
14 have specific questions for him, now would be the time  
15 to do it.

16 But let me, again, to get things started  
17 and frame the question, let me start with the first  
18 question: whether the statistically significant  
19 differences between INTERGEL solution and control can  
20 be considered to be clinically significant.

21 And I'll open it to the panel to address  
22 that question and ask questions to the sponsor or FDA.

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1 DR. D'AGOSTINO: Let me start maybe a  
2 little bit further back than where you are right now,  
3 but I think the question of surrogate versus endpoint  
4 is an important one. I mean, I think that the  
5 adhesions is an appropriate endpoint. If it isn't,  
6 then we're wasting our time.

7 Am I comfortable in making that  
8 assumption, that everybody thinks that the adhesions  
9 is all right?

10 Then the question that I have and want to  
11 begin the discussion is one of the things that bothers  
12 me, and I keep hearing, I think, different things from  
13 the FDA versus the sponsor, was the shift from the  
14 modified to the unmodified or whatever the R stood  
15 for, was that analysis not included in the package  
16 that went to the previous panel? It wasn't discussed,  
17 but was it included?

18 And when did that analysis come?

19 See, I'm bothered by the notion that you  
20 have an endpoint in a protocol and you direct your  
21 analysis to that, and then you later on -- not a  
22 subset -- but later on you shift to a new endpoint,

1 and when did that shift come? Was it FDA suggested?

2 DR. KRAUS: That data was presented to the  
3 January 12, 2000 panel.

4 DR. D'AGOSTINO: So it's not completely --

5 DR. KRAUS: Slightly different than what  
6 was presented in the January or June 12 or June 2nd  
7 amendment, but basically the same data.

8 DR. D'AGOSTINO: So it's not a completely  
9 off-the-wall, brand new thing that we're facing.

10 DR. KRAUS: No.

11 DR. D'AGOSTINO: And then the other  
12 question, just to go on if you don't mind when I have  
13 this here, but I'd be happy to give it, with this  
14 pooling question I understand -- I think I understand  
15 -- what the FDA's concerns are, but I think also that  
16 good statistics practice would argue that you can, in  
17 fact, reasonably pool the data if you do the  
18 randomization within groups and so forth and you have  
19 an analysis that indicates that the treatment effects  
20 are pretty stable across the items you're pooling.

21 So I do, again, think I understand what  
22 the FDA's arguments are, but I do think that if I'm

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1 making sense and if people are agreeing with me, I  
2 think the U.S. and the European, pooling those  
3 together and looking at analysis does make sense to  
4 me, and again, I stand to be corrected, but I think  
5 that's -- from what I heard, I think that's a  
6 reasonable approach.

7 CHAIRMAN RAMSEY: Go ahead.

8 DR. GONZALEZ: My question, it's more of  
9 an observation. I just want to know if the FDA and  
10 the sponsors feel the same way on it, but, you know,  
11 in looking at the presentations this morning, there  
12 was a concern of prospective versus retrospective, and  
13 my question is from what I can gather -- and I'm just  
14 trying to make sure that that's my correct perception  
15 -- from what I can gather, the agency's definition of  
16 retrospective is the pulling out of the data from data  
17 that had been prospectively collected.

18 Am I correct on that assumption?

19 CHAIRMAN RAMSEY: Do you want the agency  
20 to respond to that?

21 DR. GONZALEZ: Yeah, whoever feels --

22 CHAIRMAN RAMSEY: Okay.

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1 DR. WITTEN: The point that was made about  
2 the retrospective AFS score, yes, was pulling out  
3 those data points and then collapsing them into  
4 another score.

5 CHAIRMAN RAMSEY: Go ahead. Dr. Shirk.

6 DR. SHIRK: Well, I guess I've got several  
7 questions, but they all sort of revolve around the  
8 initial study design. It seems to me that a lot of  
9 the problem that we're seeing with the statistical  
10 analysis comes from the fact that the initial pilot  
11 study was basically based totally on adhesions, and  
12 that the scores were fairly high, and you could see a  
13 significant drop, you know, from the treatment group  
14 to the initial group.

15 So that the initial study was based and a  
16 statistical model was based on basically treating  
17 patients with adhesions and seeing what happens  
18 afterwards.

19 The study then went on. The final study  
20 basically incorporated a group of patients that  
21 include a large group of patients that had no  
22 adhesions to begin with, and then to see what those

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1 adhesion -- what kind of adhesions those procedures  
2 ended up with.

3 These are obviously procedures with known  
4 adhesive complications, but to me it obviously shows  
5 that we'd have had an easier time with just all  
6 adhesion patients and seeing how we drop off.

7 The problem is the number of parameters  
8 that are involved with this thing and how do we  
9 statistically handle the number of parameters?  
10 There's no control on surgical technique. There's no  
11 control on the procedures done or materials used in  
12 the procedures. Each of these have significant  
13 factors as far as adhesion formation.

14 And then you've got two groups of  
15 patients, one group that has adhesions and you're  
16 trying to see how many adhesions didn't reform, and  
17 then a group of patients that basically had no  
18 adhesions who then basically formed adhesions.  
19 Certainly the new indications are basically almost  
20 aimed at that small subgroup of patients that had  
21 dense adhesions to begin with and then didn't reform  
22 them, and how can we make a statistical statement on

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1 a small subgroup of patients in the study versus, you  
2 know, using the whole group of which, you know, two  
3 thirds of them didn't have any adhesions to begin  
4 with.

5 CHAIRMAN RAMSEY: Would you like either  
6 group to respond or just comment for us?

7 DR. SHIRK: Well, I think, yeah, I guess  
8 first of all I'd like Ralph to respond to that.

9 DR. D'AGOSTINO: No, I think that's --

10 DR. SHIRK: And then the group.

11 DR. D'AGOSTINO: I think that's important.  
12 I didn't want to go on and on, but that's where I was  
13 heading also. You have 80 percent with basically  
14 nothing at baseline. Some of them develop adhesions.  
15 You have I think it's 26 individuals, if I have the  
16 right numbers. Twenty-six individuals had moderate-  
17 severe adhesions to begin with, and is that the group  
18 of real interest?

19 And I did mention it earlier today, and I  
20 though the sponsor said they were going to respond to  
21 it later on. I don't find the numbers very  
22 compelling. As a statistician, I'm surprised there's

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