

1 would like to make at this point is that the design of the
2 study, as has been stated previously, was not statistically
3 powered to look at the sensitivity of the device. In fact,
4 the definition of sensitivity or accuracy of predicting bad
5 outcomes was not agreed upon by the sponsor and the FDA
6 prospectively.

7 For the safety of the device, there were three
8 neurologic sequelae, three infants who had seizures in the
9 immediate postpartum period, one in the test group and two
10 in the control. There were five deaths, four from severe
11 congenital, life-threatening anomalies. There were two in
12 each, test and control group. Then, there was one infant
13 that was apparently normal, that Dr. Garite mentioned, that
14 died that was in the test group.

15 There were some ecchymoses noted in the test and
16 control group. There were more in the test group than in
17 the control, transient pressure marks, and there were no
18 thermal or optical complications, which is important
19 information to us when you consider the clinical review we
20 are doing.

21 As far as maternal safety, there seemed to be no
22 difference between the two groups with the use of the
23 device.

24 This concludes my discussion of safety, however,
25 since I have just mentioned the deaths and neurologic

1 sequelae, I would just like to take a minute to look at
2 extremely small portions of the tracings from two of these
3 patients. I think they are valuable in understanding some
4 of the issues we are discussing here today.

5 I am going to leave my slide on because our
6 computer has a tendency to turn off and then need to be
7 completely rebooted. So, one of us is going to come up and
8 push buttons just to keep the computer running. I just want
9 to be able to use the laser pointer without worrying hitting
10 anybody in the eye.

11 So, this is patient 3042, right here. Again, I
12 really just took a small segment. The method of delivery
13 for this patient was vaginal. The outcomes upon delivery
14 were 3, 7 and 8 at 10 minutes. The postpartum course was
15 complicated by tension pneumothorax that was discovered
16 alter, then a grade 4 hemorrhage and eventually death. The
17 infant was taken off life support after it was noted that
18 the neurologic damage was too severe.

19 The time of delivery was 8:18 in the morning and
20 the time of this tracing is 6:30 in the morning. So, this
21 is the fetal heart rate. This is the oximeter, and these
22 are the contractions. There is an internal scalp electrode
23 on and external uterine pressure monitor, and then the fetal
24 scalp electrode. The contractions are occurring about every
25 minute and a half. Of course, we can't report on intensity

1 because it is an external monitor. The fetal heart rate is
2 about 170. Here is 150; here is 180. So, it is about 170.
3 There are late decelerations with every contraction, and
4 there is no beat to beat variability. The oximeter reading
5 -- this is 40 and this is 60, and it is the same grade
6 levels that you use when you are looking at contractions.
7 So, 40 would be 40 percent, 60 would be 60 percent. So, it
8 is reading somewhere around 50 percent, the oximeter
9 reading.

10 My point in showing this tracing is that, you
11 know, is the tracing non-reassuring fetal heart rate and it
12 is appropriate to continue because of the oximeter reading?
13 Or, is it actually an ominous tracing and it is time to make
14 a decision based on the fetal heart rate?

15 As pointed out by the company, I think when you
16 are looking at fetal heart rate tracings and when you are
17 considering this particular device it is critical to
18 remember that we are talking about an adjunct to the fetal
19 heart rate tracing monitor, and that we are not going to be
20 using the oximeter in isolation.

21 This patient had pregnancy induced hypotension and
22 delivered at 36 weeks. She had a cesarean section for non-
23 reassuring fetal status. The arterial cord pH was 7.17.
24 The Apgars were 7 and 9. There was a grade 4 hemorrhage and
25 seizures. The time of delivery was seven o'clock in the

1 evening, and the time of this tracing -- this says 5:00 p.m.
2 but the notes that were given in our PMA said 4:30. I know
3 that because here is the time of randomization, right here,
4 and that was noted to be 4:30 -- a small difference.

5 So, this is, again, the fetal heart rate, the
6 oximeter tracing, and then the contraction monitor. It is
7 an internal scalp electrode, an internal uterine pressure
8 monitor and then the oximeter. There are contractions about
9 every minute. At this point, they are not very high in
10 intensity but they are very frequent. The fetal heart rate
11 is about 140. There is decreased beat to beat variability.
12 There are a few variables.

13 I think what is important -- then, I just want to
14 point out here is the oximeter reading. It is at 30 right
15 when the oximeter was placed. Then it drops to below 30.
16 Here is the line that is 30, right between 30 and 40. It
17 stays there for several minutes and begins to recover again
18 at the end, and it does recover in the next few minutes.

19 I think what is important to consider here is that
20 this meets the definition of non-reassuring which, according
21 to the algorithm, requires some intervention. And, I think
22 what we need to think about is are the definitions of non-
23 reassuring and reassuring for the sensor readings and the
24 instructions for response that are in the labeling
25 appropriate and sufficient enough for this particular

1 device.

2 There was the unexpected finding of cesarean
3 sections for dystocia. Again, this tells you the number of
4 patients who delivered. There were 94 in the test group and
5 43 in the control who delivered for the indication of
6 dystocia by cesarean section.

7 The discussion today focused on four different
8 possibilities that might help explain why there was an
9 increased rate of cesarean sections done for dystocia in the
10 test group: The possibility that the investigator was
11 sectioning for dystocia but was really more concerned about
12 the fetal heart rate tracing; the idea that dystocia was,
13 indeed, the true diagnosis and that the proper diagnosis was
14 unmasked by the use of the oximeter and the fetal heart rate
15 tracing; the possibility that labor was slowed as a result
16 of having the device in place; and the possibility that the
17 risk factors for cesarean section were not the same between
18 the test and control groups.

19 I think the sponsor has adequately proved that the
20 labor, indeed, was not slow and that the risk factors were
21 well-matched. So, I am not going to discuss those two
22 points but I do want to look a little bit at investigator
23 bias and the proper indication.

24 The sponsor evaluation for the correct diagnosis
25 was to look at partograms of all the patients who underwent

1 cesarean sections for dystocia. This was done in a blinded
2 fashion. In other words, partograms were created for all
3 people in the test and control group, without documenting on
4 the partogram whether they were in the test or control
5 group. Then, these were reviewed by two of the clinical
6 investigators who didn't know in advance either.

7 According to that evaluation, it looks like both
8 groups were appropriately sectioned for dystocia and there
9 was no mismatch between the two groups.

10 We think there might be some additional
11 information that would be useful to us. This is information
12 that we do not currently have. The partogram study was a
13 valuable study. It could be even more valuable, or we could
14 get additional information if, instead of just looking at
15 the patients who were cesarean sectioned for dystocia, we
16 looked at all the patients who were cesarean sectioned in
17 the pilot, pivotal and randomized portions of the trial as a
18 way to get away from knowing that the diagnosis ultimately
19 was dystocia. This way, you really wouldn't know what the
20 patient was sectioned for; you would just be examining the
21 partograms and they could again be looked at for the
22 presence or absence of dystocia.

23 As alluded to, it would be valuable or nice to
24 know if the labors were adequate. Unfortunately, this
25 information, it looks like, wasn't collected during the

1 study, and there may be other information that would be
2 useful for us to have with regards to investigator bias and
3 we look forward to panel discussion about that particular
4 issue.

5 I think another finding that is important to
6 consider when you are looking at the results of cesarean
7 sections for dystocia is the number of patients who
8 underwent assisted vaginal delivery for each one of the
9 different indications.

10 This graph shows the number of patients who had an
11 assisted vaginal delivery for each of the different
12 indications -- non-reassuring fetal status, fetal
13 intolerance to labor and dystocia, dystocia and other. The
14 light colored column is the test group and the darker, pink
15 column is the control group. You can see that in both the
16 NRFS and the dystocia indications the rates of assisted
17 vaginal deliveries were the same, which is definitely a
18 discrepancy between this and the results and the outcomes
19 for the patients who had cesarean sections.

20 We have looked at a few other things to try and
21 better understand why there were more cesarean sections for
22 dystocia. We looked to see if the use of terbutaline was
23 matched between the control and test groups; whether the
24 registration times were matched; whether there was dystocia
25 present before randomization and if that was matched between

1 the test and control groups; whether there were any
2 differences between the investigator sites in terms of the
3 outcomes or the reasons for cesarean section; whether the
4 complication rates between the two groups were the same; and
5 not the risk factors but the number of patients who had risk
6 factors for cesarean section were equal between the two
7 groups. And, there seemed to be no difference in any of
8 these for the test and control group.

9 The discussion of proper indication -- part of it
10 was that it looks like that there is a shift between
11 cesarean section for non-reassuring fetal status and
12 cesarean section for dystocia, but the overall section rates
13 stay the same and, you know, I think we agree with that. At
14 this point, however, I think it is premature to explore this
15 option until we further and fully explore the possibility
16 for investigator bias.

17 Again, just to help us understand and think about
18 different parts of the study results when having the panel
19 discussion, I want to highlight two differences between the
20 baseline and the pivotal study.

21 Now, in the baseline study it was observational.
22 So, there was no intervention at all. The inclusion
23 criteria were the same, and the algorithms that were used to
24 manage the patients were the physicians' own algorithms.
25 So, they were not the algorithm as defined by the protocol.

1 Serious adverse events were defined as an adverse
2 event that requires major medical or surgical treatment
3 outside the realm of routine obstetric and neonatal care.
4 Examples for the neonate included hypoglycemia, respiratory
5 disorder and sepsis.

6 As you will note here, there is 6 percent adverse
7 event rate in the baseline study and a 14 percent adverse
8 event rate in the randomized, controlled trial.

9 As far as the overall cesarean section rates in
10 the baseline group, the cesarean section rate overall was 20
11 percent. I apologize, it may be blank in your handout. In
12 the test group of the randomized, controlled trial it was 29
13 percent and in the control group it was 26 percent. Which
14 difference between the test and control group led to these
15 different findings, either the adverse events or the
16 cesarean section rates, I think is very difficult to know,
17 and that is why it is important to keep these findings in
18 mind when considering the study conclusions.

19 A brief mention about the logistic regression
20 analysis, the company did look at several different reasons
21 why there may have been this unusual finding as far as the
22 cesarean section rates for dystocia. One of the things that
23 they discovered was that if you compared cesarean section
24 rates for dystocia in the test group and epidural placement
25 at less than 5 cm, you came out with nearly significant

1 interaction between the two.

2 The reason why we are looking at this in the
3 context of the labeling and patient population is because
4 this turns out to be 700 out of the 1000 patients who had
5 epidurals placed at less than 5 cm. So, I think we don't
6 have an answer yet but we are in the process of exploring
7 this with the company to help better understand it because
8 it might affect the labeling for the patient population.

9 In summary, we have a device that has the
10 potential to give us more information about the fetus in
11 labor, and in this randomized, controlled, carefully
12 designed study the use of the device gave us some
13 unanticipated results. We certainly look forward to panel
14 deliberation.

15 Thank you. I will entertain any questions.

16 CHAIRMAN BLANCO: Thank you. Yes, I have a
17 question. When you looked at the baseline versus pivotal C-
18 section rates, did you analyze the 20.1 percent versus the
19 other, and is there a statistically significant difference
20 between the C-section rates?

21 DR. MITCHELL: Yes.

22 CHAIRMAN BLANCO: I am sorry, is that, yes, you
23 analyzed it, or, yes, there is a difference?

24 DR. MITCHELL: I am sorry, yes, to both questions.

25 CHAIRMAN BLANCO: Thank you.

1 DR. ROY: Could you further amplify what the
2 reasons for the C-section were in the baseline?

3 DR. MITCHELL: Oh, you mean the breakdown? No, I
4 personally don't have that. This was the overall cesarean
5 section rate. The sponsor will be happy to answer that
6 question for you. I don't have the breakdown in that of how
7 many were for NRFS; I was just looking at the overall.

8 CHAIRMAN BLANCO: Any other questions from the
9 panel members?

10 [No response]

11 Thank you very much. We have actually a couple of
12 minutes. Go ahead.

13 DR. EGLINTON: Just because Dr. Mitchell said that
14 the FDA is still working with the company to clarify some of
15 the logistic regression analyses, I had a question -- the
16 reason why I asked if you had your database here and could
17 you do another analysis today.

18 On page 2-134 is the discussion about the
19 interaction between test group assignment to pulse oximetry
20 with epidural placement under 5 cm leading to cesarean
21 section for dystocia. Therefore, I have another regression
22 I would like you to perform. My question is, is this
23 statement true? I will read the statement. This is
24 analogous to your statement that is in the PMA: The
25 observed cesarean rates for NRFS plus FILDYS indicate that

1 the effect of test group assignment, i.e., assigned to FHR
2 only, on the cesarean rates for NRFS plus FILDYS exists
3 primarily for subjects with epidural placement occurring at
4 cervical dilations less than 5 cm. It is the other side of
5 the less than 5 cm dystocia coin. It should be true.

6 CHAIRMAN BLANCO: We will go ahead and get that
7 answer after lunch. Any other questions from the panel
8 members for the company that they would like to see answered
9 when we start our after lunch session? Yes?

10 DR. DIAMOND: I have one question, and maybe they
11 were talking about two different things, but I understood
12 when the company gave their presentation that when the
13 tracings were reviewed, they knew which group the patients
14 were in but the partograms that Dr. Mitchell was just
15 referring to, she said that it was done in a blinded
16 fashion; they didn't know the assignment. Are those two
17 different things?

18 DR. GARITE: Yes. Dr. Nijland reviewed the case
19 report forms that were filled out by the research nurse and
20 the fetal heart rate tracing. We made up partograms
21 separately on patients who had cesarean section for
22 dystocia. Those are labor curves. So, you plot out
23 dilation and station on a graph and then those were totally
24 blinded as to group assignment.

25 CHAIRMAN BLANCO: I had a couple of questions that

1 maybe we can answer in the afternoon. Dr. Porreco, your
2 data on slide 35, do you have similar data for the control
3 group? This is where you have the test group and you divide
4 them out.

5 Then, on your slide number 41, one of the things
6 that you referred to is that it is better to get the right
7 diagnosis because you can take time and you don't have an
8 increased risk of complications from rushing to section. I
9 would ask do you have, from your data in your study, any
10 evidence of increased rate of complications in the patients
11 that went to cesarean section for non-reassuring fetal heart
12 rate pattern compared to the ones that had dystocia? Are
13 those clear?

14 DR. PORRECO: Yes.

15 CHAIRMAN BLANCO: Thank you. Anyone else who has
16 any questions?

17 DR. D'AGOSTINO: A question on the threshold of 30
18 percent, the ROC analysis is only on 46 subjects, 50 points
19 and what-have-you -- lots of variability. Is there any way,
20 or have you done it, in terms of the clinical study that --
21 again retrospectively, but if you had varied that a bit it
22 wouldn't make a difference or would make a difference? How
23 sensitive is it? I mean, some of the tracings, and what-
24 have-you, might indicate that you put an awful lot on 30
25 percent. Others may indicate that 30 percent is a ballpark

1 figure. Is there something you can do with the data to give
2 us some indication of that?

