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FOOD AND DRUG ADMINISTRATION
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SIXTY-FOURTH MEETING

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5 Montgomery Village Avenue
Gaithersburg, Maryland

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with Operative Hysteroscopy

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1 P R O C E E D I N G S

2 DR. BLANCO: We will go ahead and begin
3 this morning's open session.

4 We will begin with a presentation and some
5 introductory remarks from Mr. Colin Pollard, Chief,
6 Obstetrics and Gynecology Devices Branch.

7 Mr. Pollard.

8 Room Air and Gas Emboli Associated
9 with Operative Hysteroscopy
10 Introductory Remarks
11 Colin Pollard

12 MR. POLLARD: Thank you, Dr. Blanco.
13 Ladies and gentlemen of the panel, distinguished
14 audience: I want to thank all of you for making
15 time on your busy schedules and coming, some of you
16 from quite far, to Gaithersburg, Maryland, for this
17 meeting.

18 [Slide.]

19 Today, we are here to discuss a rare but
20 potentially life-threatening adverse event, namely,
21 room air and gas emboli that occur during operative
22 hysteroscopy. In particular, we are asking the
23 panel as we explore this issue and consider ways to
24 improve the awareness of our colleagues, as well as
25 to foster research in this area that might shed

1 additional light on the subject.

2 [Slide.]

3 Many of you are aware of Ethicon's
4 decision last September to voluntarily withdraw its
5 VersaPoint system from the market and then, after
6 having worked with FDA, to review the data, to
7 return the system to market in late January.

8 This market return was accompanied by
9 action on the part of the firm to beef up the
10 labeling on a variety of clinical use aspects. As
11 you will hear in just a minute, we believe that
12 this was a prudent action on the part of the firm
13 precipitated by a series of reports received in
14 1999 and 2000.

15 We hope that the presentations you hear,
16 as well as input from the open public hearing, will
17 help with the discussion questions we have prepared
18 for you. Our hope is that this discussion will
19 help FDA as it considers further steps to
20 understand this risk and to take steps to mitigate
21 it.

22 I would also like to acknowledge the help
23 of Ethicon and many other manufacturers in
24 providing FDA with input to prepare for this
25 meeting. I also recognize that although not all of

1 you are planning to address the panel during the
2 open public hearing, many of you have a vested
3 interest in the outcome of these discussions.

4 I know that with all the expertise in this
5 room, Dr. Blanco will, if at all possible, provide
6 an opportunity later this morning for comments.

7 First of all, I think I have gone over the
8 panel charge. The panel charge really is to get as
9 much discussion of this topic to help focus FDA on
10 what the panel believes are the important aspects
11 of this adverse event that we found, as well as we
12 are looking at this instrumentation.

13 [Slide.]

14 A few words of clarification that I hope
15 will help with the discussion to come. We have a
16 very diverse audience and I know how easy it is to
17 slip into vernacular that can sometimes lead to
18 misunderstanding on the part of some. I would ask
19 all of you to try to be as clear and unambiguous
20 during your discussions.

21 First, just in case there is any
22 misperception, we are talking today about adverse
23 events occurring during operative hysteroscopy, not
24 diagnostic hysteroscopy. In diagnostic
25 hysteroscopy, CO2 gas is the preferred distention

1 medium, and the risks of CO2 emboli are fairly well
2 appreciated.

3 During operative hysteroscopy, a liquid,
4 such as normal saline or glycine or one of several
5 others, is used for distention, for control of
6 bleeding, as well for clearing the surgical field
7 for visualization and removal of surgical bits of
8 tissue.

9 We believe that the risk of room air and
10 gas emboli under these surgical conditions is not
11 nearly as well understood or appreciated.

12 Secondly, we would ask you to be clear
13 about your terminology. There are certain aspects
14 of the technology and the events that could get
15 people confused. I would just like to mention a
16 couple.

17 First of all, in terms of the emboli, we
18 are using the terms room air and we are using the
19 term gas, and we are differentiating between the
20 two, and you will hear in the discussions to come
21 why we differentiate between the two. We would
22 hope that during the course of the discussion that
23 we could maintain that, so that we understand one
24 versus the other.

25 Also, you will hear terms like

1 vaporization versus desiccation. You will hear
2 terms like cut versus coag versus blend. The first
3 two really refer to tissue effects. The latter,
4 cut/coag/blend, these are settings on the ESU
5 generator. Even though they may be related to each
6 other, I would hope that you could try to maintain
7 some clearness about that.

8 Finally, we are talking about unipolar
9 systems, as well as bipolar systems, and clearly,
10 that is going to be one of the aspects of the
11 discussion, so that to the degree that you can,
12 maintain that clearly, as well.

13 Finally, we are talking about multiple
14 device systems, and the clinical setup for
15 operative hysteroscopy by OR personnel involves
16 several different kinds of equipment. These are
17 typically made by different manufacturers and
18 labeling instructions for setup and use are
19 typically not nicely integrated. This makes for
20 the possibility of human error and human factors
21 issues. It also complicates FDA's job in
22 determining what is the right amount of labeling
23 for each device.

24 Lastly, you will be hearing about FDA
25 systems for reporting problems. The mandatory

1 device reporting, the so-called MDR system, and our
2 voluntary MedWatch system. Neither of these are
3 perfect systems, but we will be asking you for
4 ideas that may help or facilitate better reporting,
5 so we can continue to learn.

6 [Slide.]

7 So, what we are asking you, first of all,
8 is to consider the problem that we are going to be
9 presenting before you today and all its
10 permutations, to consider the data that has been
11 collected from a number of different sources, to
12 consider the solutions, the ones that we have
13 already embarked on with the VersaPoint system, as
14 well as possible ones in the future, and in
15 particular, we are looking to the panel for advice
16 in how we are handling this situation, and we are
17 also recognizing that there are other interested
18 parties who have a part to play in this - the
19 American College, the American Society of
20 Reproductive Medicine, the American Association of
21 Gynecologic Laparoscopists, and others, and FDA
22 sometimes can play a facilitating role in helping
23 bring attention to this issue, so we would ask you
24 for advice on that, as well.

25 [Slide.]

1 As you know, we have got some questions, I
2 am not going to get into them now, so from this
3 point we are going to go to the first presentation.

4 Any questions?

5 DR. BLANCO: Any questions for Mr.
6 Pollard? If not, we will go ahead and we will have
7 representatives of industry present first. I
8 believe that Dr. Richard Isenberg, Director,
9 Medical Affairs, for Ethicon will be the first
10 presenter.

11 May I ask you a question while we are
12 waiting for this to be set up? Is someone going to
13 address or will you address in some introductory
14 remarks the different processes that went through
15 when this issue came up?

16 MR. POLLARD: Yes. Following the Ethicon
17 presentation, Dr. Corrado, Julia Corrado in our
18 branch, will go over what we did, and you will get
19 an opportunity to question her about that, as well.

20 DR. BLANCO: Thank you.

21 DR. ISENBERG: Good morning. I am Richard
22 Isenberg. I am the Director of Medical Affairs at
23 Ethicon, Inc. I am responsible for the Gynecare
24 Division of Ethicon, our Gynecology Medical Device
25 Product Division.

1 DR. MUNRO: I am Malcolm Munro. I am a
2 professor in the Department of Ob/Gyn at UCLA. I
3 am a consultant to Gynecare, as well as a number of
4 other companies that may be involved in the
5 discussion today.

6 DR. BLANCO: For the record, you need to
7 elaborate. Did they pay your way here, and did
8 they pay an honorarium to you?

9 DR. MUNRO: That's correct.

10 DR. BLANCO: Thank you.

11 Presentation by Ethicon

12 Richard Isenberg, M.D.

13 DR. ISENBERG: On behalf of Ethicon and
14 our parent corporation Johnson & Johnson, I would
15 like to thank Dr. Blanco, the panel, FDA for giving
16 us the opportunity today to come and present the
17 results of our investigation over this last year
18 into air and gas emboli associated with operative
19 hysteroscopy.

20 I will be spending a few minutes this
21 morning recounting the sequence of events that led
22 up to our withdrawal of the device and our
23 reintroduction of the device this winter. Dr. Munro
24 will be speaking to some of the basic science
25 elements and also discussing the recommendations of

1 the International Scientific Panel which we
2 convened in October.

3 [Slide.]

4 Ethicon is the sole worldwide distributor
5 for the Gynecare VersaPoint electrosurgical system.
6 This is a bipolar electrosurgical device operating
7 in saline that allows for treatment of intrauterine
8 pathology, such as myomas, polyps, adhesions, and
9 septa.

10 Ethicon acquired this device from
11 Gynecare, Inc., out of Menlo Park, California, in
12 1998, and we have been marketing the device since
13 that time. The device, however, has been on the
14 market since 1996 in the United States.

15 [Slide.]

16 Over the course of 1999 through 2000, we
17 received 7 spontaneous reports from the field, 7
18 complaints of suspected air and gas emboli
19 associated with use of our device in operative
20 hysteroscopy.

21 In each of these cases, the patients
22 experienced an abrupt decline in cardiovascular
23 function associated with hypoxemia, and a decrease
24 in end-tidal carbon dioxide. One additional case
25 had been reported to Gynecare, Inc., before we

1 acquired the device in 1997. On evaluation of that
2 case, it was determined that the event was most
3 likely associated with the use of an argon beam
4 coagulator during a concomitant laparoscopy, and
5 not the hysteroscopic procedure.

6 [Slide.]

7 While all of the patients in each of these
8 cases did well, responding briskly to anesthesia
9 resuscitative efforts, and that there were no
10 serious sequelae or complications, and certainly no
11 fatalities, Ethicon nonetheless felt that this
12 series of complaints potentially amounted to an
13 issue of patient welfare.

14 Not wanting to put patients at risk, and
15 yet wanting to investigate this issue further,
16 Ethicon voluntarily withdrew the device from the
17 market in September of the year 2000.

18 [Slide.]

19 Upon withdrawal of the device, we notified
20 FDA and other regulatory bodies around the world,
21 and began a multi-prong investigation into the role
22 that the procedure may play in these events, the
23 role the devices may play in these events, and into
24 the events themselves in order to better understand
25 them.

1 This investigation took several
2 approaches. We first performed a search of the
3 worldwide literature, looking at air and gas emboli
4 in surgical subspecialties including gynecology,
5 focusing on operative hysteroscopy.

6 The product of that literature review has
7 been published in the Journal of the American
8 Association of Gynecologic Laparoscopy in the May
9 2001 issue. While it hasn't quite hit the
10 newsstands yet, I do have courtesy of the Journal,
11 advance copies for anyone who is interested.

12 Ethicon also hired an outside consultant
13 to explore in more detail each of these cases. The
14 physicians were interviewed. In most cases, the
15 anesthesiologists were also interviewed, and a
16 large set of data collected on each of the cases.

17 [Slide.]

18 This eye chart, and I apologize for that,
19 it is not better in your handouts I realize, does
20 summarize some of the questions that we compiled as
21 a questionnaire, and I actually have magnified a
22 few of the questions here.

23 [Slide.]

24 It was a broad-based questionnaire
25 intended to identify risk factors and to identify

1 the role of the device and the hysteroscopic
2 procedure in these events.

3 [Slide.]

4 Within three weeks of the withdrawal,
5 Ethicon convened a panel of scientific experts in
6 hysteroscopic surgery, electrosurgery, anesthesia,
7 and cardiopulmonary medicine, and charged them
8 specifically with reviewing the findings of each of
9 the cases, reviewing the literature review, and
10 recommending to Ethicon a research approach that
11 would be valid, reasonable, and sufficient to
12 justify our saying that our device was safe.

13 [Slide.]

14 Upon evaluation of the seven cases, the
15 panel concluded that of the seven, four were most
16 likely due to air embolism. As Dr. Pollard
17 mentioned, it is important to differentiate between
18 embolism of room air and embolism of gas by
19 activation of the electrosurgical devices.

20 In these cases it was thought that air
21 entered the uterus and entered the uterine
22 vasculature either through air bubbles coming in
23 through the fluid flow lines, pumped in
24 mechanically by pumps, or potentially forced in, in
25 a piston type effect as the hysteroscopic device

1 was inserted and reinserted into the uterine
2 cavity.

3 In three of the cases, the panel concluded
4 that the events may have been associated with
5 embolization of electrosurgically created gases.

6 [Slide.]

7 The panel rendered several consensus
8 statements. First, the panel observed that
9 spontaneously reported cases, complaints, did not
10 generate true incidence rates. Indeed, the true
11 incidence of air and gas emboli in operative
12 hysteroscopy, both monopolar and bipolar operative
13 hysteroscopy, is altogether unknown. It would be
14 inappropriate as a result, based on this series of
15 cases, to conclude that the risk of gas embolism
16 with the VersaPoint device is higher than any other
17 hysteroscopic electrosurgical device.

18 The panel also stated that in all
19 likelihood, based on the basic science,
20 understanding of the interaction between these
21 electrosurgical devices and tissue, monopolar and
22 bipolar devices would likely have the same risk of
23 gas embolism. I will say that I am using the term
24 "monopolar" synonymous with "unipolar."

25 [Slide.]

1 The panel recognized a series of risk
2 factors for room air embolism and gas embolism.
3 First, introduction of air into the uterine cavity
4 as one might find with high-flow or pressurized
5 gas. We are all familiar with the experience with
6 the carbon dioxide-cooled, sapphire tip YAG lasers,
7 inadvertent use of laparoscopic insufflators during
8 hysteroscopy, and as I mentioned, the piston effect
9 of instrument insertion, failure to purge bubbles
10 out of the inflow lines also increases the risk of
11 room air embolism, inadequate flushing of the
12 uterus allowing accumulation of bubbles, patient
13 positioning, most notably the Trendelenburg
14 position, and excess intrauterine pressure during
15 the procedure. Enhanced access to the uterine
16 vasculature would also pose a risk as in pregnancy,
17 as in large myomata. Finally, penetration into the
18 myometrium during the course of a myoma resection
19 would also pose a risk.

20 [Slide.]

21 The panel made several recommendations to
22 Ethicon. First, in terms of a research strategy,
23 the panel acknowledging the accepted safety of
24 monopolar devices in hysteroscopy, recommended that
25 Ethicon investigate and compare the performance of

1 the VersaPoint device to established monopolar
2 devices with the assumption that if we could
3 demonstrate comparability, we would be able to
4 speak of relative safety.

5 The panel also recommended that we revise
6 our instructions for use in order to incorporate
7 enhanced warnings advising the surgeon about how to
8 prevent, detect, and aggressively intervene in the
9 face of room air and gas emboli.

10 The panel also recommended that we work on
11 our part to further educate our users and committed
12 to drive the medical community likewise to address
13 these issues.

14 [Slide.]

15 In accordance with the panel's
16 recommendation, in October, we embarked upon a
17 research protocol which involved two primary in
18 vitro tests comparing the VersaPoint devices to
19 representative monopolar devices, assessing the
20 volume of gas produced and the rate of gas
21 production per unit time, and as well,
22 characterizing the gases produced by activation of
23 these devices in an in vitro setting.

