

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

OBSTETRICS AND GYNECOLOGY DEVICES PANEL
SIXTY - FOURTH MEETING

Monday, May 21, 2001

1:00 p.m.

Gaithersburg Holiday Inn
5 Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Jorge D. Blanco, M.D., Chairman
Joyce Whang, Ph.D., Executive Secretary

MEMBERS

David F. Katz, Ph.D.
Nancy C. Sharts-Hopko, Ph.D.
Subir Roy, M.D.
Mary Jo O'Sullivan, M.D.
Mary Lou Mooney, R.A.C.,
Industry Representative
Stanley Reynolds,
Consumer Representative

TEMPORARY VOTING MEMBERS

Michael Neuman, M.D., Ph.D.
Machelle Allen, M.D.
Ralph B. D'Agostino, Ph.D.
Gary S. Eglinton, M.D.
Jay D. Iams, M.D.

FDA

Nancy C. Brogdon

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1 PROCEEDINGS

2 DR. BLANCO: We will call the meeting to
3 order so that we don't get too far behind schedule.

4 Let me run through a few things in calling
5 the meeting to order. First of all, let me remind
6 everyone, including panel members, that they would
7 like for you to sign in. There are some sign-in
8 sheets outside, if you would please fill in your
9 name and affiliation so that we have some idea of
10 who was here.

11 We will have a session for an open public
12 forum, and we will ask you please to not make
13 comments from the audience but to be recognized by
14 the chair, and to always use one of the microphones
15 so that we can all hear you and, since this is all
16 being recorded, so that we can record you for
17 posterity. At the same time, before you speak at
18 least the first time when you introduce yourself,
19 please make sure that you make a statement about
20 any kind of conflict of interest and any kind of
21 financial disclosure. That means including whether
22 anyone paid for your travel here; whether you are
23 being paid a per diem; whether you have a
24 relationship with a company as a consultant or have
25 received any kind of compensation from the company.

1 After having said that, the first thing
2 that we would like to do is let everyone know who
3 is on the panel, and we will go ahead and begin
4 from my right-hand side. We will go around and
5 please state your name and your affiliation or what
6 you do.

7 MS. BROGDON: I am not a member of the
8 panel. I am Nancy Brogdon, the Division Director.

9 DR. WHANG: If I might just interject,
10 Nancy Brogdon was recently named Director of the
11 Division of Reproductive, Abdominal and
12 Radiological Devices. She is a microbiologist who
13 was most recently the Deputy Director of the
14 Division of Ophthalmic and Ear, Nose and Throat
15 Devices. In that division, she has been a
16 scientific reviewer and has held various division
17 management positions, including interim director,
18 for a total of 21 years.

19 DR. NEUMAN: I am Mike Neuman, from the
20 Memphis Joint Program of Biomedical Engineering of
21 the University of Tennessee and the University of
22 Memphis.

23 DR. KATZ: I am David Katz, from Duke
24 University, where I am in the Department of
25 Biomedical Engineering.

1 DR. D'AGOSTINO: Ralph D'Agostino, from
2 Boston University, biostatistician.

3 DR. SHARTS-HOPKO: Nancy Sharts-Hopko,
4 Professor of Nursing in the College of Nursing at
5 Villanova University.

6 DR. EGLINTON: Gary Eglinton, Ob/Gyn, New
7 York Hospital Medical Center of Queens.

8 DR. ALLEN: I am Machelles Allen, Director
9 of Ambulatory Ob/Gyn at Bellevue Hospital and New
10 York University.

11 DR. ROY: Subir Roy, Professor of Ob/Gyn,
12 School of Medicine, University of Southern
13 California.

14 DR. WHANG: I am Joyce Whang. I am a
15 reviewer and the executive secretary of this Ob/Gyn
16 panel.

17 DR. BLANCO: I am Jorge George Blanco --
18 used to be in academics and now I am just a
19 physician.

20 DR. IAMS: I am Jay Iams. I am in
21 maternal fetal medicine on the faculty of Ohio
22 State University in Columbus.

23 DR. O'SULLIVAN: I am Mary Jo O'Sullivan,
24 Internal Fetal Medicine at the University of Miami,
25 in Florida.

1 MS. MOONEY: I am Mary Lou Mooney, Vice
2 President of Clinical, Regulatory and Quality for
3 SenoRx, and I am the industry rep.

4 DR. WHANG: I will just interject again
5 because Mary Lou Mooney is a new industry rep for
6 this panel. She is currently Vice President of
7 Clinical, Regulatory and Quality for SenoRx, Inc.,
8 which is a women's health company that is
9 developing interventional devices for the diagnosis
10 and treatment of breast disease. Ms. Mooney
11 received her Master's degree in biomedical science
12 from Drexel University in Philadelphia. She has 20
13 years of medical device experience.

14 MR. REYNOLDS: I am Stanley Reynolds. I
15 am the consumer rep.

16 DR. WHANG: I think that needs an
17 introduction too. He is a clinical microbiologist
18 and supervisor of the Immunology and Virology
19 Section of the Department of Health of the
20 Commonwealth of Pennsylvania, where he has worked
21 for 26 years. He is the consumer rep for the FDA
22 Microbiology Devices Panel, and has served as
23 acting consumer rep for other panels, including us
24 today.

25 DR. BLANCO: Welcome, everyone. Nice to

1 see some of the familiar faces, and welcome to the
2 new members.

3 I need to make a few other housekeeping
4 announcements. The FDA press contact for this
5 portion of the meeting is Colin Pollard. He is
6 Chief of Obstetrics and Gynecology Devices Branch.
7 Colin, would you please stand? If you need some
8 press contacts, he is the individual to contact.

9 Moving along, I just want to remind
10 everyone that we don't need any outbursts. If you
11 feel you just have to say something, please motion
12 and we will try to recognize you at the appropriate
13 time. That never happens with the panel so that is
14 really more for the public folks.

15 Now I will turn the meeting over to Joyce
16 with some other announcements.

17 DR. WHANG: First, an announcement about
18 the remaining panel meetings which have been
19 scheduled for this panel for this year. The July
20 meeting has been cancelled. The October 15-16
21 meeting is the next scheduled meeting.

22 We have several temporary voting members
23 today, and I will just read to you their
24 appointment to temporary voting status: Pursuant
25 to the authority granted under the Medical Devices

1 Advisory Committee Charter, dated October 27, 1990,
2 as amended August 18, 1999, I appoint the following
3 individuals as voting members of the Obstetrics and
4 Gynecology Devices Panel for this meeting, on May
5 21, 2001, Machel H. Allen, M.D., Ralph B.
6 D'Agostino, Ph.D., Gary S. Eglinton, M.D., Jay D.
7 Iams, M.D. and Michael Neuman, M.D., Ph.D.

8 For the record, these individuals are
9 special government employees and consultants to the
10 panel or other panels under the Medical Devices
11 Advisory Committee. They have undergone the
12 customary conflict of interest review and have
13 reviewed the material to be considered at this
14 meeting. This is signed by David Feigal, Jr.,
15 M.D., M.P.H., who is the Director for the Center
16 for Devices and Radiological Health.

17 I also have the conflict of interest
18 statement for today's meeting. The following
19 announcement addresses conflict of interest issues
20 associated with this meeting, and is made a part of
21 the record to preclude the appearance of an
22 impropriety. To determine if any conflict existed,
23 the agency reviewed the submitted agenda and all
24 financial interests reported by the committee
25 participants. The conflict of interest statutes

1 prohibit special government employees from
2 participating in matters that could affect their or
3 their employers' financial interests. However, the
4 agency has determined that participation of certain
5 members and consultants, the need for whose
6 services outweighs the potential conflict of
7 interest involved, is in the best interest of the
8 government.

9 We would like to note for the record that
10 the agency took into consideration certain matters
11 regarding doctors Michael Neuman and Gary Eglinton.
12 Dr. Neuman reported an interest in a firm at issue
13 but in matters that are unrelated to today's
14 agenda. The agency has determined, therefore, that
15 he may participate fully in the panel's
16 deliberations.

17 Dr. Eglinton reported an imputed interest
18 with firms at issue in an involvement related to
19 fetal pulse oximetry. Since the interest is
20 imputed to him through his employer and not his
21 personal interest, the agency has determined that
22 he may participate fully in today's deliberations.

23 In the event that the discussions involve
24 any other products or firms not already on the
25 agenda for which an FDA participant has a financial

1 interest, the participant should excuse him or
2 herself from such involvement and the exclusion
3 will be noted for the record.

4 With respect to all other participants, we
5 ask in the interest of fairness that all persons
6 making statements or presentations disclose any
7 current or previous financial involvement with any
8 firm whose products they may wish to comment on.

9 There will be transcripts and videos
10 available for today's meetings. For videos,
11 contact Video on Location. The number is 301-984-5823. Or,
12 Video Visions at 301-438-8724. For
13 transcripts, contact Miller Reporting Co. at 202-546-6666.
14 And, there are fliers on the tables out
15 front.

16 If there are any presenters to the panel
17 who have not already done so, they should provide
18 FDA with a hard copy of their remarks, including
19 overheads. Sharon Lappalainen -- Sharon, please
20 stand -- will collect these from you at the podium.

21 DR. BLANCO: Thank you. Moving right
22 along, let me go ahead and it is a pleasure for me
23 to introduce Mr. Colin Pollard, Chief of Obstetrics
24 and Gynecology Devices Branch, who will give us
25 some introductory remarks on the issues at hand for

1 resource as well as the time and energy of the
2 panel, we used our discretion not to hold panel
3 meetings for those two other PMAs.

4 We also reclassified home uterine activity
5 monitors from Class III premarket approval to Class
6 II special controls. In conjunction with this
7 action, we also issued a guidance document. The
8 agency is currently looking at implementation of
9 the patient registry requirement, a special control
10 the panel recommended and FDA agreed with.

11 [Slide]

12 I would now like to turn to the first
13 topic of today's agenda. About a year ago FDA
14 approved a fetal oxygen saturation monitoring
15 system, the first of a kind. It is intended to be
16 used for women with singleton pregnancies, cephalic
17 presentation, and inactive labor after membranes
18 have ruptured who have a non-reassuring fetal heart
19 rate pattern.

20 Today we are asking the panel to look at
21 this monitor and, in particular, the PMA supplement
22 from Mallinckrodt for its revised post-approval
23 study plan. We don't typically bring PMA
24 supplements before the panel, and you might
25 consider this one even more unusual since the new

1 post-approval study plan before you today is
2 arguably, thanks to the efforts by NIH, more robust
3 than what was envisioned by the panel when it made
4 its recommendation in January of 2000.

5 But there are nearly four million babies
6 born in the U.S. each year and, no matter how you
7 envision the acceptance of this monitor in clinical
8 practice, there is the potential for a significant
9 percentage of the babies to be monitored during
10 labor with this technology. And, given the
11 reservations expressed by the panel and reflected
12 in a number of conditions of approval of the PMA,
13 when we released this product to market in May of
14 last year, we believed it is important to ask the
15 panel for its input in helping us make the best
16 decision.

17 [Slide]

18 In introducing this agenda item to the
19 panel, I would like to cover a few things. I know
20 this will be familiar territory to many of you so
21 please bear with me; I think it will be worthwhile.
22 I will briefly, I hope, go over some of the history
23 of our approval of this device. I will highlight
24 the decision itself and some of the key conditions
25 to the approval. Lastly, I will review the panel

1 charge. There will be an opportunity for questions
2 at the end.

3 [Slide]

4 In reviewing our approval decision last
5 year, I will touch on some elements of FDA's
6 initial review of the PMA. I will review some of
7 the discussion points of last year's panel meeting,
8 as well as some additional analyses we did after
9 the panel meeting, before approval. Finally, I
10 will go over the key aspects of the approval
11 itself.

12 [Slide]

13 When FDA approved the PMA for this device,
14 we looked at many things. We looked particularly
15 carefully at the accuracy of the sensor in terms of
16 bias from the true value and precision. We also
17 looked at practical issues of registration error
18 and posting time, all with an eye on what do we
19 tell the clinical user about these aspects.

20 We also looked, obviously, at the pivotal
21 study the sponsor presented to support the PMA.
22 This was a randomized, controlled trial of about a
23 thousand patients, with approximately about 500 in
24 each arm. As most of you know, this study
25 presented us with some fairly complex questions.

1 FDA tried to distill our concerns to a handful of
2 key questions relating to safety in terms of both
3 maternal and fetal adverse events and
4 effectiveness, both with respect to the primary
5 outcome measure as well as an unexpected finding
6 that challenged the significance of the primary
7 finding.

8 [Slide]

9 We brought the PMA for this device before
10 the panel in January of last year. FDA crafted
11 several questions for the panel to consider. I
12 will go over those in a second. Following
13 deliberations, the panel, with a 10-1 vote,
14 recommended to FDA that the PMA be approved. The
15 panel also identified several conditions to this
16 approval recommendation regarding the labeling as
17 well as post-approval studies.

18 [Slide]

19 Let me first review some of those initial
20 panel discussion questions. First, focusing
21 primarily on the pivotal clinical trial, we asked
22 the panel to consider what patients were monitored.
23 We asked about the accuracy of the monitor and how
24 the sensor functioned in posting fetal SpO2 values
25 on the tracing.

1 As I will show you in a moment, cesarean
2 deliveries for a non-reassuring fetal status were
3 lower in the experimental arm and we also saw a
4 relatively commensurate rise in cesareans for
5 dystocia. We asked the panel to help us think
6 about these findings.

7 Blood oxygen saturation of the normal
8 fetus is typically in the range of 30-70 percent.
9 We asked the panel to help us look at how fetal
10 pulse oximetry related to conventional fetal heart
11 rate tracings, especially in light of the
12 recommended clinical cut-off value of 30 percent.

13 Finally, we asked the panel about the
14 reported adverse events and whether that data
15 signaled anything significant when evaluating the
16 two study arms.

17 I can't possibly do justice to the panel
18 discussion that day, and we did our best to bring
19 back as many of you as possible for our
20 deliberations today.

21 [Slide]

22 Let me just first show you a table that
23 probably captures the most troubling aspects of the
24 pivotal trial that led ultimately to our
25 requirement for a post-approval study. Here you

1 see, within the first box, the primary study
2 endpoint of cesareans for non-reassuring fetal
3 status, approximately 5 percent in the experimental
4 arm and 10 percent in the control arm. You also
5 see in the bottom box that the overall cesarean
6 delivery rate was essentially unchanged. You see
7 the study arm using fetal pulse oximetry had
8 commensurately more cesarean deliveries for
9 dystocia-related indications. For us, this called
10 into question the overall clinical significance of
11 the individual findings.

12 As I mentioned, I can't really go over all
13 the ways the panel looked at this data but the
14 panel ultimately believed the study demonstrated,
15 as is required for a PMA, that use of the monitor
16 did produce a clinically significant result and
17 recommended approval of the PMA. The conditions of
18 that recommendation were reflected in the FDA
19 approval order.

20 [Slide]

21 But before FDA was ready to approve the
22 monitor several questions remained to be answered.
23 We looked at the data in various ways to see
24 whether bias, either in the patient selection or
25 clinical behavior, could explain the increase in

1 cesareans for dystocia. No evidence was found of
2 significant bias, but it must be admitted that this
3 kind of search is limited by the available data and
4 this is a difficult thing to pin down.

5 Besides the post hoc analysis of the
6 partograms that was done to verify that most of the
7 subjects delivered by cesarean for dystocia in both
8 arms truly met the definition of dystocia, FDA also
9 asked the sponsor to look at duration of labor to
10 see whether the sensor itself might slow progress
11 of labor. These analyses also failed to explain
12 the unexpected finding.

13 We also looked at a number of other
14 questions about this monitor, mostly trying to
15 better understand the recommended 30 percent cut-off value
16 and the relationship, if any, between
17 fetal heart rate patterns and low fetal oxygen
18 saturation. These and other analyses are described
19 in the summary of safety and effectiveness document
20 that was provided in the background package you
21 received a few weeks back.

22 [Slide]

23 The next five slides give a quick overview
24 of our approval decision and emphasis on some of
25 the key conditions of our approval, namely, an

1 adjunct only to fetal heart rate monitoring; the
2 indication for a non-reassuring fetal heart rate
3 pattern, plus a specified management protocol for
4 using that information; labeling constraints on
5 claims related to the cesarean sections, namely, if
6 the company is going to speak to the cesarean
7 section issues from the study they have to inform
8 users that there was no overall effect on the
9 cesarean delivery rate; and the post-approval study
10 requirements which are the topic of today's
11 discussion.

12 [Slide]

13 Up here on the slide you see the full
14 aspects of the indications for use, the key aspects
15 being an adjunct to fetal heart rate in the
16 presence of a non-reassuring fetal heart rate
17 pattern.

18 [Slide]

19 The management protocol -- I am not going
20 to go through this with you but, first of all,
21 related to the fetal heart rate classification as
22 well as managing the patient in face of non-reassuring fetal
23 heart rate and high or low oxygen
24 saturation. You have that in your handout.

25 [Slide]

1 The post-approval studies were two, one
2 for human factors to look at aspects of just
3 clinical use of the device and proper
4 interpretation, as well as the general use study
5 which the panel recommended to look at the
6 indications for sensor placement, cesarean delivery
7 rates, maternal infection; to look at the 30
8 percent cut-off value, its duration, its
9 relationship to fetal risk; the issue of dystocia
10 and adequacy of labor, as well as some neonatal
11 outcome information.

12 [Slide]

13 After we made this decision, we also did
14 our best to reach out to other parts of the Public
15 Health Service as well other interested parties.
16 After the panel meeting last year, FDA did some of
17 its own outreach efforts. In February of last year
18 we visited the Maternal Fetal Medicine Unit Network
19 to inform them of the panel's recommendation and
20 our plans to approve this monitor. We tried to
21 convey our concern that whereas we believe that the
22 sponsor had sufficient information to approve the
23 device, we saw this only as the beginning for a
24 device like this with the potential to be used for
25 thousands, if not millions, of labors. As you will

1 see today, although there might have been
2 differences of opinion about the FDA decision
3 itself, the Network took to heart our concerns and
4 the panel concerns and plans to conduct its own
5 large, randomized trial. We are fortunate to have
6 Kathy Spong, coordinator of the MFMU Network, here
7 today to describe this massive effort.

8 In our own small way, FDA has been able to
9 help by providing some technical support for the
10 study. Sandy Weininger, from our Office of
11 Science and Technology, who was already a key
12 member of the PMA review team, is working with Dr.
13 Spong to develop software for the data acquisition
14 involved in this study. We have continued to work
15 with Dr. Spong as this research project progresses.

16 We have also tried to keep ACOG up to date
17 and up to speed on approval developments, briefing
18 them and providing them with important background
19 materials. Most recently, I met with the ACOG Ob
20 Practice Committee, in February, explaining to them
21 how we went through our approval process. As you
22 know, Dr. Susan Raymond was at our panel meeting
23 last year representing the College, although later
24 this morning we will hear from George Macones
25 representing the College.

1 [Slide]

2 Now to the PMA supplement itself. As I
3 mentioned at the beginning, this supplement
4 describes the post-approval study plan that is an
5 alternative to what we envisioned when we approved
6 the device a year ago. There is no change to the
7 human factors study, but Mallinckrodt now proposes
8 to replace its earlier general use study with a new
9 plan to use data from three separate studies. They
10 will present a more streamlined general use study,
11 probably more akin to a patient registry, that can
12 perhaps, in light of the other two studies, be more
13 focused; a dystocia study that is planned by a few
14 of the original investigators from the pivotal
15 study I just discussed; and a large three-arm
16 randomized clinical trial to be sponsored by NIH's
17 MFMU Network. This will be described in more
18 detail a little later this morning by Dr. Spong.

19 I think I should note that our evaluation
20 of this third part is not to critique the study.
21 The plan is pretty far along, as I understand it,
22 and although Dr. Spong could speak to this herself,
23 changes to the plan are done by the Network itself.
24 Rather, we are asking the panel whether
25 Mallinckrodt's plan to use data from some or all

1 this study, as it is described to us, addresses any
2 of the concerns raised by the panel last year when
3 it recommended that the sponsor develop a post-approval
4 study plan.

5 [Slide]

6 Finally, I turn your attention to the
7 discussion questions in your folder. Although FDA
8 prepared these to help your deliberations on this
9 three-part study plan, I would like at this point
10 to acknowledge the help of Dr. Iams in our earlier
11 interactions on this plan. Dr. Iams has agreed to
12 be chief discussant on the panel for this post-approval
13 study plan, although I know he is going to
14 have lots of help from several others of you. I
15 hope that you all will work with Dr. Blanco to help
16 the panel discussion in the end, and with the help
17 of Dr. Whang, your exec. sec., and Dr. Blanco, your
18 panel chair, we will ask for a panel recommendation
19 on this PMA supplement. Thank you for your
20 attention, and are there any questions?