3 CHAIRMAN BLANCO: Any other questions?

4 [No response]

5 One other thing, was there a standardized length
6 of time that the fetal FSpO2 monitor had to show 30 percent
7 or above or below to call it whatever percentage you were
8 going to call it? Do you understand the question?

9 DR. SWEDLOW: Yes.

10 CHAIRMAN BLANCO: All right?

11 MS. YOUNG: Just a quick clarification, Dr.

12 Garite, when I asked about the nurse being one-to-one
13 continuously by the mother's bedside I think you said that
14 the study nurse was and that probably after a woman has been
15 found to have a non-reassuring heart rate a nurse would be
16 likely to be assigned to her. Well, I would like to be a
17 bit more precise about that. Does the use of the device
18 actually require one-to-one staff-patient ratio for the
19 woman continuously throughout the labor?

20 CHAIRMAN BLANCO: Please come to the microphone.

21 DR. GARITE: I think it is better for a nurse to
22 answer.

23 CHAIRMAN BLANCO: Identify yourself.

24 MS. TOWNSEND: I am Nancy Townsend, study nurse at
25 Vanderbilt. I want to clarify the question. Is the

1 question does the device require one-on-one nursing? Is
2 that your question?

3 MS. YOUNG: My question is does the device require
4 one-on-one staff nurse to be at the patient's bedside, not
5 somewhere else looking at a video picture somewhere?

6 MS. TOWNSEND: No, I do not believe it does. When
7 I was the study nurse for this study, several of the nurses
8 who had patients in the test group -- although it was ideal
9 to have just one patient at the time the tracing became
10 significantly non-reassuring, many of the nurses did have
11 another patient in addition to this one. And, the study
12 nurses were not present at the bedside continuously. The
13 study nurses were required to be present on labor and
14 delivery. I want to make sure that that is clear. So, to
15 answer your question, no, the staff nurse was not one-on-one
16 in all cases with this monitor. It did not require that.

17 CHAIRMAN BLANCO: Yes?

18 DR. IAMS: I have one more regarding the
19 definition of fetal intolerance to labor. I did not see a
20 standardized --

21 CHAIRMAN BLANCO: Let's go ahead and answer those
22 after lunch. Okay?

23 DR. SHARTS-HOPKO: I don't know which one of you
24 wants to take this, but in the training manual there is a
25 page where you talk about what happens when the pulse

1 oximeter doesn't match the fetal scalp sampling, and that
2 raised in my mind the question does Mallinckrodt think that
3 clinicians should be doing fetal scalp sampling along with
4 the use of their device?

5 CHAIRMAN BLANCO: Okay. Any other questions from
6 the panel before we break for lunch?

7 DR. IAMS: There is one more. How many adverse
8 outcomes defined as fetal acidosis were there in the total
9 study group?

10 CHAIRMAN BLANCO: Okay. Well, it looks like the
11 sponsor and company won't get much of a lunch today, but we
12 do appreciate your hard work.

13 [Laughter]

14 For the panel members, let me remind you that all
15 of our deliberations are public record and, therefore, we
16 should not deliberate any of the issues when we go off to
17 lunch. We are having lunch, therefore, in the back room of
18 the restaurant next door, and we will reconvene promptly at
19 one o'clock and be back on track, hopefully.

20 [Whereupon, at 12:12 p.m., the panel recessed for
21 lunch, to reconvene at 1:04 p.m.]

1 AFTERNOON PROCEEDINGS

2 CHAIRMAN BLANCO: Let's call the meeting back to
3 order. The way that we are going to do this, we are slated
4 to start at one o'clock for the panel deliberations but we
5 are going to take ten minutes to hear some of the answers as
6 best we can. We need them very short and to the point on
7 some of the questions that were asked earlier on. Again,
8 remember, some of the questions were really more appropriate
9 discussion issues that we will discuss. What I think I
10 would ask you to concentrate on is the answers to specific
11 numbers and those kinds of issues. Okay? Are the company
12 folks ready?

13 DR. SWEDLOW: I believe so.

14 CHAIRMAN BLANCO: Remember to identify yourself
15 the first time for those folks up front.

16 DR. SWEDLOW: My name is David Swedlow. I will do
17 my best at compressing these questions.

18 CHAIRMAN BLANCO: Can you use the mike?

19 DR. SWEDLOW: These are in no special order,
20 except the ones I wrote down. There was a question, and I
21 will paraphrase it, was the accuracy spec. good enough? I
22 think that will take time to answer and we will do it later.

23 There was a question about the ten patients who
24 had difficulty -- oh, that was already answered.

25 There was a question about interactions with early

1 epidurals that was asked by Dr. Eglinton. I believe I have
2 the answer to that, and I would like to show it, if I might.

3 CHAIRMAN BLANCO: Please, go ahead.

4 DR. SWEDLOW: I believe that the question can be
5 paraphrased by saying was there a similar association
6 between C-section for either non-reassuring fetal status or
7 FILDYS or the combination in control patients early versus
8 late epidural. That is, if there is a similar kind of
9 sorting that takes place or differentiation, then that is
10 evidence -- I believe I am quoting -- evidence that it is
11 really better diagnosis. I hope that that is the right
12 question.

13 I offer you in answer three different approaches,
14 just because it is kind of overwhelming. I also apologize
15 for the manual approach; I just couldn't get it together
16 quickly enough.

17 This is a similar analysis to the table that you
18 mentioned. Specifically, for non-reassuring fetal status C-
19 sections and C-sections for the combination of fetal
20 intolerance to labor and dystocia. The top is non-
21 reassuring, the bottom is this grey zone of FILDYS. The top
22 of the top is late epidurals, epidurals placed at or later
23 than 5. The bottom one are early epidurals. So, for non-
24 reassuring, using a similar analysis as is in that table,
25 there is a pretty strong association between early epidurals

1 and the sectioning for distress; p equals 0.005. In the late
2 epidurals, that doesn't exist; p equals 2.5.

3 When you look at FILDYS alone -- the numbers are
4 kind of small so I am not quite sure, that could be a type 2
5 error. Who knows? But in early epidurals for FILDYS as
6 well there is an association in early epidurals for
7 sectioning for FILDYS, in other words, for distress alone or
8 for FILDYS alone the answer is it is the same kind of
9 diagnostic.

10 Since I like to combine rather than split, I did
11 the combination and this is the combination of the previous
12 two. We are now talking about a C-section for either
13 distress or FILDYS, and it is the same two numbers; they are
14 just added together for convenience. And, when you do C-
15 section for either one of these two combined, in the early
16 epidurals the p value is 0.004 and not significant -- well,
17 I basically in the late epidurals.

18 So, I believe the answer to your question is yes,
19 if I understood it correctly.

20 CHAIRMAN BLANCO: All right, moving on to some of
21 the other questions.

22 DR. SWEDLOW: There was a question about breaches.
23 They were excluded not because it doesn't work in breaches -
24 - it actually works terrific in breaches, but since we are
25 talking about specifically a behavioral study there didn't

1 seem to be any point, so we excluded them.

2 Dr. D'Agostino asked about subsets. That is
3 always a risky thing to do, to do post hoc analyses.
4 Nevertheless, off the record, we did them all that we could
5 think of. We looked at evaluable patients by various
6 criteria, for example, patients in the test group who
7 actually had a sensor put in, because there were 39 people
8 who never got a sensor for various reasons -- the same
9 results. I mean, taking them out had no impact.

10 We looked at nullips; we looked at mulips -- the
11 same result. We looked across sites. You know, there were
12 small differences in the number but, basically, the answer
13 is this was a very uniform and very robust finding, or set
14 of findings across multiple subset analyses. Without the
15 details, I can't really answer the question any better than
16 that.

17 Can you identify the patient without -- I am not
18 sure what this question is.

19 DR. GARITE: Can I address that? There was a
20 question -- and if this is out of order, please correct me,
21 Dr. Blanco, but as I remember it, the issue was what do you
22 do with the patient who goes below 30 percent but then
23 recovers to about 30 percent, in terms of protocol.

24 Our best answer is the same thing you do with a
25 non-reassuring tracing where you make a decision to do

1 something like an intervention and then the tracing becomes
2 reassuring. You have to use the clinical data and the whole
3 picture, but in general if it becomes reassuring before you
4 intervene and you are reassured, then you continue.

5 CHAIRMAN BLANCO: Well, let me pin you down a
6 little bit more on that because I think that also addresses
7 the issue of how long they have to be above 30 or below 30
8 to say one way or another, and in the study the patient fit
9 the criteria of the non-reassuring fetal heart rate tracing,
10 and then had the scalp pO2 electrode -- sorry, whatever,
11 fetal scalp sensor. How long did it have to be below 30 or
12 above 30 to decide that you were going to act one way or
13 another?

14 DR. SWEDLOW: The best way to answer the question
15 really is to use an analogy of how long does a fetal heart
16 rate tracing have to be abnormal or normal before you change
17 from either going to do something or not going to do
18 something? Essentially, it is a dynamic issue. Using fetal
19 heart rate monitoring, if the fetal heart rate is either
20 sufficiently abnormal or worrisome --

21 CHAIRMAN BLANCO: Let's go back. You know, the
22 issue is here you have the study, and in your test arm your
23 patient has a non-reassuring fetal heart rate pattern, and
24 at that moment, let's say, for one minute that you have your
25 sensor on your pO2 is less than 30 percent.

1 DR. SWEDLOW: Do you want to handle that?

2 DR. GARITE: Yes. It was not defined for a
3 specific period of time but, in general, an inadequate
4 tracing was reverted to the heart rate for management. Your
5 question is how long is inadequate and we don't have a
6 specific definition in the protocol for that. So,
7 basically, if the clinician did not feel that he or she had
8 adequate SpO2 tracing without a definition they reverted to
9 the heart rate tracing.

10 DR. ALLEN: Along that same line, I thought I read
11 in there that it had to be at a particular percentage for
12 ten minutes.

13 DR. GARITE: No.

14 DR. ALLEN: No?

15 DR. GARITE: No, the European studies have shown,
16 in an analysis of duration of SpO2, that you have to stay
17 below ten minutes to have a reasonable likelihood of a
18 metabolic acidosis, but the operational definition for the
19 study was that it did not return above 30 percent at any
20 time between two contractions, which is remarkably similar
21 to what was shown in the Dallas group study -- Houston group
22 study, excuse me, for two minutes. So, sort of like that.

23 DR. SWEDLOW: I would like to make one more
24 comment on this particular question. I don't want to
25 belabor it, but I think it is very important for everybody

1 to understand that a normal saturation does not guarantee a
2 good baby, and we have no intention of saying that. What a
3 normal saturation says is the baby is well oxygenated now.
4 It doesn't say anything about what happened before you
5 started; it doesn't say anything about what will happen
6 twenty minutes from now. It only says, just like in the
7 operating room when you put a pulse oximeter on the finger,
8 what is the baby's oxygenation at this moment in time or,
9 you know, over the last few seconds.

10 CHAIRMAN BLANCO: Yes, but the issue is really how
11 the study was performed and when you had below 30 percent,
12 how long did you have to be below 30 percent to say, "I'm
13 calling off and I'm reverting back to interpreting the strip
14 to decide whether I am going to do a section or not." That
15 is the issue.

16 DR. SWEDLOW: Right, and that was unspecified
17 because we wanted to test the real-world behavior of what
18 people would do in the real world.

19 DR. GARITE: Only one other comment -- I am sorry
20 to drag this out. If it was below 30 percent for the time
21 you had, it was below 30 percent. If it was above 30
22 percent at the time you have, that fulfilled the reassurance
23 criteria. Now, if for the next contraction and contraction
24 after that you had no data, you then reverted to the fetal
25 heart rate tracing.

1 CHAIRMAN BLANCO: Let's go ahead and move on with
2 some of the other questions. I can refresh your memory. One
3 of the questions was, was the epidural rate in hospitals
4 included in the study similar in the rest of the population
5 as the 95 percent in the study population?

6 DR. SWEDLOW: We do not have that data explicitly.
7 Our clinical investigators believe that the answer is yes.

8 DR. DIAMOND: Jorge, can I follow up on your
9 question?

10 CHAIRMAN BLANCO: Yes, go ahead.

11 DR. DIAMOND: How often in the test arm did
12 patients have pO2 below 30 and then go back up? In reality,
13 retrospectively how often did that happen?

14 DR. SWEDLOW: We did not count that. We did not
15 go back and do that retrospective analysis. I cannot answer
16 your question.

17 CHAIRMAN BLANCO: The other one was the C-section
18 rates, baseline versus in the actual study, which were
19 significantly different. Do you have any idea as to an
20 explanation for that?

21 DR. SWEDLOW: Yes. The bottom line answer is we
22 believe that the nature of the study, the patient selection
23 process of the study and the characteristics of the study
24 between baseline and the randomized, controlled trial were
25 sufficiently different to say that they were different --

1 different population. The nature of consent and the
2 structure of the study for the baseline was an observational
3 study. No randomization occurred; no thing happened to the
4 mom. We believe that it was such a low threshold for
5 getting consent that we simply see a different population,
6 and the randomized control was randomized; it was
7 interventional; there was something that was going to
8 happen. We believe that the nature of the patient being
9 approached, or the nature of the level of concern was
10 different. That is why in the final analysis we feel that
11 the two groups to compare really need to be concurrent,
12 randomized, control groups, the RCT rather than the
13 baseline.

14 We did find small find small differences -- we did
15 find differences, they are not small. Interestingly, the
16 percentage of patients in the baseline with mild to moderate
17 variable decelerations was 63 percent in the baseline and 53
18 percent in the randomized, controlled trial. This is
19 significant. I have no idea, other than the nature of the
20 consent, why that is true but Tom apparently does.

21 DR. GARITE: I was just going to make that same
22 point. The motivation to include a patient in the pulse
23 oximetry trial could not be removed completely from the
24 study even though we had objective criteria. So, you know,
25 roughly 70-90 percent of patients will have at least mild

1 variable decelerations. So, if that is one of the inclusion
2 criteria, which it was, some sites were not motivated
3 sufficiently by just the criteria to randomize such a
4 patient and they needed a little bit more significantly
5 worrisome a pattern, and that is why you see that
6 statistical difference there.

7 DR. SWEDLOW: Then, finally, there were secular
8 trends that occurred. The baseline study was done in "year
9 one" and the randomized control started at the end "year of
10 two," and by the time that occurred, the secular trend, at
11 least in managed care, was pretty dramatic. It went from 30
12 percent to almost 50 percent, and I believe that that plays
13 a role in the selection of patients although, again, I can't
14 prove it.

15 CHAIRMAN BLANCO: Anyone on the panel remember any
16 specific question that they have not had answered?

17 DR. O'SULLIVAN: I asked you about the number of
18 patients who really had O2's below 30 who went to section.

19 DR. SWEDLOW: And the answer again is that we did
20 not explicitly count and survey for that variable. I cannot
21 answer you unless we go back and do an analysis of every
22 single chart specifically looking for that.