24 [Slide.]

25 This diagram describes the laboratory

1 setup. Fresh, morbid bovine cardiac tissue was
2 soaked in a representative solution, either saline
3 or glycine, and over it suspended an inverted
4 filled graduate cylinder, which served as a
5 collection chamber.

6 This allowed for measurement of the volume
7 of gas produced per time and allowed us also to
8 collect gas for evaluation with mass spectrometry
9 and other measures to characterize the gases that
10 composed the product.

11 The representative electrode was activated
12 and moved in strips across the surface to generate
13 the gas.

14 [Slide.]

15 This rather complex graph depicts the data
16 that we collected in terms of gas rate of
17 production in cc per minute. You will notice the
18 first five bars in purple are the VersaPoint
19 device. The remainder are monopolar devices. It
20 is important to emphasize that these devices were
21 evaluated as systems, a given electrosurgical
22 electrode in combination with a given RF generator
23 at a given wattage.

24 We drove the VersaPoint devices at maximum
25 wattage in order to identify the worst case

1 scenario in terms of gas production. With the
2 monopolar devices, in some settings we drove them
3 at maximum, in other settings we drove them more
4 closer to the normal usage setting.

5 [Slide.]

6 The conclusion drawn from this data is
7 that the rate of gas production for the VersaPoint
8 electrodes is comparable to that of the monopolar
9 electrodes and in many cases lower.

10 [Slide.]

11 Another eye chart, I apologize, but it is
12 reproduced largely in your handout. This table
13 describes the results of the gas composition
14 analysis. We have, in this column, the gases
15 produced by the VersaPoint activation, and here a
16 monopolar device.

17 If you look closely, line by line, almost
18 to the mole percent, there is equality in the mole
19 percentage of gases produced.

20 Highlighted for you here are the chief
21 gases that were produced by activation in this
22 model - 49 to 51 percent hydrogen. Most of the gas
23 produced here was hydrogen followed by carbon
24 monoxide and carbon dioxide with a percentage also
25 oxygen.

1 It is worth noting that a very small
2 percent, between 1.4 and 2.3 percent were nitrogen.
3 The remainder was composed of a series of
4 hydrocarbon gases.

5 From this data, we derive, I believe, what
6 is probably the most important conclusion of this
7 study, namely, that these gases produced by the
8 electrosurgical devices are highly soluble gases.
9 That is in direct contradistinction to nitrogen,
10 the chief component in room air.

11 [Slide.]

12 I believe we are all aware that nitrogen
13 comprises 78 percent of room air, nitrogen being
14 high insoluble, if embolized in the form of room
15 air, would likely persist in the bloodstream. This
16 may indeed account for the high morbidity and
17 mortality associated with room air embolism as
18 reported in the world literature, not just
19 gynecologic, but involving virtually every surgical
20 subspecialty.

21 By contrast, with such a small percentage
22 of gas produced by these electrosurgical devices
23 falling in an insoluble category, it may be that
24 these emboli of electrosurgically produced gases
25 would have a less severe clinical consequence.

1 [Slide.]

2 Taking all these elements of the
3 investigation together, the literature search, the
4 investigation of the individual cases, the
5 recommendations of the panel, the benchtop
6 research, Ethicon determined that no changes were
7 required to the VersaPoint device itself or its
8 waveform, that we did have a responsibility to
9 enhance the warnings and indeed added a section
10 entitled "Warnings Applicable to Air and Gas Emboli
11 Hazards."

12 At the beginning of February, we returned
13 the VersaPoint device to the market.

14 At this point, I would like to turn the
15 discussion over to Dr. Munro.

16 Malcolm G. Munro, M.D.

17 DR. MUNRO: Thank you.

18 [Slide.]

19 Dr. Blanco, members of the panel, it is an
20 honor to be able to represent a panel of my peers
21 and colleagues, for indeed this was a
22 multidisciplinary effort. The material that was
23 distributed previously has been modified somewhat,
24 so please don't be alarmed if your handout doesn't
25 exactly follow the structure of the presentation,

1 but in order to make things more clear, we have
2 embellished some of the images to help you and
3 members of the audience have a better understanding
4 of what is going on.

5 [Slide.]

6 The overview is we will just try to review
7 the difference between bipolar and unipolar
8 systems, describe the effects of radiofrequency
9 electricity on cells and tissue as a way of trying
10 to understand where the panel was coming from with
11 respect to giving guidance to Ethicon and in
12 interpreting the results of these at least early
13 data, and then to review the recommendations that
14 were created by the panel following review of all
15 of this material that you had already presented to
16 you this morning.

17 [Slide.]

18 With respect to the differences and
19 similarities between bipolar and monopolar systems,
20 there are a number of similarities. Each uses
21 radiofrequency alternating current, and one could
22 really say that all systems are bipolar, there are
23 two electrodes in each system.

24 The differences really relate in part to
25 the location of the second electrode. Bipolar

1 electrodes--and this is one that might more likely
2 by seen at laparoscopy--both electrodes are near
3 the tissue, so the only part of the patient that is
4 involved is that which is near the electrode.

5 This is to be distinguished from the
6 monopolar systems where there is an active
7 electrode up here and a dispersable electrode here,
8 and virtually all the patient that is between the
9 two is involved in the circuit.

10 The reduced impedance with bipolar
11 electrodes allows for the use of conductive
12 distention media at hysteroscopy, and conductive
13 distention media may be physiologic in nature, and
14 therefore have some important safety considerations
15 perhaps should intravasation of the fluid occur.
16 If there is saline or similar materials
17 circulating, the woman in this case is less likely
18 to become hyponatremic than if hypotonic, non-electrolytic
19 media are used.

20 [Slide.]

21 Now, if we look at this graphically, for
22 those of you who do a little better with graphics,
23 this is a monopolar/unipolar hysteroscopic system
24 now, and we have an active electrode, which is up
25 here, and a dispersive electrode in the red box.

1 Some people call that a return electrode, but in
2 fact, radiofrequency has no directionality, it goes
3 back forth, it is oscillating, or any alternating
4 current really fits that description.

5 [Slide.]

6 Over here we have a device that is not
7 widely marketed or no longer marketed at least in
8 the United States, called the Conceptus ERA sheath,
9 and this company moved the dispersive electrode
10 from the patient's thigh, for example, to the
11 cervical canal. That also was called a bipolar
12 system. It is just that the second electrode is in
13 a different spot. With the VersaPoint, we see that
14 the dispersive electrode is a tiny one, but the
15 second electrode is right near the active
16 electrode.

17 [Slide.]

18 The effects of radiofrequency electricity
19 on cells and tissue is the next component.

20 [Slide.]

21 This graphic describes the alternating
22 nature of the two poles of an alternating circuit
23 like the one that is powering the lights in this
24 room today, and that creates on an oscilloscope
25 this oscillating image as the polarity moves, and

1 you can see why there is no directionality to the
2 current, because it just goes back and forth, and
3 that speed and radiofrequency is 500 kilohertz or
4 500,000 times per second.

5 [Slide.]

6 Generators produce the output from a wall
7 circuit, which in the United States is generally
8 about 60 hertz, and convert it into this 500,000
9 per second frequency, and there are either high
10 voltage outputs that are often called coag, they
11 are a modulated current that takes advantage of
12 Ohm's law and pushes the voltage to a very high
13 level, or the other part of the generator, the so-called cut
14 side can be modulated, producing blend
15 currents or, in the pure form, at a given wattage,
16 have the lowest voltage of any of these currents.

17 [Slide.]

18 Now, let's translate now to tissue. So,
19 what happens? RF current causes rapid oscillation
20 of the proteins, all the cations and anions within
21 the cells, and the kinetic energy that results from
22 this is converted to heat within the cells, so it
23 is not an electrode that heats the tissue, it is
24 the oscillation of the proteins, we believe,
25 anions, cations in the cell that is converted to

1 heat, and in that sense it is similar to a laser.

2 Rapid elevation of the intracellular
3 temperature to 100 degrees centigrade or more
4 results in steam formation because of the large
5 water component of any cell. That steam results in
6 cellular expansion and an explosive vaporization.

7 If the temperature does not reach 100, but
8 is fairly elevated, say, over 70 degrees, rather
9 than cellular expansion, one gets dehydration and,
10 if you will, cellular contraction or desiccation as
11 the water is removed from the cell, and the protein
12 bonds also are broken down and can form coagulation
13 or an amalgam of tissue.

14 [Slide.]

15 Now, if we again do this in a graphical
16 context, here are the anions and cations. Here is
17 what would happen with the direct current, and here
18 is this oscillation at half a million times per
19 second or so. If it is slowly heated, we get a
20 drying or a desiccation and coagulation. If it is
21 rapidly heated, we get vaporization.

22 Of course, if that occurs in a fluid
23 media, we get the formation of bubbles as this gas
24 moves into the fluid media.

25 [Slide.]

1 This is the picture that Dr. Isenberg
2 showed you of collecting gas, and one of the
3 questions asked is how is the vapor pocket--sometimes I call
4 it the steam envelope--formed.

5 [Slide.]

6 Well, let's start. One has to deliver
7 energy to the tissue, and one does that, of course,
8 with an electrode, and here are some unipolar
9 electrodes that are relatively large, so that they
10 provide a relatively low power or current density
11 to the tissue and therefore tend not to, in normal
12 circumstances, elevate the cell intracellular
13 temperature to more than 100 degrees centigrade.

14 On the other hand, here are a number of
15 so-called vaporizing electrodes. This one is a
16 needle. This is a thin loop. This is a thick
17 loop. Here is one that I call multiple-edge
18 density because there are multiple electrodes along
19 each of those ridges.

20 [Slide.]

21 Now, if we now think of this vapor pocket
22 or this vaporization that we showed you on the
23 cellular level, and look at this in a tissue level,
24 what happens is we get vaporization with this
25 multiple-edge density electrode. We get

1 vaporization over this wide swath of tissue. The
2 resulting gas that is formed then forms this set of
3 bubbles.

4 If we look at a needle electrode, smaller
5 tissue electrode interface, one has a smaller vapor
6 pocket, but a vapor pocket nonetheless.

7 [Slide.]

8 So, basically, these two are similar, and
9 I think one of the big concepts to get is we are
10 not heating up a loop electrode making it hot and
11 cutting it through like a butter knife or a hot
12 knife, we are vaporizing. Vaporization is
13 occurring with cutting electrodes, with these great
14 big vaporization electrodes.

15 So, both RF electrosurgical cutting and
16 both vaporization are achieved by the same process,
17 vaporization, and the byproduct is the production
18 of gas.

19 [Slide.]

20 Now, let's look at this a little bit
21 differently. This is the typical voltage that we
22 throw out. Here is the multiple-edge density
23 electrode that we just showed you in an animated
24 fashion. Here is the loop electrode, the same type
25 of approach. If we look at the tiny little video

1 clip here of a loop electrode, you can see the gas
2 being produced as this loop electrode is being
3 pulled through the tissue.

4 [Slide.]

5 Now, I mentioned the other electrosurgical
6 tissue effect that one can get, and that is
7 desiccation in case we have the same output, same
8 current, not all gynecologists and urologists, et
9 cetera, use the same current, but this effect can
10 be achieved with the same current. All that is
11 happening here is we are having a larger tissue
12 interface.

13 Fulguration is really not practical in
14 fluid media because it requires very high voltage
15 and arcing to tissue that is really not feasible in
16 fluid media, at least with current technology.

17 [Slide.]

18 Let's look at this one other time. Here
19 is our steam envelope, and here is the energy
20 pathway, because if this is the unipolar/monopolar
21 system, the dispersive electrode is somewhere out
22 here, so the directionality of the current, if you
23 will, goes back and forth this way.

24 Here is monopolar bulk vaporization. This
25 is a vaporizing electrode, and this is just a case

1 that I did not that long ago. You can see the
2 bubbles to the point of even obscuring the field
3 that are being produced.

4 [Slide.]

5 Just so that you can see that that is a--well, we
6 will just carry on. I have added another
7 piece there, but it looks the same from another
8 surgeon.

9 [Slide.]

10 In the bipolar devices, we have the same
11 vapor pocket, we believe. The difference is the
12 energy pathway. The energy, of course, here is
13 going back and forth between the two electrodes and
14 doesn't traverse through the patient, as we
15 described. This is the way it is depicted in
16 Gynecare literature, educational literature, and
17 here is a picture of it occurring in the
18 endometrial cavity.

19 There is the electrode. There is a myoma
20 there to the lower right of the screen, and you can
21 see the bubbles being produced.

22 [Slide.]

23 Now, to come back to this slide, just to
24 look at it a little deeper--and we can spend an
25 enormous amount of time on this slide--but just to

1 look at it a little deeper, if we now look at those
2 two, the box on the left is a loop electrode at
3 about 100 watts, and the box on the right is one of
4 these multiple-edge density or vaportrodes at 300
5 watts. The gas production there fits the
6 description that I just gave you.

7 Here it is on the Force FX, slightly
8 different numbers, but basically the same relative
9 production. A lot of the other electrodes in the
10 middle are desiccating electrodes that have been
11 pushed to outputs far beyond where they would be
12 typically used in clinical use. So, what those
13 numbers mean clinically is hard to know.

14 There is one area that we have had a
15 little difficulty explaining, and that is looking
16 at the monopolar loop at 100 watts and the
17 VersaPoint loop at 200 watts, and those of you that
18 have looked at this will see that there is a
19 substantial difference between the two.

20 We have tried to think of a number of
21 reasons for these differences, which we don't think
22 are clinically significant because of the
23 solubility to the gases, but we are still trying to
24 understand why there is a difference.

25 [Slide.]

1 So, what we felt was that after looking at
2 these data, that the amount of gas generated by
3 tissue vaporization is probably a function of the
4 power density, the amount of fluid in the tissue or
5 the cell, and the relationship between the active
6 electrode and the tissue.

7 It is not a function of the location of
8 the second or dispersive electrode or likely the
9 conducting medium. Now, there is one caveat here,
10 is that we may not be able to measure all of the
11 gases being produced. There may be water vapor
12 produced. If that is the case, it probably goes
13 back into solution very quickly, but it is possible
14 that there are differences between these two.

15 The composition of the gas is a function
16 of the tissue undergoing vaporization, and is not
17 related to the design of the electrode be it
18 monopolar or bipolar.

19 [Slide.]

20 So, finally, the panel recommendations--and I have
21 tried to make them a little easier than
22 in the initial PowerPoint summary and categorize
23 them into patient, facility, physician, and
24 intraoperative precautions, and if we start with
25 patients first, we know that the risk of gas

1 embolism may be greater with the increasing
2 duration of surgery, with myomas that penetrate the
3 myometrium maybe because of the greater access to
4 larger vessels, and for that reason, the surgeon
5 must be somewhat judicious in counseling and
6 selecting patients considering all kinds of other
7 medical and surgical options.