21 DR. BLANCO: Thank you, Mr. Pollard.
22 Moving right along, our next section in this
23 meeting is the open public hearing. We have
24 notification that there are two speakers who would
25 like to speak. Let me just remind you, if there

1 are any others, after we finish with these two we
2 will allow you to come up. Again, let me remind
3 you to introduce yourself and note any type of
4 conflict of interest that you might have with any
5 of the companies or with this particular device.
6 The first speaker that I have is Dr. George
7 Macones, from the University of Pennsylvania,
8 representing the American College of Obstetricians
9 and Gynecologists.

10 Open Public Hearing

11 DR. MACONES: Thank you. Thank you for
12 having me here today. My name is George Macones.
13 I am from the Division of Maternal Fetal Medicine
14 at the University of Pennsylvania. I am here
15 representing the American College of Ob/Gyn and the
16 Committee on Obstetric Practice.

17 ACOG has paid my way here. So, that is
18 one of my conflicts of interest, I suppose. The
19 other one is that our site actually recruited for
20 one of the fetal pulse oximetry studies a few years
21 back. I wasn't involved in that at all and have no
22 financial conflict about it but we did recruit a
23 few patients at our site.

24 I want to say some very brief words about
25 ACOG's view on the fetal pulse oximeter.

1 Certainly, it has been something that the College
2 has followed very closely and with great excitement
3 to see how things develop. However, based on the
4 recent study that was published by Tom Garite that
5 Colin so nicely summarized, ACOG is really not
6 ready to embrace or endorse the use of the fetal
7 pulse oximeter in any way for routine use.

8 I think what ACOG would like to see, and I
9 am hopeful that will come out of the meeting today,
10 are really some well-designed clinical studies to
11 answer a couple of important questions.

12 The first, again as Colin mentioned, the
13 problems with the Garite study were that while
14 there was a reduction in the rate of C-sections for
15 non-reassuring fetal heart rate tracings, we had
16 these funny results about the increased C-section
17 rate for dystocia. I think that any postmarketing
18 study or future clinical trials really need to look
19 at that very, very carefully before ACOG is willing
20 to, again, endorse such a product.

21 Equally as important, and something that
22 really couldn't be answered adequately in the
23 initial clinical trial, is whether or not there is
24 a significant rate of false-negatives with the
25 fetal pulse oximeter, in other words, having a

1 reassuring fetal oxygen saturation when the fetus
2 is actually doing poorly. I think that needs to be
3 also a significant part of any future studies that
4 are done to assess the safety of a fetal pulse
5 oximeter.

6 So, that is really ACOG's current view.
7 There may be some official documents coming out in
8 the upcoming months that go through this in a
9 little bit more detail, but that is the current
10 view of ACOG. I would be happy to answer any
11 questions.

12 DR. BLANCO: Thank you very much. Let me
13 just say one other thing that I forgot, and the
14 speaker was very kind to fit within that, each
15 public speaker has a maximum of five minutes for a
16 presentation.

17 No questions? If not, we will move on to
18 the second speaker. The second speaker that we
19 have at this time is Dr. Barry Schifrin. Dr.
20 Schifrin?

21 DR. SCHIFRIN: I may need a second to hook
22 myself up here. My name is Dr. Barry Schifrin. I
23 am a maternal fetal medicine physician. I am
24 currently the Director of Obstetrics and Gynecology
25 Residency at Glendale Adventist Medical Center. I

1 am not here representing anything other than my own
2 opinion and some passionate involvement for the
3 last thirty years on the subject of fetal
4 surveillance during labor. I had the privilege of
5 being one of the invited speakers when the device
6 was initially considered.

7 [Slide]

8 I would like to begin with a quote and end
9 with a quote.

10 DR. BLANCO: Dr. Schifrin, just for the
11 record we need to know whether you have any
12 conflict of interest, any involvement with any
13 companies that might potentially --

14 DR. SCHIFRIN: I have no attachment to any
15 company that I know of, and my only potential
16 conflict of interest is an intellectual one.

17 DR. BLANCO: Thank you.

18 DR. SCHIFRIN: I would like to open and
19 leave with two quotes. One is by Piet Hein: Our
20 choicest plans have fallen through; our airiest
21 castles tumbled over because of lines we neatly
22 drew and later neatly stumbled over.

23 Fetal monitoring, as almost everybody in
24 this room knows, is attendant to a number of
25 problems, viewed with considerable passion about

1 its use and value. It was originally introduced
2 with the most glorious objectives only to
3 understand that some of those objectives would not
4 only not be realized but could never be realized.
5 But the problem with the fetal monitor has to do as
6 much with the conception and those expectations as
7 it did with what it actually does.

8 So, when it was introduced to the market
9 it was introduced with the notion that we had a
10 technique for recognizing asphyxia. We would
11 identify these decelerations and we would go in and
12 rescue the fetus. That simply does not work. What
13 we have come to understand is that monitors work,
14 if they are going to work, in a different way and
15 that they answer the question of how are you doing
16 more than they answer the question of do you need
17 to be rescued. For this purpose, you will need to
18 be driven by overall patterns and not simply the
19 presence or absence of decelerations. The third
20 feature is that fetal rescue has almost no place in
21 contemporary monitoring. You have to use the
22 monitor not to see how close you can come to
23 disaster but how to keep the baby out of harm's
24 way.

25 [Slide]

1 Of all of the expectations of fetal
2 monitoring, and all of the various statistics, and
3 all of the various impediments to its realization,
4 this I suspect -- I submit that the problems with
5 the precepts of monitoring, what it is designed to
6 do, is in fact one of the most misunderstood
7 features of, in fact, how it works.

8 [Slide]

9 I draw your attention to the published
10 heart rate patterns that were used for the study.
11 I am sorry, this is essentially the criteria that
12 Mr. Pollard showed a little while ago. I have just
13 made it into a table and circled for your
14 convenience those parts of the their descriptions
15 that are missing. Where you see "NS" up there --
16 and I would be happy to give you a copy of this --
17 is what is missing from the description of the
18 heart rate patterns as described in the published
19 study by Garite. I submit that it is simply not
20 reasonable or possible to make an interpretation of
21 the significance of the heart rate pattern on the
22 basis of the tracings so designated; that there is
23 often significant information missing and on the
24 basis of the information one could come up with, as
25 I have tried to show here, reasonable expectation

1 of the significance of the decelerations.

2 [Slide]

3 I share with you here a feature of heart
4 rate patterns that has been known for at least the
5 last 25 years, and that is the relationship of
6 decelerations and the type of decelerations with
7 the position of the fetal head. Babies in the
8 occiput posterior position are far more likely to
9 have decelerations in heart rate; have much longer
10 labors; have far more molding of the fetal head
11 than are babies in the occiput anterior position.
12 I would submit that, based on these and other data,
13 there is a link between heart rate pattern, between
14 dystocia, between patient selection and you need to
15 pay attention both to the type of heart rate
16 pattern and to the position of the fetal head.

17 [Slide]

18 The typical thing that we are trying to
19 prevent is the slide I present for you here. In
20 the top panel you see a series of variable
21 decelerations with stable baseline rate with
22 variability. There is a prolonged deceleration
23 here, and because of pushing in the second stage
24 and attempt to outrun the fetal distress, the baby
25 is involved in this acute ischemic event.

1 I would like to reassure you on the basis
2 of what information I do have and on the basis of a
3 great deal of clinical information that up until
4 this very point the oxygen saturations are, in
5 fact, normal and that this has as much to do with
6 the philosophy of pushing during the second stage
7 as it does with its oxygenation. The babies, as
8 most babies that are injured during labor, are
9 really injured not by progressive hypoxia or
10 recurrent systemic hypoxia but recurrent,
11 intermittent ischemic events, some of which are
12 very prolonged and some of which are not so
13 prolonged.

14 [Slide]

15 I share with you here a tracing of a
16 previously normal baby who suffers during labor and
17 acute ischemic attack. Those of you with some
18 familiarity with tracings will know that from this
19 perfectly normal standpoint this baby's tracing is
20 hopelessly compromised, an event that takes but
21 several minutes, and this notion of this
22 progressive systemic hypoxia with a gradual fall in
23 either pH or pulse oxygen saturation is not likely
24 to prevent this kind of injury.

25 [Slide]

1 Let me, in the last minute, discuss the
2 implications or the most obvious inference of the
3 use of pulse oximetry, and that is simply to
4 increase or to decrease the cesarean section rate.
5 I would like to submit that there has been no claim
6 that it would increase the outcome of the baby so
7 monitored. It is simply an effort to change the
8 cesarean section rate. I would like to suggest
9 that decreasing the cesarean section rate must
10 increase the length of labor, the duration of the
11 second stage of labor, the risk of VBAC failure,
12 the birth weight, the risk of fetal distress,
13 trauma, shoulder dystocia -- a whole bunch of
14 things must increase -- must increase -- as a
15 result of attempting to decrease the cesarean
16 section rate, this specially during labor.

17 [Slide]

18 I leave you with Thomas Pynchon who said,
19 if they can get you asking the wrong questions they
20 don't have to worry about the answers. I think
21 these answers are of crucial importance, that we
22 need to maintain safety throughout this and that
23 the implications of this device, based on systemic
24 hypoxia, based on progressive fall in oxygenation
25 for the purpose of simply decreasing the C-section

1 rate needs to be reevaluated. Thank you very much.

2 DR. BLANCO: Thank you, Dr. Schifrin. Any
3 questions from the panel?

4 [No response]

5 Thank you. At this time I will call for
6 any other public speaker that would like to address
7 the panel concerning this question. Is there
8 anyone in the audience who would like to come
9 forward at this time? I guess not, so we will go
10 ahead and move on with our panel information and
11 discussion. The next item on the agenda is a
12 presentation by Mallinckrodt. I believe that Mr.
13 Simon Thomas, former director of perinatal
14 marketing and former senior director of perinatal
15 research and development, Nellcor business unit of
16 Tyco healthcare's respiratory division will address
17 the panel.

18 Presentation by Mallinckrodt

19 MR. THOMAS: Good afternoon, Dr. Blanco,
20 panel, distinguished friends and colleagues. As
21 the Chairman has said, I am Simon Thomas. I was
22 formerly the director of marketing; before that,
23 the head of R&D at Mallinckrodt, then owned by
24 Mallinckrodt and now owned by Tyco. So, as Colin
25 said, much of the subsequent work in doing post hoc

1 analyses and trying to figure out what was going on
2 was done by myself and my staff. So, it is a
3 pleasure to be here again and talk to you about how
4 we evolved, if you will, from the post-approval
5 study that was presented at the time of the device
6 approval to where we are today.

7 By the way, just by way of financial
8 disclosures, I am no longer an employee of
9 Mallinckrodt, now called Tyco. My travel here will
10 be reimbursed by them but I am not being paid to
11 give this presentation.

12 [Slide]

13 Briefly, I am going to go over some of the
14 conclusions from all parties from the pivotal RCT,
15 some of which you have already heard; the questions
16 we asked ourselves; and then our three-pronged
17 approach to providing answers via the general use
18 study, the dystocia study to be presented by Dr.
19 Porreco, and use of some data from the NIH study
20 which Dr. Spong is going to talk about.

21 [Slide]

22 The conclusions that I believe we pretty
23 much came to after the RCT were that it was a
24 large, well executed study. I think I recall a
25 compliment to that effect from the panel meeting.

1 That adding fetal oxygen saturation to fetal heart
2 rate monitoring improves the accuracy of fetal
3 assessment; continuation of labor is safe when the
4 saturation is more than 30 between contractions;
5 use of the sensor is safe for mom and baby. We
6 know that cesareans for fetal distress went down.
7 There was no change overall, and that begs the
8 obvious question of why did cesareans for dystocia
9 go up. Dr. Porreco is going to address that last
10 one in more detail.

11 [Slide]

12 So, again, we are left with these
13 unanswered questions partly from the panel
14 discussions and partly from just our own
15 deliberations.

16 What is the effect of SpO2 monitoring on
17 cesareans on general use? How safe is it when in
18 general use? Are non-reassuring heart rate
19 patterns, especially variables, a marker for
20 increased risk of dystocia? And, an interesting
21 one here, can cesareans for dystocia be reduced
22 with a dystocia-specific management protocol
23 involving the use of fetal oxygen saturation? Dr.
24 Porreco will speak more about that shortly. Then,
25 how long can the fetus tolerate a saturation below

1 30 percent or less than 25 percent or less than 20
2 percent? The only conclusion, obviously, from
3 these questions is that we need additional studies.

4 [Slide]

5 So, we propose that data from three
6 separate studies be used to answer the six
7 questions which the FDA required of us in the
8 approval order. The six questions are shown in the
9 column on the left. Each column says which study
10 provides primary data and secondary data for which
11 of the questions. So, I think this gives a
12 reasonable overview that the general use study
13 basically records indications for placement;
14 records cesarean section rates; looks at
15 infections; looks at neonatal outcomes and
16 stratifies the analysis by epidural or not
17 epidural. It doesn't really get at the adequacy of
18 labor question.

19 The dystocia study specifically gets at
20 the adequacy of labor question and also records the
21 information, which is shown by the Xs in those
22 boxes for the other questions.

23 The NIH study -- we have asked to use data
24 from the blinded arm, blinded saturation arm of the
25 NIH study to specifically answer the question about

1 how long can the fetus saturation be below 30
2 percent before risk of injury, but I believe that
3 the NIH study will also provide data associated
4 with these other questions. But the only one that
5 we are particularly interested in is the data from
6 the blinded arm to answer the how long and how low
7 question.

8 [Slide]

9 Moving on to talk a little bit about the
10 general use study -- and, these are in your
11 handouts so if you can't read it just follow along
12 on the printed one. The intent here is to document
13 the impact of OxiFirst use in Ob practice following
14 introduction to general use at various study sites.

15 This is a non-randomized, prospective
16 observational study recording the clinical practice
17 impact of OxiFirst use. We will prospectively
18 gather data from 1700 patients at about four sites.
19 So, this is in many ways a little bit more than a
20 registry, at least by my understanding of how
21 registries are traditionally done, because patient
22 consent will be required and we do have a
23 prospective definition of what data are being
24 gathered and how it is going to be analyzed.

25 The primary objective is to document the

1 impact of OxiFirst use on operative delivery rate
2 versus historical data from the same sites.
3 Secondary, document the indications for use;
4 compare the outcomes with OxiFirst with and without
5 epidural anesthesia; document the immediate
6 neonatal condition; and document the distribution
7 of indications for cesareans when the device is
8 used.

9 [Slide]

10 So, in this general use study the
11 enrollment criteria from the fetal heart rate
12 perspective are identical with the device's
13 approved labeling. Basically, you have one of
14 these heart rate patterns. That is what makes you
15 eligible for use of the device per labeling, in
16 addition to the vertex presentation, appropriate
17 dilation, etc. So, that gets you into the study.

18 The ones shown up at the top in green are
19 kind of less concerning than the ones in black at
20 the bottom, which are more concerning. Once the
21 device is used, the black section and the green
22 section map into the Class II and Class I heart
23 rates as we defined them in the RCT, and then
24 management proceeds using the now well-known
25 matrix, again, from the official product labeling

1 where the use of the oximeter is particularly
2 relevant when you have a Class II heart rate and,
3 based on the saturation readings between
4 contractions, you either continue labor or perform
5 other evaluations to ultimately deliver the baby.
6 So, it really is general use exactly per the
7 labeling.

8 [Slide]

9 Site inclusion criteria -- obviously,
10 willing and able to provide historical cesarean
11 delivery rate data. Without that we can't do the
12 analysis. It was suggested actually by Dr. Iams, I
13 believe, in a conference call that we pick some
14 sites with a fairly high cesarean section rate in
15 order to maximize the opportunity of seeing some
16 overall impact. So, we added that to the site
17 selection criteria, and we would like that they be
18 reasonably active sites so this study won't take
19 too long to do.

20 Patient inclusion criteria -- basically
21 admitted to the unit with the expectation of
22 delivery. Excluded -- planned elective cesareans
23 and unwilling to provide consent.

24 [Slide]

25 Variables -- the usual maternal

1 demographic data: epidural, reason for use,
2 specific heart rate pattern or not, and in the case
3 report form there is a space to write in what the
4 other indications might be -- mode of delivery and
5 indication for delivery, outcomes, device-related
6 adverse events and significant adverse events
7 regardless of relationship to the device.

8 Then, for the historical variables we will
9 collect the overall C-section rate and the
10 indication for that C-section rate if it is
11 available at the site. Many sites don't keep that
12 data, in which case we obviously can't get it.

13 [Slide]

14 We are providing study definitions for the
15 indications of delivery. This one, again, is
16 straight out of the product labeling. Basically,
17 it says that you no longer have reassuring
18 saturation in the presence of a class II fetal
19 heart rate.

20 [Slide]

21 We are also providing definitions for
22 dystocia, or a definition for performing a delivery
23 for dystocia which is as you can read here. These
24 are very similar, if not identical, to the
25 definitions we used in the post hoc analysis of the

1 RCT data to determine that these babies delivered
2 for dystocia did, indeed, have true dystocia --
3 basically no change in dilation; no change in
4 descent and failed induction. The only addition we
5 used here, since this is prospective, is that we
6 are suggesting that the physician only consider
7 delivery for dystocia when there has been no change
8 in dilation in the presence of adequate labor. It
9 is defined thus. This is the general use study.
10 We will be capturing what the physician does and
11 there is no third-party audit or review to confirm
12 compliance with these definitions. They are really
13 for guidance.

14 [Slide]

15 We have a few more boxes for reasons for
16 delivery: fetal intolerance to labor combined with
17 poor progress. This is, again, what was used in
18 the randomized, controlled study -- ominous fetal
19 heart rate, self-evident, and other.

20 [Slide]

21 Study size -- it is powered to detect a 3
22 percent change in the overall C-section rate
23 against a historical rate of 25 percent and that
24 requires around about 1750 patients. So strictly
25 speaking, the null hypothesis is that the cesarean

1 birth rate is 25 percent. So, you have greater
2 than 95 percent power to detect a 3 percent
3 increase or decrease. If we find that the
4 hospitals meeting other criteria have historical
5 rates that differ significantly from the 25
6 percent, then we will change the sample size
7 appropriately, and our expectation is to perform
8 this study at a minimum of medium to large
9 community type hospitals to best try and capture
10 the impact in the general obstetrical population.

11 [Slide]

12 Study duration is expected to be about a
13 year including training, if required. That assumes
14 a 75 percent consent rate. This will be extended
15 if recruitment is slower than expectations. The
16 analysis plan is, as you see, to evaluate the
17 demographics and study entry characteristics to
18 show that the population is stable over time.
19 Then, measure the proportion of cesarean
20 deliveries, the mix of indications, neonatal
21 condition, AEs and SAEs. Thank you for your
22 attention.

23 DR. BLANCO: Thank you very much. Are
24 there any questions for Mr. Thomas?

25 DR. D'AGOSTINO: Could you just go over a

1 little bit why three studies versus one?

2 MR. THOMAS: Yes.

3 DR. D'AGOSTINO: And how will the three
4 studies, if they don't supply sort of a smooth flow
5 of information, be viewed as a sample?

6 MR. THOMAS: Let's go back.

7 [Slide]

8 The reason we proposed using data from
9 three separate studies rather than one is, quite
10 frankly, because we couldn't figure out the best
11 way of designing a single study that would provide
12 information to answer these six questions with the
13 degree of rigor that both ourselves and the agency
14 were happy with. That is it kind of in a nutshell.

15 Also, after the device approval, a group
16 of investigators approached us and said they wanted
17 to do the so-called dystocia study. That is when
18 we started thinking that the dystocia study will
19 really address this question rather well. Shortly
20 thereafter, I believe a member from the MFMU
21 Network called and said they were thinking about
22 doing their study. So, again, one aspect of that
23 study would seem to answer one question
24 particularly well. So, that is kind of how we
25 evolved from one study to three.

1 The second part of your question, what if
2 they don't fit together -- we have the backup which
3 was the single study that was proposed to the FDA
4 prior to the device approval. I don't think it is
5 quite as elegant as the way these three work
6 together. Specifically, it is not as rigorous on
7 the duration of low saturation and adverse neonatal
8 outcome. It was more of a case control approach
9 rather than truly having a natural history study,
10 if you will.

11 DR. D'AGOSTINO: With the historical
12 controls, will there be analysis and data on the
13 characteristics of the historical controls?

14 MR. THOMAS: To the extent that we can get
15 it, yes.

16 DR. D'AGOSTINO: You don't have the sites
17 selected yet?

18 MR. THOMAS: No, but some of the site
19 selection criteria will be, you know, what is the
20 quality and quantity of data they can provide from
21 historical cases.