23 DR. IAMS: The other one was the definition of
24 FILDYS. What does FIL mean?

25 DR. GARITE: When we did the baseline study, we

1 asked the clinician to specifically define whether a
2 cesarean section was done for the primary indication of
3 concern over the fetal heart rate tracing or non-reassuring
4 fetal status for dystocia alone, or whether the decision for
5 performing the section for dystocia was accelerated by some
6 concern over the fetal heart rate tracing. It was a
7 clinician's designation without specific criteria, and that
8 remained in the randomized phase.

9 CHAIRMAN BLANCO: All right.

10 DR. SWEDLOW: And, because of that we did analyses
11 with FILDYS included with distress and with dystocia and by
12 itself -- no impact.

13 MS. YOUNG: I have just a quick question on the
14 issue of comfort, patient comfort. I might have missed
15 this. Did you actually evaluate patient comfort? And, if
16 you did, how did you evaluate it? On the issue of comfort
17 also, it seems to me that if 95 percent of the women have an
18 epidural anesthesia, they are not going to feel anything
19 anyway really and, so, they are going to be comfortable.
20 So, in fact, was the sensor or the device put in before an
21 epidural was given or after an epidural was given?

22 DR. SWEDLOW: I am pretty sure that the answer to
23 your first question, did we explicitly evaluate patient
24 comfort, is no. If somebody knows otherwise, please state
25 so. That is correct.

1 The second question I believe is what fraction of
2 patients had their epidural placed before randomization, and
3 I believe the answer is 84 percent or 85 percent. Almost
4 everybody had their epidural in before they met they
5 criteria and were randomized. So, it is an untestable
6 question basically.

7 CHAIRMAN BLANCO: All right, Mike?

8 DR. DIAMOND: The other question I had asked was
9 about the patients whose oxygen fell below 30. The protocol
10 said that they would then have evaluation of accelerations
11 and fetal scalp pH's. The question was in how many patients
12 was that done. Was that something you were able to
13 identify?

14 DR. SWEDLOW: Yes, if I can find it. Bingo!
15 There were 15 scalp pH's in the test group, and I believe
16 there were 25 scalp pH's in the control group. That is not
17 right -- can I hold off on that until I can find it? I am
18 sorry.

19 CHAIRMAN BLANCO: That is fine. All right, well,
20 why don't we go ahead, while you are looking for that. Are
21 there any other questions you want to answer right now? If
22 not, we will start with what we need to do, which is begin
23 the discussion.

24 DR. SWEDLOW: Sir, the answer is scalp pH, 15 in
25 test, 26 in control. Scalp stimulation -- I am going to

1 give you percentages because the numbers are big -- 41
2 percent in test, 211, and 43 percent in control, and
3 vibroacoustic stimulation 34, or 7 percent in test, 9 percent
4 or 47 in control. It is slide 22 in your package.

5 DR. DIAMOND: I am sorry, but the issue was not
6 just how many were done but --

7 DR. SWEDLOW: What was the outcome in those?

8 DR. DIAMOND: -- in the protocol description there
9 was something to be done after the oxygen was not
10 reassuring. So, the question was then how many of those,
11 after that was done, then went on to cesarean section as
12 opposed to reassurance and you were able to hold off?

13 DR. GARITE: One of the things that the data does
14 not deal with is what happened after that event. So, a lot
15 of patients would have, for example, no data on the
16 saturation or low saturation, have a positive acoustic
17 stimulation, and then the data would recur. So, the
18 majority of these patients had a cesarean section or vaginal
19 delivery unrelated to that particular event. So, we don't
20 have that specific data.

21 CHAIRMAN BLANCO: Let's go ahead --

22 DR. THOMAS: Dr. Blanco, you asked a question
23 relating to slide number 35 in Dr. Porreco's presentation
24 relating to the relative outcomes for C-section for dystocia
25 and C-section for non-reassuring. I have that data, if you

1 would like to see it. My name is Simon Thomas, from
2 Mallinckrodt.

3 CHAIRMAN BLANCO: Please.

4 DR. THOMAS: This is basically the same chart as
5 you saw in slide 35, presented by Dr. Porreco, but this time
6 we look at the control group only and distinguish between
7 various outcome measures for C-sections for non-reassuring
8 and C-sections for dystocia. As was the case in the test
9 group where the oximetry was used, although the numbers are
10 fairly small in most of the rows, you can see that in
11 general the percentages of these undesirable outcomes are
12 lower in the C-section for dystocia group than in the C-
13 section for non-reassuring group. Does that answer your
14 question?

15 CHAIRMAN BLANCO: Yes, thank you.

16 **Panel Deliberations**

17 Let's go ahead and begin the discussion questions.
18 Panel members should have this in their packets and,
19 essentially, the first issue falls under effectiveness. Let
20 me go ahead and read the question, and we will go ahead and
21 try to discuss it after that.

22 The sponsor selected a fetal oxygen saturation of
23 30 percent, FSpO₂, between contractions for a laboring woman
24 with a non-reassuring fetal heart rate tracing, as the
25 clinical cut-off above which intervention may be delayed.

1 The 30 percent FSpO2 clinical threshold was determined from
2 animal studies and is supported by an ROC analysis of human
3 observational studies with 50 pairs of data points, fetal
4 scalp blood pH and FSpO2, from 46 patients. This data
5 showed that 81 percent of the time, when FSpO2 was less than
6 30 percent, fetal scalp blood pH was less than 7.2.

7 The first question is, a) has the sponsor selected
8 the correct threshold?

9 I am going to read all of number one and then we
10 will go back to each of the parts.

11 The sponsor also conducted many performance
12 characteristics studies. During those studies, it was found
13 that in an animal model, piglet, the average bias between
14 individual SaO2 and SpO2 readings was negative 0.6 percent,
15 with a standard deviation of 4.8 percent.

16 In sick infants and children the average bias was
17 negative 1.9 percent, with a standard deviation of 5.4
18 percent.

19 The measurement precision of the monitoring system
20 was 4.7 percent.

21 The sponsor concludes that the average difference
22 between fetal SpO2 from the N-400 and blood SaO2 in the
23 range of 15 percent and 40 percent is negative 0.6 percent,
24 and the typical variation between these readings is 4.7
25 percent. Thus, for example, at a true fetal SaO2 of 30

1 percent, 67 percent of the FSpO2 readings can be expected to
2 fall between 25 percent and 34 percent FSpO2. This also
3 means that at a true fetal SaO2 of 30 percent, 95 percent of
4 the FSpO2 readings can be expected to fall between 20
5 percent and 40 percent.

6 b) Is this level of accuracy clinically
7 acceptable for this monitor?

8 During the pivotal study, the sensor registered an
9 FSpO2 signal 67 percent of the time, median. The clinical
10 management matrix requires that the monitor be used as an
11 adjunct to the conventional fetal monitor. It also states
12 that the fetal oxygen saturation be considered non-
13 reassuring if the FSpO2 tracing stays below 30 percent
14 between contractions or is not available despite
15 adjustments.

16 c) Is the reported registration time of 67
17 percent, median, sufficient for clinical evaluation of the
18 tracing?

19 d) Is the sponsor's recommended management matrix
20 appropriate? If the device is approved, should the sensor
21 be indicated for use only with the matrix?

22 I will go ahead and start out with the discussion.
23 One of the things that was of concern in 1996, and I have
24 the advantage, as several of you have, of having been at
25 that meeting. One of the questions that was very concerning

1 to the panel at that time was the small number of
2 comparisons between scalp pH's and the sensor data.
3 Essentially, the study that you have produced with 46
4 patients and 50 points -- when you really nail it down to
5 the important number of points, I believe it is either 13 or
6 16 that fall in the quadrant of importance and of interest
7 for the study.

8 One of the recommendations that was made multiple
9 times at that session was that more data should be obtained
10 for this particular setting. And, the panel recognizes the
11 difficulty in the United States with the lack of use of
12 fetal scalp pH monitoring, however, there are other places
13 where it is being utilized. I wondered why we have no
14 further data along these lines.

15 Then, added on to the question that Dr. Diamond
16 asked -- I have forgotten which group had 15 and which group
17 had 25, but did you look at the data for your own group of
18 patients where you had both an FSpO2 and a scalp pH value to
19 correlate and to add to those numbers? That is one of my
20 concerns and I wonder if you have any data for that.

21 DR. SWEDLOW: Let me answer the second question
22 first because it is easier. There were 15 scalp pH's -- 15
23 patients had, I think it was 34 scalp pH's in the test
24 group; 25 in the control. Obviously, we can't do anything
25 about the control group. There were 8 blood gases in which

1 -- I am sorry, there were 8 scalp pH values in which there
2 was simultaneous measurement of both. Unfortunately or
3 fortunately for the babies, all 8 were normal. They all had
4 normal pH -- so, useless information from that point of
5 view. There is nothing more to say; they were just normal.

6 The reason why we did not continue to do ongoing
7 studies is because -- and this is going to sound self-
8 serving, I admit, but it is the truth -- those sites that we
9 felt very strongly could do high quality studies to gather
10 more patients were already so convinced, in Germany in
11 particular, that it worked because is significantly reduced
12 their rate of scalp pH's that is was very difficult to find
13 somebody who was sort of willing and able to do the same
14 study over again. It is really hard to find people who will
15 do really high quality, rigidly controlled -- we did not
16 even attempt to do it in the United States because of what
17 Tom said and because our general feeling, after discussing
18 with our investigators, is that it would be hopeless to
19 first try and find enough sites to get sufficient numbers
20 and sufficient quality. And, rather than flail around,
21 trying to do a physiologic surrogate, we felt that the best
22 way of testing whether the threshold was correct was the
23 randomized, controlled interventional trial. In essence, if
24 we have picked the right threshold, then the results, that
25 is the desired reduction of sections for distress without

1 injury to the babies -- it is sort of a res ipsa loquitur
2 argument. That is the best we can do.

3 CHAIRMAN BLANCO: The floor is open for
4 discussion. Dr. D'Agostino, go ahead.

5 DR. D'AGOSTINO: I had asked before lunch about
6 the variability in the data. There are ways of looking at
7 it to get an idea of just how firm this 30 percent is. You
8 could do resampling type of techniques or, so-called, boot
9 strap.

10 The discomfort I have is that it is based on small
11 numbers and the proof of the pudding is in the clinical
12 trials, but the clinical trial doesn't have, as I read it
13 here, a rigid procedure for determining when the 30 percent
14 has been exceeded long enough, and so forth. You can say it
15 is like the real world. Unfortunately -- you could argue
16 there is efficacy and effectiveness -- the real world is
17 what clinicians will do, and what have-you, but it is nice
18 to have something rigid in the clinical trial so you can
19 then see what the clinical trial did.

20 And, back to this 30 percent, I have discomfort
21 with the 30 percent and I don't know how it impacts on later
22 interpretations, but I do think, getting to this question,
23 that there is a lot of discomfort with the 30 percent, and
24 they could have done something to sharpen it up.

25 DR. IAMS: Jorge or Ralph, along those same lines,

1 when you say there is a bias -- and all the statisticians
2 talk about the comparison between the 30 percent value and
3 the scalp pH, are you talking about one moment in time? One
4 second worth of 30 percent on your strip? And, would it not
5 mean more or less if you have one minute of 30 percent
6 versus 10 minutes of 30 percent, or one minute of 20 percent
7 versus 10 minutes of 20 percent?

8 No one is going to interpret this as a one point
9 in time for the last 5 seconds; "it's been 18, I'm going to
10 do something. I'm going to look at it for at least 5 or 10
11 minutes." I would think that would make the data analysis
12 much easier, if we were to ask you to find not just how many
13 times it went below 30 but find how many times it went below
14 30 and stayed for what you consider to be a reasonable
15 length of time, and then tell us what happened. You know,
16 statistics look at this as a number. We look at it as a
17 series of numbers over time without change. Somebody ought
18 to know how to analyze that in an elegant way.

19 DR. GARITE: Remembering that the pivotal study
20 was, indeed, a behavioral study rather than a study designed
21 to directly compare the data of saturation with outcome, I
22 think there are a couple of indirect ways of looking at this
23 question within the pivotal study that I would like to refer
24 to.

25 One addresses the behavior and the accuracy of the

1 outcome, which was the sensitivity and specificity analysis
2 that I presented earlier, which would suggest that at least
3 compared to electronic fetal heart rate monitoring the
4 behavior of cesarean section as a predictor of an expected
5 depressed or acidotic baby was a better predictor than the
6 heart rate monitor.

7 In addition, we did an analysis of 18 patients
8 with falsely reassuring SpO2 data, at least alleged by the
9 behavior, that is, they did not do a section and we had
10 either a depressed or acidotic baby, and we used a low five-
11 minute Apgar score of pH less than or equal to 7.1. In that
12 analysis, there were 18 patients. Seven of them had normal
13 Apgar's with an acidosis. In a study that we did, if a baby
14 had a normal Apgar over 7 at 1 minute and 7 at 5 minutes but
15 had an acidosis there was no correlation with bad outcome at
16 all. Three had normal blood gases and, of course, a baby
17 that has depression may be depressed from things other than
18 asphyxia, and these were normal blood gases. Two had
19 respiratory acidoses only. Four had no posting of the SpO2
20 in the last 45 minutes to an hour, at least 45 minutes. One
21 was a protocol violation where, indeed, the FSpO2 was low
22 but nothing was done. The final one was, in a sense, true
23 falsely reassuring, except there were prolonged
24 decelerations and there was no posting for the last 30
25 minutes.

1 One of the things I was concerned about as a
2 clinician was how often are we going to be told by the
3 machine that the baby is okay and then get a bad baby. I
4 would rather not err in that direction. So, in our analysis
5 of these 18 significantly depressed babies with low 5
6 minutes or less than 7.1, it seemed quite reassuring that
7 this 30 percent threshold did seem to work.

8 CHAIRMAN BLANCO: All right. Let me step back a
9 minute and remind the panel that we are supposed to be doing
10 the deliberations. If we have a specific question for the
11 company we should ask that, but we need to be the ones doing
12 the discussion among ourselves. Okay? So, we do need to
13 have some discussion.

14 Do we have any other comments on what the panel
15 members think about this as the threshold or whether it is
16 correct or not in answer to question 1a)? Mike?

17 DR. NEUMAN: Yes, I would like to take it from a
18 different point of view, and I would like to ask the panel
19 to discuss whether any threshold is appropriate. It seems
20 to me we are looking at a very complex physiologic system
21 and trying to set a value -- really trying to make a binary
22 decision, yes or no.

23 If we look at a little history on fetal monitoring
24 itself, back in the early days where we had -- what did they
25 call it? -- type one, type two and type three decelerations

1 and it was so simple; if you had a particular pattern the
2 fetus was bad, and if you didn't it was all right, and look
3 where that has gone. I am thinking more in terms of
4 certainly this number 30 or some rather diffuse band around
5 it is important, but I am wondering if a fetus desaturates
6 to 20 percent for a period of 5 minutes or a fetus
7 desaturates to 20 percent for a period of 5 minutes, can
8 these be considered equivalent?