8 [Slide.]

9 The next is that there are no known
10 preoperatively applied techniques or methods for
11 reducing the risk of gas embolus at hysteroscopy,
12 but there are some approaches that the committee
13 really didn't have time to deal with, but would
14 like to deal with - suppression, endometrial
15 suppression. There is some of us who believe that
16 this may be an issue, reducing trauma to the cervix
17 by predilation with osmotic dilators might have an
18 impact.

19 [Slide.]

20 With respect to the facility, the facility
21 must have resources. The resources include
22 appropriate anesthetic monitoring equipment for
23 end-tidal CO₂, et cetera, must have a fluid
24 management system and protocol, and be able to
25 control intrauterine pressure, as well as measure

1 the balance of fluid deficit.

2 That is not specifically for gas emboli,
3 but that is a general approach for any type of
4 hysteroscopic procedure, and that these OR staff
5 must be trained in fluid management, but specific
6 to this question, in gas line purging. You heard
7 Dr. Isenberg say that we believe that maybe some of
8 these incidents that were identified might have
9 been related to gas being caught in the line and
10 being forced into the uterus.

11 [Slide.]

12 If something happens that is adverse, the
13 appropriate resuscitative capabilities should be
14 accessible to the staff, and the hysteroscopic
15 equipment should be complete and functional with
16 appropriate variety of electrodes and functional
17 generators.

18 [Slide.]

19 With respect to physician preparation, the
20 surgeon should be trained in the principles of
21 hysteroscopic surgery, which I think is fairly
22 obvious, and must employ good judgment in patient
23 selection, and this is redundant, but to emphasize
24 size, number, the depth of penetration of a myoma
25 might be factors that might cause one to think of

1 another approach other than hysteroscopic
2 approaches or to stage hysteroscopic approaches, so
3 that it is not all done in one procedure.

4 [Slide.]

5 Anesthesiologists need to understand the
6 risks of hysteroscopic surgery and how they may
7 differ from other fluid media-based endoscopic
8 surgery like cystoscopy. Nitrous oxide may enlarge
9 the size of air bubbles and should be avoided when
10 possible in operative hysteroscopy, and if a
11 patient is considered at high risk for gas
12 embolism, to consider controlled ventilation, end-tidal CO2
13 monitoring, and perhaps even precordial
14 doppler monitoring.

15 [Slide.]

16 The team should be oriented to
17 communicate, particularly the surgeon and the
18 anesthesiologist.

19 [Slide.]

20 In the surgery, prior to commencing
21 surgery, the doctor should be sure that the
22 electrodes are there, that the patient monitoring
23 and all the issues we talked about are in effect,
24 that the fluid monitoring system is there and the
25 staff that are there are trained.

1 We have talked about the Trendelenburg
2 position. We are not totally sure, all of us,
3 whether that is a major issue, but it is one that
4 we are generally agreeing to minimize, and that the
5 air must be purged from the system before
6 connecting the various tubes to the hysteroscope.

7 [Slide.]

8 How does one minimize air in the
9 endometrial cavity? Well, patient positioning,
10 minimizing instrument exchanges, minimizing the
11 exposure of the dilated cervix to air, keeping the
12 cervix occluded after dilation.

13 Fluid management, there should be Y-connectors on
14 inflow lines, the lines should be
15 purged, the bags shouldn't be allowed to run dry,
16 if possible, and the pumps should be turned off
17 during bag exchanges to avoid pressing air into the
18 endometrial cavity.

19 [Slide.]

20 If gas gets into the endometrial cavity,
21 of course, the surgeon often can't see, and also
22 recognizing that this is a normal byproduct, as you
23 saw, of electrosurgical vaporization of fluid. So,
24 if excessive bubbles or pockets of gas are
25 identified, active fluid outflow may aid in purging

1 them.

2 One should operate at the lowest
3 intrauterine pressure required for adequate
4 visualization of the field.

5 [Slide.]

6 If suspected gas embolism occurs, the
7 surgeon must be prepared to interrupt the
8 procedure, to deflate the uterus, and if
9 cardiovascular compromise, to implement appropriate
10 resuscitative measures.

11 Finally, the procedure must be terminated
12 if the patient's condition warrants.

13 [Slide.]

14 So, in summary, we felt that all the
15 evidence that we have been able to determine from
16 review of the literature and review with peers,
17 that the hysteroscopy remains a safe procedure.
18 Air embolism is rare, potentially catastrophic, and
19 is associated with any procedure involving the
20 endometrial cavity including Cesarean section and
21 D&C, that gaseous embolisms that are not air,
22 arising from the products of electrosurgical
23 vaporization, occur with an unknown frequency, they
24 seem to be rarely, if ever, associated with
25 permanent sequelae.

1 The in vitro evidence suggests that there
2 are no clinically significant differences between
3 monopolar and bipolar systems in the volume or the
4 composition of electrosurgically created gases.

5 Thank you.

6 DR. BLANCO: Thank you very much.

7 First of all, before we continue, I would
8 like to compliment the company Ethicon on what
9 appeared to be a very measured and very appropriate
10 response to the information that you received. I
11 think you should be complimented on that and your
12 approach in trying to solve the problem.

13 I also enjoyed your presentations. If you
14 wouldn't mind, I don't know if the panel has any
15 questions of fact that they would like to ask
16 either of the two presenters at this point. Subir.

17 DR. ROY: It seemed that the greatest gas
18 production occurred with the highest setting in
19 terms of wattage. Is there any clinical utility to
20 those high settings? I mean is there any reason
21 for having the 300-watt settings?

22 DR. MUNRO: With what I call the multiple-edge
23 density electrode, in effect, that is like an
24 array of four or five electrodes sitting beside
25 each other, and you can almost look at them as

1 independent electrodes. In order to vaporize
2 tissue, in order to generate the power density, a
3 tissue electrode interface sufficient to elevate
4 the intracellular temperature, you need relatively
5 high power, at least initially, at least initially
6 to develop the envelope.

7 Afterwards, quite frankly, the setting on
8 the machine doesn't necessarily affect what is
9 being put out. The power tends to fall quite
10 rapidly off, but that varies a lot with the
11 generator that is being used.

12 But you are right with respect to the
13 desiccating electrodes, there is no reason to be
14 running them that high, and they were pushed, there
15 was a decision made they were pushed to try to see
16 what is the worst case scenario. That is why I
17 took the boxes and circled some areas that were not
18 worst case scenarios, but more reflected clinical
19 use to show how they more fell into line with what
20 I showed you.

21 DR. BLANCO: Thank you. Any other
22 questions? Mike.

23 DR. NEUMAN: I would just like to comment.
24 First of all, I would like to compliment the firm
25 for simplifying the biophysics of electrosurgery,

1 so we can all understand it. On the other hand, I
2 think you left off a few things that perhaps you
3 want to consider in further evaluation of these
4 devices.

5 First of all, even though the
6 radiofrequency effect involves high-frequency
7 currents, I believe there is still a lot of just
8 ordinary, what we call "Joule" heating that is
9 associated with the process, and you are doing some
10 burning, as well as vibrating molecules, and all
11 that sort of thing, and I think you need to take
12 that into consideration.

13 The other process, in view of the fact
14 that you are concerned about gas generation, is
15 electrochemical processes, because, in fact, you
16 may be oxidizing and reducing various components
17 especially water at these electrodes, and that can
18 contribute a lot to especially the hydrogen
19 production that you indicate.

20 The final comment I would like to make is
21 with regard to the wattage settings on the
22 generators. Indeed, whatever the generator is set
23 at is the power available, but the real question
24 and the real relationship that you want to look at
25 in some of the reports that you provided, you had

1 gas per unit volume of tissue or mass of tissue.

2 The real thing you want to look at is the
3 actual power dissipated in the tissue, and to look
4 at, if you will excuse me for being technical a
5 very short time, just so that the people will know
6 what to look at, look at reflected power or
7 standing waves, probably standing waves are not
8 appropriate in view of the frequency you are using,
9 but you are, when you deal with a radiofrequency
10 system, some energy goes down and some comes back.

11 Just think of the laser, for example. If
12 all of the energy of the laser went to destroying
13 the tissue, to ablating the tissue, you wouldn't
14 see it because there would be no light coming back.
15 Some light comes back and similarly with these RF
16 things, it comes back.

17 So, if you wanted to clean up your data
18 and reduce those error bars, I think this may help
19 you to do that.

20 DR. BLANCO: Thank you.

21 Any other questions?

22 [No response.]

23 DR. BLANCO: I wonder if I could ask one
24 question in terms of the speed with which the gases
25 are dissolved into the liquid. You mentioned that

1 most of the liquids produced by the procedure are
2 gases that are fairly easily dissolved in the
3 liquid, but yet you still were able to measure some
4 gas production.

5 Do you have any data on how quickly these
6 gases really do dissolve?

7 DR. ISENBERG: That is a very good
8 question, Dr. Blanco. The issue it seems would be
9 the rate of dissolution in the bloodstream, and for
10 that, there is very little evidence available.

11 We have reviewed the literature for
12 solubility indices for these gases and do have data
13 that we could share with FDA, we didn't bring it
14 here today, on solubility in water, in saline, and
15 at least in animal models in blood, that does show
16 many-fold differences in the solubility
17 coefficients for these gases certainly as compared
18 to nitrogen.

19 DR. BLANCO: Thank you. Michael.

20 DR. DIAMOND: Just one other comment is
21 that when these gases are generated, they are not
22 all necessarily going to go into the circulation in
23 some mechanisms, and so the issue may not only be
24 how much is generated, but what happens to it
25 relative to whether it stays in either cavity,

1 whether the device or the electrodes, their shape,
2 their configuration alters the amount that might be
3 able to egress back out the cervix or egress out
4 through the fallopian tubes, but the total
5 dissipation of the gas at locations other than just
6 entering the circulation.

7 DR. BLANCO: Thank you. Any other
8 comments or questions?

9 [No response.]

10 DR. BLANCO: Let's go ahead and proceed on
11 with the next speaker.

12 The next presentation is by the FDA. I
13 believe Dr. Julia Corrado, Medical Officer for the
14 Obstetrics and Gynecology Devices Branch, will be
15 presenting.

16 Presentation by FDA

17 Julia Corrado, M.D.

18 DR. CORRADO: Hi everybody. Good morning.

19 I guess what I would like to do, which is
20 not a part of my slide presentation, is give you
21 all a verbal summary of how the FDA staff reviewed
22 the voluntary withdrawal of the VersaPoint device.

23 The working staff in the Office of Device
24 Evaluation became aware of these events in early
25 November, and we convened a working group among

1 ourselves, consisting of electrical, chemical, and
2 biomedical engineers, myself, and an
3 anesthesiologist.

4 We reviewed the reports that had been sent
5 to us by the company and also the conclusions of
6 their own advisory panel. Some of the things we
7 reviewed were as follows. We have heard from Drs.
8 Munro and Isenberg of some of the conditions, sort
9 of the intraoperative management decisions that
10 were made in the cases under question.

11 I will summarize--again, I apologize, I
12 don't have a slide on this--we looked at the
13 following variables. We looked at the electrode
14 that was chosen for the procedure. We looked at
15 patient position. We looked at the frequency of
16 removal and reinsertion of the hysteroscope to the
17 extent that that information was available.

18 We looked at whether or not the surgeon
19 recalled or had kept records on whether there was a
20 large fluid deficit during these cases.

21 We looked at the method of distention of
22 the uterus and specifically, I mean obviously
23 saline was used at a distending medium, but in some
24 cases, a blood pressure cuff was placed around the
25 bag of distending fluid, and the fluid forced into

1 the uterus, and the pressure was not monitored.

2 In all cases, myomectomy was the procedure
3 that was undertaken. In one case, nitrous oxide
4 was used as part of the anesthetic regimen.

5 We also looked to the extent that we could
6 at duration of the procedure.

7 We concluded that there was a
8 preponderance of certain variables that we felt
9 might have contributed to these events. We looked
10 at the use of the zero degree vaporizing electrode.
11 I do not have the exact numbers, I believe that in
12 four or five out of the seven cases, that electrode
13 was used exclusively or in conjunction with another
14 electrode.

15 There were I believe four or five cases in
16 which the conclusion was reached that there had
17 been a significant fluid deficit of 1,500 or 2,000
18 cc. A blood pressure cuff was used in a number of
19 the cases to force fluid into the uterus, and
20 several of the cases were relatively long in
21 duration, 1 1/2 to 2 to 2 1/2 hours.

22 We also looked at the bench testing that
23 the company performed, as you have heard from Dr.
24 Isenberg. We asked the company for additional
25 information on the relative solubility of the gases

1 generated in the different distending media, and
2 then we worked with the company on the labeling,
3 and we will talk about that a little bit at the end
4 of my talk.

5 We felt that it was important that the
6 risk of room air or gas embolism should be made
7 more prominent on the labeling for the product, but
8 we did agree with the company that given the
9 uncertainty as to whether or not these are room air
10 or device generated gas emboli, the relative low
11 morbidity of these events, the steps that they took
12 to improve their labeling, and the reintroduction
13 letter that they issued when they released the
14 product again were substantial actually and we felt
15 acceptable to reintroduce the device.

16 Independently, FDA decided at that time
17 that it would be a good idea to take a generic look
18 at the risk of room air and gas embolization using
19 both bipolar and unipolar systems, and that is why
20 we are here today, to get our panel's expert advice
21 on whether or not this is a generic problem or
22 whether the changes to the labeling for the
23 VersaPoint device are really all that is necessary
24 to protect our patients.

25 At this time, I will begin my

1 presentation. I would just like to digress for
2 half a minute and recognize Dr. Schroeder, an
3 anesthesiologist who is joining us this morning,
4 because my presentation will make the point
5 repeatedly how important anesthesiologists are in
6 diagnosing and treating these events, and
7 furthermore, in documenting these events in the
8 literature.

9 I would also like to acknowledge Mr. Jay
10 Houser from Karl Storz Company, who has been kind
11 enough to come and give us a presentation on
12 unipolar hysteroscopic electrosurgery.

13 I would also like to make a special
14 acknowledgment of Dr. Isaac Chang of the FDA staff.
15 He is a biomedical engineer in our Office of
16 Science and Technology, and he has I could say
17 cooperated, I could say coached, but he has greatly
18 helped me prepare for this presentation.

19 This panel doesn't need a lecture in some
20 of the things I am going to discuss. I acknowledge
21 their prominence and expertise, nevertheless, I
22 thought it was useful to review some basic
23 principles before focusing on the points that FDA
24 staff would like their input on.

25 [Slide.]

1 Pulmonary embolism can evolve from a
2 number of circumstances, physiology is one of them,
3 negative intrathoracic or maybe more properly
4 negative intravenous pressure in the vascular
5 system versus in the uterus, and the vascularity of
6 the particular tissue under treatment.

7 [Slide.]