22 DR. O'SULLIVAN: In regard to your
23 historical controls, if I understood you correctly,
24 they were going to be predominantly retrospective
25 and you are trying to get data that may not be

1 available.

2 MR. THOMAS: Right.

3 DR. O'SULLIVAN: Did I get that clear?

4 MR. THOMAS: Yes, the historical control --

5 basically, the key data element is what is the
6 overall C-section rate for the last year or so.

7 DR. O'SULLIVAN: But the problem I have
8 with that is that you are not looking at patients
9 concurrently.

10 MR. THOMAS: I understand.

11 DR. O'SULLIVAN: And, therefore, your
12 ability to retrieve data is going to be much better
13 in your study population and you may not be able to
14 answer the question.

15 MR. THOMAS: That is why the only absolute
16 requirement is that the site can provide their
17 historical C-section rate for all indications.
18 Most every site I have spoken to, they have that.
19 They may not have anything else but they track
20 that.

21 DR. BLANCO: Let me interrupt for a minute
22 because I think you are kind of answering and
23 asking different questions. From what I can gather
24 from what you said, Mr. Thomas, what you are going
25 to be looking at historically is that you want to

1 make sure you have centers that have a relatively
2 high cesarean section rate so that it will help in
3 terms of the numbers of patients required, plus be
4 more likely to show if there is a difference. I
5 think what Dr. O'Sullivan is referring to is more
6 other data that may be going on. I guess the issue
7 would be once you know that the center has
8 sufficient percentage of C-sections to be included
9 in the study, could you collect patients that are
10 not put in the study concurrently rather than
11 retrospectively. Does that help, Mary Jo?

12 DR. O'SULLIVAN: That is exactly what I am
13 asking because I think it is much more reliable.

14 MR. THOMAS: Well, from the data
15 management point of view it would obviously
16 increase the size --

17 DR. O'SULLIVAN: There is no question that
18 it will increase the size of your study, but your
19 historical retrospective data is, first of all, at
20 a different time period. It is not concurrent.
21 You won't get the same amount of data in that group
22 as you will in the study group. And, it would seem
23 to me to make much more sense to do them both
24 prospectively because you can get much better data
25 and, at the same time, the physicians are

1 practicing in the same fashion if they are or not
2 using the monitor.

3 MR. THOMAS: I understand your point.

4 DR. BLANCO: Go ahead, Dr. Iams.

5 DR. IAMS: I have a question along the
6 same lines regarding the entry of patients into
7 this study. You assume apparently a 75 percent
8 acceptance rate and a 25 percent decline rate.

9 MR. THOMAS: Right.

10 DR. IAMS: In other words, you are going
11 to approach everybody who comes in labor --

12 MR. THOMAS: Pretty much.

13 DR. IAMS: So, Dr. O'Sullivan is asking
14 about can we track those who decline.

15 MR. THOMAS: Right. Well, it is not so
16 much those that decline, it would be those that --

17 DR. IAMS: Are never approached?

18 MR. THOMAS: No.

19 DR. IAMS: Because you don't have somebody
20 on site to ask them when they come in?

21 MR. THOMAS: There is that group but we
22 approach everybody but probably only 25 percent, or
23 a third of them, will meet the indications for use
24 of OxiFirst and then get OxiFirst.

25 DR. IAMS: Right.

1 MR. THOMAS: So, it is really those who
2 give consent to be in the study but who do not meet
3 the entry criteria for OxiFirst use that I think
4 will be of most interest. It would be at least a
5 concurrent control group.

6 DR. IAMS: So, they will be asked upon
7 arrival at the hospital, should they meet the entry
8 criteria, if they would like to join --

9 MR. THOMAS: Right.

10 DR. IAMS: Will they be asked again now
11 that you have met the entry criteria, we are ready
12 to do it. Is that the point at which a woman will
13 sign a second consent?

14 MR. THOMAS: At the moment, the study plan
15 is that she only gives one consent.

16 DR. IAMS: Just once?

17 MR. THOMAS: Because the use of the device
18 is per the labeling and per the hospital standard
19 practice. So, they are not getting an unusual or
20 experimental treatment.

21 DR. IAMS: I agree with Dr. O'Sullivan.
22 Although historical controls are certainly
23 important, that is a very interesting group to have
24 some knowledge about also. I was involved in a
25 study a long time about various preventive

1 strategies for prematurity where the group that
2 declined entry into the study actually did quite a
3 bit better than anybody who said yes, for reasons
4 that no one ever quite figured out, except these
5 women seemed to know they didn't really need that
6 intervention, or whatever. So, you really never
7 know if they are as comparable to those who said
8 yes. It may not represent the group of women who
9 said yes, or the doctors who allow their patients
10 to say yes.

11 MR. THOMAS: Well, it certainly won't be
12 comparable in having non-reassuring heart rates --

13 DR. IAMS: Right. Well, that is okay but
14 the ones who have non-reassuring heart rates -- the
15 other question about this in addition to just the
16 issues of study design has to do, in this era of
17 heightened scrutiny about informed consent, if
18 someone says no at any point in this, are you
19 really allowed -- if we were to ask you, well, just
20 track and see how those women who said no do -- I
21 know you can't gather any information from them but
22 couldn't we, please, know what happened to the
23 women who declined participation in the study; what
24 was their cesarean section rate? A few years back
25 I would have said, well, we can just kind of find

1 out. We will get the delivery mode, and that is
2 it. I am not so sure today that you can even do
3 that -- MR. THOMAS: I would agree.

4 DR. IAMS: -- with human subject review
5 being what it is. Do you think that is possible at
6 all?

7 MR. THOMAS: I think that would be up to
8 the individual site IRB. Certainly, the more
9 conservative ones I have come across recently, I
10 agree with you, they would say no.

11 DR. IAMS: So, that is going to make
12 concurrent controls somewhat difficult --

13 MR. THOMAS: Well, in the group that
14 explicitly says no to being in the study, my
15 opinion is they are lost. There is nothing you can
16 do. The interesting group is that group that says
17 no to being in the study -- or, says yes to being
18 in the study but which don't meet criteria for
19 placement of OxiFirst. But, remember, that group
20 is also similar to the group that is going to be
21 studied by the NIH.

22 DR. IAMS: Well, that is another issue --

23 DR. BLANCO: Can I cut it a little bit
24 short? Narrow it down, if you would, both of you
25 and then we will move on because we have some other

1 questions on this side. To make sure that it is
2 clear, what you all are suggesting is concurrent
3 controls. Are you suggesting folks who fit the
4 criteria but decide not to use the experimental
5 protocol, that they should be followed, data
6 collected on them, or, are you saying all folks
7 that are coming in should have data collected? I
8 am trying to narrow it down for them.

9 DR. O'SULLIVAN: The women who come in,
10 fulfilling the criteria for the study, the group
11 that agrees to the study with internal monitoring
12 versus a group that refuses to be internally
13 monitored but is willing to have data collection.

14 DR. BLANCO: Okay.

15 DR. IAMS: I guess my take would be a
16 little different. My expectation, when we approved
17 this, was that you would be able to do what in
18 effect the Group B strep protocol has apparently
19 now done, and you should be able to track as is now
20 coming out with GBS. Introduction of this protocol
21 for management has resulted in dramatic declines in
22 the rate of GBS, neonatal sepsis. Obviously, that
23 is a different subject but that is ultimately the
24 real-world test that this device really has to
25 show. If I am reflecting the sense of the panel

1 last time, we ought to be able to say the device
2 was introduced into XYZ hospital on January 1 of
3 2002 and within a year or so, whatever, their rate
4 of cesarean sections overall dropped. We didn't
5 just trade indications around; we saw a decline.
6 If we don't see that, this device is going to lose
7 its conditional approval. As a researcher, I am
8 sympathetic to what Dr. O'Sullivan wants, but the
9 bottom line is if it doesn't work in XYZ hospital
10 there is really no reason to go any further.

11 DR. BLANCO: Let's move on to a couple of
12 other questions. Gary?

13 DR. EGLINTON: I think you are assuming a
14 risk here that may not serve your interests well.
15 It wasn't published in the Garite paper, but as I
16 recall, at last year's meeting when you did the
17 pilot phase, the run-in phase, you had a cesarean
18 rate for non-reassuring fetal status of 5 percent.
19 When you did the randomized, controlled phase in
20 the control group that doubled to 10 percent,
21 nominal figures. Therefore, the difference -- I
22 remember having a big discussion about this -- was
23 that in the pulse oximeter group the cesarean rate
24 remained the same and it doubled in the control
25 group. Now, if you see the same kind of effect

1 here, that your cesarean rate for dystocia is
2 actually increasing during this time frame and you
3 have no concurrent controls, you are in trouble.

4 Is there evidence that that may, in fact,
5 be true or that may be a fact? There is. If you
6 look at the data from the Maryland Indicator
7 Project, it is clear that there is a secular trend
8 toward increasing cesarean today. So, you may have
9 a major problem doing this as historical controls.
10 I don't think you will satisfy a single nay-sayer
11 who reads the paper.

12 MR. THOMAS: It would depend on how
13 dramatic the change was, but I take your point.

14 DR. BLANCO: Dr. Allen?

15 DR. ALLEN: Just a point of clarification
16 in the inclusion and exclusion criteria for the
17 patients, does that mean that you will be including
18 women who have non-vertex presentations less than
19 36 weeks with placenta previa?

20 MR. THOMAS: No.

21 DR. ALLEN: Those were the exclusion
22 criteria originally.

23 MR. THOMAS: Right. No, only women who
24 meet or have the potential to meet the criteria for
25 OxiFirst use will be recruited.

1 DR. ALLEN: The other question is will we
2 address question number six in today's presentation
3 about the duration of an SpO2 less than 30 percent
4 impact on outcome?

5 DR. BLANCO: We can certainly discuss
6 that, so we can bring that up in the panel
7 discussion session. I would like to add that I was
8 actually going to ask a question and I was waiting
9 for other folks. I think we have a question over
10 here, but, you know, one of the concerns that I
11 have in hearing what you are planning is, if my
12 memory serves me correctly, there was a fair amount
13 of concern about how the 30 percent value had been
14 arrived at. There was a great deal of concern by
15 the panel that the amount of information to arrive
16 at that particular number was somewhat limited.

17 One of the things that the panel, I
18 believe, had recommended was that a lot more
19 information would be gathered on that to make sure
20 that the correct number was being used because, as
21 clinicians realize, everyone tends to think numbers
22 are magical and, therefore, that is the right thing
23 and if you have 30 percent you are okay, and it was
24 rather limited.

25 Now, I don't know, maybe there has been a

1 lot more data that I am not familiar with that has
2 come out, but I don't see in any of these proposals
3 anything looking at -- other than what you said
4 where there is eventual fetal damage, but it still
5 uses that hard and fast number to see whether that
6 number really is a correct number to use.

7 MR. THOMAS: Two comments, not two
8 answers, one, this study and, indeed, the dystocia
9 study uses the device per its approved labeling,
10 therefore, it has to use 30 percent.

11 DR. BLANCO: That is not my question.

12 MR. THOMAS: I realize that. The data to
13 answer your question, I believe, will come most
14 effectively from the blinded arm of the NIH study
15 because the results of the RCT, as you may recall,
16 showed that there was actually a significant
17 reduction in the number of babies with severe
18 metabolic acidosis in the test group. So the other
19 problem we are faced with is that extrapolating
20 those results and, indeed, our experience in the
21 marketplace today has been that we haven't seen any
22 bad outcome babies and, as such, it is hard to get
23 the data to answer this question in a group who has
24 been monitored and managed with the oximeter.

25 DR. BLANCO: But it sounds like you are

1 not going to look at that issue, which bothers me.

2 MR. THOMAS: We have not thought of a
3 really good way of looking at it except from the
4 natural history type study, exemplified by the NIH
5 sham arm.

6 DR. BLANCO: I think we have another
7 question or comment.

8 MS. BROGDON: I just wanted to clarify the
9 approval status of this application. It was fully
10 approved by FDA as opposed to conditionally
11 approved. One of the conditions was that the
12 sponsor do a post-approval study. Once the study
13 results are in, we would be expecting the sponsor
14 to modify labeling as necessary based on the
15 findings. If the findings were adverse and we
16 decided it was adverse to public health and safety,
17 or something on that order, then we would have to
18 decide whether the approval should be withdrawn
19 but, basically, the status right now is that it is
20 fully approved.

21 DR. IAMS: Can I reply to that? My use of
22 the word conditional is probably not within the
23 guidelines of FDA use of that term, but I am quite
24 sure that last year the panel's view was
25 conditioned upon questions to FDA that ran along

1 the lines of if this device fails to reduce the
2 cesarean section rate, as promised, can the FDA,
3 without finding adverse things -- if it simply
4 fails to perform, can FDA withdraw its approval?
5 And, the answer we heard was, yes, we can, not
6 because it did something we didn't expect or had an
7 adverse outcome but, rather, because it simply
8 didn't perform in the marketplace the way it was
9 expected to, and that is why the vote was 10-1. If
10 that hadn't been said, it would not have been a 10-1 vote.

11 MS. BROGDON: I think what the agency
12 usually says is, first of all, it looks to see if
13 labeling changes would address accurately the
14 safety and effectiveness of the device as the study
15 demonstrates. If we couldn't come to a
16 satisfactory resolution then, yes, we would need to
17 look at withdrawing approval. It is not an easy
18 thing for the agency to do.

19 DR. BLANCO: Well, let me add to Dr. Iams'
20 comment that I think the panel had the concept that
21 the approval was conditional on the conditions
22 being met, and conditions being met was a lot more
23 information about those issues -- the 30 percent
24 issue and so forth. So, just to go on record as

1 having said that. Dr. D'Agostino?

2 DR. D'AGOSTINO: Yes, not a question but
3 just to reinforce that. I thought that we were
4 talking about a study that would put the whole
5 package together and not three pieces with this
6 ambiguity that may result from trying to interpret
7 it.

8 MR. THOMAS: I don't think there is too
9 much risk of ambiguity from having three separate
10 pieces --

11 DR. D'AGOSTINO: I don't want to continue
12 but, I mean, I think the historical control --

13 DR. BLANCO: We are kind of getting into
14 discussion and I will take the prerogative here and
15 we will move on. I will just add that, probably
16 agreeing with Ralph, if you don't ask the questions
17 that meet the conditions, then I am not sure you
18 have met the conditions. But in any case, let's
19 move on. Mr. Pollard wants to say something and
20 that always takes precedence.

21 MR. POLLARD: Thank you, Dr. Blanco, I
22 appreciate it. I just wanted to try to clarify
23 this because, you know, I am trying to recollect
24 myself from the January, 2000 meeting. I know
25 there were these very specific concerns. I don't

1 believe the concerns were postured in the context
2 of if they don't show this would the PMA be
3 withdrawn. So, there I kind of beg to differ a
4 little with you. I think, certainly, the panel
5 approval recommendation was conditioned on the
6 expectation that the company would conduct this
7 post-approval study to look at the cesarean
8 sections. It wasn't conditioned on the outcome of
9 it, and I don't think we really got at what would
10 we do if A, if B, if C came from that study.

11 Nancy has kind of gone over with you how
12 we look at post-approval studies. Obviously, the
13 first thing we look at is does the current labeling
14 stand up vis-a-vis our new findings? Obviously,
15 there is that possibility but, to be perfectly
16 frank, it is a fairly rigorous bar, if you will, to
17 pass regarding whether the results of that study
18 would somehow put the approval of the PMA itself in
19 jeopardy.

20 DR. BLANCO: All right, let's move on.
21 Our next speaker is Dr. Richard Porreco, principal
22 investigator of the dystocia study,
23 Presbyterian/St. Luke's Medical Center, Denver,
24 Colorado. Please remember to state any conflict of
25 interest, or anything.

1 DR. PORRECO: Thank you, Dr. Blanco. My
2 name is Rich Porreco, and I don't have any
3 personal financial ties with Mallinckrodt, Tyco but
4 they did pay my expenses here.

5 [Slide]

6 As you have heard, the published study
7 from the November Grey Journal showed efficacy in
8 decreasing cesarean birth rates for non-reassuring
9 fetal status.

10 [Slide]

11 It was shown to be safe for mother and
12 baby. It showed better sensitivity and specificity
13 for some newborn outcomes but, as has been
14 mentioned here multiple times, there was no change
15 in the overall cesarean rate due to increase in
16 cesareans for dystocia.

17 [Slide]

18 Here is the outcome table, reproduced once
19 again for you, showing that the mode of delivery,
20 in the upper part of the slide, was not different.
21 The indications for cesarean were, indeed,
22 different with the decreases, as indicated, for
23 NRFS, non-reassuring fetal status, and the increase
24 for the single indication of dystocia.

25 [Slide]

1 There are four potential explanations for
2 the cesarean rate for dystocia being increased as
3 seen from the RCT database. There are imbalance
4 and risk factors for dystocia, the impact of the
5 device on labor progress, investigator bias and,
6 finally, that non-reassuring fetal status may be an
7 unrecognized marker for dystocia.

8 We went back and redid a critical analysis
9 of the RCT database, given its limitations, to try
10 to understand this finding as best we could, and
11 that was the subject of my presentation in Reno
12 this year. I am not going to recapitulate that for
13 you, but simply tell you that we concluded after
14 that critical analysis that the most logical
15 explanation for the increase in cesareans for
16 dystocia in the sensor group, the oximetry group,
17 from the RCT database is that inclusion criteria
18 selected patients who were at increased risk for
19 dystocia, that is non-reassuring fetal heart rate
20 patterns, used for study entry arm marker for
21 dystocia, that improved assessment of the fetus
22 during labor allows for continuation of labor which
23 might otherwise be prematurely interrupted by
24 cesarean for non-reassuring fetal status.

25 [Slide]

1 And, that a prospective study design to
2 investigate dystocia with the use of the fetal
3 pulse oximeter is needed to confirm or refute these
4 observations from the RCT.

5 [Slide]

6 So, in the next couple of minutes let me
7 tell you about the study that we proposed, given
8 the context of our experience with this device. It
9 is a non-randomized, prospective cohort study,
10 observational to evaluate the incidence and
11 management of dystocia in a nulliparous population
12 with non-reassuring fetal heart rate pattern and
13 the use of a pulse oximeter; 500 subjects in 5
14 centers, most of them participating in the RCT
15 previously.

16 [Slide]

17 The variables of interest are obviously
18 heart rate patterns, the diagnosis of dystocia, the
19 various interventions for abnormal progress of
20 labor, and delivery mode, indications, delivery and
21 neonatal outcomes.

22 [Slide]

23 The purpose was to examine the
24 relationship between non-reassuring fetal heart
25 rate patterns and dystocia, and to examine if the

1 application of a prospective protocol for the
2 diagnosis and management of dystocia affects
3 maternal and neonatal outcomes.

4 [Slide]

5 Secondary objectives were to look at
6 whether certain variables, certain non-reassuring
7 patterns predict dystocia more than others, for
8 example variable decelerations and, as Dr. Schifrin
9 showed you earlier this afternoon, whether these
10 patterns predict dystocia in the active phase of
11 labor, whether position of the occiput and fetal
12 heart rate patterns and dystocia are associated,
13 and the outcome of labor, immediate newborn outcome
14 and its association with non-reassuring fetal heart
15 rate patterns and normal oximetry and dystocia or
16 lack of dystocia, as the case may be.

17 [Slide]

18 The design is two cohorts of eligible
19 patients, one that never develops Class II patterns
20 during labor and the second cohort of eligible
21 patients that do, indeed, develop these Class II
22 patterns.

23 [Slide]

24 Inclusion criteria are similar to the RCT
25 data, with the exception that, since we are looking

1 at dystocia as a primary issue of interest, we are
2 looking only at nulliparous patients in this study
3 with singleton gestations near term.

4 [Slide]

5 Exclusion criteria are identical to the
6 RCT exclusion criteria.

7 [Slide]

8 Non-reassuring fetal heart rate patterns,
9 by definition, once again, are modified from the
10 RCT and you will note as I go through these -- I am
11 not going to read them all for you -- that any even
12 modestly abnormal pattern might be in inclusion
13 criteria because they may progress on to a Class II
14 pattern. The ones that have asterisks, starting
15 with number 6, would fit the definition of a Class
16 II pattern.

17 [Slide]

18 These are all in your hard copy.

19 [Slide]

20 Especially of note are the variable
21 decelerations with various characteristics of
22 concern and, finally, supraventricular tachycardia,
23 congenital heart block -- all the lists that have
24 asterisks are Class II patterns.