9 CHAIRMAN BLANCO: Well, I am going to take a
10 slightly different tack, Michael. I am not sure that this
11 question is really even pertinent. The fact is that was the
12 number that was picked by the company, the investigators, to
13 make their decisions and what we are interested in is the
14 overall data as to what they set out to do.

15 We are asking this question because we are almost
16 falling into the same issue of is the FSpO2 reflecting of
17 what is going on with the fetus in terms of its pH and its
18 oxygen status, and so forth. And, at the time that we were
19 discussing this, in 1996, that was felt to be an almost
20 unanswerable question because of the very small number of
21 babies or fetuses that might fit into that.

22 So, I think the fact is 30 was the number that was
23 picked, and the issue is does this number discriminate for
24 the endpoint that was chosen to look at by the company to
25 see whether this monitor works. So, I am not sure whether

1 20, 33 -- whatever -- I mean, 30 was what was picked. That
2 is what we need to work with, and does it work?

3 DR. D'AGOSTINO: I was trying to say something
4 similar to that. There is a question here before us, then
5 there is a bigger question of what happened in the clinical
6 trial. And, I think the question before is that you could
7 find an awful lot of fault with the 30 percent when you get
8 to the clinical trials, how it is all put together. Maybe
9 if we could get some specificity on how it is put together -
10 - the 30 percent falls very much in the background. I think
11 I am with you in terms of how to view this, and I am not
12 excited about the 30 percent; I am very excited about how to
13 look at those clinical trials.

14 DR. CHATMAN: Is this strictly a matter of
15 labeling that we are talking about? You know, the study is
16 the study; they chose 30. So, that doesn't mean that it
17 needs to be marketed with that 30 percent being an absolute
18 cut-off line. You know, you don't want clinicians to think
19 -- there is always a danger, of course, in getting
20 clinicians to think that if there is a number out there they
21 can use that number. But, just like Dr. Neuman says, that
22 is not the case in biology. It doesn't happen that way.
23 So, are we talking about two different things here? Are we
24 talking about the study itself, or are we talking about how
25 we are going to have the company label the instrument for

1 marketing? Those are two different things.

2 The other thing that I am concerned about is the
3 outlier, that last baby that Dr. Garite mentioned -- a
4 clear-cut outlier here, a baby with evidently normal pO2's
5 but it didn't turn out so well. That is in 508 babies. So,
6 how many are there going to be in 10,000 babies -- this kind
7 of thing? When you use that really, you know, hard number
8 of 30 percent, then you may end up with more. I think it is
9 a matter of integrating all kinds of information before you
10 decide to do or not to do. But, the study stands as it is
11 now.

12 DR. ALLEN: On slide 24, where it says
13 continuation of labor with a reassuring O2 sat, it looks to
14 me as though -- and tell me if I am misinterpreting this --
15 if you look at the acidotic, if you add up the 28 with a
16 cord pH of less than 7.1, cord pH of less than 7.05, or cord
17 pH of 7.0 -- explain that to me.

18 DR. SWEDLOW: They are nested. In the control
19 group, for example, the 11 at 7.05 are contained within the
20 26.

21 DR. ALLEN: So, to interpret this, 28 infants were
22 acidotic in spite of reassuring -- what are the O2 sats for
23 these?

24 DR. SWEDLOW: Do you want me to answer the
25 question?

1 CHAIRMAN BLANCO: Well, I am going to intervene
2 and I am going to say what was the purpose of the study and
3 what is the indication that the company is going to market
4 this device for? That is, it is going to say that if you
5 use it and state it, it will lower cesarean section rates.
6 I think the discussion we are getting into is we would all
7 love to have a sensor that tells us whether the baby is
8 hypoxic, acidotic, and so forth, but the fact is that that
9 is not the issue before the panel. The issue before the
10 panel I think is did the use of this instrument lower the
11 cesarean section rate? That is what the study was designed
12 to do in a specific set of patients.

13 So, I would like to hear from a few other folks,
14 but I think we are going to spend a lot of time on trying to
15 figure out whether this correlates with pAO2 or not. I
16 mean, I would actually hope that that is not the way the
17 machine is going to be utilized because that is not the
18 indication that is being sought.

19 DR. ALLEN: So, what do we do about 1a) about the
20 correct threshold?

21 CHAIRMAN BLANCO: Well, I suggested that I don't
22 think it makes any difference. That is the threshold they
23 picked for the study and that is the one they have got.

24 DR. WOLFSON: I have really a question and a
25 comment. First of all, what do we know about the

1 reflectance system that has already been approved for
2 clinical use in terms of their overall accuracy and how it
3 compares with this particular methodology? That is my one
4 question.

5 My other is, or more along the lines of a comment,
6 I think knowing the correlation with the actual acid base
7 status of the fetus is part of the safety issue. I think
8 Dr. Garite has made a very important point from a clinical
9 perspective, and I think the investigators have demonstrated
10 a significant shift in the cesarean section rate relative to
11 non-reassuring fetal heart rate tracings. The question is
12 what is going to be our false-negative rate? When are we
13 going to be reassured by this machine and continue the labor
14 and be incorrect, and find ourselves with an acidemic baby
15 that is depressed? And, I think that falls under the safety
16 perspective of this particular thing. So, I think it is
17 pertinent to this panel.

18 CHAIRMAN BLANCO: Anybody else want to comment?
19 Subir?

20 DR. ROY: Well, the thing that frustrates me is
21 that I have heard the discussion that we are using this 30
22 percent cut-off but it is not an "all or none;" it is a
23 clinical decision; there is no way that they have been able
24 to uncouple how long a time it was that way, that then led
25 to or kept them from performing a C-section. Until we know

1 that, how do we know that that is the branch point?

2 CHAIRMAN BLANCO: So, what you are saying is the
3 amount of time needs to be defined that the reading is, or
4 something to that effect?

5 DR. ROY: Well, we need to know how it was
6 actually used. They have to be able to tell us that this
7 was the algorithm and when this set of factors were met, it
8 then translated to a behavior -- C-section or no C-section.
9 Then, the issue of false negatives comes out of that as
10 well. But, right now, I don't know -- it just seems almost
11 whimsical as to how this 30 percent business was used,
12 unless they can go back to the data and extract it and give
13 us some numbers.

14 DR. DIAMOND: That is the point I think I was
15 trying to make before with my question as to what was done
16 at certain times. There was a protocol but it was as a
17 guide and we don't know how often it was followed. We don't
18 know in which situation it was or wasn't followed. So, it
19 makes it very hard to know is this really the correct cut-
20 off.

21 DR. WOLFSON: Could I make another comment? I
22 think that from a scientific standpoint, if you look at what
23 we do clinically in obstetrics and gynecology, or
24 specifically in obstetrics, there are a lot of studies that
25 appear in our literature where we respond and alter our

1 behaviors as clinicians on data sets that are the same size,
2 and sometimes even smaller than what was presented here.
3 So, I think that the overall data, both the physiologic data
4 and animal models as well as the one clinical study, give us
5 a reasonable view with respect to a 30 percent threshold,
6 and I think that overall initially that is a perfectly
7 stable place to be, and I think the data supports it.

8 CHAIRMAN BLANCO: But I think you were the one
9 that mentioned that you are unsure whether that will be
10 predictive of fetuses that may be academic where you will
11 continue to watch them.

12 DR. WOLFSON: Well, I was questioning the accuracy
13 in terms of how we function clinically with other monitors,
14 because clearly we have other approved monitors that are
15 utilized clinically, and I was just adding in that I think
16 that the threshold as a value, whatever threshold is
17 ultimately used, is still pertinent relative to knowing the
18 safety of the device in terms of calculating its false-
19 negative rate.

20 CHAIRMAN BLANCO: Gary, what do you think?

21 DR. EGLINTON: Well, there are other data in the
22 early part of section two of the PMA, from other studies
23 that are not part of this PMA, offering some reasonable
24 assurance. For example, 1100 paired umbilical artery and
25 venous samples, from Dilde, Thorpe, East and Clark, offering

1 some support. Now, they did a calculation assuming a split
2 preductal blood flow.

3 But, on page 2-24, their data showed that when the
4 predicted preductal arterial blood SaO2 was greater than or
5 equal to 30 percent significant umbilical arterial acidemia
6 rarely occurred in their series, with an incidence of only
7 1.6 percent, which is pretty reassuring, and 30 percent
8 sounds pretty good. When predicted preductal arterial blood
9 SaO2 was less than 30 percent, umbilical artery acidemia is
10 present in 10 percent of their cases, 56 out of 536. So,
11 again, we are left with a lower predictive value positive or
12 abnormal. When umbilical artery acidemia is present, the
13 predicted preductal arterial blood SaO2 is usually less than
14 30 percent, in their series 86 percent of the cases.

15 I mean, there is a fair amount of support embodied
16 in those 1100 cases for 30 percent being a reasonable number
17 for human fetuses.

18 Then, there is another, further study from Germany
19 just discussing the time below 30 percent, and I think, as
20 much as we can get it, in combination of human blood gas
21 data and animal interventional data, that the value of 30
22 percent probably is important. It may be fuzzy but it is
23 probably important.

24 CHAIRMAN BLANCO: Any other comments on 1a)?

25 DR. D'AGOSTINO: It is a difference between is it

1 a correct threshold versus is it a reasonable threshold,
2 from the data. It does have some support. It sounds
3 reasonable. Is it scientifically correct, the actual
4 endpoint number that we would all agree with? No. So, I
5 mean, I don't know how we are going to handle voting on
6 this, and so forth, but I think there is a fuzziness about
7 it.

8 CHAIRMAN BLANCO: I think the issue, when you
9 bring up voting and we will talk about that later on, but we
10 vote on the PMA and there may be conditions or no
11 conditions. We are not going to vote on each of these
12 questions. These are just to give the FDA some background
13 information, as well as the company, on things that are
14 raised by the panel and we will go from there.

15 DR. D'AGOSTINO: If that is the case, thank you
16 for clarifying that. But, if that is the case, then all the
17 more the issue about how this gets put together and the
18 algorithm for use is extremely important, and less so in
19 answering the question as it is written.

20 CHAIRMAN BLANCO: Anyone else? If not, let's move
21 on to 1b): Is this level of accuracy clinically acceptable
22 for this monitor? Any comments on the accuracy?

23 DR. ALLEN: Well, I will start off with my concern
24 that it seems to me, the way I read this, that 33 percent of
25 the time the actual pAO₂, or equivalent thereof, is either

1 below 25 percent -- 50 percent of the time it is not exactly
2 accurate according to reading the quote here, that when the
3 true O2 sat is 30 percent you will get a reading somewhere
4 between 25 and 34 -- 67 percent of the time it is between 25
5 and 34 and 33 percent of the time it is outside that range,
6 and that is a little bit disturbing.

7 DR. IAMS: That is the same question that got me
8 to the comment I made before about time analysis of this
9 over a period of time. If you tell me that it is outside
10 those ranges but it is over a period of 10 minutes, that at
11 minute 1, minute 3, minute 7 and minute 10 it is basically
12 pretty much the same, then that number is a statistical
13 truism that has no clinical importance to me at all. But
14 when you first look at it you think that is not accurate
15 enough. It looks like the 30 percent threshold was
16 correctly picked from the data that was available but the
17 second part of this, the 1b) issue here, makes you concerned
18 until you think about the way it would be used clinically,
19 which is not as a single point of time; it will be used over
20 time. And, we haven't seen that kind of information in the
21 PMA. We haven't seen every 10 minutes, you know, what
22 percentage of the time is it less than 30 over a period of
23 10 minutes at a time or 15 minutes at a time.

24 DR. CHATMAN: Dr. Blanco, is this question simply
25 a matter of whether or not registration of data is present

1 in 100 percent of cases, and it is in 67 percent of cases
2 and it is not in 33 percent of cases? Is that what this
3 question is?

4 CHAIRMAN BLANCO: No, that is the next question.
5 This is really looking at -- there is some variability, as
6 with any instrument, with this instrument, and these are the
7 numbers of variability that they found. Is that good
8 enough? Is that variability narrow enough that you get a
9 reasonable number?

10 You know, to me, again, if you go back to the
11 clinical setting -- and it is what Dr. Neuman pointed out --
12 at which point in labor do you say a fetus is acidotic
13 enough that you need to deliver it, and we have surrogates
14 for that -- scalp pH may be a surrogate for that but that is
15 not a true arterial pH that we can look at. So, I think the
16 issue is, is this identifying accurately enough the babies
17 that are of interest for the study? I think that is what
18 they are trying to do. Does anyone have any other ideas?
19 Subir?

20 DR. ROY: Getting back to what was just said about
21 duration -- I am a gynecologist; I apologize for that in
22 this setting --

23 [Laughter]

24 -- but this system of assessing the pO2 is a more
25 acute assessment than a pH, is it not, as customarily

1 obtained through scalp pH? Yet, clinically what we relate
2 to poor outcome is scalp pH, recognizing that it is not the
3 acute arterial pH. And, that is where I think just having a
4 pO2 less than 30 percent acutely may not necessarily
5 translate to a bad outcome unless it exists for a duration
6 of time during which you get the metabolic change reflected
7 by a low venous pH. So, I think that is where the coupling
8 is that needs to be unraveled out of this data set, whether
9 that was or wasn't met, leading to whether C-sections were
10 performed or not performed, and with the false negatives
11 falling out because they should have been sectioned, let's
12 say, and weren't.

13 CHAIRMAN BLANCO: Nancy?

14 DR. SHARTS-HOPKO: Well, I was going to comment
15 and say that the last statement in that paragraph above
16 question b) suggests sort of the converse issue as well,
17 that whenever you have a reading of 30 you don't really know
18 what you have. And, that just led me to wonder about the
19 stability of the machine over time, which is another issue
20 that hasn't been raised.

21 CHAIRMAN BLANCO: Well, I am not sure that I agree
22 with you on that. I mean, the whole point -- trying to
23 refresh my memory back to 1996 -- was the idea that there is
24 a very small number of fetuses that are going to fall in the
25 category where you are going to have an acidemic fetus.

1 Therefore, that really couldn't be studied, and the issue
2 was can we, in the setting of a non-reassuring fetal heart
3 rate, say, okay, we have an FSpO2 of 30 or above and we
4 think that means the fetus is okay so we can keep going.
5 Okay?

6 Whereas, I think we are trying to look at the
7 meaning of below 30 and that wasn't originally what was
8 aimed at, and I think the bigger group is the group above
9 30, and is it accurate that you can keep going in the face
10 of a non-reassuring fetal heart rate monitor, with a FSpO2
11 of 30 or above?

12 DR. SHARTS-HOPKO: Well, that is germane to what I
13 am saying --

14 CHAIRMAN BLANCO: Right.

15 DR. SHARTS-HOPKO: -- if you have a reading of 30
16 but you have this range around 30 which might be the true
17 sat and you have the non-reassuring heart rate, you don't
18 really know what you have.