8 There are iatrogenic risk factors. These
9 are risk factors over which the medical team has
10 control including the pressure on the inside of the
11 uterus, the degree of cervical dilation, whether or
12 not we repeatedly insert and remove instruments.

13 I believe that Dr. Munro mentioned the
14 pistonlike effect of shoving instruments in the
15 uterus under pressure with significant cervical
16 dilation. The degree of tissue trauma, and that
17 is, to what extent are venous channels going to be
18 open, duration of the procedure, and again patient
19 position may be a factor.

20 [Slide.]

21 Electric equipment-related risk factors
22 include the configuration of the electrode, the
23 size and the shape of the electrode, the
24 temperature that is achieved during the treatment,
25 and the extent of vaporization.

1 [Slide.]

2 When we are performing operative
3 hysteroscopy, the surgeons are usually pretty
4 intent on looking at the tissue, making sure that
5 they see what they are treating and what they are
6 excising.

7 We rely to a large degree on our
8 anesthesiologists to alert us to signs that the
9 patient is suffering some type of compromise. We
10 have already heard about decreased oxygenation,
11 oxygen saturation, and decrease in end-tidal carbon
12 dioxide. What is not there, and I am sorry, I
13 apologize, hypotension should also be on this
14 slide.

15 [Slide.]

16 Intraoperatively, there is a combination
17 of anesthesiology maneuvers and surgeon maneuvers
18 to treat a suspected room air or gas embolization.
19 This is not an all-inclusive list, but it includes
20 the following: interrupting the procedure,
21 achieving intubation if the patient is not under
22 general, and assisted ventilation, resuscitation
23 depending on the degree of cardiopulmonary
24 compromise, if necessary, achieving central I.V.
25 access, repositioning a patient into what I believe

1 is left lateral decubitus position, but Dr.
2 Schroeder can correct me if I am wrong, and
3 considering occluding the cervix and the vagina, at
4 a minimum removing the instruments that are
5 facilitating possible entrainment of room air in
6 the vagina through the cervix and into the uterus.

7 [Slide.]

8 Now, I am going to switch topics and just
9 briefly summarize where FDA has played a role in
10 this technique of operative hysteroscopy. In 1989,
11 FDA approved the first unipolar system for
12 operative hysteroscopy. In 1996, we approved or
13 cleared--I apologize--cleared for marketing the
14 VersaPoint system, and in 1997, FDA gave market
15 clearance to a device that was manufactured by
16 Conceptus. It operates as a bipolar device, it was
17 somewhat of a hybrid device. The reason it is
18 parenthetical now is that it was not used for very
19 long, and it is our understanding that it not
20 actively marketed right now.

21 Again, I apologize for the elementary
22 nature of my slides, but nevertheless, I am going
23 to go ahead and give my talk as I had planned it.

24 [Slide.]

25 This is just a schematic of the direction

1 of the current in bipolar hysteroscopy. Again, I
2 am a clinician, I am not an engineer. I will
3 certainly try to use the correct terminology.

4 What you don't see here is a ground plate
5 that we will see with the unipolar system.
6 Essentially, the current is generated, delivered to
7 the electrode, the active electrode, which is at
8 the tip, delivers the current to the tissue. The
9 current is then rerouted to the return electrode,
10 which is very proximal to the active electrode.
11 So, the current essentially doesn't go through the
12 patient's body except for the target tissue.

13 [Slide.]

14 I am going to give a hypothetical of what
15 FDA staff believes is happening during bipolar
16 tissue treatment. Again, desiccation is not
17 something that we would commonly do using bipolar
18 instrumentation, and I am going to attempt to
19 convince you of why we believe this is the case.

20 Because you must use saline when you do
21 bipolar operative hysteroscopy, you must use
22 saline, it is not option, saline is a conducting
23 medium, and the way we view it is that when we are
24 using saline, we can lose current through the
25 distention medium. Therefore, we are not

1 effectively delivering energy to the issue in
2 question.

3 All of the current does return again to
4 that return electrode, which is the purple area
5 above that white section in between the two
6 sections of the tip of the electrode, but again you
7 see a lot of energy being lost in the saline
8 distention medium. This is with bipolar treatment.

9 [Slide.]

10 During vaporization, a pocket consisting
11 of water vapor is created around the tip of the
12 electrode. Water vapor is not a good conductor.
13 Therefore, the way we view it is that the bulk of
14 the energy is being delivered to the target tissue.

15 It is then being routed around that vapor
16 pocket, back to the return electrode. We believe
17 that this is how the bipolar instrument is intended
18 to work, that it works more effectively in a vapor
19 pocket than without a vapor pocket, and it is
20 because the property of that vapor pocket is that
21 it is not going to conduct current through it.

22 [Slide.]

23 Now, I won't spend any time on this. The
24 ground pad is what Dr. Munro referred to as his
25 dispersive electrode, I believe. The current is

1 delivered to the tissue, into the tissue, routed to
2 the ground, and then the way I have this diagram,
3 back to the generator. Again, the difference is
4 that it is going through the patient to that
5 dispersive electrode.

6 [Slide.]

7 Glycine is just the example I am going to
8 be using of a non-conducting liquid medium. What I
9 am trying to show here is that when we are using
10 unipolar generators, the energy is delivered to the
11 tissue, it does not get dispersed into the
12 distention fluid because it is a non-conducting
13 fluid, and therefore, this is an efficient way to
14 deliver the energy to the tissue.

15 [Slide.]

16 This is something that maybe you didn't
17 expect to see. It is a diagram of what we believe
18 would happen if you attempted to use a unipolar
19 generator and saline as your distention medium.
20 Once again, we believe that we would lose energy
21 through the distending medium. We would not have
22 an effective impact on our tissue. In order to get
23 tissue impact, we would have to increase the power
24 to the extent that it could be dangerous for the
25 patient, and she may sustain an injury at the site

1 of that ground pad.

2 [Slide.]

3 This is a list of some complications of
4 operative hysteroscopy using the unipolar and
5 bipolar systems. In general, they are shared
6 complications with the exception of hyponatremia.
7 I won't spend more time than just to mention
8 obviously perforation fluid absorption, what
9 happens with fluid absorption using hypertonic
10 solutions is hyponatremia with the unipolar systems
11 and pulmonary edema in the bipolar system,
12 infection, and then the last item is air and/or gas
13 embolization. That is the reason we are here
14 today, to decide what is the relative role of each
15 of these and how do the two types of systems differ
16 with respect to that relative risk.

17 [Slide.]

18 We heard about the eight reports of the
19 VersaPoint events. It is uncertain whether or not
20 these were room air or gas emboli. FDA took what
21 we thought was a conservative approach when we did
22 our analysis. We assumed that they were all
23 generated by the device. That has certainly by no
24 means been proven, and we feel that we will never
25 know, but nevertheless, we wanted to make sure that

1 we considered whether or not the device posed a
2 significant risk.

3 As several people mentioned, the company
4 responded promptly, and we very much appreciate
5 that.

6 [Slide.]

7 In terms of labeling, these were the types
8 of things that the company proposed and we worked
9 with them on. To just emphasize, in the labeling,
10 the importance of appropriate patient selection,
11 the importance of as low pressure intrauterine as
12 possible, and continuous flow, how important it was
13 to monitor fluid balance, and to have resuscitative
14 capability.

15 This is really gratuitous. Most people
16 performing operative hysteroscopy are well aware of
17 this, but nevertheless, because some of these
18 factors may have been involved in these events, we
19 thought it was important to just reemphasize them.

20 Air entrainment was noted in several of
21 the cases of the VersaPoint adverse events. We
22 intended the operators to be advised not to
23 reinsert the instrument unnecessarily, not to
24 exaggerate Trendelenburg, and to avoid the use of
25 nitrous oxide anesthesia although that was only

1 used in one of the cases of the ones that we
2 evaluated.

3 [Slide.]

4 To keep things in perspective lest we
5 think that air and gas embolization are unheard of
6 using the unipolar system, these are examples of
7 two articles that have appeared in the published
8 literature. They certainly are few and far
9 between, but nevertheless, these are two examples
10 of what appear to have been either room air or gas
11 emboli that occurred with the use of unipolar
12 hysteroscopic electrosurgery.

13 I have got a couple of others that
14 essentially are Letters to the Editor of a couple
15 of anesthesia journals, and let me also again point
16 out here for all the gynecologists, these were all
17 reported in anesthesiology journals.

18 I did not find anything specific to room
19 air and gas embolization in operative hysteroscopy
20 in the gynecologic literature. My search may have
21 been imperfect, but I was not able to come up with
22 them, with unequivocal room air or gas
23 embolization.

24 [Slide.]

25 I guess I would like to wrap up with an

1 effort to highlight what FDA staff sees as some of
2 the important differences and similarities between
3 these two systems.

4 We would argue that in the bipolar system,
5 you can only use saline as your distention medium.
6 You cannot use glycine. In the unipolar system, it
7 is possible to use either/or, but if you use a
8 conducting medium in the unipolar system, it will
9 be a very inefficient transfer of energy, and again
10 result in using excessive levels of current to get
11 a tissue effect.

12 With respect to desiccation and
13 vaporization, it is our view that in the bipolar
14 system, vaporization--I am not attempting to tell
15 the company how it designed its device or how it
16 works--but the way we see it, you really need to
17 get that vapor pocket when you are using the
18 bipolar system in order for it to work as it is
19 intended.

20 In the unipolar system, vaporization will
21 occur depending on the intracellular temperatures
22 that are achieved. Other differences in the two
23 systems are electric field strength and obviously
24 electrode placement.

25 [Slide.]

1 The similarities in the environment in
2 which we find ourselves now or the indication, the
3 use of radiofrequency energy, the potential to
4 generate vapor in both types of systems, and in my
5 view, the inherent risk of room air embolization
6 with operative hysteroscopy using either type of
7 system, and if that is not a correct assumption,
8 then, we certainly need to be guided in that
9 direction.

10 [Slide.]

11 Our role here we think is to assess the
12 risk of room air embolization during unipolar and
13 bipolar hysteroscopy and of device-generated gas
14 embolization during unipolar and bipolar
15 hysteroscopy.

16 We want to respond commensurate with the
17 risk. We don't want to place undue burdens, we
18 don't want to make a mountain out of a mole hill,
19 but we also, although the morbidity of the events
20 that were reported was relatively low, we all here
21 have a very healthy respect for a pulmonary
22 embolism and would like to avoid that absolutely.

23 How should we look at decreasing this
24 risk? We think that it may be worthwhile to
25 undertake some research on both types of systems to

1 again try to quantify some of what I have described
2 as qualitative differences, to beef up the
3 labeling.

4 Should the unipolar manufacturers include
5 labeling similar to what the VersaPoint
6 manufacturer has put into its labeling now, and
7 what everyone has when they use that device, and
8 also to increase clinician awareness.

9 We are a little bit concerned that
10 clinicians who have gone from unipolar system to
11 the bipolar system think, great, I am not using a
12 hypotonic solution anymore, therefore, you know, my
13 biggest risk factor is eliminated and I can just
14 relax and not really think too hard about what I am
15 doing here and what the risks of this procedure may
16 be.

17 My last bullet here is an attempt to
18 introduce our next speaker, who is Sharon Dillard,
19 who will talk about MDR reporting, how FDA gets
20 reports on events like this and how it decides what
21 really rises to the top and what requires action on
22 our part.

23 I will be happy to answer any questions
24 the panel may have, and I may wish to call on my
25 biomedical engineer depending on the questions.

1 DR. BLANCO: Thank you very much, Dr.

2 Corrado.

3 Any questions? Mike.

4 DR. NEUMAN: Just for the purpose of the
5 record, and maybe your biomedical engineer will
6 need to help you with this, you had some very
7 elegant drawings of the electric fields, and it
8 appeared to me that this was more than just a
9 cartoon, that it was probably a computer
10 simulation. Could you clarify that for us?

11 DR. CORRADO: Yes, and I will ask Dr.
12 Chang to take the podium now, but he does computer
13 simulations of electrosurgery in different types of
14 tissue, and therefore he is very versed in creating
15 this type of diagram.

16 DR. CHANG: Hi. I am Dr. Isaac Chang. I
17 am from the Office of Science and Technology in the
18 Center for Devices and Radiological Health.

19 DR. NEUMAN: Let me just ask another
20 question about the unipolar electrode when it is
21 placed with a saline distention fluid. I think
22 your simulation showed that a large amount of
23 current is going through the saline.

24 Would that current be large enough to
25 cause vaporization of the saline and produce a

1 vapor pocket similar to what was shown with the
2 bipolar electrode, and then if that occurs, would
3 the unipolar electrode be just as directional as
4 the bipolar?

5 DR. CHANG: For the simulation that was
6 presented, that is with the unipolar catheter
7 assuming that you have a saline solution, and it is
8 assuming a tissue with the conductivity
9 approximately the same as what you would find in
10 the uterus.

11 What we found in our models is about 90
12 percent of the current that is ablated actually
13 goes into the saline. However, given the way it is
14 being used with a considerable amount of movement
15 of the fluid, we don't really expect to see or we
16 don't anticipate seeing a large amount of bubble
17 formation.

18 We personally think that the bubble forms
19 because you are heating medium, whether it be a
20 fluid or a tissue, giving a significant amount of
21 energy with the high e-field strength, and that
22 causes the local temperature to actually rise.

23 I guess sort of in concert with what was
24 said before, once the temperature reaches above a
25 certain point, 100 degrees C., you get the

1 formation of bubbles, so in answer to your
2 question, even though a significant amount of
3 current appears to be going into the saline,
4 because the saline is a fluid and is likely to
5 move, we don't anticipate there being a large gas
6 formation.

7 DR. NEUMAN: Can I ask one more question?

8 DR. BLANCO: Just so that we don't get off
9 on a tangent, I mean it is my understanding, and
10 Dr. Levy has confirmed this, that typically, unless
11 you had a hanging bag error, you would not use
12 saline for unipolar, and you would not use glycine
13 for bipolar, so before we get into the physics or
14 the biomechanics of these things, I mean that is an
15 error in hanging the appropriate solution rather
16 than something in the system, rather than something
17 of the particular physics, so I don't want to get
18 off on that if you agree with that too much.

19 DR. NEUMAN: I will ask my question off-line.

20 DR. BLANCO: Okay. Thank you.

21 Any other questions at this point?

22 DR. LEVY: Just from the standpoint of
23 looking at medical errors, however, it would be
24 reasonable to look at those scenarios and look at

1 the kinds of injuries that could occur when someone
2 does hang the wrong solution. So, I don't think we
3 are totally off base in looking at those things,
4 but we must understand that that is not the way
5 they are designed to be utilized.

6 As FDA considers doing some research into
7 medical errors, however, that is something we may
8 want to look at. From a clinical standpoint, if
9 you tried to use monopolar electrosurgery with the
10 saline solution, you would get no tissue effect.
11 The surgeon would be screaming up and down it's not
12 working, it's not working, something is wrong, and
13 they would ultimately figure it out, we hope.