25 [Slide]

1 Interventions -- these patients are
2 monitored electronically and will meet label
3 indications for the pulse oximeter. Vaginal
4 examinations will be done at a minimum every two
5 hours, and partograms of dilatation and station
6 will be made, and position of the vertex and
7 effacement will also be noted. Oxytocin
8 augmentation is as noted. And, these management
9 plans were sort of bargained out over a committee
10 of interested investigators and we arrived at a
11 consensus that we could all live with. Abnormal
12 progress is no progress in the active phase for
13 more than two hours, and no active phase within 12
14 hours of ruptured membranes requiring placement of
15 an intrauterine pressure catheter.

16 [Slide]

17 If the patient has non-reassuring fetal
18 status and normal pulse oximetry, that is 30
19 percent or greater between contractions, then the
20 natural evolution of that labor will be allowed to
21 unfold. There will be an assisted vaginal or
22 abdominal delivery if we get non-reassuring fetal
23 status and abnormal oximetry, or we don't get any
24 information from the oximeter and there is nothing
25 reassuring for normal scalp pH about the subsequent

1 fetal heart rate trace despite any maneuvers to
2 correct same.

3 [Slide]

4 The definitions of dystocia -- we, as a
5 consensus, felt that three hours in the face of
6 adequate uterine activity would be a definition of
7 dystocia during the active phase, no progress, or
8 no descent at full dilatation after two hours, and
9 three hours is permitted if an epidural was felt to
10 be impeding expulsive efforts; inability to achieve
11 active phase after 12 hours of adequate uterine
12 activity with oxytocin.

13 [Slide]

14 The variables of interest are listed on
15 this slide. Specifically note the labor summary
16 includes fetal heart rate tracings, delivery
17 summary as you might expect, and serious adverse
18 events.

19 [Slide]

20 There will be an independent review of
21 fetal heart rate tracings confirming normal entry
22 criteria and fetal heart rate pattern, assigned
23 either to Class II or non-Class II status and,
24 finally and importantly, confirming compliance with
25 labor management in the face of abnormal progress.

1 [Slide]

2 The analysis is based on data retrieved
3 from the RCT database, and we would anticipate
4 approximately two-thirds of the patients would
5 develop Class II patterns and that they may
6 experience a cesarean for dystocia 20 percent of
7 the time, whereas non-Class II patterns would have
8 a cesarean birth rate for dystocia 10 percent of
9 the time, and 500 patients should be sufficient to
10 confirm or refute the hypothesis.

11 That concludes my remarks, Dr. Blanco, and
12 I would be happy to entertain any questions.

13 DR. BLANCO: Thank you. Any questions for
14 Dr. Porreco?

15 DR. IAMS: I have one. Rich, there has
16 been some research from the University of Alabama,
17 Birmingham primarily but other places I imagine as
18 well, regarding definitions of dystocia and waiting
19 a little bit longer to declare labor to be
20 unsuccessful. Have you thought about using some of
21 those definitions as that literature has evolved?

22 DR. PORRECO: As I alluded quickly, the
23 group of us sat together and tried to bang out
24 something we all could live with not only from our
25 own personal views on dystocia and management of

1 labor, but the fact that in many of our settings
2 what we could sell to the attending physicians and
3 patients. Indeed, there was a contingent that
4 wanted four hours, for example, of active phase
5 arrest. As you know, two hours has sort of been
6 the traditional time period in active phase. The
7 epidural issue of impending expulsive efforts was
8 discussed at length. I think what we arrived at
9 was a workable, doable, practical way that we think
10 we can get this study done, and I see this as sort
11 of a synthesis of the opinions expressed by the
12 investigators rather than adopting anybody else's
13 opinion on exactly how to do this.

14 DR. BLANCO: Dr. Eglinton?

15 DR. EGLINTON: Are the Class II heart rate
16 patterns those with asterisks?

17 DR. PORRECO: Yes, that is correct. Those
18 would fit in that grey box that you have seen on
19 the previous slides.

20 DR. EGLINTON: So, in that sense then the
21 underlying hypothesis is that persistent late
22 decelerations, decreased variability and
23 tachycardia with decreased variability might be
24 patterns associated with dystocia?

25 DR. PORRECO: That is correct.

1 DR. EGLINTON: Then, the instructions for
2 investigators' package, it looks like the
3 investigator is asked to rank the heart rate
4 patterns in some fashion, choosing that which is
5 the worst heart rate pattern that develops in
6 labor.

7 DR. PORRECO: That is the way the case
8 report forms will be filled out, but independently
9 reviewed.

10 DR. EGLINTON: Right. My concern with
11 that is, without meaning any disrespect but let's
12 just construct a hypothetical -- we have a lady who
13 has four hours of flat heart rate of 180 beats per
14 minute. Then we have another lady who has a
15 perfectly normal heart rate pattern but for her
16 final two pushes in the second stage has two severe
17 variables. Which one is worse? On your scheme the
18 second one is number 9; it is lower on the scale --

19 DR. PORRECO: Oh, no. I don't think that
20 the listing is a ranking.

21 DR. EGLINTON: But there are no
22 instructions for how the investigator ranks them.
23 How does the investigator choose which is, in
24 quotation marks, the worst pattern?

25 DR. PORRECO: Oh, I see what you mean.

1 What I think we are referring to with the word
2 pattern is that someone may initiate a non-Class II
3 pattern initially and develop one and then they
4 would be ranked as a Class II patient. So, what I
5 am saying is that the worst pattern that they
6 develop during labor is what ranks them as either
7 Class II or non-Class II, not a ranking among Class
8 II's.

9 DR. EGLINTON: You may want to look at the
10 work sheet because on that page the instructions
11 are to choose only one. So, if a lady has a flat
12 tachycardia for two hours and then has severe
13 variables the investigator cannot check both of
14 those boxes.

15 DR. PORRECO: Oh, I see. Your point is
16 taken. Thank you.

17 DR. BLANCO: I am going to make a comment.
18 It appears that you are going to look at the non-Class II
19 patterns, which is really kind of a non-indication use for
20 this particular device. While I
21 believe that you are doing that to see whether
22 these patterns may lead to dystocia, I have some
23 concern that after having done that this will lead
24 folks to broaden the indications for what this
25 device is utilized for without looking at the

1 endpoint for which the device was put together.
2 Can you address that? Did you understand that?

3 DR. PORRECO: I am not sure. There are
4 entry criteria which are not Class II, and the
5 reason that those are more modestly selected is
6 because for that group of patients there may be
7 some progression to Class II patterns, and it is in
8 that progression that we believe are found the
9 dystocia patients. So, you are concerned that if
10 we broaden the use of it -- I am sorry, I guess I
11 don't understand.

12 DR. BLANCO: You are not looking at the
13 endpoint. If I understand you correctly, you are
14 looking at the non-Class II's because you think
15 they will lead to Class II's. Okay? That is what
16 I just heard you repeat.

17 DR. PORRECO: That is correct.

18 DR. BLANCO: Well, why don't you wait
19 until they become Class II's before they are
20 eligible to be in the study? My concern is that
21 once you have a published study with a broadened
22 indication of what this device is used for there
23 will be a lot of people who will use it for those
24 issues when you are not really looking -- I mean,
25 unless I missed it, you are not necessarily looking

1 at this other than to see whether those patients
2 have more dystocias. Is that right?

3 DR. PORRECO: We think that the entry
4 criteria as currently labeled for this device --
5 among those entry criteria are a group of patients
6 that have patterns that predict dystocia, but not
7 the whole group. The entry criteria enrich the
8 population of dystotic patients and it is probably
9 the severe variables -- at least that is what we
10 showed from the critical analysis of the RCT data -- that
11 are going to predict dystocia. There are
12 patients which don't have severe variables, to use
13 my example, who would otherwise meet entry
14 criteria. It might be confusing to physicians and
15 they would want to know what the status of fetal
16 oxygenation is, but ultimately will not predict
17 dystocia.

18 DR. BLANCO: Yes, but that is not really
19 an indication for the device and that is not really
20 the issue you are addressing with your study.

21 DR. PORRECO: The device is currently
22 indicated for any non-reassuring fetal status
23 pattern, not all of which are Class II.

24 DR. BLANCO: I did not think that was the
25 indication. I thought the indication was for that

1 narrow group of patterns.

2 DR. PORRECO: Well, for our study entry
3 for this dystocia study we don't know at time zero
4 which ones are going to evolve into a Class II
5 pattern.

6 DR. BLANCO: What I am asking you is why
7 don't you wait until they evolve into a Class II
8 pattern? What is the benefit of including this
9 broadened definition for your study? Maybe I am
10 missing the whole point.

11 DR. IAMS: I thought this was a different
12 question but maybe it is the same one, is this
13 study going to answer the question of whether the
14 device itself increases the rate of dystocia? Is
15 that still an open question in your mind?

16 DR. PORRECO: No, I don't believe the
17 device itself increases the rate of dystocia. I
18 think that the improved knowledge of fetal status
19 and labor allows the evolution of labor --

20 DR. IAMS: I understand that but the
21 increase in dystocia from the randomized trial has
22 to have a couple of explanations, I guess. One,
23 you simply, as you just said, allow women who were
24 going to get a cesarean for dystocia with
25 electronic fetal monitoring alone who got sectioned

1 for non-reassuring fetal status and you move them
2 from one category to the other. I guess if that
3 were the only explanation you would have to say
4 those women are going to get a cesarean anyway.
5 The only question is timing, and this device,
6 again, would not make a significant contribution if
7 you simply changed the duration of labor before an
8 inevitable cesarean, one for incorrectly diagnosed
9 fetal distress which would have been dystocia if
10 allowed to go on, and the other one for directly
11 diagnosed fetal distress.

12 What I hoped was going to be the case was
13 that there were some unexplained dystocia cases,
14 maybe related to labor management, that would
15 simply disappear when this device was introduced in
16 the broader clinical practice.

17 DR. PORRECO: We think that a uniform
18 approach to dystocia, obviously from our study
19 criteria, will address the issue of improper labor
20 management, for lack of a better term. That
21 people, indeed, are allowed to progress
22 appropriately or not progress appropriately, and
23 given enough time to do so, and given adequate
24 uterine activity to do so. So, I think we will be
25 taking that variable out of the equation that we

1 couldn't answer from the RCT data.

2 DR. IAMS: Well, that goes back to my
3 first question about the Alabama data. If we don't
4 wait enough for those dystocias to resolve, which
5 is the thrust of what they have been publishing --
6 if we just let these people labor a little longer
7 they will get around the corner and keep on going
8 safely. You may be pulling the plug too soon and
9 end up with RCT-2. You are going to have the same
10 C-section rate with different names on it but it
11 isn't going to change, and that is ultimately the
12 bottom line. That is why the device was created.

13 DR. BLANCO: Right. I think allowing
14 knowledge in the general community that fetal
15 status unequivocally is good, is normal, is
16 reassuring will allow us to tell patients that they
17 can, indeed, go three hours in the active phase of
18 labor with adequate uterine activity and not be
19 concerned because a lot of times those patterns are
20 confusing and people bail out too soon. I think
21 that ultimately will be the clinical impact.

22 Anything else? We are kind of getting
23 into discussion but it is probably good to get some
24 interchange. Any other questions? Yes?

25 DR. O'SULLIVAN: I brought this up the

1 last time and I want to bring it up again. I
2 think, for what it is worth, using patients that
3 you are doing inductions on is really not a good
4 idea. The reason I say that is that they are a
5 different group of patients altogether rather than
6 spontaneous onset of labor. They, indeed, may have
7 additional problems for why they would either
8 arrest or develop fetal distress, and it bothers me
9 that once again they are included here.

10 DR. PORRECO: Well, first of all, as you
11 will recall, in RCT there were inductions in both
12 groups. Secondly, I am not sure how it is in
13 Florida, Dr. O'Sullivan, but the induction rates,
14 especially among nulliparous patients, are very
15 high in our community hospitals around the country
16 and in my community and we would be excluding a
17 large number of patients if we didn't allow for
18 inductions to be included. I, as the messenger,
19 will tell you that the hospitals in my community
20 have induction rates of nulliparous patients of
21 about 40-60 percent.

22 DR. BLANCO: Let's move ahead. Thank you,
23 Dr. Porreco. Next on our schedule is Dr. Kathy
24 Spong, Chief of Pregnancy and Perinatology Branch
25 of all these other initials in the Department of

1 NIH, and I will leave it at that.

2 Presentation by NIH

3 DR. SPONG: Thank you.

4 [Slide]

5 I would like to present the randomized,
6 controlled trial of fetal oximetry, also known as
7 the FOX trial, which is being put up by the NICHD
8 Maternal Fetal Medicine Unit Network.

9 [Slide]

10 The subcommittee is listed here, and
11 without the help of Steve Bloom and Greg McPherson
12 and Elizabeth Tarm this would not be nearly as put
13 together as it is today.

14 [Slide]

15 The MFMU Network, for those of you who
16 don't know, is a national network of high risk
17 obstetrical units. Currently, there are 14 centers
18 across the country that meet certain criteria, and
19 are funded on 5-year cycle grants.

20 [Slide]

21 These are the current 14 centers that run
22 the Maternal Fetal Medicine Unit Network, and when
23 this study was designed, it was designed as the
24 Network was transitioning into its cycle from 2001
25 to 2006. The previous Network had a little over

1 90,000 deliveries per year and we now have over
2 120,000 deliveries per year.

3 [Slide]

4 The primary aim of the FOX trial is to
5 measure the impact of fetal oximetry as an adjunct
6 to conventional electronic fetal heart rate
7 monitoring on the overall cesarean delivery rate.

8 [Slide]

9 The secondary aims are as follows: To
10 measure the rates of cesarean delivery for dystocia
11 and fetal distress; to measure infant safety, and
12 we are using a composite outcome; to measure
13 infection rates, including chorioamnionitis,
14 endometritis and infant sepsis; and to measure the
15 rates of cesarean delivery in patients with
16 abnormal fetal heart rate patterns.

17 [Slide]

18 Our study will include two different
19 phases. The first is an implementation phase
20 during which time we will get the equipment, train
21 the centers and certify the centers, and the trial
22 phase.

23 [Slide]

24 The study has a three-arm design. After
25 randomization the patient will be randomized to one

1 of three arms. One arm is electronic fetal heart
2 rate monitor alone, and that is called the no
3 device group. The second arm is the electronic
4 heart rate monitor with a blinded FSpO2, the masked
5 device group. The third is the electronic heart
6 rate monitor with the known FSpO2, and that is the
7 open device.

8 [Slide]

9 The assessments that we are going to be
10 able to obtain from these different trial groups
11 include that in the groups between the open and the
12 masked oximetry groups we will be able to assess
13 the effect of fetal pulse oximetry on cesarean
14 rates and on infant safety. In addition, the
15 masked group will allow us to determine the effects
16 of untreated fetal oxygen desaturation. Finally,
17 the no device group will give us an assessment of
18 the effects of sensor insertion on maternal-fetal
19 infections and dystocia.

20 [Slide]

21 Randomization will occur by a central
22 computerized randomization access by the telephone,
23 using the simple urn method, and will be stratified
24 by clinical center. After randomization, the
25 research nurse will prepare dedicated equipment to

1 function as an open device, masked device or a
2 device that is not turned on, depending on which
3 arm they are randomized to.

4 [Slide]

5 The inclusion criteria are nulliparous
6 patients who are singleton, with cephalic
7 presentations at greater than 36 weeks gestation,
8 in labor, between 2-5 cm of cervical dilatation
9 with ruptured membranes, and all of them have
10 internal fetal heart rate monitors.

11 [Slide]

12 There are many exclusion criteria, notably
13 any need for immediate delivery, any reason a
14 patient should not deliver vaginally.

15 [Slide]

16 Intrapartum management -- the research
17 nurse, again, will configure the oximeter and serve
18 as a technical resource person, but will not make
19 any medical judgments or have any input as to the
20 medical management of the patient. For the masked
21 arm, the sensor will be adjusted to maintain the
22 pulse rate display but the saturation rate will be
23 blinded; it will not be displayed. All of the data
24 will be continuously collected via laptop, and the
25 intrapartum management will be done at the

1 discretion of the attending physician.

2 [Slide]

3 Interpretation of the oximetry is at the
4 discretion of the clinician, with the recommended
5 interpretation as it is labeled where reassuring is
6 when it returns to greater than 30 percent between
7 contractions and non-reassuring when it remains
8 below 30 percent for the entire interval between
9 two contractions.

10 [Slide]

11 In addition, the attending physician may
12 do any of the following for non-reassuring fetal
13 heart rate tracing, including altering the position
14 of the mother, hydration, correction of
15 hypertension, scalp pH and amnioinfusion and
16 anything else listed above.

17 [Slide]

18 The primary outcome is cesarean delivery
19 for any indication.

20 [Slide]

21 Secondary outcomes include the indication
22 for the cesarean delivery, forceps delivery,
23 chorioamnionitis and length of hospital stay.
24 Fetal secondary outcomes include any intrapartum or
25 neonatal death; the length of the hospital stay;

1 birth weight; Apgar score at 5 minutes. All
2 patients will have umbilical cord gases obtained
3 and those will be evaluated. If the neonate needs
4 to be incubated in the delivery room without the
5 presence of meconium; all NICU admissions; hypoxic
6 ischemic encephalopathy; a fetal vulnerability
7 index, which is a composite. Neonates with early
8 onset neonatal sepsis; neonatal seizures; and any
9 facial marks from the sensor.

10 [Slide]

11 How feasible is it to do this trial? The
12 total number of deliveries in the prior Network was
13 90,000. As I mentioned, we now have over 120,000
14 so these still apply. The data source from this is
15 Maternal Fetal Medicine Unit C-section registry.
16 The number of nulliparous patients was estimated at
17 40 percent from our cesarean section registry, as
18 well as from the vital statistics report, and the
19 number of patients who would meet the inclusion
20 criteria was estimated to be about 76 percent, and
21 that data is from UT Southwestern. The consent
22 rate we took from the Mallinckrodt study, which was
23 50 percent, which gives us over 13,000 patients
24 available per year when we only had 90,000
25 patients. So, we certainly could do this trial.

1 [Slide]

2 We anticipate enrolling 10,074 women, and
3 from that sample size it allows the detection of a
4 15 percent change in the overall cesarean section
5 rate; a 33 percent change in the cesarean rate for
6 a non-reassuring fetal heart rate tracing; a 25
7 percent change in the cesarean rate for dystocia; a
8 20 percent change in chorioamnionitis rate; and a
9 42 percent change in the incidence of fetal safety
10 composite.

11 [Slide]

12 The data is managed by the biostatistical
13 center, and weekly transmission to the Maternal
14 Fetal Medicine Unit biostatistical coordinating
15 center or data center will occur from each of the
16 individual network centers. This data is then
17 uploaded and merged with the ongoing database. The
18 BCC looks at all of the data and weekly edits for
19 clarification to each center, as well as audits
20 comparing data across forms, which are run at
21 regular intervals, and data quality reports are
22 issued monthly in the Network.

23 [Slide]

24 The oversight committee for the Maternal
25 Fetal Medicine Unit Network in each trial ongoing

1 include the MFMU Network steering committee, the
2 advisory board, the data safety and monitoring
3 committee, as well as the institutional review
4 boards at each clinical center.

5 [Slide]

6 So, the FOX trial is a large-scale, multi-center,
7 randomized clinical trial of fetal pulse
8 oximetry which allows for the evaluation of fetal
9 oximetry on the overall cesarean section rate,
10 infant safety, maternal fetal infections, dystocia
11 and in the presence of abnormal fetal heart rate
12 patterns.

13 [Slide]

14 The goal of the MFMU Network is to improve
15 the outcome of infants and their mothers.

16 [Slide]

17 There were three questions that were posed
18 for our trial from the FDA and I would like to
19 address each of these three questions in turn.

20 First, will the FOX trial provide useful
21 data on the currently improved indication? A
22 subset of the 10,000 women will have abnormal fetal
23 heart rate tracings, and it is estimated that the
24 size of this group will be at least 2000 women.
25 So, yes, the FOX trial will be able to provide this

1 information on the currently improved indication.

2 [Slide]

3 Will the FOX trial's masked group provide
4 information towards further understanding of the
5 validity of the 30 percent cutoff? We will have
6 over 3000 women in the masked arm. That masked arm
7 will give significant data on the natural history
8 of fetal oxygen saturation values, and information
9 on the prognostic significance of the 30 percent
10 cutoff will be obtained.

11 [Slide]

12 Finally, will labor management protocol in
13 the FOX trial allow for meaningful interpretation
14 with respect to management protocol in the approved
15 labeling? Physicians will be instructed to use the
16 device in accordance with its labeling. In
17 addition, a computer archive will allow for the
18 measurement of whether physicians comply with the
19 management portion of the labeling.

20 I would be happy to answer any questions.

21 DR. BLANCO: Thank you, Dr. Spong. Go
22 ahead.

23 DR. SHARTS-HOPKO: I am not clear on why
24 the masked arm will validate the 30 percent level
25 if we are operating now on the hunch that people do

1 cesareans prematurely.