19 CHAIRMAN BLANCO: But I will go back -- I keep
20 saying 1996 all the time, and there were other folks there,
21 and part of the issue that was discussed back then is just
22 that whole point, and it is a point we are getting bogged
23 down in. We are trying to correlate what it really means in
24 reference to the fetal paO2, and I think confusing the panel
25 is that a lot of that was brought up in the presentations in

1 terms of the data but the reality of the study, because it
2 was thought that that would be difficult to do, was to look
3 at just that quadrant of non-reassuring fetal heart rate
4 monitoring, FSpO2 above 30 and can we reduce the sections in
5 that setting. Okay? That was really the issue. It wasn't
6 are we going to predict hypoxia, or are we going to predict
7 acidosis? None of that. It was just can we lower the
8 section rate in this particular group because a lot of
9 clinicians -- I think I may be quoting Dr. Garite here, at
10 this point, a lot of clinicians will take a non-reassuring
11 fetal heart rate tracing and go to a C-section because of
12 the climate and that is the clinical standard now in the
13 States, and we want to be able to reduce that rate. Okay?

14 So that is why I made the comments earlier on
15 about what the percentage is may not be that critical if all
16 we are looking at is the C-section rate. Mike?

17 DR. NEUMAN: I think this, just as any other
18 measurement that we do in medicine or anything else for that
19 matter, has a certain amount of noise associated with it.
20 You don't get an absolute value; you get a value plus/minus
21 something. Here, it is listed as the standard deviation of
22 4.7 percent. I would be a little concerned about that
23 because, first of all, we don't even know if the error is
24 normally distributed, but I think that this is really a
25 labeling issue and that the accuracy, or whatever you want

1 to call it, of this measure needs to be clearly stated to
2 the clinicians who use it.

3 In terms of the question of whether this accuracy
4 is sufficient, it seems to me any additional information
5 that we can have on our patients that will help us in making
6 a decision, as long as we understand the limitations of that
7 information, would be useful.

8 CHAIRMAN BLANCO: Gary?

9 MR. JARVIS: That is close to a point I wanted to
10 ask about. Do we know that the error distribution is
11 normal, is a Gaussian distribution? At an SaO2 of X is the
12 distribution of error of the FSpO2 about that true value, is
13 it normally distributed? We are assuming that based on
14 having a number for a standard deviation. Is that true?

15 CHAIRMAN BLANCO: Go ahead. Yes, you can answer
16 the question.

17 DR. MANHEIMER: I am Paul Manheimer. I am a staff
18 scientist at Mallinckrodt. Before I put this up, I just
19 want to address a point on the precision and your point,
20 actually, Dr. Iams, I think, on time. The value that we
21 post up here of 4.7 percent is based on individual
22 observations about this pO2, either two sensors compared to
23 each other or sensors compared to blood draws in animals, or
24 sensors compared to blood draws on little kids. Those are
25 individual snapshots.

1 The way the sensor is being used in the test
2 protocol is looking at the value in between contractions,
3 and there is an intervention of some degree if the sat is
4 not reassuring, and you look to see what happens in the next
5 contraction, if your intervention was successful or not, the
6 same way as fetal heart rate tracings are looked at.

7 So, by the time you have looked at several
8 contractions, several values of that FSpO2. So, the
9 individual precision value of 4.7 gets multiple observations
10 and you tend to be more at the bias level of precision, not
11 exactly the bias level but you have multiple observations of
12 that FSpO2.

13 The question of whether or not it is normally
14 distributed, I want to look at where that 4.7 comes from.
15 It is from the dual sensor studies in which we placed two
16 sensors simultaneously on a fetus, and we plot here the
17 occurrence of the difference between FSpO2 readings on the
18 two sensors in a cumulative graph, and we see the most
19 common difference is one or two sat points, and the standard
20 deviation of this difference is 6.6, I think. The single
21 sensor equivalent would be 4.7. That is where it is coming
22 from. So, we do assume a normal distribution of differences
23 here, and this has the general shape and behavior of what
24 you would expect of an absolute difference of two sensors.

25 CHAIRMAN BLANCO: Thank you. Any more comments?

1 DR. DIAMOND: Can I just ask a question about
2 this? This is done at what FSpO2?

3 DR. MANHEIMER: This is over the full range of
4 FSpO2's that we monitored in a number of kids. So, I don't
5 think a lot of these got down to less than 30. So, these
6 are mostly healthy kids, 30 and above.

7 DR. DIAMOND: And, are there differences in this
8 curve from the data that you have at different --

9 DR. MANHEIMER: I don't recall us having enough
10 data points in the less than 40 to draw a conclusion.

11 DR. EGLINTON: Extending this, I think I
12 understand what you are saying, then if we are looking at a
13 snapshot in time, the instant that a measurement is made
14 with two monitors applied to the same fetus, at that instant
15 we can record these numbers; we can calculate a standard
16 deviation of 4.7 percent. But, we should be able to count
17 on regression toward the mean, and we should wind up with an
18 infinite series of observations regressing toward the bias
19 number of 0.6. So, at any given moment we are not really
20 worried about the true value being over 30 -- I mean the
21 FSpO2 display being over 30 when the SaO2 is actually 25. I
22 mean, if this really were a snapshot system, then at an SaO2
23 of 25 there would be a 16 percent probability that the FSpO2
24 would display 30 or greater. But it is not a snapshot
25 system; it is a continuous sampling series and averaged.

1 So, over time it should be no different than one percentage
2 point.

3 CHAIRMAN BLANCO: And that also makes the issue of
4 the length of time that it is at a certain percentage more
5 important.

6 DR. EGLINTON: What is the firing rate on the LED?
7 How many times per minute, per second?

8 DR. SWEDLOW: It is 1636 flashes per second. I
9 think the real question is how many -- over what period of
10 time is the display data averaged, and my recollection is
11 that it is 40 seconds. So, this is not a fuzzy -- you saw
12 the printout. These are not noisy numbers. This is quite
13 smooth and you can actually detect very small changes. We
14 struggled with the FDA staff on how to state in the label
15 the accuracy and this is what we negotiated. None of us,
16 either side, is actually terribly happy with it.

17 CHAIRMAN BLANCO: Jay, you had a comment?

18 DR. IAMS: No, I just think we are done with this.
19 That is all.

20 CHAIRMAN BLANCO: That sounds wonderful!

21 [Laughter]

22 I am always happy to entertain that thought.
23 Let's move on to c) then.

24 Is the reported registration time of 67 percent,
25 median, sufficient for clinical evaluation of the tracing?

1 Anybody want to start, take off on that?

2 DR. O'SULLIVAN: There are a couple of things I
3 would like to bring up here at this point. Number one, the
4 situation under which you described that this monitor can be
5 used, and that is that the head has to be at least station
6 minus 1 -- am I correct? Minus 1 or minus 2?

7 DR. SWEDLOW: The protocol specified that it was
8 at minus 2 or below. It is difficult to place when it is
9 higher up. It doesn't not work; it is just difficult.

10 DR. O'SULLIVAN: Okay. So, part of the problem is
11 going to deal with patients who might be above that station,
12 and the other part of the problem is going to deal with the
13 fact that about a third of the time, if I understand this
14 correctly, you cannot get an accurate tracing. Am I correct
15 on this?

16 DR. SWEDLOW: May I answer?

17 CHAIRMAN BLANCO: Please.

18 DR. SWEDLOW: The success rate for obtaining
19 readings was 95 percent. That is, in those patients in whom
20 an attempt was made, 95 percent of them were able to obtain
21 readings quickly. The registration time is over the period
22 of the case. If it is a ten-hour case, for example, what
23 fraction of that ten hours was posting? So, lots of things
24 go into that -- does the mother roll over? Does the sensor
25 fall out? Does the mother go to the bathroom? The success

1 rate is 95 percent.

2 CHAIRMAN BLANCO: This is really not an important
3 issue --

4 DR. O'SULLIVAN: That is why I couldn't understand
5 it before.

6 CHAIRMAN BLANCO: Yes, it is not that you can only
7 get a number in 67 percent, it is over a period of time and
8 if you have it for one hour you may get whatever 60 percent
9 times 60 minutes is -- in that 36 minutes you get a reading.
10 I think this goes back to the issue of how much do you need
11 in terms of a reading to make the decision. You know, for
12 how long. Do you understand? I think that is the
13 difference. So, I mean, I don't think the issue is whether
14 it is 67 percent.

15 DR. IAMS: So it is the same thing as we just did
16 before. Over time, if you tell me that it records two out
17 of every three seconds, then I will never know that it has
18 lost a third of its data. But if you tell me that these
19 other events are fairly frequent, which you just told me
20 they are not, you know, where I miss ten minutes out of
21 every twenty and then I get it for twenty, that is
22 completely different. So, that 95 percent figure says that
23 if I walk in a room and a patient has one of these devices
24 on, I have a 95 percent chance of being able to read the
25 tracing when I walk in there or a 67 percent chance.

1 CHAIRMAN BLANCO: Go ahead.

2 DR. GARITE: There is one way of looking at that,
3 and that is what happens if you eliminate the information
4 from patients where adequate data wasn't recorded, and the
5 results of the trial did not change. So, the patients with
6 good data remained --

7 CHAIRMAN BLANCO: But answer this, Tom, whenever
8 you had a patient admitted into the study, non-reassuring
9 fetal heart rate tracing, you put in the sensor and then you
10 took a reading. Now, we have already established that the
11 panel thinks it is important to have established a length of
12 time that the reading was stable, and that that hasn't been
13 provided and it may be something you want to look at. But
14 now, at what percentage of the patients did you get a
15 reading when you inserted it as opposed to you couldn't get
16 any kind of information for a set period of time. I think
17 that is what you are asking. Right?

18 DR. SWEDLOW: Of the insertions, 95 percent were
19 successful in getting readings. During a case, if the fetal
20 heart rate was normal and the sensor had moved and the
21 reading stopped, there was no reason for the nurse or the
22 physician to go in and readjust it because you weren't going
23 to do anything; it is a normal fetal heart rate so you don't
24 do anything. However, if the fetal heart rate became
25 abnormal and they needed a reading, all they needed to do

1 was tweak it a little.

2 CHAIRMAN BLANCO: Yes, as you said, this is
3 somewhat misleading. I think the issue is when you are
4 going to put a monitor in and you need a reading, what is
5 the percentage of time you are going to get a reading. And,
6 what you are saying is that it was 95 percent of the time.

7 DR. SWEDLOW: That is correct.

8 DR. CHATMAN: This is not relevant.

9 DR. WOLFSON: Were you saying, therefore, that the
10 registration time being 67 percent was also because clinical
11 circumstances didn't require the reading to begin with so
12 the clinicians let it ride?

13 DR. SWEDLOW: I am suggesting that might be part
14 of it. The distribution is simply reporting of fact. That
15 is what it was.

16 DR. WOLFSON: So, the most important is the
17 proportion of time you were able to achieve a reading, which
18 is 95 percent of the time.

19 DR. SWEDLOW: That would be my position as a
20 clinician.

21 DR. WOLFSON: Yes.

22 CHAIRMAN BLANCO: Gary?

23 DR. EGLINTON: If you look in volume II on page 2-
24 102, you will see the distribution of the monitoring time
25 and the legend shows you the number. The median is 67

1 percent.

2 CHAIRMAN BLANCO: Somebody correct me if I am
3 wrong, but I think the issue that I think needs to be looked
4 at is not how long could you keep a constant reading -- I
5 mean, the fetal heart rate monitor doesn't keep a constant
6 reading and lots of things happen -- but it is when you are
7 evaluating a patient and you need a reading, how often can
8 you get that reading, rather than if the patient is on it
9 for three hours can you keep it for all three hours? Is
10 that correct or do people disagree with that?

11 DR. DIAMOND: These were being placed on when
12 there was a non-reassuring fetal heart rate tracing, but
13 what was the range of time that it took from the time it was
14 placed to be able to get a reading -- a median and a range,
15 to get some idea? Ninety-five percent of the patients
16 within five minutes, or did it take in some patients an hour
17 to get an adequate reading?

18 DR. SWEDLOW: I believe they were all within five
19 minutes because nobody had the patients to keep tweaking.

20 CHAIRMAN BLANCO: If there are no other comments
21 on this one -- I think we are done with this one. Let's go
22 to d).

23 Is the sponsor's recommended management matrix
24 appropriate? If the device is approved, should the sensor
25 be indicated for use only with the matrix?

1 I don't know whether anybody wants the matrix
2 refreshed in their minds.

3 DR. IAMS: Refresh us.

4 CHAIRMAN BLANCO: In volume I, part 2, page 2-62.
5 But if you remember, basically the matrix was divided into
6 three fetal heart rate patterns, one normal, one ominous and
7 then the one in the middle, the non-reassuring and,
8 essentially, in the normal no indication for use and I don't
9 think the company is seeking an indication for use there; in
10 the ominous, no indication for use, the company is not
11 seeking an indication there; in the non-reassuring, the
12 matrix then said if the FSpO2 was above 30 percent, we would
13 continue to observe. If it were below 30 percent, we would
14 then revert back and act based on the fetal heart rate
15 monitor tracing. Did I say that correctly?

16 DR. SWEDLOW: Yes, and it is put in English --

17 CHAIRMAN BLANCO: I thought I said it in English.

18 DR. SWEDLOW: Oh, you did but for the readers,
19 slide 17 from this morning is, I think, a whole lot easier
20 to read. And, this is what we would propose essentially as
21 the instructions for use.

22 CHAIRMAN BLANCO: Comments? Discussion? No
23 comments? No discussion? This is an awfully quiet panel!

24 DR. O'SULLIVAN: Admittedly, this may be the
25 matrix under which it would be proposed that the company

1 market it. On the other hand, once this becomes available
2 that is not what is going to happen. It is going to be used
3 as much as, if not more than the fetal heart rate monitor by
4 itself. This is my concern. I mean, my concern is that it
5 is going to be used far more often. It is like most
6 anything we do, gadgetry being what gadgetry is and how much
7 physicians love to play with gadgets, I really have some
8 strong feelings that this is going to get used a lot more
9 often than what the recommendations of this matrix are.

10 CHAIRMAN BLANCO: Well, you know, that is always a
11 problem and I share your concern, and we are not going to go
12 into what instruments have been discussed here many, many
13 times for just that very issue. I think the problem that we
14 face every time we look at one of these is that we have to
15 look at the indications that are sought, and we have to act
16 on whether there is scientific evidence for that indication,
17 and we can't control what everyone else is going to do with
18 it. Believe me, I share your concern more than you probably
19 realize. Dr. Schultz, do you want to make any comment on
20 off-label use at this point?

21 DR. SCHULTZ: Well, I don't think I can say it any
22 better than you did. I think what you need to do is look at
23 the indication that is being sought, and I think the other
24 control that you have is in terms of training and in terms
25 of other things to try to make sure, as best as possible,

1 that people will understand what the correct uses are and
2 what the shortcomings are. I think that is basically a
3 matter of labeling and a matter of training together.

4 CHAIRMAN BLANCO: Let me just bring this up,
5 again, we have to look at the data and what the indication
6 is. I don't think that we talked about indication
7 specifically but we need to because I have a concern. The
8 original indication for use and the way the study was
9 designed and statistically approached was to do indication
10 one in volume one, page -- well, just the very summary of
11 safety and efficacy information data.