14 DR. CORRADO: We used those examples to
15 try to highlight the differences between the two
16 systems, and what it was inherent in the electrode
17 placement that makes it necessary to use saline
18 with the bipolar system and a non-conducting fluid
19 in the unipolar system, I certainly didn't intend
20 to suggest that it was optional, but I intended to
21 show that hypothetically, if you attempted to use
22 it this way, this is what would happen.

23 DR. BLANCO: I think the issue is that as
24 we get into the discussions, there are clearly two
25 items or two areas that we need to look at. Some

1 FDA to provide leadership in addressing medical
2 device-related risks not only in the premarket
3 activities, which you are quite familiar with, but
4 also in the postmarket portion of the medical
5 device life cycle.

6 To this end, I will be providing you with
7 a very brief overview of FDA's medical device
8 adverse event reporting program. I will provide
9 some additional comments on MDR reports describing
10 air or gas emboli that occur during operative
11 hysteroscopy using fluid insufflation medium, and I
12 will briefly touch upon some of postmarket options
13 commonly used by FDA to help us better understand
14 and address new or emerging medical device related
15 problems and any related public health issues and
16 concerns.

17 [Slide.]

18 FDA's adverse event reporting program
19 consists of both mandatory and voluntary
20 components. Mandatory reporting requirements apply
21 by law to device manufacturers, device importers,
22 and user facilities. These reporting requirements
23 are specified in Title 21 of the Code of Federal
24 Regulations. It is Part 803, and it is entitled,
25 "Medical Device Reporting," and throughout this

1 presentation, you will hear me say MDR quite a bit,
2 and that is what I mean.

3 Manufacturers under MDR must report deaths
4 and serious injuries if a medical device may have
5 caused or contributed to the event. They must also
6 report to FDA certain types of device malfunctions.

7 User facilities, as defined by the MDR
8 regulation, for example, hospitals, nursing homes,
9 outpatient surgical and diagnostic facilities, and
10 so forth, must report device-related deaths and
11 serious injuries, and they must report those to the
12 manufacturer or to FDA if they do not know who the
13 manufacturer is.

14 FDA-regulated user facilities are not
15 required to report device malfunctions, however,
16 FDA encourages these user facilities to report
17 voluntarily any medical device-related problem of
18 concern including use error to the device
19 manufacturer as a public health initiative.

20 You should be aware, and I am sure almost
21 everyone here may be aware, that the private
22 offices of physicians and dentists are not subject
23 to mandatory reporting requirements.

24 [Slide.]

25 FDA also maintains a voluntary reporting

1 system. The agency recognized that health care
2 professionals are often the first to recognize
3 device problems with medical devices, and we know
4 that there may be some problems of concern that do
5 not meet our mandatory reporting thresholds, very
6 important ones in some cases, but under the
7 voluntary system, physicians, any type of health
8 care professional can report in confidentiality, if
9 that is necessary, any type of device-related
10 problem or concern.

11 DR. BLANCO: I wonder if we could go ahead
12 and continue without the slides. We are running a
13 little late on time. So, please, if you would go
14 ahead and continue with your verbal comments.

15 MS. DILLARD: No problem.

16 Although the specifics of the MDR
17 reporting regulation are really beyond the scope of
18 this discussion, in general, symptomatic air/gas
19 emboli experienced during operative hysteroscopy
20 will generally meet FDA's mandatory adverse event
21 reporting thresholds.

22 That is, when a user facility, a device
23 manufacturer, or an importer becomes aware that
24 such an embolytic event has occurred, even if use
25 error is thought to have contributed to such an

1 event, they must report in accordance with the
2 requirements specified in the medical device
3 reporting regulation.

4 [Slide.]

5 In any discussion of medical device
6 reporting, it is important to take notes of both
7 the strength and limitations of FDA's MDR system.

8 [Slide.]

9 With regard to recording medical device
10 related adverse incidents, the system is quite
11 robust and FDA receives approximately 100,000
12 adverse event reports per year, and the system is
13 internationally considered to be one of the best of
14 its type in the world.

15 It is one of many tools used by FDA
16 scientists to monitor and identify emerging
17 problems and public health concerns and the
18 information reported to the FDA continues to
19 represent a unique and powerful surveillance tool
20 that serves an important role in assisting FDA in
21 both recognizing and addressing important medical
22 device-related issues.

23 [Slide.]

24 It is also important to clearly recognize
25 the limitations of the system, and although MDR is

1 a powerful signaling tool, for the most part, the
2 information submitted to the agency consists of
3 unconfirmed attributions, the reports typically
4 contain very little information regarding
5 definitive cause and effect of a given incident,
6 and it is widely recognized that any passive
7 surveillance system is subject to substantial
8 under-reporting.

9 There are also biases, such as press
10 coverage or even a recent FDA inspection that can
11 result in increased reporting compared to the
12 status quo of certain events or certain problem
13 categories.

14 [Slide.]

15 With that in mind, I would like to remind
16 us all to resist the temptation to treat any
17 information reported into our system as data from a
18 controlled clinical trial.

19 [Slide.]

20 As a result of the biases inherent in the
21 system, MDR information cannot be used to reliably
22 predict population-based incidence or prevalence
23 for any given device-related problem or failure
24 mode.

25 It also cannot, and should not, be used to

1 differentiate "good" firms or products from "bad"
2 firms or products.

3 With that in mind, I, like others before
4 me, would like to take a moment today to note the
5 efforts that Ethicon has made to assure that
6 required MDR reports were submitted to the agency,
7 that follow-up actions were taken as required under
8 FDA's quality system regulation, and to acknowledge
9 Ethicon's willingness to further discuss and
10 explore operative hysteroscopy issues in this
11 public forum in order to further the shared goal of
12 reducing the occurrence of device-related air or
13 gas emboli during operative hysteroscopy.

14 [Slide.]

15 Well, what has been reported to FDA with
16 regard to the issue at hand? We were curious early
17 on and we searched the adverse event database for
18 reports describing embolytic events specifically
19 associated with operative hysteroscopy performed
20 with fluid insufflation.

21 The search covered the time period from
22 1996 to the present, and the search included all
23 possible candidate devices, that is, in addition to
24 electrosurgery systems, we looked at hysteroscopes,
25 insufflation systems, and any other type of

1 endoscopic surgical instrumentation that might be
2 involved in such an incident, and the only reports
3 that met our tech search criteria were associated
4 with bipolar or bipolar type electrosurgical
5 systems.

6 [Slide.]

7 No reports of air or gas emboli associated
8 with the use of monopolar or unipolar
9 electrosurgical electrodes during operative
10 hysteroscopy procedures appear to have been
11 reported to FDA through either the voluntary or
12 mandatory reporting system from 1996 to the
13 present.

14 One report was received for an embolytic
15 event involving the use of the Conceptus ERA
16 sleeve, which is what we have previously referred
17 to as that hybrid bipolar type device, and that
18 report was received in June of 1998.

19 Between July of 1999 and the present,
20 eight events involving air or gas embolism have
21 been reported in association with the use of the
22 VersaPoint bipolar electrosurgical system during
23 operative hysteroscopy.

24 Three reports were received in 1999, four
25 reports were received in 2000, and the most recent

1 report was submitted in April of 2001.

2 [Slide.]

3 Interesting, but what does this mean?

4 FDA and MDR report reviews allows us the
5 opportunity to consider reported information on
6 adverse device-related events in order to determine
7 if that information requires further FDA follow-up
8 action in order for us to meet our regulatory
9 mandate to address device safety, efficacy, or
10 public health related concerns.

11 Sometimes the concerns raised in the MDR
12 reports are easily explained or answered and
13 sometimes they are not, and that is that the data
14 and clinical information that will be necessary to
15 definitively address certain concerns especially
16 regarding new or unusual issues or rare events, may
17 not yet be available.

18 Drs. Isenberg and Munro have provided
19 detailed information related to the reported events
20 of concern, and Dr. Corrado has talked a bit about
21 some of the internal workings that FDA undertook to
22 address those concerns, but from a more general
23 perspective, the MDR reports have served their
24 signaling function, and they motivate us to
25 consider what factors might explain the differences

1 in these observed reporting patterns associated
2 with air or gas embolism in conjunction with
3 operative hysteroscopy.

4 [Slide.]

5 Again, MDR reports typically raise more
6 questions than they allow us to easily answer, and
7 you might be thinking that only nine events appear
8 to have been reported to FDA, however, FDA takes an
9 interest when even a few reports of a serious but
10 potentially preventable device-related complication
11 are received.

12 I would like to mention some of the
13 questions raised by the MDR report review, some of
14 which may have been touched upon all or in part by
15 the previous speakers, and some of which are
16 embedded in the discussion questions the panel has
17 before it today.

18 I do not intend for the panel to discuss
19 these questions at this time. These examples are
20 simply meant to illustrate the postmarket thought
21 process.

22 For example, does the observed reporting
23 pattern suggest that there may be a real difference
24 between the occurrence of air/gas embolism during
25 operative hysteroscopy using a fluid insufflation

1 medium between unipolar and bipolar electrosurgical
2 systems.

3 I couch my words carefully because on my
4 end of the spectrum, things that shouldn't be done
5 are often done, and so we want to focus this on
6 when things are being done correctly.

7 Are the incidents of concern such rare
8 events that there are actually are no other
9 incidents to report? Based on our understanding of
10 the biases involved in reporting, we do not expect
11 that the majority of such events have been
12 reported, and as mentioned earlier today, there are
13 case reports in the medical literature describing
14 embolytic events associated with the use of
15 unipolar electrosurgical electrodes during
16 operative hysteroscopy.

17 Are there concomitant device use factors,
18 device design issues, or possibly functional
19 differences between bipolar and unipolar
20 electrosurgical system configurations that could
21 account for the observed reporting pattern?

22 Is it possible that clinicians generically
23 consider gas or air emboli formation to be a
24 procedural complication associated with endoscopy,
25 and in this case operative hysteroscopy, rather

1 than a potential device-related complication, and
2 as a result, they do not recognize that such events
3 should be reported to the device manufacturer under
4 MDR.

5 Unlike monopolar electrosurgical
6 electrodes used in operative hysteroscopy, the use
7 of FDA-cleared bipolar electrodes for hysteroscopy
8 is comparatively new and may be increasing. Is
9 there heightened clinical awareness and interest
10 that would account for the reporting differential,
11 that is, are there problems being reported in
12 association with the use of bipolar electrodes that
13 would not be reported if the same type of event was
14 experienced in association with the use of a
15 monopolar electrode?

16 [Slide.]

17 I am sure everyone has questions they
18 could add to this list, but the most provocative
19 question from a postmarket perspective is now that
20 we know the firm's response to the reported events
21 involving the VersaPoint electrosurgical system,
22 does FDA need to do more at this time?

23 [Slide.]

24 We consider our postmarket authorities to
25 be a complement to our premarket programs for

1 medical devices, and with respect to postmarket
2 questions and issues, such as those that have
3 brought us together today, FDA has at its disposal
4 a relatively wide variety of both regulatory, as
5 well as non-regulatory options, that we can use to
6 help us better identify, understand, and address
7 public health concerns in an appropriate manner.

8 Like today, we can raise these questions
9 and issues of concern before a panel of our expert
10 advisors. FDA can issue directed inspections of
11 manufacturers and user facilities. Section 522 of
12 the Safe Medical Devices Act provides FDA with the
13 discretionary authority to order manufacturers of
14 certain classes of devices brought to market
15 through FDA's premarket notification or 510(k)
16 process to conduct postmarket surveillance studies.

17 Such discretionary authorities are used
18 judiciously, but they may be appropriate when a
19 public health question can be clearly specified and
20 a clear clinical or regulatory need for obtaining
21 the data necessary to answer such questions can be
22 established.

23 Based on recognized device-related
24 problems including use error-related concerns, FDA
25 can issue public health notifications, such as

1 alerts and advisories. We publish information on
2 manufacturer-initiated recalls and safety alerts,
3 and we have a number of educational options at our
4 disposal.

5 As appropriate, FDA, working in concert
6 with regulated industry, professional practice
7 organizations, academia, or other government
8 agencies can sponsor professional meetings to
9 stimulate research and information exchange on
10 topics of device-related public health concern.

11 We publish and peer review medical and
12 scientific journals and we frequently work with
13 outside organizations to develop educational
14 information or programming designed to help health
15 care professionals recognize and reduce the
16 occurrence of preventable device-related problems.

17 Most recently, CDRH has received blanket
18 clearance through OMB to conduct what we call a
19 Rapid Response Survey. These are limited surveys
20 of user facilities, professional practice
21 organizations, individual health care
22 professionals, or other targeted groups, and they
23 are designed to help us quickly gather information
24 on postmarket questions without having to go
25 through lengthy survey approval processes.

1 Panelists, in your package of reference
2 materials, you have some examples of these types of
3 actions that have been taken by FDA with respect to
4 other device issues.

5 [Slide.]

6 In conclusion, I would like to thank you
7 for your attention and I hope this very brief
8 overview of FDA's postmarket surveillance programs
9 and postmarket initiatives proves useful as you
10 deliberate the questions at hand today.

11 DR. BLANCO: Thank you very much.

12 Are there any questions of fact? We have
13 got to keep them brief. We are running a little
14 late.

15 DR. SHIRK: My question would be why was
16 your literature study so limited back to '96? It
17 is a problem since I have been working with this
18 thing for a long, long time, and started the
19 endometrial ablation studies back in the early
20 1980s, you know, that we have known about clear
21 back in the 1980s.

22 Certainly the laser ablation thing was
23 obviously operator error with the insulation of
24 either carbon dioxide gas or CO2 through coaxial
25 cable into the cavity under high pressures and

1 rapid volumes, but Don Chapman back in 1986 had a
2 paper about air embolism and two cases that were
3 reported, so these cases obviously extend back
4 beyond 1996.

5 I think that your literature search
6 probably should have gone back before then, and
7 these questions have been asked for a long time.

8 MS. DILLARD: I agree with you, and just
9 so you understand, in order to do this search and
10 do it effectively, it is not as simple as it might
11 sound on the outset. There were about 2,500
12 candidate reports that had to be hand-read in order
13 to determine what was in those reports and if they
14 were suggestive of the types of events that we were
15 looking at.

16 Because the bipolar device, the VersaPoint
17 was introduced in 1996, we did our search from '96
18 forward in order to have a comparison over that
19 time frame, but your points are well made.

20 DR. SHIRK: Another question is are there
21 any literature things in the urological literature
22 that comprise the same thing, since this is
23 borrowed equipment from urology, and urology has
24 been using monopolar and bipolar electrical devices
25 in the bladder for over 50 or 60 years, and are

1 there any similar problems with air and this type
2 of technology in the urological field?

3 MS. DILLARD: Those are good questions,
4 and quite frankly, that is why we are here today,
5 to call upon your expertise to guide us, so that we
6 understand whether we are dealing with a selective
7 risk or an equal risk between the use of these
8 types of devices, and I don't know if my colleagues
9 from ODE have anything to add.