2 DR. SPONG: I am not saying that it will
3 validate anything. I am saying you will have a
4 body of evidence that will give you a natural
5 progression as to what happens to fetal oxygen
6 saturation during labor without acting upon it,
7 without a physician being able to act upon it
8 because they will not know that data.

9 DR. SHARTS-HOPKO: But they are going to
10 do what they believe is clinically appropriate
11 without seeing that data.

12 DR. SPONG: Based on the fetal heart
13 tracing, yes.

14 DR. SHARTS-HOPKO: Right.

15 DR. ALLEN: Just to follow-up on that,
16 just from reading the article published by Garite,
17 based on the fetal heart rate tracing intervention
18 occurs before the SpO2 gets down to 30. So, you
19 are actually intervening before you can even
20 collect the data that we are interested in.

21 DR. BLANCO: Do you want to make a comment
22 on that?

23 DR. SPONG: I am merely here to present
24 our study as how it is being done. If it happens
25 to meet the post-marketing guidelines as you have

1 set forth, then I think that is what I am here for.

2 DR. O'SULLIVAN: I think one of the things
3 that the blinded arm will do is that in each of
4 these institutions they are going to have a value
5 of having used the fetal pulse oximeter. That, in
6 and of itself, may change the way they think
7 regarding fetal heart rate tracings. So, this
8 information, since it is blinded, may provide what
9 happens when they don't have the pulse oximeter,
10 have changed perhaps practice by virtue of using
11 the equipment, and we can begin to see whether, in
12 fact, they get into trouble by doing that. I mean,
13 this is one way of looking at it.

14 DR. IAMS: Clarification about the monitor
15 alone, the electronic fetal heart monitor, that
16 group is not going to have a sham device?

17 DR. SPONG: No.

18 DR. IAMS: Okay. The second question is,
19 is there any financial support from any of the
20 people who make this device for the Network study?

21 DR. SPONG: Ask that one more time.

22 DR. IAMS: Are any of the companies who
23 manufacture the device providing any financial
24 support or other support for the study done by the
25 Network?

1 DR. SPONG: Not that I know of.

2 DR. BLANCO: Any other questions,
3 especially questions of fact, before panel
4 discussion?

5 DR. IAMS: One more. I think I know the
6 answer to this but when will the safety data from
7 these studies, which is what we are talking about
8 here, be available for the FDA and the public to
9 review?

10 DR. SPONG: All of the data from the
11 Maternal Fetal Medicine Unit Network belongs to the
12 Maternal Fetal Medicine Unit Network steering
13 committee. At the discretion of the steering
14 committee, they would make that data available to
15 the FDA.

16 DR. IAMS: I was thinking about what
17 calendar year.

18 DR. SPONG: We anticipate this study
19 beginning in the fall, and we expect that it will
20 be a two- to three-year study and data won't be
21 available until the study is completed.

22 DR. BLANCO: Along those lines, does the
23 Network plan to look at safety issues, and if they
24 see something in terms of safety of how the design
25 is set up or the device is being used, will there

1 be a preliminary release of that data?

2 DR. SPONG: You mean ongoing --

3 DR. BLANCO: Right.

4 DR. SPONG: Certainly, the data safety and
5 monitoring meets regularly and will go over all
6 safety issues. If they were to find something that
7 required the study to be stopped then, yes, that
8 would be brought up. I don't believe they would
9 release anything unless the study were to be
10 stopped.

11 DR. BLANCO: Any other questions?

12 [No response]

13 Thank you very much. We appreciate your
14 presentation as we appreciate the presentations of
15 all of today's speakers. Despite running a little
16 longer on some, we have run a little shorter on
17 others so we are still on schedule.

18 Panel Discussion

19 The next step in the agenda is to go over
20 the discussion questions and then have some panel
21 discussion. You should have the questions posed by
22 the FDA in your packet.

23 When the FDA approved the PMA for the
24 OxiFirst monitor on May 12, 2000, a post-approval
25 study was required to assess how the use of this

1 monitor would impact cesarean deliveries, as well
2 as to evaluate several other important variables
3 within general clinical practice. Per FDA's
4 approval order, the post-approval study should
5 address the following parameters: indications for
6 OxiFirst sensor placement; cesarean section rates;
7 maternal infection rates; duration that fetal
8 oxygen saturation can remain below 30 percent
9 before risk of fetal injury; adequacy of labor;
10 neonatal outcomes, e.g., cord blood gases, Apgar
11 scores, etc.

12 In the PMA supplement subject to this
13 panel discussion, Mallinckrodt has proposed a post-approval
14 study plan based on the three separate
15 studies: Study A, three-arm multi-center,
16 randomized trial conducted by NICHD's Maternal
17 Fetal Medicine Unit Network, with some technical
18 consultation from Mallinckrodt; Study B, general
19 use study sponsored by Mallinckrodt; and Study C,
20 dystocia study conducted by some of the original
21 OxiFirst investigators and partially underwritten
22 by the company.

23 So, now we come to the questions and they
24 have it divided into each of the studies. So, for
25 Study A, which is the NICHD Maternal Fetal Medicine

1 Unit Network, number one, in the NIH study, the
2 OxiFirst sensor will be placed in subjects for
3 indications beyond what is in the approved
4 labeling, i.e., non-reassuring fetal heart rate
5 tracings. Will the proposed NIH study provide
6 useful data, per the panel's earlier
7 recommendation, on the currently approved
8 indication? If not, are there patient subsets that
9 can be analyzed?

10 That is the first question. Anybody care
11 to take a look at that and begin the discussion?
12 If not, I will go ahead and pick someone. So, Dr.
13 Iams, why don't you go ahead and make some comments
14 on this first question?

15 DR. IAMS: Well, I think the first
16 question I have about this comes from the last
17 question I asked Dr. Spong, and that is simply a
18 matter of timing. The NIH study is going to take a
19 long time. So, regardless of what question you ask
20 it, unless there is a profoundly disturbing safety
21 issue where the data safety monitoring committee
22 will come forward, I think you are going to see
23 results from the Network study -- what? Four
24 years, Cathy, would probably be the end of the
25 study? And, in my experience with network trials,

1 the data doesn't become instantly available at four
2 years and one day when the trial closes. There is
3 a series of prioritized analyses that are done, and
4 it would probably be more like four or five years.

5 So, I am not sure, as a general comment,
6 whether the NIH study is ever going to be the place
7 where either the FDA or the company should expect
8 to go and find timely answers. In fact, that was
9 one of the underpinnings of the panel's
10 recommendation to go ahead and approve this last
11 time, that it would simply take too long for a
12 well-conducted, properly powered randomized trial
13 to produce results, and many of us thought that it
14 would be more appropriate, given the safety
15 information we have, to go ahead and try to get
16 those results from clinical trials.

17 So, I think my only question would be does
18 FDA expect the NIH study to provide the answer to
19 this question? I think you should not. The safety
20 issue -- certainly, you are going to need big
21 numbers like that and you might have to wait that
22 long unless something more worrisome comes up.

23 DR. BLANCO: And added to that, I think
24 the questions the Network is asking are very
25 important questions and they are probably a lot

1 broader than the narrow issues in terms of the
2 indications and the approval by the FDA. So, I
3 think eventually that study is much more likely to
4 prove or disprove or at least address the issue of
5 how this device should be used, and I think that
6 will be very useful but I don't think it is going
7 to address the issues or the concerns that the
8 panel members had when they voted for approval of
9 the device with conditions. Gary, do you have some
10 comments on that?

11 DR. EGLINTON: I don't think we are
12 looking at study designs that are going to answer
13 very many questions that are important to the
14 questions that were raised in the last two years.
15 I mean, people aren't going to be happy with these
16 results with the study design.

17 As Dr. Schifrin says often -- I have
18 listened to him say it for over twenty years, if
19 you get people to ask the wrong question, who cares
20 what the answers are. I don't think we have the
21 right questions before us today.

22 From the NIH study, do I understand
23 correctly that women in labor with no indication
24 for the device will have the device inserted? Is
25 that right? Did I understand that right, Dr.

1 Spong?

2 DR. SPONG: Yes, it is for --

3 DR. BLANCO: I am sorry, identify yourself
4 again.

5 DR. SPONG: Cathy Spong, NICHD. Yes, it
6 is for women meeting the inclusion criteria, and
7 included in the inclusion criteria is not any type
8 of abnormal fetal heart rate tracing.

9 DR. EGLINTON: So, a lady could go through
10 her entire labor with no fetal heart rate
11 abnormality but does have the pulse oximeter?

12 DR. SPONG: Yes.

13 DR. EGLINTON: And in the general use
14 study we are talking about non-concurrent controls.
15 We are looking --

16 DR. BLANCO: They have got it set up study
17 by study. So, let's stay with the NIH study and
18 then we will come back for the other study. That
19 way, we will be somewhat organized.

20 I don't know if anyone else wants to jump
21 in and say anything, but what I am hearing folks
22 say is no, this study isn't going to really come in
23 a timely enough manner, nor is it directly
24 addressing the conditions that the panel had
25 concerns with when they approved the PMA. Anyone

1 want to shoot that down one way or another?

2 MS. MOONEY: I think just one thing we
3 should keep in mind when we are looking at this
4 study is that the sponsor was only looking for the
5 NIH study to address the percent oxygen level, the
6 30 percent. That is adjunctive or additional to
7 the general use study. So, I think maybe we should
8 focus on how useful the NIH study will be for that
9 one particular variable that the FDA was interested
10 in.

11 DR. BLANCO: Subir?

12 DR. ROY: I think one aspect of the NIH
13 study that may prove to be useful is to determine
14 whether the use of the device increases the
15 dystocia rate.

16 DR. IAMS: I think that is right. The NIH
17 study will give us information about a number of
18 issues, not necessarily those that we posed last
19 time, but the first is timing -- none of those are
20 going to be back any time soon. But it will give
21 us valuable information about infection rates both
22 in mother and baby and about the influence of the
23 device on dystocia, and perhaps about other, as yet
24 to be determined, characteristics of the pulse
25 oximeter that may identify women at risk for

1 dystocia or fetal distress. There are all sorts of
2 interesting things that will come out of that, but
3 really for purposes of this discussion the question
4 is what does it answer? It will answer safety
5 issues but not in a timely fashion.

6 DR. BLANCO: Let's go ahead and address
7 that. I think that is a very good point that you
8 made, that that was one check point that they had
9 from the study and I think the study will get a lot
10 of information.

11 So, the very next question, number two,
12 the SpO2 cutoff specified in the OxiFirst labeling
13 is 30 percent. Will the sham arm of the NIH study
14 provide information towards further understanding
15 of the validity of this cutoff value?

16 That is the information that may be
17 gathered and, again, I think, as Dr. Iams points
18 out and as has been clearly stated, it is not going
19 to be terribly timely. This is a crucial issue and
20 I bring back the concern again. This was a big
21 issue for me at the time that it was approved.
22 There was a limited number of data points that were
23 being utilized to arrive at this 30 percent cutoff
24 in terms of comparison between the 30 percent and
25 actual scalp pH's done on babies.

1 So, the issue is will any kind of a
2 longitudinal study where 30 percent is used as a
3 cutoff and the device is used as is being intended
4 really answer the issue of whether 30 percent is
5 the value that should be used. To me, that doesn't
6 seem to make sense, and I don't think we have
7 addressed the issue of 30 percent and how that was
8 arrived at, and we are not addressing it with any
9 of the three studies as far as I can tell. Maybe I
10 am missing something. Anybody else want to
11 comment?

12 DR. IAMS: George, I have a little
13 different memory of the 30 percent number. I
14 recall not being completely convinced that it was
15 okay but my general sense of the previous panel
16 meeting was that there was a large body, maybe not
17 a totally convincing body but a large body of
18 evidence that that was a reasonable threshold, if
19 you had to pick one, and I didn't come to this
20 meeting thinking, boy, I hope they address that 30
21 percent issue. That, to me, is a relatively minor
22 point. The risks of the device, to me, more
23 appropriately relate to does it cause dystocia and
24 are there infectious risks that somehow have not
25 been identified previously. I grant you, that is

1 an important question but I didn't come away from
2 the last presentation, in January 2000, with a lot
3 of concern about that.

4 DR. BLANCO: Okay. Dr. Eglinton is next
5 and then we will go over to this side.

6 DR. EGLINTON: At the time of the last
7 panel meeting I was not aware, but I have since
8 become aware that there are over 330 published
9 articles on pulse oximetry, articles or abstracts,
10 and there is a fairly sound body, large body of
11 information suggesting that somewhere below 40
12 percent, in the 34-40 percent range in both sheep
13 and in humans is where the lactate level begins to
14 rise, the pH begins to fall and metabolic acidosis
15 takes place.

16 But I think the next step is we come back
17 to Dr. Schifrin's question, so what? So, yes,
18 there is a relationship between pulse oximetry and
19 30 percent direct intra-arterial monitoring --
20 those are highly correlated -- and relationship to
21 the scalp pH of 7.2, but the question then extends
22 to so what? What is the clinical correlation?
23 What is the importance of that golden number? It
24 is like $p < 0.05$ is golden but why? So, 30
25 percent is well established in physiology. I don't

1 know that it is established in terms of clinical
2 outcome.

3 DR. BLANCO: Then do you think that this
4 study or any of the other studies will gather the
5 data that would satisfy you that it has a clinical
6 meaning?

7 DR. EGLINTON: I think we have to go back
8 and talk to Dr. Havercamp and turn all the monitors
9 off --

10 [Laughter]

11 -- that is the only way you are going to
12 find out realistically.

13 DR. IAMS: Given the indications, George,
14 for entry into the NIH study, I don't think you
15 have any idea how many of those babies whose pulse
16 ox is below 30 -- that is simply an unknown so we
17 have no way of knowing whether the study will
18 produce that data or not.

19 DR. O'SULLIVAN: There is another issue
20 about below 30, and that is, you know, is it below
21 30 for 2 minutes total and that is it for the whole
22 tracing, or does this pulse ox intermittently go
23 below 30 at multiple points in time? Does that
24 cumulative effect of the periods of time it is
25 below 30 versus 2 minutes below 30 or 5 minutes

1 below 30, i.e., the intermittent so-called
2 recovery, is that important to the long-term
3 outcome of the baby, or is it the prolonged period
4 of time? I think we might get that information
5 but, again, in five years.

6 DR. BLANCO: Ralph?

7 DR. D'AGOSTINO: I think the answer to the
8 question is no, but one of the things that I was
9 trying to ask at the beginning with one of the
10 early speakers is how do we put all this together?
11 I mean, what is really compelling with the three
12 studies? Is the 30 important? Is the use study
13 going to give useful information? I mean, it may
14 go negative, negative, negative in all of them.
15 But if we go positive on one, how compelling and
16 how important are some of the other issues such as
17 this 30? I mean, is this so important that we need
18 to see a mounted study for it? If this doesn't
19 work, how does the FDA react to a positive study
20 for the use, and so forth? Maybe we should wait
21 until we go through A, B and C and ask that
22 question, but I am confused in terms of trying to
23 see what is really important and how one puts a
24 final package together.

25 DR. BLANCO: Michael?

1 DR. NEUMAN: I would like to speak against
2 my profession, if I may, because I think we have
3 done everyone a disservice by creating
4 instrumentation that gives a single number, and
5 then we all think of it as our gasoline gauge on
6 our automobile and when the little pointer goes
7 below a certain mark it is time to go to the
8 station and put more gasoline in the automobile.

9 We are dealing with a very complicated
10 mechanism here, the physiology of the fetus or even
11 the maternal fetal unit, and how can we expect to
12 have a single number tell us whether things are
13 good or not? If we could have done this, we could
14 have done what my long-time friend Jacques Roux
15 used to say about fetal monitors -- all they need
16 is a green light and a red light, and when the
17 green light is on everything is all right and when
18 the red light is on you are in trouble. But we
19 can't do that.

20 And, I think one of the beauties of the
21 middle arm of the NIH study is that it starts
22 looking at what are the numbers when clinicians are
23 concerned? We don't know why they are concerned,
24 and we certainly expect that different clinicians
25 are going to be concerned in different ways, but we

1 start to look at the overall picture together
2 rather than just a single number. I think a single
3 number is an oversimplification of a very
4 complicated problem.

5 DR. IAMS: I would like to agree with
6 that, Michael, but the backdrop of this particular
7 device, to me, begins with the fact of electronic
8 fetal heart rate monitoring. It exists. It is in
9 practice, and has resulted in, we assume, a higher
10 than appropriate rate of cesarean section for fetal
11 indications, indicating fetal compromise. That is
12 where this all starts. It is ingrained in our
13 culture and we could not stop electronic fetal
14 monitoring tomorrow if we wanted to. It is there.

15 Even though Dr. Schifrin would probably
16 have us interpret the tracings better than we do
17 now, the fact is we don't interpret them very well
18 and we have an inappropriately high cesarean rate,
19 and that is where this device has its origins
20 really, in the fact that the C-section rate is too
21 high.

22 I say I agree with you but obstetrics has
23 a history of assuming that more accurate measure of
24 something translates automatically into improved
25 care. I sort of sense that that might be a logical

1 conclusion from your comments, but that is not the
2 case in obstetrics. Accurate measurements have
3 reliably not improved the outcome of pregnancy for
4 women, starting with x-ray pelvimetry and urinary
5 and serum estriol and on and on, and you can keep
6 right on going. But we have assumed that the
7 better the data, the more good will come to our
8 patients and, in fact, the opposite has often been
9 the case.

10 So, this device, to me, lives or dies on
11 the question of does the cesarean rate, which we
12 assume to be too high based on inappropriate
13 interpretation of electronic monitoring -- does it
14 reduce the cesarean section rate? If it does, it
15 is a great advance. If it doesn't, then I would
16 hate to see us approve it or, shall we say maintain
17 its approval, simply because it gives us more
18 accurate information by which to judge the course
19 of labor. We have been there with that sort of
20 argument and we have failed repeatedly to improve
21 outcomes for babies and mothers. So, to me, the
22 question is do the proposed studies answer that
23 question about will the cesarean section rate go
24 down?

25 And, I think we can quibble about the fine

1 points of the various studies that have been
2 proposed, but the use study and the dystocia study,
3 I think, are good places to start. We have argued
4 about some of the details but I think that is
5 exactly what the company has to do to justify their
6 product. If they don't do it, then the product
7 really should simply not be used.

8 DR. BLANCO: Any comments from anyone
9 else? Any other issues specifically addressed to
10 number two? If not, we will go ahead and move
11 quickly to question number three.

12 Will the labor management protocol
13 employed in the NIH study allow for meaningful
14 interpretation with respect to the management
15 protocol in the approved labeling? Nancy?

16 DR. SHARTS-HOPKO: I think it will provide
17 that information but we have already noted that it
18 is going to take a long time.

19 DR. BLANCO: Dr. Spong, would you like to
20 make a comment?

21 DR. SPONG: I would like to make a
22 comment, if I may.

23 DR. BLANCO: Please.

24 DR. SPONG: Again, Cathy Spong, NICHD. I
25 realize that you are concerned with the timeliness

1 of the study and how long it will take our study to
2 be done. But, in truth, I think that is how long
3 it will take any study to be done and I don't
4 really think four years is a long time when you
5 look at what you are going to get in four years
6 from that trial.

7 Understand that our trial was not designed
8 to address these questions in the post-marketing
9 approval. Our study was designed to ask the
10 question and design the best trial to answer the
11 question. Although I appreciate it will take four
12 years to get that, in fact, as I noted, we could
13 get it done in a year given financial support to be
14 able to implement the study and get the patients
15 enrolled. We have the patients to be able to
16 complete it in a year, however, that is not going
17 to happen and it will take two to three years in
18 order to enroll the patients. But no study that
19 you start now isn't going to take at least two, if
20 not three, years to get done. So, yes, it is a
21 long time but in reality for any randomized,
22 controlled trial that is how long it will take.

23 DR. BLANCO: Don't misunderstand us, I
24 don't think that anyone is asking that it be any
25 faster than what it really has to be in order to be

1 able to gather the appropriate and good data. I
2 will speak for myself but I think the panel members
3 feel likewise, we sit here and we make
4 recommendations. Industry goes to a lot of trouble
5 and tries to design and works very closely with
6 FDA. FDA puts in a lot of time working with
7 companies to try to arrive at appropriate studies
8 that answer questions. And, we certainly don't
9 want to be in the way of progress and the use of
10 devices that might benefit babies and women but, at
11 the same time, our votes I guess really do count
12 and we are concerned that our votes not be the
13 wrong way, and if they are the wrong way that they
14 be reversed and that devices, if they are useful,
15 be out there even more, and if they are not, not be
16 there for very long, not helping and possibly
17 hurting. So, I think we have different purposes in
18 what we are trying to do and what you are hearing
19 is that difference in desires and purposes. Dr.
20 Allen?