12 Here, it says when used in conjunction with fetal
13 heart rate monitoring under a specified protocol, the system
14 has been demonstrated to be safe and effective at, one,
15 reducing the rate of C-sections performed for non-reassuring
16 fetal status and, two, more accurately predicting postpartum
17 neonatal conditions than the use of fetal heart rate
18 monitoring alone.

19 Well, I would be opposed to that, number two,
20 being included as an indication because that is where you
21 are going to open the door to not what the study was
22 designed to do. That is what was agreed on in 1996, that it
23 was going to look at reduced cesarean section rate. That is
24 the most we can do. I mean, you can't, I don't think, if
25 you have proven efficacy for the indication you seek, then

1 not approve something because it is going to be misused by
2 people out in the community.

3 Any comments? Welcome, all comments.

4 DR. IAMS: Jorge, I have a question. Given the
5 predictable behavior of physicians that Dr. O'Sullivan
6 described, and the uniform affirmative shaking of heads
7 around the room, are we not allowed to think about that in
8 terms of conditions attached to an approval?

9 CHAIRMAN BLANCO: Oh, we can do anything we want.

10 DR. IAMS: I don't want a condition for use but,
11 unlike a lot of other things, cesarean section is a very
12 frequent event in the United States. It would not take very
13 long for the impact of this sort of device to be tracked
14 following its introduction. You could watch -- does it get
15 used in people outside the boundaries? Does the cesarean
16 section rate overall go down? Does the cesarean section
17 rate overall go up? It would not take a rocket scientist to
18 design an observational study to watch what happens.

19 CHAIRMAN BLANCO: Yes. First of all, the panel
20 can make the recommendation that conditions be applied to
21 the PMA. Conditions could be anything from very specific
22 labeling that this is not to be used in any other way but in
23 this very specific matrix that we are looking at right now.
24 I think the other issue is one of post-market analysis and
25 looking at what information is brought in and making sure

1 that the data is still gathered as to how it is being used.

2 So, there are conditions that can be placed that
3 we can look at when we vote. I will just take a minute now
4 out of the discussion to explain that at the end what we
5 will do is we will vote either to approve the PMA as it
6 stands, and the machine as it stands, with the indication as
7 stated, or to disapprove it, or to approve it with
8 conditions. Then we can discuss the conditions and vote on
9 the conditions, whatever the panel feels would be the
10 appropriate, correct recommendations. Yes, Dr. Wolfson?

11 DR. WOLFSON: I was just going to say just to
12 answer the question is the sponsor's recommended management
13 matrix appropriate, I would say yes. Then relative to that,
14 if the device is approved, should the sensor be indicated
15 for use only with the matrix? I think what I hear and what
16 I believe is yes. That is a labeling issue as well.

17 DR. CHATMAN: Is there any room for specifically
18 defining non-reassuring fetal heart rate pattern? Is there
19 any room for that?

20 CHAIRMAN BLANCO: Well, the matrix includes the
21 definitions. Do you agree with those, or do you want to add
22 any, subtract any? The matrix has definitions in it.

23 DR. CHATMAN: Well, maybe I am talking about
24 labeling again.

25 CHAIRMAN BLANCO: Okay. It seems like everybody

sgg

1 is pretty much in agreement that the matrix needs to be
2 applied and the indication needs to be very narrow to the
3 specific issue that was looked at and answer obtained. Am I
4 expressing the committee's wishes on that? Okay, I think we
5 answered that one. We are moving along just great! I keep
6 trying to convince myself.

7 Let's go ahead and tackle number two. We still
8 have some time before our scheduled break. Again, I will go
9 ahead and read it. It will be put up in the slides for you;
10 you can follow along:

11 Effectiveness is defined as a reasonable assurance
12 that, based upon valid scientific evidence and in a
13 significant portion of the target population, use of the
14 device for its intended uses and conditions of use, when
15 accompanied by adequate directions for use and warnings
16 against unsafe use, will provide clinically significant
17 results. In other words, as proposed in this PMA
18 application, the fetal oxygen saturation monitor is
19 effective if valid scientific evidence shows clinically
20 significant results when it is used as an adjunct to
21 conventional fetal monitoring for women in labor with term
22 gestation and a non-reassuring fetal heart rate pattern.

23 Question a), in the experimental arm of the
24 pivotal study where the sensor was used, the cesarean
25 section rate for women with non-reassuring fetal tracing, 5

1 percent, 23/508, is lower than the cesarean section rate in
2 the control arm, 10 percent, 51/502. Is this finding of
3 decreased sections for NRFS clinically significant?

4 There were several unexpected findings from the
5 pivotal study -- well, let's just tackle that one first.
6 Well, no, we did the other one the whole number; let's do it
7 the same way.

8 There were several unexpected findings from the
9 pivotal study: The cesarean section rate for dystocia in
10 the experimental arm, 19 percent, 94/508, is higher than the
11 section rate in the control arm, 9 percent, 43/502, for the
12 same indication.

13 There was no difference in the number or
14 percentage or assisted vaginal deliveries for NRFS between
15 the experimental arm and the control arm.

16 The overall cesarean section rate in the
17 experimental arm and control arm of the pivotal study
18 increased when compared to the section rate in the initial-
19 phase baseline observation study.

20 b) Do these unexpected findings, and the
21 explanations provided by the sponsor for these findings,
22 mitigate the clinical significance of the 50 percent
23 decrease in cesarean sections for NRFS?

24 Anyone care to make some comments on 2a), 2b)?

25 DR. ALLEN: I will start off. As a clinician, I

1 think it is great to actually have information to inform why
2 you are doing what you are doing. If the outcome is a
3 cesarian, to be able to know that I am doing a cesarean for
4 a specific reason -- fetal hypoxemia, then I like that.

5 Shall we go on to b) or leave it alone?

6 CHAIRMAN BLANCO: Well, why don't we see what
7 other people's comments are? Gary?

8 DR. EGLINTON: The only thing that troubles me
9 greatly about this, on the surface of it, it is an ideal
10 outcome -- a randomized, controlled trial that has a power
11 calculation satisfied at a 50 percent reduction, as
12 anticipated. The part about it that troubles me though is
13 that in the study group there was no decrement in the
14 cesarean rate for NRFS compared to the baseline study upon
15 which the power calculations were based. Rather, the
16 cesarean rate for unsatisfactory fetal tracings doubled in
17 the control group.

18 So, the basis for the difference is a doubling of
19 NRFS and FILDYS cesareans in the control group, not a
20 halving in the study group. So, yes, they are different but
21 it is because it went up in the control group.

22 CHAIRMAN BLANCO: Other comments?

23 DR. D'AGOSTINO: I think commenting on the study
24 and then the analysis procedure, I think the analysis was
25 quite rigorously done and I think quite defensible. So, I

1 don't think the question hinges on sort of the appropriate
2 analysis. I think the variable they went for looks
3 extremely good, but you do have to interpret the study as a
4 whole and we just heard one problem, that you would have
5 anticipated something slightly different in terms of the way
6 the rates went, and you also have this potential bias or
7 this potential problem with the dystocia and trying to look
8 at the overall cesarean rates not changing.

9 So, divorcing the two questions, I think that
10 looking at a) one can say that I think it is a clinically
11 significant finding. The study was powered. It is when you
12 get to going through these unexpected findings that the
13 discussion really has to get a little bit more detailed.

14 CHAIRMAN BLANCO: All right. Any other comments?
15 Mike?

16 DR. DIAMOND: I had asked the question earlier
17 about how many ominous tracings ended up being in the two
18 groups. I was told there were about 15 or 16 in each. If
19 those are actually in the NRFS groups, then actually in the
20 test group you only have about 8 or 9 patients, as opposed
21 to 38 patients. So that difference is even much more
22 significant than the sponsors are making out. I assume I am
23 interpreting that correctly. Nonetheless, I too am
24 concerned that when you add everything back together, the
25 overall cesarean section rate of the entire group is no

1 different.

2 CHAIRMAN BLANCO: Jay?

3 DR. IAMS: That is my comment. This is a
4 behavioral study, and the behavior of the physicians was to
5 do as many cesarean sections with this device as they did
6 without it, even though the rationales are better. The
7 bottom line is the C-section rate didn't go down, and I am
8 still kind of confused by that. I understand it. You know,
9 it is not like I need to ask more questions about it, but if
10 you plot out a little schematic of why should that happen,
11 it doesn't make sense that if you have enough patients that
12 that trend should stay the same.

13 I don't think that is what the sponsor wants to
14 say and that is not what we want to say, that if we
15 introduce this device into practice that the C-section rate
16 will stay the same and we will all feel much better why we
17 did some of them. We want there to be a decline in the C-
18 section rate without compromising safety, and it does appear
19 that this device could do. There must be something about
20 the behaviors of who got entered into the study. All these
21 other things are indicative to me of a well-done trial. The
22 study is not too perfect. It is really reflective of all
23 good clinical trials; there is always something unusual that
24 comes up in every honestly presented trial and, you know,
25 this is just one more of those examples where there is

1 always something that you didn't anticipate.

2 Anyway, the bottom line is the C-section rate
3 didn't change, and until we get more comfort with that it is
4 hard to say that the device does what it was proposed to do.
5 I think it is promising and it looks to be safe, although we
6 haven't talked about that yet --

7 DR. D'AGOSTINO: Yes, it did.

8 DR. WOLFSON: It did do what it was proposed to
9 do. We ended up doing cesarean sections for what we
10 believed, based on the monitor, were for more appropriate
11 reasons. So, we still allowed vaginal deliveries to occur
12 in the face of non-reassuring tracings where we otherwise
13 would have taken them to cesarean much earlier, like the
14 example that Dr. Boehm gave.

15 I think that the proposal is fulfilling it. In
16 terms of where we would wish to be, that the cesarean
17 section rate would decline overall because we are doing
18 inappropriate cesareans because of the fetal heart rate
19 tracing, no, it didn't demonstrate that. And, that may be
20 not where we are going to go.

21 DR. IAMS: There are a lot of issues about
22 physician behavior and interpretation of data that is very
23 difficult to tease out, but there is a long list of
24 obstetrical interventions, starting with x-ray pelvimetry,
25 maternal urinary estriol, electronic fetal monitoring,

1 uterine contraction monitoring, and the bottom line is what
2 happened to the endpoint they were introduced for?

3 DR. WOLFSON: No, no, my main concern --

4 DR. IAMS: It looks like it might make it but --

5 DR. WOLFSON: I think this one is going to make
6 it, but my real concern with the study is that the
7 physicians were watching the tracing because that was
8 supposed to be the primary tool. This is an adjunct. And,
9 even though the analysis demonstrated -- let me back up.
10 The physicians were watching the tracing. The fetal heart
11 rate tracing was, indeed, quite worrisome like, again, the
12 example that Dr. Boehm gave. Some physicians were like Dr.
13 Boehm and they were able to walk out it out, and he got a
14 baby that was good and he had a vaginal delivery. Other
15 clinicians are actually prepared to watch this tracing with
16 consistent late variable decelerations that become ever more
17 dramatic and see that it is a reassuring saturation and hang
18 in there. So, the tendency, it seems to me, still is that
19 these physicians are bailing by calling it dystocia.

20 CHAIRMAN BLANCO: Didn't they present us data that
21 purported to say that that wasn't the case?

22 DR. WOLFSON: I agree, and I think they presented
23 a very good case to say that that is not the case. But it
24 fascinates me when you go back to the issue of individual
25 behavior and somewhere in there is going to be a tendency to

1 basically pull the plug on the situation.

2 CHAIRMAN BLANCO: But then what you are saying is
3 a self-defeating argument because now we introduce this
4 monitor and we have it, and people are going to bail out and
5 just use a different diagnosis.

6 DR. WOLFSON: No, no, no.

7 CHAIRMAN BLANCO: I don't share the sponsor's
8 great desire to make sure I am correct on why I did the
9 section if it turns out that I am still doing the same
10 number of sections.

11 DR. WOLFSON: No, no, I understand what you are
12 saying but the thing that still fascinates me about this
13 tool is that we already know that we are doing cesarean
14 sections for non-reassuring fetal heart rate tracings. The
15 monitor has not made us do more cesareans; it has reduced
16 the number we are doing. I don't know what to do with the
17 dystocia data, but I think that, again, it does clearly
18 demonstrate that we have an additional piece of information
19 that when properly used will probably reduce the number of
20 cesarean sections that are done for non-reassuring
21 electronic fetal monitoring tracings. And, that is the big
22 bugaboo. It reduces, in a sense, the false-positive rate
23 for electronic surveillance of fetuses during labor.

24 Now, the other side of the coin I don't know yet.
25 I mean, the dystocia question, I think, is simply just the

1 proverbial red herring of this particular study. When we
2 have the opportunity to do post-market evaluation we are
3 going to find that it is going to vanish.

4 CHAIRMAN BLANCO: Well, let me just add that you
5 inserted a "probably" there as opposed to "will." Okay?

6 DR. WOLFSON: Oh, yes.

7 CHAIRMAN BLANCO: Which means that you are not so
8 sure, number one. Number two, I mean one of the things, as
9 Jay pointed out, this is really a well-done study. I mean,
10 all kudos to the company, and all that, and I am sure it
11 cost a lot of money and a lot of time, and everything else,
12 and it is very well done, but you still have to face the
13 data and you have to face the facts. You know, if everybody
14 as so well randomized and the two groups were not
15 dissimilar, why in the world did we get this finding, and
16 why is there no difference in the overall C-section rate?

17 I personally, despite their good arguments, think
18 that basically obstetricians and gynecologists -- and I hate
19 to say this and go on public record saying that, but I think
20 obstetricians and gynecologists make up their mind they are
21 going to do a cesarean section on someone because they think
22 something isn't right and basically it is a matter of what
23 you are going to call it, whether it is for the non-
24 reassuring fetal heart rate or for dystocia, or for
25 whatever. So, I have some real concerns. You know,

1 everything was done so well; everything was matched so well,
2 then why do we have this big difference? I mean, it is not
3 a little difference; it is a big difference.

4 DR. SHARTS-HOPKO: Jorge, I would like to comment
5 on that. I am also very unsettled by that cesarean section
6 rate related to dystocia, but I think, although the
7 scientific data doesn't support it, clinically we know that
8 a planned cesarean is a better experience for all the people
9 involved than a hysterical, screaming cesarean.

10 CHAIRMAN BLANCO: Actually, I asked the company,
11 and I think they need to go on record because they told me
12 offhand, but that was why I asked the question, and they
13 said it is better to have the right diagnosis because you
14 can take your time and go to a planned C-section and, you
15 know, everything will turn out better. So, my question was
16 do you have evidence from your study that it turned out
17 better? Did you have a lower rate of complications in your
18 patient population in the dystocia group that was in the
19 test versus the control group that was in the non-reassuring
20 fetal heart rate patter? What I was told was no, but I
21 would like for them to see if they can answer that question.