10 DR. BLANCO: I am not sure that you are
11 going to be able to tell that, as you yourself
12 cautioned, adverse reports are not going to give
13 you necessarily numbers whether they are similar in
14 the bipolar versus unipolar.

15 I know you are not implying that, but I
16 think that the point that Dr. Shirk is making, that
17 Dr. Levy also whispered in my ear, is that when you
18 have devices that have in the market before,
19 reports may have occurred when it was new, people
20 are more comfortable with it, and they know, well,
21 these are not that major or dramatic, so they may
22 not be reporting them anymore, whereas, this being
23 a relatively new device, they may be more likely to
24 report this.

25 I think we need to be careful not to make

1 the assumption that simply because there have been
2 no reports with unipolar methodology since the
3 bipolar methodology was introduced, that that means
4 that the unipolar methodology does not cause some
5 similar problems as a possibility.

6 Am I kind of paraphrasing what you were
7 saying?

8 DR. SHIRK: Right.

9 MS. DILLARD: Absolutely, and I hope Dr.
10 Corrado's point was made, as well as mine, that
11 that is the case.

12 Dr. Shirk, just from my perspective, when
13 you said "literature," I was thinking of the
14 medical literature, not my MDR reports, so my
15 answer was geared that way, and I just want to
16 clarify that point.

17 DR. SHIRK: I was speaking of medical
18 literature. I mean there are reports in the
19 medical literature that date back to 1986, when
20 Chapman put a report in of two cases, so, you
21 know, there are reports in the medical literature
22 involving other energy sources and hysteroscopy
23 that have been associated with air embolism.

24 DR. BLANCO: Thank you.

25 In the interest of time, let's go ahead

1 and proceed.

2 The next part of the meeting is the open
3 public hearing. I have two individuals that have
4 stated that they have an interest in speaking
5 before the panel. We will allow it if there are
6 others that want to speak. Please limit your
7 remarks to five minutes.

8 The first individual who has registered
9 that they have an interest in speaking before the
10 panel is Jay Cooper, Dr. Jay Cooper, President of
11 the AAGL.

12 Dr. Cooper. [Pause.] It appears that he
13 is not here today, so we will move on to the next
14 speaker, Jay Houser, Market Director, Karl Storz
15 Endoscopy.

16 Please remember to state conflict of
17 interest.

18 Open Public Hearing

19 MR. HOUSER: My name is Jay Houser. I am
20 Director of Marketing, Product Development, and
21 Research Development with Karl Storz Endoscopy.

22 Karl Storz Endoscopy is the world leader
23 in durable medical endoscopic products distributing
24 worldwide. My background also is formation from 21
25 years of experience in endoscopic surgical products

1 including Conceptus, where I was Director of
2 Marketing and developing their product.

3 I want to thank the panel and the FDA for
4 allowing me to speak today. I also would like to
5 thank Dr. Keith Isaacson from Mass. General
6 Hospital, who has provided me with additional
7 information he would like to have verified, or
8 excuse me, presented.

9 [Slide.]

10 The first thing I want to do in my
11 presentation really from a layman's terms is not so
12 much to go into the electrophysiology and actions
13 of monopolar except in comparison to bipolar, but
14 really to give some historical perspective from our
15 point of view on monopolar electrosurgical
16 resectoscopes.

17 I say that in the aspect I will also refer
18 to bipolar because Karl Storz has been very
19 interested in bipolar resectoscopes and treatment
20 of the uterus for some time. Because of that, we
21 have been watching very carefully what safety
22 measures we must incorporate in looking at this
23 product line.

24 [Slide.]

25 One of the benefits I guess and detriments

1 of being the last speaker on today's schedule is
2 that I am going to be redundant on a number of
3 slides, so I will make them quick, at the same
4 time, hopefully, the previous speakers will have
5 independently verified some of the things that I am
6 presenting.

7 [Slide.]

8 We have all discussed the complications of
9 operative hysteroscopy and most of these have all
10 been well documented in one form or another.

11 [Slide.]

12 The main causative factors generally found
13 in the literature are long operative procedure
14 times, which we have discussed, high intrauterine
15 pressure, and that has a caveat, is that previous
16 and most of the studies, the actual intrauterine
17 pressure was not actually documented or what role
18 it plays and actually in this case, in gas embolism
19 absorption.

20 We do know that deep intravasation into
21 the myometrium during operative procedures
22 increases the risk for intravasation and thus, by
23 association, may also have a play in absorption of
24 gas. We know that heavy vascularization of the
25 endometrium, particularly in myoma, generally is an

1 increased risk for absorption of fluid.

2 [Slide.]

3 Monopolar energy resectoscopes, a very
4 similar slide. This is just a depiction of the
5 energy path. Things that we do know is that in
6 order to use monopolar energy, you must use a non-
7 electrolytic solution, primarily glycine, sorbitol
8 or mannitol, the primary solutions.

9 We do know that bubbles do occur and that
10 generally is a result of heat transfer and forming
11 a vapor pocket in order for the energy source to
12 work. However, bubbles do appear. They are less
13 than those seen in bipolar devices. I do have four
14 videotapes all keyed for about a 20- to 30-second
15 visualization if you would like at the end of my
16 procedure, we can do those very quickly and you can
17 see exactly what the differences are clinically.

18 [Slide.]

19 Bipolar resectoscopes, primarily in
20 devices, the Conceptus ERA bipolar sheath device.
21 There are bipolar electrodes which are being looked
22 at to be distributed independently, which fit onto
23 monopolar systems, which are similar to activity as
24 the Conceptus sheath. They are hybrids. The
25 Gynecare VersaPoint system.

1 There are differences in the site of
2 current transfer, and we know that the current path
3 now is between the active electrode, through the
4 electrolytic solution and back to the return
5 electrode.

6 [Slide.]

7 Activation of bipolar electrode is
8 somewhat dependent on the high resistance around
9 the electrode to create sufficient power. This
10 occurs because the power in the tissue is lower
11 generally and you must allow sufficient power to
12 force the current through the saline to the tissue
13 and return again.

14 The consequence of that is bubbles do
15 occur generally by heat or vapor in the development
16 of this resistance, and they are generally of
17 larger volume, however, what is the question is
18 what value or what parts does that larger volume
19 play in the increased reported incidents so far of
20 gas embolism.

21 [Slide.]

22 A little bit of history here. First of
23 all, the resectoscope was first used as reported I
24 think in about 1978 with Dr. Robert Neuwirth. Over
25 the years subsequent to that, there were not

1 reported incidents, and that is the most important
2 part is reported incidents of gas or air emboli was
3 not mentioned in the gynecologic literature on
4 resectoscopic surgery.

5 [Slide.]

6 However, laser came into play, and in
7 1997, Dr. Philip Brooks reported 7 cases of venous
8 air emboli events, cause unknown whether it was air
9 or gas emboli, 7 case reports, 5 to 7 which were
10 death.

11 Again, 1988 and 1989, previous to that,
12 Dr. Loffer, Dr. Baggish, Dr. Danielle also reported
13 deaths again related to the product of laser used
14 in saline.

15 All of these procedures, there were
16 numerous bubbles of large volume that were also
17 produced.

18 [Slide.]

19 Laser declined after these reports, and
20 again so did the incidents of reported air emboli
21 or gas emboli, although there were some ancillary
22 reports after that, primarily in anesthesia
23 journals at this point, and some of this may be
24 attributed to some increased vigilance, however,
25 there were no known deaths reported.

1 [Slide.]

2 In 1997, the ERA Bipolar Resectoscope
3 Sheath was introduced by Conceptus, developed by
4 Dr. Keith Isaacson. During subsequent use with
5 this product, Dr. Isaacson had the hair-rising
6 experience of experiencing a gas or air emboli
7 during a procedure. Things that he noted was that
8 he was using normal saline, there was no monitoring
9 of intrauterine pressure. There was definitely
10 increased bubble volume during the procedure.

11 After this point in time, except for a
12 study which I will present in a minute. Dr.
13 Isaacson discontinued the use of the ERA Bipolar
14 Resectoscope due to the fear of gas and air emboli.

15 [Slide.]

16 During this period of time, after
17 reporting this to Conceptus, Dr. Isaacson went into
18 a short pilot study which was discontinued by the
19 company as they decided to discontinue
20 manufacturing of the Conceptus sheath.

21 The following comments are directly from
22 Dr. Isaacson on the pilot study. Basically, the
23 use of saline is of benefit over non-electrolytic
24 solutions due to the risk of hyponatremia with
25 those solutions; that the physics of the bipolar

1 system can be used in saline because it creates the
2 vapor bubble around the electrode. The wattage
3 necessary is really not any different than that of
4 the unipolar system or monopolar system.

5 The intrauterine pressure necessary to
6 create distention is higher or as high, so that any
7 gas that may be created by the hysteroscopic
8 electrode may enter the venous system and return to
9 the right heart.

10 [Slide.]

11 He also agrees that upon the clinical
12 significance of this, bubbles are unknown, they
13 consist of basically the same concept and
14 development that Gynecare has studied, they diffuse
15 into the venous system, however, of question is if
16 the accumulation is greater than the rate of
17 diffusion, which has already been brought up in the
18 panel, the signs of gas/air embolism may occur.

19 The exact mechanism for this is still
20 unclear, with two possible causative factors that
21 he reported. One is increased bubbles and
22 unanswered questions as to the intrauterine
23 pressures and what roles they may or may not play
24 in the intravasation of the gas and liquid. This
25 was suggested by Perry in his paper.

1 [Slide.]

2 In 1998, FemRx/Gynecare also introduces
3 bipolar resectoscope. During this period of time,
4 again we see a rise in air or gas emboli, again the
5 mechanism is unknown. Common factors are bipolar,
6 which creates more bubbles, normal saline
7 distention, and unrecorded or unknown intrauterine
8 pressure recordings.

9 [Slide.]

10 In conclusion, certainly, there is a need
11 to understand the differences now of incidence of
12 gas/air emboli between the monopolar and bipolar
13 systems.

14 The incidence and significance
15 particularly are the formation of bubbles. The
16 risk that might be associated with each of these
17 varying conditions under different intrauterine
18 pressures, does that play a role.

19 Very lastly, I just pose a question.
20 Since these bipolar systems are now also going to
21 be marketed to urologists, should there be a
22 similar warning or question as to a study of those,
23 which are independent of this group.

24 I would like to show tape number 1 just
25 for about 30 seconds, if we could.

1 DR. BLANCO: I am sorry, let me interrupt
2 you. Are the tapes simply showing bubble
3 formation?

4 MR. HOUSER: Yes, that's all.

5 DR. BLANCO: We have seen that, I mean I
6 think one of the other speakers, so unless you
7 think there is something really to be learned extra
8 from that, I think we saw lots of bubbles.

9 Is that all right with the panel? Does
10 anybody want to see more bubbles? Let's move on
11 then.

12 MR. HOUSER: That's fine. Thank you very
13 much.

14 DR. BLANCO: Any questions of fact?

15 [No response.]

16 DR. BLANCO: Okay. Thank you very much.

17 Anyone else from the audience would like
18 to have any comments? Please introduce yourself
19 and any conflict of interest, and let's try to keep
20 it brief, so we can discuss.

21 DR. BRILL: I will try to be brief.

22 Andrew Brill from the University of Illinois,
23 Professor, Ob-Gyn.

24 I am a consultant for Gynecare, and they
25 have accommodated my travel with an honorarium for

1 today.

2 I want to share a couple thoughts in
3 listening to this morning's presentations and give
4 what I think is my viewpoint on some of the bigger
5 issues.

6 I had the luxury of being on the expert
7 panel after the voluntary withdrawal of the device,
8 and I think that in addition to looking at whether
9 there is a difference between monopolar or bipolar
10 devices, as a group, and I think we have heard
11 either directly or indirectly this morning, we have
12 concerns about physician behavior and this whole
13 amalgam that has been presented here.

14 Whether we can or cannot legislate or
15 control physician behavior is a difficult issue to
16 grapple, but we surely had a number of issues with
17 pressure, we have heard about lack of monitoring of
18 pressure, lack of monitoring of fluid deficit, poor
19 patient selection, large fibroids, deep intramural
20 myomas, mismatching between electrodes and myoma
21 size. This has nothing to do with bipolar versus
22 monopolar technology.

23 Another issue. We don't have any
24 scientific evidence whether bipolar technology is
25 indeed vaporogenic. You heard from Mack Munro that

1 we should look at electrosurgery as fundamentally
2 the same process regardless of whether you have
3 electrodes close together or some distance apart,
4 and it is actually the tissue change that creates a
5 vapor pocket.

6 So, to think of this as a bubble-generating device
7 is something that is
8 observational, it is not based on science.

9 Another issue that has been brought up by
10 Dr. Blanco, and that is observation bias. Here, we
11 have a new procedure, a new technique, we are all
12 concerned about changes. As long as a Kaplan graph
13 is being generated, anesthesiologists are sensitive
14 to changes within the operating room. A change in
15 end-tidal CO₂, a sudden drop in blood pressure,
16 maybe a transient change in oxygen saturation,
17 boom, we have a gas embolus.

18 The question is, is this clinically
19 significant or is it an observation? We don't know
20 the answer to that question. I think we all have
21 to accept that whenever you do intrauterine
22 electrosurgery, you create at least microemboli
23 through the circulation, and as long as
24 compensatory measures of the body are sufficient,
25 there is no clinical sequelae.

1 Now, the fact is, is that all these cases
2 were stopped because of fear, and that represents
3 prudence, however, we don't know what would
4 happened, and it may be that a number of these
5 observational events are physiologically
6 significant at that moment, but they have no
7 adverse sequelae, especially when you look at the
8 incredible solubility of the combustibles that are
9 created by electrosurgery in the uterus.

10 Now, my final point is what about bubble
11 formation, looking at monopolar versus bipolar
12 loops. Well, part of the difference in these
13 devices is the electrode configuration. Granted,
14 they both have the same shape and they have the
15 same contour, but the truth of the matter is, is
16 that the bipolar loop is a stout, thick loop
17 compared to a very fine wire, which is the
18 monopolar loop.

19 So, we have a big issue here, and the
20 issue is surface area, a larger surface area, more
21 vaporization, more bubbles. What does that have to
22 do with vaporigenicity of the technology? Nothing.
23 What does it have to do with the observation of
24 monopolar or bipolar necessarily? Not anything.
25 Just the fact that you have different surface area,

1 different electrode configurations, different
2 productions of gases based on the amount of tissue
3 that is vaporized per unit of time.

4 So, in summary, this is very unclear-cut
5 this morning. It is an amalgam of clinical issues,
6 it is an amalgam of technology concerns. For me,
7 and being part of this panel and part of this
8 process, I walk away with a heightened concern
9 about operative hysteroscopy in a fluid environment
10 using energy, period. Energy is going to create
11 vapor, and if it overwhelms the physiology of the
12 human body, it will become a clinically significant
13 gas embolus.