21 DR. ALLEN: I would just like a
22 clarification for question number three. What are
23 we really asking? Will the labor management
24 protocol employed by the NIH study allow for
25 meaningful interpretation of the management

1 protocol in the approved labeling, and how do they
2 differ? How the management protocols in the
3 original randomized, controlled trial -- other than
4 that one is randomized, controlled and prospective
5 and in the FOX trial everybody gets the sensor?

6 DR. BLANCO: Well, I think the management
7 protocol is not addressing whether you get the
8 sensor; it is addressing what you do with the
9 information --

10 DR. ALLEN: And are the interventions
11 different in the randomized, controlled from yours?
12 You just have larger numbers?

13 DR. SPONG: The physicians will be
14 instructed to use the device in accordance with
15 this labeling. They will be given the same
16 information as to how to interpret.

17 DR. ALLEN: So, we just have more power
18 with the larger numbers.

19 DR. BLANCO: And different entry criteria
20 as well.

21 DR. SPONG: In addition, a computer
22 archive will allow us to determine whether or not
23 physicians did actually comply with what was
24 recommended for them to do.

25 DR. BLANCO: Let's hear from Mr. Pollard.

1 MR. POLLARD: I just wanted to add that
2 the reason we put that question in is because we
3 were just trying to highlight that aspect in the
4 FOX trial protocol that management would be at the
5 discretion of the attending physician whereas in
6 the labeling they actually spell out a fairly
7 detailed kind of management protocol, and we
8 weren't certain whether this difference had any
9 real bearing on how we should look at that data.

10 DR. SPONG: This is Cathy Spong, NICHD,
11 again. Yes, we will be giving the physicians the
12 same information for how to use the oximeter, and
13 we will be able to collect from the computer
14 archive whether or not they did it according to
15 what they were supposed to do, but they will do
16 what they do.

17 DR. BLANCO: We are well aware of that!
18 Dr. Eglinton?

19 DR. EGLINTON: Dr. Spong, I know you do
20 not need the exercise but we appreciate your
21 getting up and down. How rigid is the FOX trial's
22 protocol for management of dystocia?

23 DR. SPONG: For management of dystocia in
24 the sense of are they told exactly what to do if
25 the patient -- how long they are supposed to sit on

1 a patient for X, Y, and Z? No, they are not given
2 explicit instructions that they must wait three
3 hours before doing X, Y or Z. There will be a form
4 filled out by the research nurse, who is not
5 involved with the medical management of the
6 patient, who will determine why that patient had a
7 cesarean delivery or an operative vaginal delivery,
8 given explicit criteria that she will go through,
9 but the medical team is not told how to manage
10 their patients.

11 DR. BLANCO: Any other comments or
12 questions at this point on this particular
13 question? No? All right, any other comments on
14 the Maternal Fetal Network study that anyone would
15 care to make at this point, from the panel?

16 [No response]

17 Let's move on then to Study B, the general
18 use study, question number four, considering the
19 nature of the clinical centers involved in the NIH
20 study and dystocia study, should the general use
21 study target different types of hospital settings
22 so as to optimize the overall information gained by
23 the sum of the three studies?

24 Just to start out, the networks are mainly
25 academic centers with a certain type of practice,

1 and I think this question addresses the issue of
2 community hospitals where practice might be
3 different and section rates might be different, and
4 so forth. So, anyone care to address this issue?
5 Dr. Eglinton?

6 DR. EGLINTON: I talked with Colin about
7 this several months ago and I corresponded with Dr.
8 Spong as well. I think it might be more useful to
9 try to find some hospitals with a cesarean delivery
10 rate of 50 percent to see what kind of impact this
11 has. It may shock you to learn that there are
12 such, but there are. When I was in southern
13 California there was a big TV expose on hospitals
14 with a cesarean delivery rate over 50 percent. You
15 can find such hospitals. Fifty percent is too high
16 obviously. That is a little facetious, but there
17 are hospitals with very high cesarean delivery
18 rates and you may have different outcomes. You may
19 have different results. I am still worried very
20 much but one of the statisticians helped me -- is
21 it the Hawthorne effect? -- if you are looking for
22 the cesarean delivery rate in this general use
23 study and you are looking at non-concurrent
24 controls.

25 DR. D'AGOSTINO: I think that was exactly

1 the whole point of the discussion about the
2 historical controls. Trying to get concurrent
3 controls is not going to be an easy task, and it
4 appears that because we don't even know what the
5 centers are, we don't know what their ability is to
6 collect data on the historical controls, how much
7 data actually exists. So, I think they are really
8 in quite a bind right now.

9 DR. BLANCO: Let me just add, I mean, that
10 is partly what the FDA would like to hear. They
11 would like to hear us make some comments as to how
12 it should be set up. So, do address those issues.

13 DR. IAMS: Well, I think there are a
14 couple of issues. I agree with Gary that you
15 should find hospitals that have a high baseline
16 cesarean section rate presumably, in part, because
17 they have a higher than appropriate rate of "fetal
18 distress" that this device might address.

19 The second issue might help somewhat with
20 the validity of your historical controls if you
21 were to approach, especially right away, the
22 centers who are no longer in the network -- the
23 network that is just in the middle of or has
24 finished a cesarean section study, Mary Jo's center
25 for instance, and several other quality research

1 units have recent data about every cesarean section
2 at their institution for several years -- how many;
3 why they happened; quite a bit of very high quality
4 historical data. I assume that they would be
5 interested in participating, starting your general
6 use study in those centers. There are about five
7 of them I think. That would be a great place to
8 go. It would be a different population than what
9 you would see from the high C-section rates but it
10 would be a group that has a very well validated
11 historical control group where you might not see
12 some of the trends and some of the data flaws that
13 you might find in some of the other places.

14 DR. SHARTS-HOPKO: Just to add to the
15 comparative data that is going to be available, we
16 were concerned in a prior discussion about the
17 people who declined to participate and declined to
18 have their data collected. But since all
19 institutions are doing aggregate cesarean rate
20 calculations every year, you can flag the people
21 who did consent to be in the study and deduct them
22 from the total and have the gross comparisons
23 available.

24 DR. BLANCO: Will that be sufficient data?
25 I got the impression from what Dr. O'Sullivan and

1 Dr. Iams were saying that you really wanted more
2 data than just simply who got sectioned and
3 possibly the indication.

4 DR. SHARTS-HOPKO: Well, it won't be
5 sufficient for anything but it will add to the
6 general picture.

7 DR. D'AGOSTINO: You want to be able to
8 explain the data afterwards and start looking at
9 different groups, and what-have-you, and if you
10 know a priori you are not going to have that type
11 of data from the historical which is, you know,
12 what you want to spend to get it, I think the idea
13 of going to centers where they do have good
14 historical data is really key. You are not going
15 to get into a randomized trial mode so you don't
16 have that way of having a prospective control, and
17 if you take those and say yes versus those and say
18 no to entering, those who say no will probably be
19 tremendously biased. So, I think you do need
20 something like a historical control from centers
21 that have good information and you can generate a
22 check list of what those variables should be.

23 DR. BLANCO: Subir, you have some
24 comments?

25 DR. ROY: I have a problem justifying

1 historical controls or considering as controls
2 those people who demur and don't want to
3 participate. What is the reason we can't recommend
4 concurrent randomized controls with a sham device?
5 That would answer the question does the device
6 itself lead to increased dystocia. It would give
7 us the direct head-to-head comparison. What is the
8 problem with that? That goes to question three in
9 terms of clinical design, but I think it gets us
10 out of this morass.

11 DR. BLANCO: Let me just address that. If
12 you throw in something that is a sham, you know, if
13 you do that somebody may say -- I don't know if
14 what you meant is that they are going to introduce
15 something that would appear to be like the monitor.
16 If you are going to do that somebody will say, no,
17 I don't want that. I think if you are going to go
18 that way, the way to possibly go might be for the
19 people who say no, I don't want to participate in
20 the study because I don't want this particular
21 experimental device to say, okay, will you allow us
22 to collect data on just what happens to you? You
23 are still probably going to find some folks who are
24 going to say no but I think you are more likely to
25 get the information concurrently if you do it that

1 way, if the concern is one of informed consent for
2 obtaining the data.

3 DR. D'AGOSTINO: That tends to be a biased
4 sample though. Why did they say no? So, you do
5 have a dilemma there. There is the design where
6 you can ask people would they be willing to have
7 the device and not give it to them on a random
8 basis, which I think is what you are saying, with
9 or without a sham. I mean, that is a great idea
10 but I thought we already approved the clinical
11 trial or approved based on the clinical trial so we
12 are in a dilemma where we can't tell them to go
13 back and run another clinical trial that is the
14 usual one for approval. I mean, I think we have to
15 be clever and the sponsor has to be clever in
16 generating information, but we are not to the point
17 of asking them for a controlled clinical trial.

18 DR. BLANCO: Any other comments or
19 suggestions? If not, let's move along to the next
20 question. I believe it is question five, what
21 would be the appropriate overall time frame for the
22 conduct of this study? Is there a need for longer
23 term tracking? Any issues there?

24 DR. IAMS: Well, I was concerned about the
25 one-month run-in or observational time frame that I

1 saw in the general use study. I think a month is
2 not appropriate. You need to find hospitals which
3 have excellent data for a year. When you do the
4 run-in, the run-in maybe should be a little longer
5 than a month, not a whole year obviously but you
6 ought to have a historical control group and then a
7 run-in that is a little more than a month.

8 DR. BLANCO: Please identify yourself.

9 MR. THOMAS: Simon Thomas. That was
10 addressed in the latest version of the protocol,
11 wherein we propose if the site is not a current
12 user of the device, they would be trained per our
13 standard procedure -- typically it takes a couple
14 of weeks. They will then have at least two months
15 to become familiar with the device before we start
16 tracking the data. In that period, exactly like
17 regular customers, clinical consultants will go
18 back and see how they are getting on and do a bit
19 of remedial training, etc., if needed. So, in
20 terms of the historical data, what we will be
21 looking for is sites which have reasonable quality
22 of historical data over, say, the last year. Then,
23 if they haven't already started using OxiFirst they
24 will get kind of three months to get trained and
25 become familiar with it, and then we will start

1 formally collecting the data for this study.

2 DR. IAMS: Good. Thank you.

3 DR. BLANCO: Any other comments on the
4 particular time frame for the tracking?

5 [No response]

6 Number six, are there any other
7 improvements that can be made to the clinical
8 protocol?

9 I was looking for the actual letter and
10 conditions that were placed, and you had it in the
11 packet, but I just might refresh your memory
12 because I guess the issue boils down, for me a lot,
13 to this question. You know, are the studies that
14 are being proposed by the company answering the
15 questions and the conditions that the panel placed
16 on the device for approval? If you look at your
17 letter in your packet, it says, in addition to the
18 post-approval requirements in the enclosure you
19 must conduct the post-approval study to assess how
20 the use of the OxiFirst fetal oxygenation fetal
21 monitoring system will impact C-section rates and
22 other important variables within general clinical
23 practice. The study will address the following
24 parameters...

25 So, one of the questions that I would

1 throw out before the panel and, again, I would
2 suggest that the Maternal Fetal Medicine Network
3 study may take too long to have the data to come
4 out to really answer that but if you want to
5 include that one, you are welcome to do so, but the
6 issues that had to be addressed, the parameters are
7 indications for OxiFirst sensor placement; cesarean
8 section rates; maternal infection rates; duration
9 that fetal oxygen saturation can remain below 30
10 percent before risk of fetal injury; adequacy of
11 labor; and neonatal outcomes; and that it be
12 stratified to look into the use of epidural
13 analgesia.

14 So, does anybody on the panel want to
15 address whether the dystocia or the general use
16 study or, I guess the third one if you want to
17 include that one when it comes out, answers these
18 conditions? What do you think, Dr. Iams?

19 DR. IAMS: Well, actually, I think the
20 studies are going to have some problems but I
21 think, given the constraints of this as a post-marketing
22 study, nor a randomized trial, that the
23 studies they proposed will address really all but
24 number four, the issue about 30 percent and fetal
25 injury. It is pretty difficult to say we will

1 definitely know the answer to that one. But the
2 other two studies I think will get where we need to
3 go. The bottom line is does the cesarean section
4 rate change, and you have to have historical
5 controls and something about concurrent controls in
6 order to account for the issues that have been
7 raised and that we don't need to mention again. If
8 those comments are taken to heart and tracked, and
9 the cesarean section rate does what you hope it
10 will do, then this device is an advance and
11 everybody is happy. If it doesn't do that, we are
12 going to be back here arguing whether or not it
13 helps us make better judgments, or some garbage
14 like that. You know, we have been there and done
15 that. I hope that is not the case.

16 DR. D'AGOSTINO: Excuse if the question
17 comes from ignorance, which it does, but could you
18 tell me how the dystocia study is really going to
19 address the questions that were put for that
20 particular problem?

21 DR. IAMS: I am not sure if I can give you
22 as elegant and answer as you would like, but the
23 dystocia study, to me, starts with that as the
24 primary goal and I think that is what I liked about
25 it, that it was a study specifically of the

1 relationship of dystocia to heart rate patterns and
2 to the pulse oximeter data. To try to tease that
3 out of any other larger study and hope that you get
4 there, I am not sure that you will. Maybe Simon --

5 DR. BLANCO: Actually, I was going to ask
6 Dr. Porreco because he was the one that presented
7 dystocia. If you don't mind coming forward to see
8 how you might answer that question?

9 DR. PORRECO: Rich Porreco. As Dr. Iams
10 said, the major deficit or limitation of the RCT
11 was that we were missing some important variables
12 in terms of labor management. Not only were
13 definitions of dystocia not prospectively outlined
14 but, more importantly I think, the management of
15 that occurrence was not outlined. I think if we
16 take patients who have an indication for sensor
17 placement as it is currently labeled, non-reassuring
18 patterns, and assign definitions and
19 assign a management protocol that everybody can
20 live with, then we can see where this dystocia
21 thing falls out. So, I think from a dystocia
22 perspective it will help answer that question in a
23 way that is doable.

24 DR. BLANCO: Any comments?

25 DR. O'SULLIVAN: One other thing, you

1 still can collect the data on the duration of time
2 -- for want of a fancy number, to mention what Dr.
3 Neuman was saying but that is what we are stuck
4 with -- for this 30 percent business. It may be 30
5 percent, it may be 40 percent or it may be 20
6 percent. Regardless, you can still collect the
7 period of time that a fetal heart with an SpO2 went
8 below 30 for the total duration of labor. You can
9 still calculate that out.

10 DR. PORRECO: We can in either the general
11 use study or the dystocia study.

12 DR. O'SULLIVAN: Right, and at least that
13 will give us some information -- how long was it,
14 how did it relate to the outcome of the baby, and
15 under what circumstances did you see it, and we may
16 find out that we have nothing to show here.

17 DR. PORRECO: Maybe Simon will want to
18 comment on that. With regard to the 30 percent, I
19 would point out that the RCT itself, in using that
20 30 percent threshold, did show improved specificity
21 for what is currently the gold standard of labor
22 management, which is electronic fetal heart rate
23 monitoring. It was more sensitive, surprisingly,
24 and more specific for several of the newborn
25 outcome parameters and, impressively, we had no

1 babies out of 500 roughly that had severe metabolic
2 acidosis.

3 DR. O'SULLIVAN: You had one, or was it
4 postnatal?

5 DR. PORRECO: Yes, added clinical evidence
6 from the RCT that 30 percent is the correct
7 threshold, if we can pick a number, red or green,
8 that might be useful. But collecting the amount of
9 time, as you know, the protocol states that if it
10 does not recover above 30 percent between two --

11 DR. O'SULLIVAN: Yes, I understand that.
12 I am not talking about that. That I understand
13 altogether. What I am talking about is the periods
14 of times at which it might go below 30, which may
15 be intermittently a stress to the baby but which
16 you might not see when the baby is born, for
17 example. That is where you would really need some
18 long-term outcome which you are not going to have.
19 But that could still be something worth collecting.
20 And, there was one baby in that study that had a
21 very poor tracing to begin with and who ultimately
22 died, and the question here is why.

23 DR. PORRECO: Do you want to address that,
24 Simon, since you know that case?

25 DR. BLANCO: I think it goes back to the

1 issue of the magic 30 percent and I always enjoy
2 your analogy, Michael, on, well, it is now empty --
3 if it is 30 percent it is now empty, and it may not
4 have to do with that. It may have to do with a
5 period of time below which it is 30 percent. It
6 may have to do with how many times it dips below
7 and recovers. I mean, it may be a lot more than
8 just anything that you can put down with a hard
9 number on it.

10 DR. PORRECO: As Dr. Eglinton mentioned,
11 physiologically we do know that at least the fetal
12 animal does not begin accumulating acid until it is
13 below 30 percent and stays there, and as soon as it
14 crests 30 percent the acid begins clearing. So,
15 there is plenty of physiologic --

16 DR. O'SULLIVAN: My point is just because
17 the acid clears and just because the baby has a
18 normal pH at birth implies, okay, nothing happened
19 to this baby during the hour or two before
20 delivery. It doesn't tell us that the baby, in
21 fact, was not severely acidotic at some other point
22 during pregnancy for example.

23 DR. PORRECO: Absolutely.

24 DR. O'SULLIVAN: This is what I am getting
25 at. You may not see this as acidosis.

1 DR. PORRECO: I couldn't agree with you
2 more but, you know, the point is that our behavior
3 in labor is to deliver these babies either with
4 forceps or abdominal delivery and rescue them from
5 some event that happened two weeks before or an
6 hour before. The best we can do with intrapartum
7 intervention is to deal with the hypoxemia that we
8 think is occurring or not occurring, and this
9 device has that impact. It is not going to address
10 the problem of an ischemic event or a hypoxemic
11 event two weeks before.

12 DR. BLANCO: Any other comments? I have a
13 comment for you Dr. Porreco. I guess I have
14 already made it but I guess I want to make it
15 again.

16 DR. PORRECO: Okay.

17 DR. BLANCO: I am concerned about the
18 broadening of the indications for use of the device
19 because, you know, I am sure that you will use that
20 and it will be published, and I just have a concern
21 that that will lead to a broader use under not the
22 indications that the primary studies developed out
23 in the community. Unless you are going to address
24 that issue specifically, which is not what I gather
25 you would do with the study, I am concerned that

1 that may lead to inappropriate use of the device,
2 which isn't going to help the company because it
3 may turn out to cause problems and so forth.

4 DR. PORRECO: You know, the experience to
5 date, and I used this during the RCT in the last
6 year and this device gets used on a relatively
7 modest sized service every third day, is not that
8 the device is used prematurely or inappropriately,
9 the question comes up why didn't they use the
10 device when you look back in retrospect. So, it is
11 a question of why didn't we ascertain --

12 DR. BLANCO: But that is like saying why
13 didn't you do a C-section --

14 DR. PORRECO: Sure. Your concern is that
15 it will be used inappropriately for a broadened
16 indication and I am saying that the experience so
17 far has been that it wasn't even used for the
18 labeled indications.

19 DR. BLANCO: Then, why are you going to go
20 and look at non-labeled indications?

21 DR. PORRECO: Well, I don't believe I am.

22 DR. BLANCO: I thought you said you were
23 going to put the device in people who did not have
24 indications for its use.

25 DR. PORRECO: No, no, no, that is probably

1 my lack of articulation.

2 DR. IAMS: George, this is a place for me
3 to respond when you whispered that comment to me
4 before, and that is that I would like to see these
5 studies get going here because otherwise we are
6 going to find ourselves with a device that has
7 trickled into general use without any additional
8 data beyond the RCT, and we will have something
9 that people have fallen in love with because it is
10 more numbers, more data, another artificial
11 threshold, and we will be resting on this flawed
12 trial. I mean, I respect you guys tremendously for
13 your efforts to tease all that data out the last
14 time. It was a very thoroughly evaluated trial,
15 but you don't want to stop with that trial and say
16 that is the cornerstone of our use of this
17 technology. We have to have more and we have to
18 have it pretty quickly.

19 I have one question about that which I
20 forgot to ask before, are there any prior review
21 restrictions or publication restrictions upon any
22 of the investigators from the company? I imagine
23 the data has to be seen by the sponsors, but if you
24 wanted to publish a study which was not favorable,
25 are there any contractual or other impediments to

1 your doing that?

2 DR. PORRECO: No.

3 DR. BLANCO: Any other comments? Gary?

4 DR. EGLINTON: Can I just ask the people
5 on the panel here how many people have this
6 technology being used clinically in their hospitals
7 now? Is anybody using it?

8 DR. BLANCO: Let's touch on the last
9 question and we will go from there. Question
10 seven, will this study help elucidate the findings
11 from the pivotal PMA study that showed more
12 cesarean deliveries for dystocia in the OxiFirst
13 arm? Any comments on this? I think we kind of
14 answered this. We sort of talked about this
15 already to some extent. Anything else that anyone
16 wants to say? Nancy?