22 DR. SHARTS-HOPKO: While they are thinking of the
23 answer, I think you would then want to look at patient
24 satisfaction data after both these different experiences.

25 CHAIRMAN BLANCO: I think that would be excellent.

1 I don't think they have that data but I think that would be
2 an excellent thing to look at.

3 MS. YOUNG: I will just make a comment here on the
4 issue of dystocia. I mean, going back to the 1980s cesarean
5 birth consensus development conference that was held, you
6 know, the conclusion was that dystocia was -- they used the
7 term -- a wastebasket term. Nobody could really define it.
8 And, I think we still can't escape that as far as the study
9 is concerned and this device is concerned, nor can we tease
10 out the potential effects of the epidural and the potential
11 effects of induction. I mean, there were quite a lot of
12 failed inductions in this as well. So, you know, there are
13 other variables that I think have the potential to have an
14 effect on the dystocia that we have seen.

15 CHAIRMAN BLANCO: Don?

16 DR. CHATMAN: Maybe the focus is a little bit
17 different from what it should be. Certainly cesarean
18 section rates are important, but if we find some kind of
19 methodology that would allow us to better assess the fetus
20 inside the uterus, that eliminates EFM or modifies EFM, we
21 are taking a step forward. So, we focus on cesarean section
22 rates, and what-not. Nobody knows what it should be but,
23 obviously, we are getting pressures from everywhere to
24 decrease cesarean section rates and perhaps the focus here
25 should go back to the baby and talk about the intrapartum

1 assessment of the fetus. That is probably the most
2 important part of this, the most important part that we can
3 get out of this I think, and that is the only reason why I
4 am in favor of it, frankly.

5 DR. IAMS: Jorge, I have to argue with that --

6 CHAIRMAN BLANCO: Let me just say that is a
7 slippery slope that we don't want to go down. That is just
8 the whole point of what Mary Jo was saying about, you know,
9 it is going to be used to evaluate the fetus and not in the
10 indication. Again, we have to go back to the original point
11 of the study. The original point of the study was not to
12 say whether the fetus is hypoxic or acidotic or not. The
13 original point of the study was, when used in this specific
14 way, did we lower the section rate? Jay, go ahead.

15 DR. IAMS: I would just say that the obstetric
16 literature over the last fifty years is pretty consistent
17 with the notion that -- fifty, sixty years now -- that more
18 data is not necessarily better outcomes. We had more data
19 when we had electronic fetal heart rate monitoring, that is
20 not necessarily better. X-ray pelvimetry is a more accurate
21 method of assessing the pelvic dimensions of the mother but
22 it is not better than manual clinical pelvimetry in
23 predicting who is going to go through labor. Uterine
24 contraction monitoring is more data about the way the uterus
25 behaves but it didn't have a benefit. So, I am not

1 impressed by any argument that says that more information is
2 necessarily better. Even though it makes very good sense to
3 my scientific side, I think we have shown that that is not
4 the case in obstetrics. And that is why the C-section rate
5 is the bottom line number, and the most impressive number in
6 the whole study is the fact that the section rate went down
7 for the indication of fetal well-being. If I were sitting
8 on the other side of the table, that is the number I would
9 point to with pride. But the flip side is the dystocia
10 number went up and that has to be somehow addressed.

11 CHAIRMAN BLANCO: Don, do you want to make a
12 comment?

13 DR. CHATMAN: No, what I am going to say is
14 obvious. The cesarean section rate didn't change. So,
15 there has to be something else here that is of value.

16 CHAIRMAN BLANCO: Yes, the crux of the point is
17 did the cesarean section rate change in a way that we think
18 is clinically useful for the patient in some way? Because,
19 I mean, that would say the subset of patients that had non-
20 reassuring fetal heart rate strips -- that it did change.
21 But what we see is that the overall rate in either group
22 didn't change. So, I mean, is there some way to look at
23 this data and to say whether that is clinically or not
24 clinically important? Do you want to make some comments on
25 that? Mary Jo?

1 DR. O'SULLIVAN: I don't know if I can comment on
2 that specifically but there are so many things that enter
3 into this garbage basket called dystocia. I know that
4 babies are bigger now than they were twenty-five and thirty
5 years ago. So that does have some impact.

6 There also is the additional unfortunate impact
7 that we have carried with us for the last twenty years, and
8 that is the data relative to two hours of arrest, which I
9 believe you guys extended, if I remember correctly, when you
10 looked at retrospectively, looking at the partograms, to
11 three hours of arrest. I would say four and if the baby's
12 heart rate is fine keep on going. But in this group of
13 patients we have no information about the utilization of
14 oxytocin, and I think that is an extremely important
15 parameter to look into.

16 We have absolutely no information, at least that I
17 have understood, about the indications for induction, and
18 why twelve hours was picked as the magic time.

19 We have no idea of what the actual practices of
20 the obstetricians involved in the study were because they
21 were doing their own thing, except for the particular study
22 itself.

23 So, there are too many other parameters in here.
24 Yes, I think everybody in this room is unsettled by the fact
25 that the overall cesarean section rate did not change and,

1 in point of fact, it probably went up in a sense but, yes,
2 that is extremely unsettling. But that is something that we
3 can look at in another way. I think that is something that
4 in the future can be looked at in terms of what we decide
5 today.

6 DR. ALLEN: I would have to agree with Dr.
7 O'Sullivan. I think when we talked about this in 1996 we
8 were talking about lowering the cesarean section rate in
9 that group of patients that had non-reassuring fetal heart
10 rate tracings, and I think the study has addressed that
11 point and has significant results.

12 I think the spin-off is a spin-off that we can't
13 really judge because we don't have the rigorous analysis
14 that Dr. O'Sullivan has just talked about that would need to
15 be addressed -- uterine pressure monitors, active management
16 of labor -- we don't know if that has been done.

17 DR. WOLFSON: Can I make one comment in terms of
18 parameters?

19 CHAIRMAN BLANCO: Sure.

20 DR. WOLFSON: I am a believe that having
21 additional information can be very helpful from the
22 standpoint that we are always dealing with a heterogeneous
23 situation in obstetrics and medicine in general. I agree
24 with Dr. Iams that certainly more data doesn't always
25 translate into better results. But, for example, one of the

1 things we learned from x-ray pelvimetry was that failure to
2 progress to dystocia, however you want to call it, is
3 heterogeneous and it isn't simply cephalopelvic
4 disproportion. So, that was the reason why the parameter no
5 longer worked because the heterogeneity finally proved it as
6 being invaluable in evaluating all labors.

7 I think the same thing is true here. This
8 particular modality has the potential, we are going to see
9 and I think it was addressed by the sponsor that not all
10 babies that have an non-reassuring fetal heart rate pattern
11 have it because of the development of an acidemia or
12 hypoxemia. Again, it is heterogeneous and this particular
13 tool allows us to further subdivide the patients whose labor
14 we are monitoring and the fetuses as to who is actually
15 having a hypoxemic event and who is not. So, I think from
16 that standpoint it is a valuable tool.

17 CHAIRMAN BLANCO: Any other comments on these
18 issues? I think the overall answer is that those of you who
19 vote will have to decide whether this isolated drop in this
20 very specific setting, as opposed to the overall drop,
21 becomes of clinical significance as a result. I do think
22 this is the crux of whether the monitor is of some benefit
23 or not. So, I think you need to be thinking about that as
24 you prepare to eventually vote on the PMA. Yes?

25 DR. DIAMOND: Could we have the sponsor respond to

1 your question about complications and adverse events in the
2 two patient populations?

3 CHAIRMAN BLANCO: Yes. Do you remember the
4 question? The question was one of the speakers said, and I
5 forgot which one it was, that it is better to go to a nice,
6 calm, predictable C-section for dystocia as opposed to the
7 circus of "I've got a fetal heart rate tracing and distress,
8 and so forth." So, my question was when you compare the
9 complication rate in the group that was in the test group
10 that was sectioned for dystocia versus the control group
11 that was sectioned for non-reassuring fetal heart rate
12 tracing, was there a difference in the complication rate
13 between those two groups?

14 DR. GARITE: Well, the endpoints that you are
15 going to have to use -- blood loss, infection, maternal
16 anesthetic complications, etc. are inconsistently coded and,
17 at least in a real quick preliminary look within our data
18 set, we are not going to be able to demonstrate that from
19 our own data. That can be culled from the literature, that
20 urgent cesarean sections have a higher rate of those
21 complications. Endometritis might go the other way. But,
22 to a certain extent, it can be culled from the literature.

23 DR. O'SULLIVAN: I think that is arguable though
24 because if 95 percent of the patients are getting epidurals
25 you are not doing the same kind of cesarean sections as the

1 literature is talking about. There is not all this yelling
2 and screaming that everybody talks about.

3 DR. GARITE: Well, it certainly reduces the
4 anesthetic accidents.

5 DR. O'SULLIVAN: Yes, it does that. It also
6 decreases the rush of trying to crash the patient,
7 inadequate prep while they are getting the levels. I mean,
8 all of that is a different issue today if you are using
9 epidurals.

10 CHAIRMAN BLANCO: Not only that -- and I am glad
11 you pointed that out because the circus is going to be with
12 the ominous patterns which we are not even looking at. I
13 mean, these are patterns where the whole point is we are
14 sitting there, thinking, "have I got a bad baby? Do I not
15 have a bad baby?" So, you are not going to want to waste
16 time but you are not going to be rushing off and, you know,
17 not necessarily throwing the patient in to do the section
18 kind of thing. That is really for more ominous patterns.
19 So, I am not sure that that really puts forth an indication,
20 which brings it back to what I said earlier, which is that
21 the issue is, is it an overall section reduction that is
22 important or is it just for that definition in that group of
23 patients?

24 Any other comments? Nobody? All right, moving
25 right along, we will move on to safety. Number three, there

1 is reasonable assurance that a device is safe when it can be
2 determined, based upon valid scientific evidence, that the
3 probable benefits to health from use of the device for its
4 intended uses and conditions of use, when accompanied by
5 adequate directions and warnings against unsafe use,
6 outweigh any probable risks.

7 From the experimental arm of the pivotal study,
8 investigators noted neonatal transient pressure marks (n+7),
9 probably caused by the sensor contact with the fetus during
10 labor. All were considered mild in severity and five were
11 resolved by discharge.

12 There were 100 neonatal ecchymoses noted in the
13 experimental arm, compared to 74 in the control arm.

14 In the fetal/neonatal population, one or more
15 adverse events were reported in 70 percent of the
16 experimental arm and 64 percent of the control arm.

17 The overall incidence of serious adverse events in
18 the baseline phase, 6 percent, was lower than in the pilot
19 and randomized clinical trial phases, 13 percent control and
20 14 percent test.

21 No adverse events attributable to optical or
22 thermal effects were noted.

23 Does the panel consider the device safe?

24 Who would like to open up the discussion?

25 DR. CHATMAN: I would because I am concerned about

1 the potential for infection. I don't know whether or not I
2 read this correctly or not, but it seems to me that in the
3 patients who had the device put in place there was an
4 inordinate increase in the frequency of febrile response. I
5 used my old computer and counted a number of events that
6 could be interpreted to be intrauterine infections of some
7 kind that may have been associated --

8 CHAIRMAN BLANCO: Do you remember where the data
9 is because I don't remember that.

10 DR. SWEDLOW: Slide 25 from this morning, no
11 significant differences between the two groups.

12 CHAIRMAN BLANCO: Okay, slide 25 shows -- let's
13 see, 40 percent -- 40 -- these are hard numbers, not
14 percentage -- 40 in the fetal heart rate monitor alone and
15 48 in the FSpO2 group. What is the denominator?

16 DR. SWEDLOW: There were 502 in the control and
17 508. So, for all intents and purposes, it is the same
18 number.

19 CHAIRMAN BLANCO: And, postpartum fever, 11 and
20 16. So, it doesn't look like there is an increased risk of
21 febrile morbidity.

22 DR. O'SULLIVAN: I have to ask a question here
23 because I come from an institution that hardly ever uses
24 anything inside the uterus anymore. Is this common? I
25 mean, I don't really know what goes on in the rest of the

1 country when it comes to obstetrical practice, but in the
2 study were most of these patients on intrauterine devices of
3 one sort or another? So, that would impact on the rate of
4 infection to begin with.

5 DR. GARITE: Virtually all patients in both groups
6 had internal scalp electrodes.

7 DR. O'SULLIVAN: And how about intrauterine
8 pressure catheters?

9 DR. GARITE: As David reminds us, all these
10 patients already had some degree of non-reassuring heart
11 rates to even get into the study. Intrauterine pressure
12 catheters? Did you ask that?

13 DR. O'SULLIVAN: Yes, because that might impact on
14 the difference between the infection rate with the device if
15 a fair number of them already had invasive monitoring of one
16 sort or another. I have to say something. I object to the
17 fact that this is not an invasive device because this is an
18 invasive device.

19 DR. SWEDLOW: For the mother, for sure.

20 DR. O'SULLIVAN: For sure, and to say that it is
21 not invasive, which I have heard several times --

22 DR. SWEDLOW: To the fetus.

23 MS. YOUNG: -- yes, but it doesn't make that
24 clear. It says non-invasive, and the assumption is that it
25 is non-invasive to the mother.

1 DR. SWEDLOW: We can make that clear.

2 CHAIRMAN BLANCO: Yes, that is something we can
3 recommend in the labeling. I think the point you are making
4 is that if you don't use intrauterine pressure catheters and
5 you put this in, at that point it could increase --

6 DR. O'SULLIVAN: It can definitely increase the
7 infection rate.

8 CHAIRMAN BLANCO: Right, as opposed to if they all
9 already had it in both groups --

10 DR. O'SULLIVAN: Exactly.

11 CHAIRMAN BLANCO: -- then it is probably not going
12 to add to the infection rate. So, the question would be do
13 we know how many had intrauterine pressure catheters in the
14 control and in the test group? While they are looking for
15 that, why don't you go ahead?

16 MS. YOUNG: Yes, my question was did you keep an
17 account of the number of vaginal examinations in each mother
18 in each study?

19 DR. SWEDLOW: Yes.

20 MS. YOUNG: And, how many vaginal exams would
21 there be? I ask this because, again, questions have been
22 raised in the last two or three years about the need for an
23 excessive number of vaginal exams, and I know that in some
24 centers there is a major effort made to decrease the number
25 of vaginal exams that are used.

1 CHAIRMAN BLANCO: I think the numbers four and
2 five come to mind. I am not sure which group had which in
3 terms of average number of vaginal exams. That is in there.

4 DR. GARITE: We have the data on IUPC, and as you
5 surmised, it was 73 percent.

6 CHAIRMAN BLANCO: In both groups?

7 DR. GARITE: Yes. It was similar in both groups
8 and the overall number was 73, but your point is well taken.

9 CHAIRMAN BLANCO: Any other comments? Does
10 anybody else want to make any comments about the safety of
11 the device? We already have a concern in that high use of
12 IUPC may have made it conflicting in terms of whether that
13 might cause infection if you don't use IUPCs. Any other
14 comments in terms of safety?