14 Thanks.

15 DR. BLANCO: Thank you.

16 Anyone else from the audience that would
17 like to make comments?

18 [No response.]

19 Panel Discussion

20 DR. BLANCO: If not, we will go ahead and
21 close the open public hearing portion, and let's
22 move right on to discussing the questions that FDA
23 has posed before us. You should have all these in
24 your packet.

25 The first discussion question is: What

1 are the underlying conditions that lead to the
2 formation of room air and gas emboli during
3 operative hysteroscopy with RF unipolar and/or
4 bipolar electrosurgery?

5 How common are room air and/or gas emboli
6 during operative hysteroscopy using RF ablation
7 technologies?

8 Are the risks essentially the same,
9 whether using bipolar or unipolar modes?

10 Are there other studies that should be
11 done to understand this risk?

12 Anyone that would like to start the
13 discussion? Go ahead, Dr. Shirk.

14 DR. SHIRK: I think the answer to this if
15 you put an esophageal doppler in and look, almost
16 everybody who is having an operative hysteroscopy
17 has got some amount of air embolism. Over my term,
18 I have done a lot of work on fluid intravasation
19 and certainly fluid intravasation occurs in almost
20 every--

21 DR. LEVY: Jerry, can I interrupt you just
22 for a second? Can I clarify, do you mean gas, and
23 not air?

24 DR. SHIRK: Gas, right, I am talking about
25 a gas, gas of some sort.

1 DR. LEVY: Okay. Just for the record, I
2 wanted to make sure that that was clear.

3 DR. SHIRK: Gas of some sort. Okay? So
4 that there are bubbles of gas going in. How the
5 bubbles are generated, as to whether they are being
6 introduced through the system or whether they are
7 being introduced by vaporization of tissue, I don't
8 think can be determined at this point.

9 Certainly, you know, all patients have a
10 certain amount of fluid intravasation, and that is
11 about a given, and it's just amount. So, again, it
12 amounts to amount, and there is no easy way from a
13 monitoring standpoint to quantify gas embolism or
14 how much gas is being introduced.

15 I know of no system where you could
16 literally quantify the amount of gas that is being
17 introduced into the system other than note that it
18 is happening.

19 The obvious problems comes when the amount
20 is significant enough to cause problems both at the
21 level of pulmonary structures and also in those
22 patients who have significant anatomic variances in
23 their cardiac system where you can have an atrial
24 defect or a ventricular defect where you can shunt
25 gas from the right side of the heart to the left

1 side of the heart and get catastrophic events by
2 air embolism to the brain. It is a very difficult
3 situation to look at over time.

4 Fortunately, these things are rare, but I
5 think we have to understand that almost all
6 patients that are undergoing those procedures are
7 going to have some amount of some form of gas going
8 into their systems, and that is pretty much a
9 given.

10 DR. BLANCO: Thank you.

11 Dr. Levy.

12 DR. LEVY: In approaching these things, I
13 think we need to look at clinically significant
14 events. There is no question that with almost any
15 medical invasive procedure, if we do adequate
16 monitoring, we will find some gas in the venous
17 system. That includes starting I.V.'s. It is
18 certainly true of neurosurgery, cardiac surgery,
19 all kinds of other things, so I think we need to
20 confine our comments and our concerns to what is
21 clinically in operative hysteroscopy.

22 So, the answer to the first bullet point
23 is it is very common, happens in everybody. From
24 there then, what can we do to reduce the clinically
25 significant risks, and that is what I think we need

1 to be concentrating on.

2 So, then, the second bullet, are the risks
3 essentially the same whether using bipolar or
4 unipolar, and I would say are the clinically
5 significant risks the same rather than the amounts
6 of gas, entrainment of gas, you know, what is going
7 on here, and I think we can't answer that question
8 yet.

9 Certainly, there were reports in the
10 literature of emboli during the monopolar era.
11 Certainly, there were cases that I personally knew
12 about of patients dying of air emboli that
13 obviously didn't generate MDRs, but they happened
14 because I was involved in those cases, not
15 personally as the surgeon, thank goodness, but I
16 know of cases that occurred well before the bipolar
17 systems came into play.

18 So, I think it will take ongoing MDR and
19 MedWatch surveillance for us to understand those
20 things. I don't think we can answer that question
21 today. I think what we need to understand is that
22 clearly, both systems create tissue effects that
23 create gas and that we need to monitor those
24 things.

25 So, that comes to the third bullet, are

1 there other studies that should be done to
2 understand the risk. In looking at what sorts of
3 studies you can do to understand the risk, I think
4 once you have created a clinical study, you have
5 really modified the risk factors to the point where
6 you are studying basic science, but you are not
7 studying what happens in patients.

8 It is very, very clear, looking at the
9 case reports, that, as Dr. Brill said, there are a
10 lot of clinician judgment errors in these cases, so
11 I think our job really probably needs to help FDA
12 focus on the second, third, and fourth questions
13 here, about what are the things that we can do to
14 keep patients safe in the current environment.

15 DR. BLANCO: Ralph.

16 DR. D'AGOSTINO: My question or response
17 to this No. 1, are they common? I mean we just
18 heard that they are common at one level, but are
19 they common in the sense of being serious, and I
20 get the impression that they aren't necessarily
21 common in terms of being serious.

22 DR. LEVY: I think one of the issues is
23 that if you are doing a patient under general
24 anesthesia, then, you are monitoring the PACO₂, if
25 you doing it under spinal or local anesthesia, you

1 are not.

2 DR. SCHROEDER: I would like to address
3 one comment and also suggest a possible bias in our
4 reporting data. As you mentioned these nine cases
5 and everything in the past several years had been
6 in the anesthesia literature solely, I can honestly
7 say that the routine monitoring of end-tidal CO₂
8 has only become standard in the past five to eight
9 years, certainly earlier in the academic centers or
10 the bigger centers that are able to afford more in
11 technological monitoring. Therefore, before that
12 time, the diagnosis of air embolism could be made
13 at autopsy or was pretty much a diagnosis of
14 exclusion. Therefore, most of these cases would
15 never have made it into our literature without end-tidal CO₂
16 monitoring.

17 DR. BLANCO: Thank you.

18 Did you want to say anything else, Dr.
19 Levy?

20 DR. LEVY: No, just to say that when you
21 look at what is clinically significant, the older
22 things in the literature are clearly air emboli
23 where the patients are dying.

24 These cases, the MDRs that we have looked
25 at--and I was part of the Gynecare Panel, and I

1 should disclose that to everybody, so that you know
2 that I have been able to look at those cases--they
3 were not clinically significant in the sense that
4 the patients all did very well. They were
5 significantly different in cases in the literature
6 of deaths being reported, and everything about
7 these patients was different.

8 There were also a lot of clinical errors
9 along the path in these patients, you know,
10 excessive fluid intake. You know, most of us would
11 stop a case at 1,000 cc of fluid deficit. Some of
12 these had 2,000 fluid deficit. The cases were
13 long. Most of us would stop a resection case at an
14 hour, some of them were two hours.

15 So, there were a lot of points along the
16 way there where I think that FDA, as well as
17 industry, can do a lot to prevent clinically
18 significant adverse events from happening by
19 educating physicians on how to do operative
20 hysteroscopy and how to avoid these things.

21 DR. BLANCO: Dr. Diamond.

22 DR. DIAMOND: I think the last comments
23 that Barbara made are very important, and I think
24 would go a long way to a lot of the issues, but
25 specifically to this question. I am less confident

1 that we know truly how often gas or air emboli
2 occur. I wouldn't be surprised, based on what I
3 have learned preparing for today's session, that
4 they occur very frequently in almost all cases as
5 others have suggested, but I really don't think we
6 know that factually.

7 I also don't think that we have a good
8 handle on if they do occur in most or all patients,
9 how much gas or air is being embolized, nor do I
10 think we have a good handle on the issues of
11 bipolar versus unipolar.

12 The studies that have been done look at
13 generation of gas, sometimes at different power
14 settings based on different practice of uses, but
15 still the question is what is getting into the
16 circulation.

17 I think there are areas where a lot of
18 additional studies could be done, perhaps by
19 comprehensive and serial monitoring of end-tidal
20 CO2's, perhaps by doppler flow studies or other
21 forms of imaging, but I think there is a large
22 amount that could be done to try to identify the
23 magnitude of the risk, the frequency of it, and
24 would better allow us to answer these questions.

25 DR. BLANCO: Any comments? Dr. Shirk.

1 DR. SHIRK: I guess one of my questions
2 would be, you know, would there be any certain
3 patient populations that are at certain risk.

4 Certainly, patients with ASD and BSD might
5 be an exclusion criteria, you know, put out on the
6 labeling as people that should be excluded from use
7 of these products just because of their increased
8 risk of shunting gas from right side of the heart
9 to the left side of the heart, which is a much more
10 serious consequence, and at what point should some
11 studies with echocardiography be done on these
12 patients that are having the procedures done.

13 DR. BLANCO: Dr. Schroeder.

14 DR. SCHROEDER: I would like to address
15 both of those issues, one, with the issue of
16 transesophageal echocardiography, and when you
17 mentioned esophageal doppler earlier, I am not
18 exactly sure if you were talking about TEE's or
19 not.

20 That is an extremely sensitive, extremely
21 sensitive mode for detecting both gas emboli and
22 turbulent flow, and sometimes merely rapid
23 administration of a crystalloid solution, such as
24 the normal saline that you all are infusing into
25 the uterus, can cause what looks like air. It is

1 in some settings very difficult to tell the
2 difference between a gas bubble that is from
3 turbulent flow and a gas bubble that is from actual
4 introduction of gas.

5 I would suggest that if there was a
6 motivation to study this, that a combination of TEE
7 with addition of end-tidal CO2 monitoring, end-tidal
8 nitrogen monitoring, which both of those two
9 are pretty standard, would be a reasonable sort of
10 combination of things to look at.

11 The end-tidal nitrogen monitoring is very
12 sensitive for air emboli, and since nitrogen didn't
13 seem to be a product of the device function, that
14 would differentiate gas from the use of instruments
15 and the other issues that were discussed, also, the
16 potential contraindication in patients who have
17 intracardiac shunts.

18 It is also well known that up to 25 to 30
19 percent of patients have a pro patent foramen
20 ovale, such that if you do have reversal of
21 pressure in the right to left atrium, you can have
22 opening of that shunt, and a patient who doesn't
23 know they have it and who has never had any type of
24 embolic phenomenon before, I think those patients
25 should be remembered.

1 DR. BLANCO: Let me make some comments,
2 kind of go in a different direction, because I
3 think that it is very commendable and we all like
4 lots of studies and lots of information, but I
5 think it is going to become very difficult again to
6 go back to what is clinically significant and what
7 really is going to give information that is
8 worthwhile.

9 I have heard several people--I don't work
10 with, I don't do these, so I am purely an amateur
11 at this--but a lot of people saying it happens all
12 the time, that you see it all the time. Well, does
13 it make any difference then if it happens all the
14 time, or is that just something that is going to
15 happen with the procedures, so I think the issue is
16 does it happen enough that it causes some type of
17 problem, that something needs to be done in the
18 utilization of the procedure. I don't know how you
19 get at that, quite frankly, for either industry or
20 for FDA. I don't know how you answer that
21 question.

22 I don't think that medical device
23 reporting or adverse reports is going to do it.
24 Quite frankly, the only experience I have had with
25 this recently is that my wife had a resection--she

1 will hate going public--and she had a broken little
2 wire loop. That was never reported, I don't think,
3 and it was inside of her.

4 I think that this poses really a great
5 problem. The other issues, we don't have a
6 denominator, and actually I had hoped that the
7 company would have given us some idea, if they have
8 it, of how often do we know that this procedure has
9 been done during these four or five periods as
10 opposed to unipolar or bipolar.

11 I think that in trying to wrap up the
12 question, I think we need to look at two things,
13 suggestions to FDA, and again it is what I alluded
14 to earlier in terms of as I see this as somebody
15 that doesn't do this, there are two issues.

16 One is the issue of obviously, physicians
17 are doing some things, and operating room personnel
18 are doing some things, that don't sound real good,
19 like having air in the tubing that takes the liquid
20 to the device, et cetera, et cetera, I won't go
21 into that, and I think that means that the labeling
22 for those particular issues really needs to be
23 strengthened to make sure that people realize that
24 that just isn't a good idea and not good surgical
25 procedure.

1 I think some folks have brought forth some
2 things, such as a deep myoma, vascularity of the
3 uterus, length of the procedure, and I don't know
4 what the data is for that and how certain we are of
5 all those different issues, but certainly that
6 should be strengthened in the labeling, so that the
7 physicians who are using, the personnel who are
8 using these are aware that these are issues that
9 may create more complications.

10 So, those are things that can be done, I
11 think through a lot of labeling, and if the panel
12 doesn't agree, please, come on back.

13 Then, the other issue is this issue of the
14 gas. I think, quite frankly, it is going to
15 behoove the company, because obviously--forgive me,
16 make sure I say my words--but obviously, this may
17 become a marketing issue among companies out there,
18 so it may behoove the company that makes the
19 bipolar to take a look at some of these issues of
20 how much gas is or is not produced and whether that
21 gas does go into the patients and whether it has
22 any significance.

23 I open it to the rest of the panel to
24 shoot my usual statements here.

25 DR. O'SULLIVAN: A couple of issues.

1 Number one, I know end-tidal CO2 has been monitored
2 for about five or six years and all general
3 anesthetics, so if that is the case and people have
4 been using unipolar techniques, one would think
5 that something would have been picked up that way.
6 That doesn't mean it is going to get reported, I
7 agree with that.

8 The second issue is relative to how you
9 could do something about this. I think that
10 sending out alerts, you know, letting people know
11 that this is a problem and that they need to pay
12 attention to it and that they need to be careful of
13 how they do the procedures and that they should
14 report it.

15 Finally, we have an obligation, I think,
16 perhaps even through the college or some other way,
17 to educate everybody who is using these techniques
18 about the risks associated with them including the
19 operating room personnel, as well as the physician
20 user.

21 I have another statement. To say that
22 they may not be clinically meaningful, I think
23 anybody who has these symptoms, who requires to be
24 in the hospital for several hours afterwards, who
25 alerts and throws everybody's heart into a mode

1 that could clearly cause some of them to have a
2 heart attack, that's clinically significant.

3 DR. BLANCO: What I meant by clinically
4 significant was that apparently, the technology
5 with TEE is there, that you are going to find even
6 a tiny little bubble that everybody, you know, Dr.
7 Shirk, Dr. Levy were saying, hey, we are going to
8 see that in everybody, they certainly don't seem to
9 be worried about it. That is what I meant, as
10 opposed to somebody where there is changes in
11 obviously physiological measurements. Okay?