17 DR. SHARTS-HOPKO: My comment is directed
18 to Dr. Spong. I have enormous respect for
19 longitudinal studies that only NIH can do and
20 really cesarean delivery is a proxy endpoint.
21 Really the outcome is neurological functioning of
22 these children later on. So, I hope that you will
23 keep going.

24 DR. SPONG: Again, this is Cathy Spong.
25 The intent is to follow the patients through

1 discharge. We do not have funding to follow them
2 long term. We would love to follow them through
3 school age but we don't have that.

4 DR. O'SULLIVAN: Can I just make a point
5 about that? It takes a huge amount of dollars to
6 do that and, while that would be the ideal way,
7 there is no question it would solve a lot of
8 issues, if you go back and you just look at the
9 history to date, I don't think there is any
10 evidence out there that we have changed anything,
11 despite everything that we are doing, in terms of
12 epilepsy, mental retardation, cerebral palsy --
13 maybe a little bit increase in cerebral palsy but
14 perhaps more related to survival of a very
15 premature infant. But to do that -- that would be
16 the ideal route to go, and it is just too
17 expensive.

18 DR. BLANCO: Any other comments? At this
19 time, what I would like to do, although we have had
20 feedback and I do like feedback from some of the
21 folks who present, let me open up the floor again
22 to solicit some comments. If there is anyone in
23 the audience who would like to make some final
24 comments in front of the panel for the record or
25 for the panel's ears, if you would come forward.

1 Dr. Schifrin?

2 DR. SCHIFRIN: Schifrin, Glendale,
3 California. It is my understanding that there is a
4 current preliminary study under way trying to see
5 the relationship of heart rate patterns to the SpO2
6 below 30. If it shall be shown that certain heart
7 rate patterns invariably predict a low SpO2 will
8 that no longer be an indication for the SpO2
9 device? Contrary, if certain of the patterns can
10 always be shown to be unrelated to a low SpO2 will
11 those in the future no longer be used as an
12 indication for the device?

13 DR. BLANCO: Well, I am not really sure
14 who would be making that decision to answer that.
15 So, I am not sure who you were directing the
16 question to.

17 DR. SCHIFRIN: Well, my understanding is
18 that the data is soon to come out that certain
19 patterns are almost invariably associated with a
20 low SpO2. If a pattern predicts a low SpO2
21 saturation, and that in itself is an indication for
22 intervention, why would you use the device?
23 Contrary, if some of these patterns are invariably
24 associated with a normal O2 saturation, then do
25 they still remain an indication for surveillance?

1 I would like to compliment Dr. O'Sullivan
2 for her comments on what is essentially patterns.
3 We are talking about the O2 patterns, some that dip
4 and some that don't dip; some that recover, some
5 that don't recover. These are, in fact, the
6 patterns and perhaps they should be called by that
7 name. Thank you.

8 DR. BLANCO: Thank you. Anyone else from
9 the audience that would like to make a comment?
10 No? Then, anyone from FDA that would like to make
11 a comment?

12 MR. POLLARD: I guess the only comment I
13 have is more like a question. As I mentioned at
14 the beginning of my presentation, we don't
15 typically bring PMA supplements before the panel.
16 In this case, even though arguably the post-approval study
17 plan has been strengthened
18 dramatically by the inclusion of the NIH study, we
19 still felt it important because we felt this device
20 itself is an extremely important device, and how it
21 progresses in the marketplace and its clinical use.
22 So, a more generalized question, is this the kind
23 of thing the panel would like to see and would like
24 to comment on in the future as we look at things
25 like this?

1 DR. BLANCO: Does anybody from the panel
2 want to respond to that? If not, the chairman will
3 take a shot at that. It depends on what you got
4 out of it. I think it depends on whether the
5 discussion that you have currently heard gives you
6 any information that you are going to act on that
7 is of benefit.

8 I notice that after we have the sponsor
9 speak next with some final comments we are supposed
10 to have a vote. I am not really quite sure what we
11 are going to vote on per se because the device is
12 already approved with conditions. I don't think
13 there is really a necessity for a vote. I think
14 the issue for me was that this maybe helps you
15 refine the conditions and helps you refine issues
16 that maybe the company and some of their
17 investigators may be able to take and refine their
18 studies to address some of the issues that we
19 brought forth. And, if that happens that is
20 probably of benefit. If it doesn't, then maybe it
21 is not. Ralph?

22 DR. D'AGOSTINO: Just a comment in terms
23 of what I would like to see, I think that what is
24 useful about it is that possibly when we are
25 looking at the approval process we might be a bit

1 glib in terms of saying, yes, approve and throw it
2 into a study, a post-marketing study. I think with
3 this type of discussion we see just how hard it is
4 to run those studies and I think it might help very
5 much in terms of what we suggest in the approval
6 process.

7 DR. BLANCO: Thank you. Any other
8 comments from anyone else? Yes?

9 MS. BROGDON: I am advised by staff that
10 it is not critical that we receive a vote on this.
11 We do have a sense of the panel.

12 DR. BLANCO: Thank you. Then, lastly, if
13 we could hear from the sponsor.

14 MR. THOMAS: Simon Thomas again. Three
15 quick comments and I hope clarifications on points
16 which have been raised during the panel discussion,
17 leading off actually with Dr. Schifrin's remarks a
18 few minutes ago. First off, I have no knowledge of
19 the study to which he is referring so I will be
20 eagerly looking for those results. Second, the
21 question he asks about fetal heart rate patterns,
22 particular patterns being associated with a low
23 saturation and the converse was explicitly
24 addressed, as part of the post hoc analysis and,
25 indeed, we found no such association. That is

1 actually summarized in the SSAD, which I believe is
2 in your package and has more detail available, if
3 you are interested.

4 One other just, hopefully, clarification
5 relating to indications for use, both the dystocia
6 study and the general use study enrolled patients
7 or used the device in patients meeting the
8 indications for use per the labeling, no
9 exceptions. It doesn't go any wider, Dr. Blanco.

10 DR. BLANCO: Thank you.

11 MR. THOMAS: And to Dr. O'Sullivan, the
12 very interesting question of how long the
13 saturation would have to be below 30 before you see
14 evidence of harm in the baby, we did do that
15 analysis looking at total time below 30 percent and
16 kind of duration of epochs below 30 percent on the
17 RCT data set, and we didn't find an association.

18 We also looked at the time interval of the
19 difference between the saturation and 30 percent,
20 the area under the curve, if you will, and again we
21 did not find an association with any of the
22 standard outcome measure in that parameter on the
23 RCT data set. This is one of the reasons why I
24 believe the blinded arm of the NIH study will be so
25 valuable to help answer this question because in

1 that group, reasonably, you would expect to have
2 some bad outcomes because people won't be using the
3 oximeter to help them get better outcomes. So, we
4 may be able to answer that question.

5 DR. BLANCO: Thank you. Any comments from
6 any of the panel members at this point?

7 DR. IAMS: Just one, George. Let me say
8 it again, hurry up and get this stuff done.

9 DR. BLANCO: I think we have given the FDA
10 a sense of what our feelings and what our ideas are
11 concerning some of the studies and the information,
12 and I want to thank everyone that participated,
13 both the panel as well as industry, FDA and the
14 speakers that spoke before us. It is always
15 enjoyable to do this as I usually learn a great
16 deal. Unless anyone has another comment, that will
17 be the end of this portion of the panel meeting. I
18 am going to look around and see whether the panel
19 members would like a small break before we go into
20 the next session. I see some nods. It is 3:51.
21 Let's try to be back here at 4:05. Thank you.

22 [Brief recess]

23 Novatrix Labor Assister Device:

24 Discussion of Regulatory Process Issues

25 DR. BLANCO: Let's go ahead and reconvene

1 the panel. I would like to introduce Mr. Colin
2 Pollard, Chief, Obstetrics and Gynecology Devices
3 Branch, who will address the panel.

4 Introductory Remarks

5 MR. POLLARD: Thank you, George. Just
6 very briefly, you are about to hear a presentation
7 from Novatrix and CareStat. Over the last three or
8 four years, and actually probably further back than
9 that, although it is about four years ago when I
10 think Novatrix first started talking to us about
11 their labor assister product, which is essentially
12 a fundopressure belt used to help women in labor,
13 the idea being that perhaps it might reduce active
14 interventions.

15 I am sure the company is extremely
16 disappointed that the study did not prove out, like
17 they had hoped, but we thought it would be a
18 worthwhile exercise to listen to just went on.
19 There were a number of early collaborations which
20 at that time especially were fairly new to FDA. We
21 worked very interactively and had what we call
22 determination and agreement meetings where we
23 actually agree on the protocol up front in terms of
24 what shows a clinical benefit, such that the
25 company can go away and know that if they prove

1 something they have a very good chance of getting
2 approval.

3 So without any more ado, I would like to
4 introduce Evelyn Lopez, who was the Director of
5 Regulatory Affairs for Novatrix when the company
6 was developing the product. Evelyn?

7 DR. BLANCO: If you would forgive me,
8 Colin, I wanted to thank both the companies and the
9 people involved for coming and presenting before
10 the panel, the panel where some of the new
11 mechanisms for which FDA is working with industry
12 to try to develop products and, as you said,
13 unfortunately, this one may not be developed any
14 further but I do want to thank the folks involved
15 for taking their time and coming here before the
16 panel to give us this kind of background. Thank
17 you.

18 MR. POLLARD: Yes, and I totally agree.
19 This is totally at the company's volition. We
20 thought it might be useful to hear and invited them
21 and it was very kind of them to do so.

22 Presentation by CareStat

23 DR. LOPEZ: Good afternoon, and thank you
24 very much for allowing us to present the
25 information. I am Evelyn Lopez. I was vice

1 president of regulatory affairs and quality
2 assurance for Novatrix Medical Co., a start-up
3 company in Carlsbad, California.

4 The information you are going to get today
5 will be presented by Dr. Howard Golub, who is
6 president of CareStat. It was our contract
7 organization who managed the study and helped us in
8 the analysis of the data. We went through the
9 entire process with the FDA, the determination
10 agreement meetings, focusing on the protocol; went
11 forward and did the study. From our end, the
12 company's end, we thought that the relationship
13 with the FDA and the interaction went very, very
14 well. Thank you.

15 DR. BLANCO: Thank you.

16 DR. GOLUB: Hi. My name is Howard Golub.
17 I am the president of CareStat. We were the
18 clinical consultants for the sponsor, which is
19 Novatrix, as Evelyn just mentioned.

20 [Slide]

21 I never thought I would be saying this but
22 at the end of my talk, I hope that all of you vote
23 against the approval of the PMA for this product.

24 [Laughter]

25 Particularly this panel, I never thought I

1 would say that!

2 [Slide]

3 Today I am going to take you through the
4 story of a medical device company. As Colin
5 mentioned, there was a very early connection with
6 FDA on not only the protocol but some of the
7 feasibility studies we did in development of
8 biologic models for determining the plausibility of
9 the device. It is a story where the device
10 basically worked on the bench and in the
11 feasibility trials. It was safe on all patients
12 for whom we used it, including the pivotal trial.
13 Unfortunately, when used in the complicated
14 clinical setting of patient management, it didn't
15 turn out to be efficacious. I am going to take you
16 through that story and I think it is constructive,
17 particularly based on the discussion I heard
18 earlier today.

19 The first thing I am going to present is
20 the definition of the clinical problem that the
21 company was trying to solve. Was the Novatrix
22 labor assister system a plausible potential
23 solution to this problem? And, we spent some time
24 actually trying to answer that question before the
25 pivotal trial was accomplished, in consultation

1 with FDA.

2 I should mention that I actually have no
3 financial interest in the company. I was asked by
4 Colin and George to come today, and I even paid my
5 own way, which is a pretty good guest!

6 [Laughter]

7 Did the device function as designed? Were
8 there any safety concerns that outweighed the
9 potential benefit that should have or could have
10 prevented us from doing the pivotal trial in the
11 first place? And, was the study protocol
12 sufficient to adequately evaluate the safety and
13 effectiveness of the device?

14 [Slide]

15 The clinical problem -- and you have all
16 talked about it today -- is that in particular
17 nulliparous women who elect epidural analgesia
18 often have prolonged second stage labor and a
19 higher operative delivery rate.

20 [Slide]

21 The mechanisms proposed for the increased
22 operative intervention rate due to epidural
23 analgesia include decreased uterine activity,
24 prolongation of the first or second stage,
25 relaxation of the pelvic musculature or decreased

1 maternal urge or ability to push, particularly
2 during second stage.

3 [Slide]

4 The clinical problem then is current
5 management strategies to shorten the second stage
6 of labor include instruments that aid in pulling
7 the baby out -- vacuum extraction, forceps.

8 [Slide]

9 C-section may be required if those vaginal
10 operative delivery methods fail, and these current
11 strategies of pulling the baby out may be
12 associated with significant complications.

13 [Slide]

14 So, in conclusion, there is evidence that
15 epidural analgesia is associated with an increased
16 rate of operative deliveries. Since epidural
17 analgesia is likely to continue to be widely used,
18 techniques capable of reducing the need for
19 operative delivery would be of value.

20 [Slide]

21 The labor assister system is comprised of
22 a processor, a tocodynamometer and a belt that goes
23 around the abdomen that inflates. The idea was
24 that the processor with the sensor of the
25 tocodynamometer detects contraction and inflates

1 the belt around the abdomen synchronously with the
2 contractions, particularly aimed at second stage
3 labor.

4 [Slide]

5 Was it plausible that the labor assister
6 system had the potential to negate the effects of
7 epidural analgesia and result in a reduction in the
8 operative delivery rate? We asked this question,
9 obviously, early on.

10 [Slide]

11 Did the device function as designed?

12 [Slide]

13 There was a development of contraction
14 detection algorithm because, obviously, a lot of
15 the efficacy was based on this ability to detect
16 contractions accurately. And, there was a
17 development of a database. The company had 1000
18 contraction database for which they used as a
19 development data set, and the initial testing on
20 the bench is with an additional 1000 contractions
21 from 74 patients, and the result was that 97
22 percent of contractions correctly resulted in
23 inflation, and 13 inflations were due to artifact
24 out of 1000.

25 [Slide]

1 Besides the contraction detection, we, FDA
2 and the company realized that it was important to
3 fundamentally ask the question in a prospective
4 sense, to evaluate this contraction detection not
5 only off recorded contractions but also a number of
6 feasibility patients, to prospectively evaluate
7 whether the belt inflated appropriately and then
8 assess if, in fact, there was an incremental
9 intrauterine pressure because if there was no
10 intrauterine pressure, which is the proposed
11 mechanism of the benefit, then we might as well
12 stop there because why do a large pivotal trial if
13 we don't increase the intrauterine pressure?

14 [Slide]

15 The feasibility study included women
16 randomly assigned to one of two protocols. One was
17 a ten-minute ON period where the device was
18 actually on and detecting for ten minutes; a
19 washout period of five minutes to allow for this
20 transition period between ON and OFF; an OFF period
21 for ten minutes, and so on. We actually used
22 ON/OFF and OFF/ON in a balanced way. The ON/OFF
23 modes were, as I mentioned, ten minutes with a
24 washout of five, and there were 14 women who had at
25 least one ON and one OFF mode.

1 [Slide]

2 There were 120 contractions identified
3 based on intrauterine pressure catheter tracings
4 during the ON modes; 26 contractions actually
5 occurred during periods where the device was paused
6 and, by protocol, the device was paused if the
7 patient was being manipulated, if the belt was
8 being repositioned because we didn't want the belt
9 to inflate when the patient was being manipulated.
10 So, those were by protocol pauses. A refractory
11 period was built in to ensure that the inflations
12 didn't happen too often. There were 94
13 contractions that should have been detected and,
14 again, 91/94 contractions in a prospective sense
15 were correctly detected. If any of you have ever
16 dealt with this signal, the company did a great job
17 on that part of it. These are second stage labor
18 contractions which are somewhat easier than preterm
19 labor contractions but, still, the company did a
20 fantastic job with this.

21 [Slide]

22 A hundred inflations occurred during the
23 200-odd minutes the devices was in the ON mode.
24 Six inflations were not evaluable because the IUP
25 signal was inadequate, leaving 94 inflations that

1 were evaluable, and 91, or 97 percent, of
2 inflations were correctly associated. So, it was
3 detecting contractions and the belt was inflating
4 appropriately.

5 [Slide]

6 In addition to that, as I mentioned, we
7 needed to assess whether we were, in fact,
8 impacting on the intrauterine pressure because that
9 was the hypothesis. And, 170 contractions, 87 ON
10 and 83 OFF, met the criteria. The primary analysis
11 used a mixed linear model so that we could separate
12 the issues because, as we know, contractions
13 through second stage tend to change character at
14 early second stage to late second stage. We needed
15 to both account for whether they were ON/OFF
16 protocol or OFF/ON. The time period that the
17 contractions were measured mattered because the
18 first ten minutes and, for example, the fourth
19 happen in 30-40. Contraction number during each
20 ten minute matters too. So, this model was
21 attempting to take into account where the
22 contractions actually happened in the course of
23 second stage labor.

24 [Slide]

25 The result was that the fitted mean for

1 the ON mode was 77.5 and the fitted mean for the
2 OFF mode was about 63, leaving about a 14 mmHg
3 difference between the situation where the device
4 was not inflating during contractions and where it
5 was.

6 [Slide]

7 So, the conclusion of the feasibility
8 study was the ON mode was associated with a
9 statistical increase, and this increase actually --
10 if you read the literature, the literature is
11 somewhat spotty but the literature is connected
12 with that 14 mmHg, 15 mmHg being approximately what
13 is reported in the literature as the decrease that
14 epidurals cause in nulliparous, otherwise healthy
15 term women.

16 So, the idea was to replace the
17 intrauterine pressure that the epidural, on the
18 average, was decreasing, and the idea then was that
19 that would reduce the negative effect of the
20 epidural on the operative delivery rate.

21 [Slide]

22 Was there a reason to believe that safety
23 concerns should have or could have outweighed the
24 potential benefits before the pivotal trial was
25 started?

1 [Slide]

2 Potential safety issues -- we were
3 obviously concerned that increased intrauterine
4 pressure would result in the potential for uterine
5 rupture or placental function problems, or
6 increased intra-abdominal pressure would result in
7 maternal abdominal organ injury.

8 [Slide]

9 The average intrauterine pressure during
10 uterine contractions is somewhere between 35-50
11 mmHg or 60 mmHg. The inflation of the belt around
12 the abdomen inside the belt was 200 mmHg but, as we
13 just showed, it resulted in about a 10-20 mmHg
14 increase in intrauterine pressure, and this
15 increase is much less in term of peak pressures you
16 see with either fundal pressure or second stage
17 pushing.

18 [Slide]

19 The risk of uterine rupture in this
20 population is rather low. It usually occurs in
21 women with uterine scarring and is extremely rare
22 in nulliparous women. In all literature searches
23 it is about 0/22,000 deliveries.

24 [Slide]

25 Women with risk factors were excluded from

1 the study, particularly uterine anomaly,
2 polyhydramnios and so on.

3 [Slide]

4 Women with evidence of utero-placental
5 insufficiency; all subjects were to undergo
6 continuous electronic fetal monitoring; use of the
7 device was to be discontinued in cases of abnormal
8 or non-reassuring heart rate; any evidence of
9 maternal or fetal complications.

10 [Slide]

11 The rupture of normal liver, spleen or
12 stomach during labor are also extremely rare,
13 usually related to PIH, which was an exclusion
14 criterion.

15 [Slide]

16 And, protocol features aimed at reducing
17 the risk was, as I mentioned, the exclusion of
18 women with any risk factor we could think of.
19 Staff was present at all times during operation of
20 the device, and there was continuous monitoring of
21 the patient. There was a data safety and
22 monitoring board that met monthly to ask the
23 question was there a safety issue long term.

24 [Slide]

25 The summary of the pre-pivotal or

1 feasibility trial is that the additional pressure
2 from the device is relatively small in comparison
3 to the increase in pressure from something like
4 just maternal pushing. Only low risk women were
5 eligible for the study, and no adverse effects have
6 been observed among 405 women using the device
7 before the pivotal trial.

8 [Slide]

9 The rationale for beginning the clinical
10 trial included that the LAS addressed an important
11 clinical problem, as we identified, which is a high
12 rate of operative interventions, particularly in
13 women who are on epidural analgesia. It was
14 plausible that the impact of epidural analgesia may
15 be overcome by the cumulative effect, which is this
16 15-20 percent in IUP for contractions in second
17 stage labor.

18 So, we were at a point where the bench
19 testing, feasibility testing and our biologic
20 plausibility arguments in terms of modeling the
21 system led us to believe that there was a rationale
22 for continuing on to the pivotal clinical trial.