15 MS. YOUNG: Yes, I would just like to say that in
16 terms of a conclusion that comes out about the safety, that
17 that be reflected in the patient video. We haven't had a
18 chance to talk about that yet but maybe when we get to
19 labeling we will talk about the patient video. But in that,
20 the device is described to the mother as being safe. There
21 is some mention of marking on the faces of the fetus.
22 Interestingly, as an aside, I noticed that in all of the
23 information, with the exception of the patient video, the
24 word fetus is used. The text of the patient video doesn't
25 talk about a fetus; it talks about the baby.

1 DR. SWEDLOW: I am not sure I understand the
2 question.

3 MS. YOUNG: Well, just on the issue of safety,
4 depending on the conclusion about the safety of this device,
5 I am asking that that be reflected in any patient
6 information materials.

7 CHAIRMAN BLANCO: You said that you had the
8 device. At this point, I think it might be useful if you
9 have some of the sensors. We don't need to look at the box.
10 A box is a box. Can you maybe pass that around and have the
11 panel members take a look at it?

12 DR. GARITE: May I give you follow-up information
13 on the previous questions?

14 CHAIRMAN BLANCO: Please, Dr. Garite.

15 DR. GARITE: The number of vaginal exams was eight
16 in the control group, mean, and nine in the test group.

17 I did want to point out one thing, that I think
18 Dr. O'Sullivan's point is very cogent but the rate of
19 chorioamnionitis in these patients having a lot of invasive
20 monitoring, or the intrapartum fever rate is on the order of
21 about 3 percent to 4 percent, and the rate of postpartum
22 endometritis with cesarean section rate of 26 percent to 29
23 is on the rate of 1.5 percent. So, the overall rate --

24 DR. O'SULLIVAN: Oh, 1.5 percent?

25 DR. GARITE: Postpartum fever.

1 DR. O'SULLIVAN: Then they must all be on
2 antibiotics. There is no way.

3 DR. GARITE: I am just giving you the number.

4 DR. O'SULLIVAN: That is not considered even the
5 standard for the country.

6 CHAIRMAN BLANCO: Well, it is one percent of the
7 overall population, not the cesarean section rate. So, when
8 you put in the vaginal deliveries, which are the predominant
9 number, that is going to lower your rate. Do you know the
10 rate for the C-section population?

11 The other thing is, the way the question is
12 framed, do we think seven marks on the cheek with the sensor
13 is a major problem? My take on that is if it saves you a C-
14 section or if it really gives you some benefit, that is
15 probably a pretty minor type of issue; that is not a big
16 problem. And, the adverse effects are not that dissimilar.
17 So, those don't seem to be major issues. Are there major
18 issues for anyone else?

19 DR. O'SULLIVAN: They are not a major issue for me
20 but what about for the patient, because patients don't even
21 like a forceps mark. They are a little upset when they see
22 a vacuum -- and you have a lot of explaining to do to let
23 them know that is going to happen and it is going to go
24 away. So, I think it is really the patient's input to that
25 one. I mean, true, I don't have any problem with it but the

1 patient might.

2 CHAIRMAN BLANCO: I think the issue there is what
3 Diony was pointing out. I think that was her issue. It
4 wasn't a real question, it was basically that the patient
5 needs to be informed that there is this possibility and not
6 just say it is safe. You know, it is nice that it is safe
7 but they need to be told that their baby may have a mark on
8 his cheek or their baby may have a mark where the monitor is
9 placed, and it will probably go away before you take him
10 home -- him or her home, but that is it. Wasn't that your
11 point, Diony?

12 MS. YOUNG: Yes, absolutely, and just following
13 along from that, and having looked at the sensor now, I
14 think that if there is time, and I assume that time isn't
15 absolutely of the essence here; it is not critical, the
16 mother could be shown the sensor, shown the device that will
17 be inserted in her, with a brief explanation.

18 CHAIRMAN BLANCO: I think that is labeling. Mary
19 Jo, if that will be acceptable in terms of labeling --

20 DR. O'SULLIVAN: No problem.

21 CHAIRMAN BLANCO: -- they need to describe the
22 percentage of times that a baby gets a mark on the face, to
23 the mother, in language that she is going to be able to
24 understand.

25 DR. ROY: How stable is it in terms of location

1 once placed, and has there ever been an occasion where that
2 LED has slipped over the eye, and what happens thereafter?

3 CHAIRMAN BLANCO: So that we sort of keep the
4 discussion among ourselves, I mean, the issue, to some
5 extent, is what they are talking about, the 60 percent of
6 time that they can get a reading in putting it in; that it
7 does fall out; it does move; and the issue is that you can
8 replace it and you can jiggle it probably or move it around
9 and get it back to put on there, and 33 percent of the time
10 it is not going to get a reading and it is some place else.
11 As far as eye data, I think the FDA has looked at that
12 preclinically. Ms. Daws-Kopp, do you want to make any
13 comment on that?

14 MS. DAWS-KOPP: We are in the process of working
15 some of that out but, as I had said in the presentation I
16 gave, the light levels and the thermal levels are pretty low
17 so theoretically we don't think there will be a problem.

18 DR. ALLEN: I had a question. In the text there
19 are several references to accidental injury in the neonates.
20 What is an accidental injury?

21 DR. THOMAS: That term refers to the coding used
22 to classify all of the adverse events. It could be coded
23 accidental injury, it could have been called an ecchymosis.
24 It is whatever the case report form was filled in as.

25 DR. ALLEN: And the uterine rupture was not in the

1 study arm? It was in the control arm?

2 DR. SWEDLOW: There was one uterine rupture and it
3 was in the control arm.

4 CHAIRMAN BLANCO: Please use the mike.

5 DR. SWEDLOW: I am sorry. The answer is yes.

6 [Laughter]

7 CHAIRMAN BLANCO: Very succinct. We appreciate
8 that. I have another issue. This is fairly stiff.
9 Perforation? Any evidence of perforation?

10 DR. SWEDLOW: Well, zero in 35,000.

11 CHAIRMAN BLANCO: You are including the European
12 data in that remark?

13 DR. SWEDLOW: Yes. I feel fairly confident that
14 had there been one we would have heard. Quickly.

15 CHAIRMAN BLANCO: All right. Any other comments
16 from panel members?

17 DR. O'SULLIVAN: This may sound dumb, and maybe it
18 is, especially as it has been used for as long as it has,
19 but if I interpret this correctly, this is alongside of the
20 cheek, and then the biparietal diameter is involved and this
21 is going to come in and it is going to increase the diameter
22 that is presenting. Now, I know this may sound very strange
23 but I question whether this 6 mm, 8 mm in any way impacts.

24 CHAIRMAN BLANCO: Whether that impacts on
25 dystocia? That is an interesting question.

1 DR. O'SULLIVAN: I am not worried about the cheek.

2 DR. SWEDLOW: Maybe I can clarify it.

3 CHAIRMAN BLANCO: Okay, let's get that clarified.

4 They looked at that.

5 DR. O'SULLIVAN: Okay, let's hear it.

6 DR. SWEDLOW: There are two comments to clarify.

7 First, there is a tactile ridge on the cable itself, and the
8 instructions and the video demonstrate -- not demonstrate
9 but say you are supposed to put it in until you feel it at
10 the cervix. When that happens -- if you will pardon the
11 expression, the big, black part is beyond the biparietal
12 diameters. It is already beyond that equator and is -- not
13 void exactly, but is in the space around the cheek.

14 The second point in terms of whether that
15 phenomenon might cause dystocia, we looked at all the
16 vaginal deliveries, both assisted and controlled, and all of
17 the C-sections, and there is no evidence of slowing at all
18 from using the sensor. So, I think we have exhaustively
19 nailed that one.

20 CHAIRMAN BLANCO: Mike?

21 DR. DIAMOND: Is it possible that sometime --
22 obviously it is possible, but it could get turned around
23 such that rather than the sensor being against the head it
24 is against the uterine wall?

25 DR. SWEDLOW: Yes, it can.

1 DR. DIAMOND: I am sure it could, but what would
2 the reading be? How would the practitioner know that that
3 has happened?

4 DR. SWEDLOW: It becomes the mother's reading
5 which, fortunately, is around 95 or 100 and becomes absurd.

6 DR. DIAMOND: Okay.

7 CHAIRMAN BLANCO: Does the panel have any other
8 comments on safety?

9 DR. SWEDLOW: The heart rates don't match. It
10 becomes the mother's heart rate. It basically reads the
11 mom.

12 CHAIRMAN BLANCO: Any other comments on safety?

13 DR. DIAMOND: Let me ask a hypothetical question,
14 not practicing obstetrics anymore, what is the possibility,
15 if I were a nay-sayer, that the reason that the cesarean
16 section rate is reduced in this patients is that the
17 protocol was such that you see an abnormal tracing in the
18 control group and you are going to have to make a decision
19 whether to go to cesarean section, that decision would be
20 made sooner. In the treatment arm you are taking the time
21 to place this device. Some of the concerning fetal heart
22 rate traces by then will have come back to normal, and no
23 longer be a concern. The oxygen being 30, maybe it goes
24 down to 26, 28; after 5 minutes while you are trying to
25 figure out what to do it comes back up to 30. What is the

1 potential that just prolonging things, and then doing a
2 fetal scalp sampling in some of the patients or doing
3 acoustic stimulation -- that just prolonging the course of
4 labor before you make a decision to do a cesarean section
5 would account for a lower rate of cesarean sections in
6 patients with abnormal fetal heart rate tracing without
7 seeing any increases in abnormalities of the fetus?

8 CHAIRMAN BLANCO: What you are asking is for them
9 to provide the data of the interval time from when the
10 decision was made to enter the patient into the study to the
11 time that the control group was sections, versus from the
12 decision time when the patient was introduced into the study
13 in the test group to when some reading was obtained from the
14 fetal scalp electrode to see whether there was a significant
15 difference in there, and then to look at how many of the
16 tracings in the fetal scalp electrode -- I am going to get
17 it right before it is over -- in the fetal scalp sensor
18 changed to reassuring and, therefore, you didn't go section.
19 Is that what you are saying?

20 DR. DIAMOND: A little bit, but let me ask it a
21 little differently, what is the likelihood that in a patient
22 with non-reassuring tracing you could wait longer and it
23 will come back to reassuring? Does that study exist in the
24 obstetrical literature here or elsewhere, where we could put
25 that into a perspective as to what percentage will come back

1 to normal without having adverse outcomes as assessed by
2 acidosis or cerebral palsy or other endpoints?

3 CHAIRMAN BLANCO: Well, I think the issue though
4 is to look at what data they are presenting because this is
5 the study that we are looking at. What we can recommend and
6 what I think the FDA needs to look at is how many times did
7 that happen in this study. In other words --

8 DR. DIAMOND: Well, it happens in every one of
9 them because in every one of them that they have an abnormal
10 tracing in the treatment group they are putting in this
11 device --

12 CHAIRMAN BLANCO: Right.

13 DR. DIAMOND: -- and then they are waiting a
14 variable length of time, based on physician behavior, and
15 some of them come back up. So, it is happening in every one
16 of them, albeit in varying extent and to degrees to which at
17 this point of time the data is not available.

18 CHAIRMAN BLANCO: Not exactly because we don't
19 know how many fetal heart rate tracings went back to
20 reassuring. You could look at that. Your issue, if I
21 understand it and if I frame it correctly, is in the control
22 group you find your non-reassuring fetal heart rate pattern
23 and you section them. Here, if you had let them go they
24 would have had reassuring patterns X number of times after
25 that and you wouldn't have sectioned them. Whereas, what

1 happened with the test group is you recognized it here; you
2 inserted the monitor. Okay? But then, the way the matrix
3 is, you are supposed to go on the monitor. If the monitor
4 is over 30, and even though it is non-reassuring, you
5 continue to watch it. The issue becomes then how many
6 reverted back to reassuring? Right? That is the only way
7 you are going to be able to look at that.

8 DR. SHARTS-HOPKO: Without that monitor you would
9 never find an IRB that would approve that study.

10 DR. DIAMOND: No, you wouldn't but are there
11 studies from other situations. Who knows? When I first
12 went into OB one of our hospitals didn't have an OR staff at
13 night. So, if we had a non-reassuring tracing we would have
14 to wait half an hour to forty-five minutes till we had them.
15 So, that would be a natural history of what happened in that
16 time course.

17 CHAIRMAN BLANCO: Dr. Garite?

18 DR. GARITE: The data was looked at with the labor
19 curves, the Kaplan-Meier survival curves, which is plotting
20 the number of patients remaining undelivered over time. We
21 analyzed those survival curves just for patients having
22 sections for fetal distress. If what you are proposing is
23 that you are delaying the delivery in some patients, you are
24 going to change that survival curve, I would think, among
25 the patients in the test group who are having sections for

1 fetal distress.

2 DR. DIAMOND: Yes, but not necessarily for
3 cesarean sections because the question is could that be the
4 reason that you ended up with fewer cesarean sections.

5 DR. GARITE: One would expect then that that would
6 change your correlation with prediction of outcome and,
7 indeed, the prediction of depression and acidosis was
8 actually better in the monitor group.

9 DR. DIAMOND: If that is what you are doing, then
10 I would say mazzeltov. I mean, the point is that you are
11 allowing patients to go to vaginal delivery who need to go
12 to vaginal delivery and sectioning the ones that are more
13 depressed. So, if that is the case, then the device is
14 accomplishing what it wants to accomplish.

15 CHAIRMAN BLANCO: Let me interrupt there. It is a
16 little bit after three o'clock; we need some break time.
17 And, that is really not part of the safety; that is really
18 more when we go back to which way to vote and whether it is
19 significant.

20 Before everybody goes, any other comments
21 specifically on the safety, or have we made all the comments
22 we want to make? I think we have made all the comments we
23 want to make. We are really keeping on time pretty well so
24 let's go ahead and keep the fifteen-minute break.

25 [Brief recess]

1 CHAIRMAN BLANCO: Let's go ahead and get started.
2 We are doing quite well on time. Yes, sir?

3 DR. SWEDLOW: We have some information if you
4 would like to hear it.

5 CHAIRMAN BLANCO: What we are going to do, we will
6 hear that and then we will go to the last question. At that
7 point, we will ask you to step back --

8 DR. SWEDLOW: Mist.

9 [Laughter]

10 CHAIRMAN BLANCO: No, you don't have to go that
11 far back. Just go into the crowd, if you will. I was
12 looking for a better word than crowd -- the audience. They
13 didn't give me this job for my couth, you know.

14 [Laughter]

15 Let's go ahead and get started. We will get to
16 your point but Dr. Eglinton wants a clarification on some
17 issues.

18 DR. EGLINTON: During the last segment I had made
19 the observation that comparing the baseline phase to the RCT
20 phase, the cesarean rate for NRFS and for FILDYS doubled
21 basically compared to the baseline phase. Now, let me ask a
22 question. Several of my colleagues here pointed out to me
23 that during the baseline phase, the patients enrolled in the
24 baseline phase were unselected. They were not high risk for
25 some reason. They did not have non-reassuring strips to