23 [Slide]

24 Was the study protocol sufficient to
25 adequately evaluate the device, the pivotal trial?

1 [Slide]

2 Prospective, multi-center, randomized
3 clinical trial -- it was an active versus sham
4 device. The sham was rather interesting in that
5 obviously we started the company did not have a
6 sham device, and this sham device had to be
7 something that both put a shroud around the belt so
8 when the belt inflated you couldn't see it. It had
9 all the bells and whistles of the device. It had
10 to make sounds as though it was inflating. And,
11 the company did a very good job in creating this
12 cart with switches so that one could randomize to a
13 belt inflation or sham device.

14 Randomization was at the onset of the
15 second stage of labor and that is a key. We
16 decided to randomize at the onset of second stage
17 labor because all kinds of stuff happens before
18 second stage labor and we wanted to ensure that at
19 entry, which is at the beginning of second stage
20 labor, the groups were equal in terms of risk.

21 [Slide]

22 So, the primary hypothesis was among
23 nulliparous women with uncomplicated pregnancies
24 who elect epidural analgesia, when compared with
25 women in the sham control group, women who use the

1 labor assister system during the second stage of
2 labor will have a reduction in the proportion of
3 deliveries that require an operative delivery.

4 [Slide]

5 An operative delivery is defined as -- and
6 this is a key question I think relevant to this
7 morning's discussion -- it includes all vaginal
8 delivery utilizing forceps, vacuum extractor or C-section.
9 One did not want to push this into C-sections. A way to
10 diminish vaginal deliveries is
11 to have more C-sections and we did not want to have
12 a situation where we basically pushed one bad thing
13 into something worse.

14 [Slide]

15 Since the choice of operative delivery may
16 vary among technicians -- clinicians -- same thing
17 --

18 [Laughter]

19 -- the occurrence of any operative
20 delivery is more relevant rather than the frequency
21 of any particular technique, and the strategy
22 prevents being misled, as I told you, by a shift
23 from one strategy to another. One really needs to
24 worry about this because we really need to identify
25 what it is we are trying to do, and you don't want

1 to have a diminishment of one bad thing and
2 increase of another bad thing.

3 [Slide]

4 This is something that we also did before
5 the pivotal trial was started. We did a pre-study
6 chart review of operative deliveries and, by the
7 way, most sites did not know their operative
8 delivery rate for nulliparous women on epidural.
9 In fact, when we got good at this, after the second
10 or third time we did this we asked the site, "guess
11 your operative delivery rate for nulliparous women
12 on epidurals."

13 Among the things you see here is something
14 a little misleading in that we, in fact, rejected,
15 along with consultation with the FDA staff -- we
16 rejected sites that had operative delivery rates
17 outside the 20-40 percent range. A publishable
18 fact is the gigantically wide range in U.S. sites.
19 We have two English sites here but they are no
20 better. In fact, in terms of operative deliveries
21 they average higher. A publishable and very
22 interesting issue is the gigantic variation across
23 sites. What you only see here are those sites
24 which we included in the study. We rejected six
25 sites that fell outside the operative delivery

1 percent. We rejected the two lows and we rejected
2 the two highs, thinking they were outliers.

3 Our job was to ask the question, in at
4 least some middle range by site, do we impact on
5 their operative delivery rate.

6 Another reason to do this, and I think
7 Gary mentioned the Hawthorne effect, is that you
8 will see, in fact, some of these sites,
9 particularly the high ones -- this was just a two-month
10 chart review before we started the pivotal
11 trial and when we did the pivotal trial their
12 operative delivery was low in both the control,
13 sham, and the active delivery. Both went down, and
14 both went down because they were paying more
15 attention to the patients that were in the study.

16 We also understood that that was a
17 potential, particularly we also understood -- when
18 I say "we" it is we and the sponsor. We were the
19 clinical consultants. We and the sponsor also
20 understood that when you are trying to impact on an
21 outcome that has such a large by-site variability
22 in the first place, then it is messy. So, there
23 were attempts to identify sites that were in the
24 20-40 percent range who had the potential that, if
25 we succeeded, we would have a clinical and

1 important outcome.

2 By the way, the reason the C-sections are
3 so low here is because these are healthy term
4 nulliparous women. Obviously, this is not the C-section
5 rate for their entire hospital.

6 [Slide]

7 The sample here is 451 or 902 patients in
8 this trial. We hypothesized a minimum clinical
9 difference of 30 percent control rate. We
10 hypothesized a 25 percent reduction would be
11 minimally required for anyone to recommend use of
12 the device.

13 [Slide]

14 Other hypotheses we looked at nulliparous
15 women -- again, we wanted to make sure that there
16 was either a reduction in duration of second stage
17 or no change because it is very easy to reduce the
18 duration of second stage by just doing a C-section
19 on everybody after ten minutes. So, we needed to
20 at least show there was no change in duration of
21 second stage at a minimum but, obviously, the
22 better hypothesis was that in fact we showed a
23 decrease in duration of second stage in the face of
24 reducing all operative delivery rates.

25 [Slide]

1 Then, there is this whole plethora of
2 additional analyses for which we have this gigantic
3 data set that allowed us to ask all kinds of
4 interesting and secondary questions, which I will
5 speed through.

6 [Slide]

7 Women in both groups received identical
8 care except for use of either the active or the
9 sham labor assister system. Obviously, because of
10 this big variation in management of these patients,
11 it was really important to, as best as possible,
12 blind the caretaker who is making the operative
13 delivery decision. In all cases, the belt was
14 initially placed during first stage and tested if
15 we could get a decent tocodynamometer signal. So,
16 the only criteria, at least device-wise, for which
17 the patients were not eligible -- and this was all
18 before randomized -- was if we could get an
19 adequate tocodynamometer signal and we had an
20 adequate tocodynamometer signal on almost
21 everybody.

22 [Slide]

23 The onset of second stage was defined as
24 the time at which full dilation and effacement of
25 the cervix was diagnosed on vaginal examination.

1 By the way, we know that that is also a little
2 messy but because this was done before
3 randomization the idea is that you would have the
4 same messiness in both groups in terms of deciding
5 exactly when second stage started. At the time,
6 the study personnel then immediately randomized the
7 woman. They were placed on the labor assister
8 study switches. As I said, there were three
9 switches and we actually had only two switches that
10 meant anything and the third switch was not
11 connected to anything, although nobody knew that,
12 including the study coordinator at the study. The
13 idea there was if the first two switches were
14 active the third one could be anywhere and not
15 matter. So, that helped in blinding the caretaker.
16 Then they turned the labor assister system on.

17 [Slide]

18 Both the active and sham devices utilized
19 the same tocodynamometer signal. When a
20 contraction was detected both devices triggered the
21 flow of air, as I mentioned before. In the active
22 it inflated to 200 mmHg and for the sham device we
23 had to inflate something; we had to move something
24 and we inflated to 5 mmHg or 10 mmHg. Now, maybe
25 it is that 5 mmHg or 10 mmHg that was the reason we

1 didn't see a difference but we don't think so.
2 There were no discernible differences in the
3 activities of the devices between the two groups.

4 [Slide]

5 randomization was performed, as I
6 mentioned, at second stage labor. It was performed
7 by the study personnel not participating or having
8 any impact on the care of the women, and
9 consecutively numbered opaque envelopes in the
10 standard way of randomizing patients were used.

11 [Slide]

12 Clinical staff was not informed of
13 subjects' study group, and women were not
14 randomized if criteria for exclusion were met prior
15 to second stage labor, as I have mentioned a number
16 of times.

17 [Slide]

18 The eligibility criteria included sort of
19 standard -- trying to get healthy term women on
20 epidural. As I mentioned before and I will go
21 through these quickly, we really did try to exclude
22 all women who had any hint or possibility for which
23 this device could lead us into trouble.

24 [Slide]

25 The screening -- this is an interesting

1 issue in terms of whether you consent a woman in
2 for a stage, and we certainly went around on that,
3 but every attempt was made to distribute literature
4 in prenatal sites so most women knew about the
5 study before they entered labor. The screening
6 form was then completed on women prior.

7 [Slide]

8 The structure -- Novatrix, the president
9 was John Bason and Evelyn you just met; we were the
10 CRO; Mike Corwin and Ted Colton were my partners
11 and we had a really good DSMB, headed by Fred
12 Frigoletto.

13 [Slide]

14 We collected a large amount of
15 information, and here it is: screening, enrollment,
16 but particularly stage two labor and delivery
17 information. The key feature here is that there
18 was some concern in terms of when this pausing was
19 done to ask the question was it used as per
20 protocol. The company developed a little key that
21 actually stored when the device was paused. So, we
22 quantitatively knew not only how much it was paused
23 for everyone but we knew when it was paused, and
24 next to each pause there was a reason for that
25 pause. We actually checked to see if that was per

1 protocol.

2 [Slide]

3 So, there were no safety concerns. It was
4 DSMB monitored throughout.

5 [Slide]

6 And, here are the results. No
7 statistically significant difference between the
8 groups in operative delivery rate at all sites for
9 all subjects. The trends were positive in three
10 sites and negative in three sites, and trends were
11 positive in some subpopulations and negative in
12 others. The key feature that you see a lot of
13 people do in a talk like this, they tell you all
14 the subpopulations where it was positive but they
15 don't mention if there is no effect overall. It
16 has to be negative in some subpopulations. So, one
17 needs to worry about that.

18 [Slide]

19 In detail, of the 902 women, 33.5 percent
20 in the active group had an operative delivery
21 versus 30.6 percent in sham or a change in the
22 wrong direction of 9.5 percent. What you can see
23 for three sites is that there was a decrease in
24 operative delivery rate and in three sites there
25 was an increase. These two sites were the English

1 sites, as I mentioned before.

2 One interesting aspect, if you remember
3 back, the chart review was about 42 percent
4 operative delivery rate in this population and both
5 these, particularly the sham group, is much lower.
6 One of the mechanisms, by the way, for reducing the
7 operative delivery rate is that we package Hal
8 from Cedars, who had a 20 percent operative
9 delivery rate with probably a similar risk
10 population, and sort of send him around to the
11 other sites.

12 [Slide]

13 But what was concerning is why this big
14 variation in result across sites. That could be
15 due potentially to some random variation. We don't
16 think so. We actually checked and if you look at
17 the by-site randomization, the groups in the active
18 and the sham group were similar in terms of risk.
19 Despite randomization, could you have ended up with
20 a difference in risk? Again, we checked that. The
21 active device may be associated with differences in
22 management between groups.

23 And, here is the interesting issue and I
24 will get to this in the succeeding slides, but we
25 think there was a very complicated interaction

1 between the management of these patients and the
2 device. The differences in rate of fetal heart
3 rate changes resulting in removal of the device --
4 there was a slight increase in percent of times the
5 device was removed from the patient due to abnormal
6 fetal heart rate tracings, about 8 percent versus 4
7 percent. The interesting thing for that is that
8 the reasons for operative delivery were no
9 different. So, they asked the active device to be
10 removed more often than the sham device, but
11 actually there was no difference in terms of reason
12 for operative delivery in terms of abnormal fetal
13 heart tracings. The difference in rate at which
14 patients or caretakers asked the device to be
15 removed -- in fact, there was a difference and I
16 will get to that.

17 [Slide]

18 The possible factors with the potential to
19 impact operative deliveries is that there is
20 potentially investigator bias where the blind was
21 broken. Again, we don't believe that actually
22 happened. Patient factors, change in pushing,
23 discomfort decreased with device use -- in terms of
24 change in pushing, we don't really have a good way
25 of measuring that, although that is possible. We

1 do have a pretty good measurement of the fact that
2 the device was used less on the active group. Even
3 though women had never seen this device before,
4 obviously, depending on the level of the epidural,
5 they used it on the average 10-15 minutes less and
6 asked that it be removed more often.

7 [Slide]

8 No differences in delay time between the
9 onset of second stage and when the device became
10 active. The active group had somewhat less usage
11 at each of the sites, as I mentioned. And,
12 assessment of subpopulation with high device use
13 only -- if you limit the subpopulation to only
14 those who used the device a lot there is still no
15 overall, across all sites effect.

16 [Slide]

17 The difference in second stage labor
18 medications, here is where we think the money is.
19 Again, there is a trend, and this is the
20 interesting part, towards increased epidural use in
21 women with the active device. So, what happened is
22 we put the active device on and if this thing was
23 inflating a lot they probably felt it more, and
24 there was a trend towards increasing epidural use,
25 which probably increased their risk of labor.

1 In terms of the bromage, a measure or
2 motor block, and in fact in those sites for which
3 there was a negative result, patients with the
4 active device had more epidural used, which is a
5 very surprising but interesting result. Also, at
6 60 and 90 minutes, because we did these tests at
7 30, 60 and 90, they felt less pain because they had
8 increased epidural. So, they were more blocked.
9 So, the idea was to use the device to help with
10 second stage pushing in women with epidural and
11 what we didn't expect is that because the patients
12 were more uncomfortable, they asked or were treated
13 with more epidural, which resulted in diminishing
14 whatever effect the device had.

15 Oxytocin use was higher in the sham group
16 so that we had higher epidural in the active group,
17 which ended up in pushing the results in the wrong
18 direction, and higher oxytocin use in the sham
19 group -- trends toward that -- which could have
20 resulted in sort of this variation across sites and
21 this potential negative effect.

22 [Slide]

23 If you look at the data, we didn't really
24 design the trial to ask this question
25 prospectively. So, all of this is post hoc

1 surmising but our guess is that there was a
2 difference between active and sham groups in sites
3 that resulted in the negative direction of
4 operative delivery rates. These differences in
5 management were not protocol violations because by
6 protocol the doctors were blinded. They were
7 managing the patients as they thought they
8 typically do.

9 It is not possible to implement a study
10 protocol to control these management decisions and
11 the company deserves a gigantic amount of credit
12 for realizing that in this particular case it would
13 not be to anyone's best interest to try to do
14 another study that would really hinder the
15 management of the patients because in order to show
16 the benefit one would really have to control that
17 management.

18 [Slide]

19 Subpopulations in the active group
20 actually had a lower operative delivery rate. By
21 the way, most of these make some amount of sense if
22 you think about them. Oxytocin for augmentation
23 versus no oxytocin because the no oxytocin patients
24 were going along fine and you are not going to
25 probably intervene, or induction which, someone

1 said today, is a different sort of patient. Slower
2 dilation rate during first stage labor; fetal head
3 position was OT because if they are OP or OA they
4 are either one way or the other. OT, potentially
5 the device could move them in the right direction.
6 And, high fetal station, which is what the device
7 is supposed to do, push you down.

8 Now, all of this has some rationale but
9 all post hoc, and it is unwise and probably
10 dangerous to pick post hoc subgroups to demonstrate
11 your case, and the company, wisely, didn't intend
12 to do that.

13 [Slide]

14 The subpopulations where the active group
15 had a lower operative delivery rate, as I
16 mentioned, had some biologic link to why -- it
17 makes sense that second stage pushing helps; it
18 probably does. This belt is just trying to help
19 you push. So, there are probably some subgroups
20 with extremely well-controlled management where you
21 would eventually show efficacy but, one, the groups
22 are not large enough and, two, one could not
23 control management that way or should not control
24 management that way. The effect size is only
25 clinically meaningful among patients with high

1 device use in those subgroups anyway.

2 [Slide]

3 So, although there is a suggestion that
4 the device may be effective in certain
5 subpopulations, if tolerated as I said, it was a
6 decision of the company to, in fact, withdraw their
7 PMA and not make the post hoc arguments that they
8 might have or could have made.

9 [Slide]

10 Overall, getting back to the original
11 outline of my story, we believe there is a clinical
12 problem. Number one, regardless of any other
13 issue, the fact that we have such a gigantic
14 operative delivery rate variance across American
15 sites is just amazing. Even if you account for
16 risk of population, that variation is there and it
17 is so much management oriented, so subject to
18 management.

19 The device functioned as designed through
20 bench testing and feasibility testing. As
21 intended, it replaced the intrauterine pressure
22 that the literature shows epidurals sort of remove
23 on the average. So, there was this plausibility
24 for why it probably should work.

25 The study protocol was sufficient. In

1 fact, it showed that if you appropriately blind and
2 put it in a setting of where the device will
3 eventually be used, it basically showed that the
4 management actually countered whatever the effect
5 of the device, resulting in an overall no effect.

6 The results of the study indicated that
7 although safe, the device was not effective in the
8 prospectively defined patient population.

9 This is a final statement, just as it is
10 unwise to post hoc pick subgroups which you don't
11 prospectively identify to make your case, I think
12 one needs to be careful about limiting labeling
13 based on post hoc analysis of subgroups you haven't
14 prospectively identified as well. I think it works
15 both ways.

16 I think it is incumbent, particularly in
17 this case as Colin mentioned -- we did a whole lot
18 of work to try and design this up front and hung
19 everything on the primary outcome, the primary
20 result. All the secondary stuff is data to support
21 the primary message. Even though we found some
22 biologically plausible subgroups where one could
23 make an argument, we knew that it is not
24 appropriate without doing another trial to make
25 that argument. The same goes for if, in fact, we

1 found the main effect, to limit labeling to some
2 subgroup that wasn't prospectively identified is
3 probably equally unwise. So, that is the story.

4 DR. BLANCO: Thank you very much. We
5 appreciate your presentation. Any questions from
6 any of the panel members?

7 DR. SHARTS-HOPKO: I do have one actually.
8 You have given us all the technical information. I
9 am just wondering if you debriefed any patients,
10 nurses or physicians about their satisfaction with
11 the device.

12 DR. GOLUB: We, in fact, did and I happen
13 to have it right here because among the questions
14 we asked was -- and I will list them -- we knew
15 that if we shoed a main effect if the patients were
16 absolutely miserable and suffering, then our case
17 would be not as strong. Overall, were you
18 satisfied with the experience of the labor assister
19 system? We made no attempt to tell the patients
20 what the pressure should be, but about 76 percent
21 said yes, they were overall satisfied in the active
22 group and 71 percent said yes in the sham group,
23 and there was about 15 percent in both groups that
24 were neutral.

25 Did you find the belt generally

1 comfortable? And, 82 percent in the sham group and
2 63 percent in the active -- as I mentioned, the
3 active patients found it less comfortable. But no
4 was about 25-29 percent.

5 Here is another interesting complicated
6 interaction in which the patients actually asked
7 for the belt to be removed more often. So, it
8 needs to be tested in a clinical situation where
9 the device will be used.

10 Did the belt give you confidence? And, 60
11 percent in the active group said yes and 40 percent
12 in the sham group said yes.

13 Do you feel the belt helped you during
14 your labor? And, 67 percent in the active group
15 said yes and 41 percent said yes. Now, I think the
16 reason for that is they felt something in the
17 active group; there was some intervention and so
18 they connected that. So, basically we did attempt
19 to ascertain that. It is very different data to
20 make heads or tails of.

21 DR. O'SULLIVAN: George, I have a
22 question.

23 DR. BLANCO: Sure.

24 DR. O'SULLIVAN: How was this belt placed
25 on the abdomen?

1 DR. GOLUB: It was placed during first
2 stage. You mean how physically? It is like a
3 rubber tube and it has Velcro in the back, and it
4 is placed right above the fundus and a toco is put
5 on in parallel. That is it. It is just a belt
6 with Velcro in the back and the belt inflates.

7 DR. O'SULLIVAN: So, it is placed at the
8 fundus.

9 DR. GOLUB: Right.

10 DR. BLANCO: Thank you all for coming and
11 making the presentations. I also would like to
12 commend you for a very nicely designed, well worked
13 out study. It was very nice to hear that. I think
14 Mr. Pollard wants to say something.

15 MR. POLLARD: Yes, I just wanted to
16 highlight, as I mentioned at the beginning, that as
17 a result of the 1997 FDA Modernization Act,
18 manufacturers now have a number of mechanisms for
19 early collaboration that are, to a certain degree,
20 binding on FDA and this company took advantage of
21 that, and other companies will as well. So, you
22 will be seeing PMAs in the future where we will be
23 sharing with you that kind of product where we have
24 entered into a binding agreement. We may from time
25 to time tap one or two of you individually to help

1 us in that. So, I just wanted to let you know that
2 as well.

3 DR. BLANCO: Thank you, Colin. If there
4 is no other business, I want to remind the panel
5 members that they can leave their confidential
6 information that was sent to them on the table and
7 it will be taken care of and disposed of. I thank
8 all of you for your attention and participation,
9 and look forward tomorrow, those of you who will be
10 here, to spend another day with you all tomorrow.

11 Thank you.

12 The meeting is adjourned.

13 [Whereupon, at 4:55 p.m., the proceedings
14 were recessed, to resume on Tuesday, May 22, 2001
15 at 10:15 a.m.]