12 DR. O'SULLIVAN: Uh-huh.

13 DR. BLANCO: Anybody else?

14 DR. LEVY: I just want to point out, too,
15 that a lot of these cases are not done under
16 general anesthesia where the PACO2 is not being
17 monitored, so in the old days of operative
18 hysteroscopy, those of us who are old enough,
19 Jerry, to have been doing a bunch of it, we did a
20 lot of it under spinal, epidural and even local
21 anesthesia, so a lot of it was being done in the
22 older days with smaller myomas, a little bit less
23 pathology, and certainly not anywhere near this
24 kind of monitoring.

25 I absolutely agree with you in terms of

1 clinical significance if patients need to stay in
2 the hospital a lot longer, but I have yet to have a
3 patient induced with propofol, who doesn't drop her
4 pressure out for a couple of minutes, and we all
5 watch that happen, we all watch the systolic
6 pressure go down to 60 and 70 maybe, you know, we
7 watch it for a while and it comes right back up,
8 and we all get a little nervous for a minute or
9 two, but I think there is a difference between that
10 and when the whole room stops, everything stops,
11 and there is something else going with the patient,
12 she becomes hypotensive and all those other things.

13 But there has been a spectrum among these
14 cases, some of which were just simply a very
15 transient event that did not really cause any
16 prolonged stay, in fact, the procedure went on, the
17 patient completed the procedure, and everything was
18 fine.

19 DR. BLANCO: When you are talking, just
20 addressing the issues that both of you brought up,
21 are you differentiating between unipolar and
22 bipolar, or risks for all, or both?

23 DR. O'SULLIVAN: All.

24 DR. LEVY: All.

25 DR. O'SULLIVAN: Because we don't know

1 unipolar. I mean it would certainly suggest based
2 upon the little bit we hear, and I, too, am totally
3 uninvolved in this, but based upon the little bit
4 we hear, that if there were unipolar problems, they
5 were not registered because people were not
6 monitoring them in the same way.

7 Now, I presume everybody is done under
8 some type of general anesthesia, am I correct?

9 DR. LEVY: No, absolutely not.

10 DR. O'SULLIVAN: I mean for operative?

11 DR. SCHROEDER: Actually, if I can address
12 that for just a moment, there are some places, and
13 certainly when I trained, spinal anesthesia was the
14 anesthetic of choice for hysteroscopy for the
15 reason that mental status is the most sensitive
16 indicator to check for what we affectionately call
17 TURP syndrome, which you get from absorption of the
18 distending medium, be it glycine or whatever it is
19 that you are using, so the addition of spontaneous
20 ventilation where a patient could be actually
21 sucking air, you could have a real negative
22 pressure in the venous system, makes this risk that
23 much greater. Some places I know it is still done
24 that way as a standard. So, certainly, in the
25 anesthesia community, this is not well known.

1 The other thing I would add is that the
2 Trendelenburg position, even general anesthesia
3 makes the risk of sucking air into the venous
4 system much greater. I just would add that to your
5 labeling instructions.

6 DR. BLANCO: Any other comments on
7 Question No. 1?

8 DR. LEVY: If I could just have one more,
9 and that is to say that the air embolism is a much
10 more serious event, and I think from FDA's
11 standpoint, the things that seem to predispose to
12 the air embolism are the issues like air in the
13 line, changing the bottles, you know, when one of
14 the bags runs out, what are the processes that the
15 nursing personnel or the operating room personnel
16 use in order to do that and make sure, because we
17 are working in a dark room, the physician really
18 isn't watching that happen, and those I think are
19 the highest risk situations for our patients.

20 That, I think deserves an alert and some
21 education, and some other things that we can do
22 right now, before we fine-tune what our knowledge
23 base is, but at the very least, those things I
24 think deserve an alert.

25 DR. O'SULLIVAN: Barbara, don't they occur

1 even when using unipolar systems?

2 DR. LEVY: Yes, any system. It is unique
3 to hysteroscopic surgery, not necessarily to
4 monopolar or bipolar.

5 DR. BLANCO: I think we are kind of
6 getting into No. 2, so let's go ahead and go with
7 that.

8 How can we improve our communication of
9 risk, as well as recommended practices for reducing
10 risk, e.g., labeling changes (if so, how?),
11 published articles, clinical training, FDA public
12 health advisory?

13 Any further comments on that?

14 DR. LEVY: My issue with the labeling is
15 that honestly, physicians don't read the labeling.
16 I mean I would love to tell you that we do, but we
17 don't, we should. But the first time we see a
18 device we are already scrubbed and, you know, there
19 is some piece of paper with fine print, the room is
20 dark, I can't see it. We just don't read the
21 labeling, so the labeling is important for hospital
22 personnel, but when we want to communicate to
23 physicians, I think we need to figure out a better
24 way to do it.

25 DR. O'SULLIVAN: I think alerts are the

1 way to go.

2 DR. LEVY: I agree.

3 DR. O'SULLIVAN: I think that that is the
4 way to do it.

5 DR. SHIRK: It is a difficult issue
6 because even the issue of fluid intravasation with
7 pressures, and stuff like that, has been an
8 extremely difficult issue to get across to the
9 people doing hysteroscopy. There is still a lot of
10 people out there who just totally ignore pressure
11 monitoring during the procedure, or even keeping
12 close track of fluid intravasation, on the amount
13 of fluid that is going into the patient, so it is
14 going to be even harder to get them to pay
15 attention to air bubbles and stuff like that in the
16 line.

17 DR. O'SULLIVAN: But this is why I think
18 alerts are important, you know, alerts and then
19 some of the educational things that can be done,
20 but certainly alerts are important.

21 DR. BLANCO: Any other comments on No. 2?
22 Dr. Schroeder, what about on the anesthesia side, I
23 mean do you see some things that could be done for
24 anesthesiologists even if we can't get the ob-gyns
25 to read the label, maybe we get the

1 anesthesiologists away from reading the newspaper.

2 Forgive me, I had to throw that in.

3 DR. SCHROEDER: I will offer one back. We
4 are the real patient advocate, you know. We are
5 protecting our patients from the surgeon.

6 [Laughter.]

7 DR. BLANCO: Thank you. Touche.

8 DR. SCHROEDER: I think education is the
9 most important thing. I would agree that FDA
10 alerts get everyone's attention a lot better than
11 everyone else. I don't mean to jump the gun on to
12 No. 3, but No. 3 says how can we improve our
13 reporting. I think by better educating--I can only
14 speak for my own side--if I know that it is
15 something to look at, something to look for, I find
16 what I look for more often than I find what I am
17 not looking for, and I am more likely to report
18 something I know the FDA is interested in. So, I
19 think that an alert type of thing will get people's
20 attention, will educate people, and we will do our
21 best to educate you.

22 DR. BLANCO: Thank you.

23 We have gone to 3 anyway, so let's just
24 read it and then we can move on and discuss it some
25 more. We can go back to 2 if anybody wants to make

1 some more comments on that.

2 3. How can we improve reporting of events
3 such as air/gas emboli? For instance, are there
4 additional communication means that would
5 facilitate MDR reporting?

6 DR. LEVY: One of my thoughts is if we
7 could have something available on a web site that
8 had a template of the information that we would
9 like to collect. One of the biggest frustrations
10 with looking at the MDRs was that the data that we
11 really wanted wasn't there, and then going
12 retrospectively and trying to figure it out was
13 very difficult.

14 If we were to create a template of
15 information that we wanted to get, and have that on
16 a web site, something that was really easy to
17 generate on-line, we might be able to get much
18 better information contemporaneously with the case,
19 so that we collected stuff that was worthwhile, as
20 opposed to looking two years ago what happened
21 during a case that you didn't happen to write down.

22 DR. D'AGOSTINO: Who is going to do this?
23 I mean I can imagine you sending out educational
24 material, and you will get a flood of cases, and
25 there will be a committee meeting a year from now

1 saying how serious the problem is, and there will
2 be an expert panel saying all the cases we looked
3 at were negligible.

4 I am concerned. There was a problem. The
5 company did handle it, and now we are seeing that
6 there are other potential problems, and so forth.
7 When we just say send out an alert, I think of an
8 alert as being some serious cases have been
9 identified as opposed to necessarily just we think
10 this might be a problem, please help us identify
11 cases that you have.

12 So, how are we suggesting that this gets
13 unfold, can somebody help me with that?

14 DR. BLANCO: Nancy.

15 DR. SHARTS-HOPKO: I do have a suggestion
16 that might help with that, and that is that the
17 relevant professional societies are the logical
18 people to advertise, look, we have a web site, this
19 is the kind of information, if you have experience
20 we are looking for within some time frame, so that
21 they are not remembering back.

22 DR. O'SULLIVAN: I think the other thing
23 is that you definitely will have an increase, there
24 is no question about that, but getting that
25 increase will also get the increase or the presence

1 of the same problem occurring in the unipolar
2 system.

3 But finally, I think it is extremely
4 important. While I don't like the idea that there
5 is enough gas generated to create some transient
6 problems, which may be related to the technique
7 itself, I certainly am concerned about the risk of
8 an associated air embolus, room air embolus, death,
9 and I think it would behoove us to follow up on
10 this and make sure that we are trying to look at
11 that, because that certainly is the worst possible
12 outcome.

13 DR. SHIRK: My question would be how big
14 is the risk.

15 DR. O'SULLIVAN: We aren't going to know
16 unless we look.

17 DR. SHIRK: If you do a C-section, you are
18 getting air emboli, I mean your room air emboli,
19 and obviously, nobody is advocating we not do C-sections.

20 DR. O'SULLIVAN: And nobody is advocating
21 we don't do the procedure. What we really need to
22 know is there is a problem. Yes, the company has
23 looked at a lot of information, but it hasn't
24 solved the problem that we know of.

25 If we are sitting here as a discussion, I

1 think it is something that we need to look at.

2 DR. SHIRK: I think the industry is
3 addressing the problem. Obviously, Ethicon looked
4 at it themselves. They are the ones that brought
5 the thing to the FDA.

6 DR. O'SULLIVAN: It hasn't solved the
7 problem. It has looked at a lot of things.

8 DR. SHIRK: It is a multifactorial
9 problem.

10 DR. O'SULLIVAN: It has looked at a lot of
11 things, agreed. I agree they have done a lot of
12 work. I commend the company for what they have
13 done. But the point is as we sit at this table,
14 the problem still is not solved--if there is a
15 problem.

16 DR. BLANCO: Subir.

17 DR. ROY: I think that my sense is that
18 the problem is one of physician and nursing and
19 personnel more so by orders of magnitude over that
20 of the devices. I would like to be proven wrong.

21 So, I think what we need is education
22 through all the usual means and persistent,
23 repetitive, repetitive, repetitive, because people
24 get sloppy and they forget. This is a human

1 problem, not a technological problem.

2 DR. BLANCO: Michael.

3 DR. DIAMOND: One additional thought and
4 it goes along with what Subir was just saying, is
5 for a lot of the things that we have been talking
6 about, I don't think physicians are fully and
7 adequately trained.

8 For example, I have participated in the
9 training of 25, 30 fellows - very good, very high
10 quality individuals who many are high-standing
11 academic physicians now, but when they came to us
12 to begin with, I would hold the operating end of a
13 laparoscope and ask where does the CO2 laser beam
14 come out of, and for years no one could tell me,
15 and that continues recently.

16 So, I think there is a problem in part of
17 our residency training where people are not going
18 over the basics, and people don't understand the
19 basics, and therefore can't extrapolate thoughts in
20 their mind.

21 One additional thought perhaps to deal
22 with some of these latter issues we are talking
23 about would be interactions with CREOG and
24 residency training as to expectations of what
25 residents ought to be able to be taught and learn

1 in that training process including assembling
2 hysteroscopes, assembling laparoscopes, generators,
3 basic fundamental information.

4 DR. O'SULLIVAN: There is a standard joke
5 in the American Board of Ob-Gyn that if you start
6 asking questions about it, it will get taught.

7 DR. BLANCO: All right. Actually, going
8 along with Dr. Diamond's comment, I mean CREOG does
9 published what are the expected things to be taught
10 to a resident. I am not sure that is included in
11 there, so it might be something that should be
12 brought up to them as included items that need to
13 be taught.

14 Any other comments?

15 Let me read 4, so we have read them all.

16 Are there additional measures that can be
17 taken by FDA, NIH, relevant professional societies,
18 et cetera, that will further add to the
19 understanding of the risks of air and gas emboli
20 during operative hysteroscopy?

21 I think we have addressed some of them, so
22 I open up the floor. Any other comments?

23 DR. LEVY: I would just like to say that
24 the basic research with the TEE's and all those
25 things, that probably is the purview of the NIH. I

1 mean I don't think that that is up to the companies
2 to have to do that kind of research.

3 It also entails certain risks to patients
4 that don't particularly convey benefits to those
5 patients. That is one of the things we talked
6 about at the consensus panel was the basic science
7 research you would like to have is costly,
8 extremely costly, but NIH might be interested and I
9 would encourage us to talk to them about creating
10 some studies that were done in the appropriate
11 centers with TEE, so that we really had a good
12 idea.

13 I mean we are extrapolating a lot of our
14 knowledge right now or a lot of what we think we
15 know to poor outcomes in patients, and I think
16 there is a lot of information we really don't have,
17 and the right studies could be done, but I don't
18 think the instrument companies and the
19 manufacturers can do them, and I think it would be
20 very difficult to do them outside the context of
21 the NIH.

22 I know my Institutional Review Board,
23 would probably no way approve a study like that.

24 DR. BLANCO: Any other comments from any
25 of the members of the panel? Yes, Subir.

1 DR. ROY: Just to reiterate something
2 Michael said. I think it is important to encourage
3 endoscopic laboratories be used, and not only in
4 residency training programs, but for clinicians who
5 are out in the field who need refreshers and things
6 like that, because I think that helps reiterate a
7 lot of the nuts and bolts of the whole process of
8 what is involved in terms of the RF systems, what
9 is involved in terms of the difference between
10 bipolar and unipolar, the use of distending media,
11 things like that, and it gives one a better
12 appreciation than when you go into the clinical
13 setting of all these different factors which are so
14 critically important to the safe performance of
15 these procedures.

16 DR. LEVY: Although I have to say that of
17 the problem cases that we saw, they were relatively
18 experienced hysteroscopists tackling the wrong
19 cases. They were judgment errors, they were errors
20 in tackling very large myomas that were more than
21 50 percent into the myometrium. There were a whole
22 lot of issues there that were judgment issues.

23 It is very hard to do a good bench model
24 for hysteroscopy that really teaches the problems
25 that, you know, you don't dilate a cervix in the

1 wet lab, you don't create much pressure in a pig
2 bladder, so there are a whole bunch of things in
3 those wet labs that are kind of difficult to teach.

4 I think we need to publish more. I think
5 we need to write more about what the problem
6 situations are, and we probably need to publish in
7 some form an analysis of these cases very
8 specifically, so that people can learn from them.

9 DR. BLANCO: Dr. Diamond.

10 DR. DIAMOND: One final suggestion from me
11 anyhow, for FDA, about the voluntary and mandatory
12 reporting processes. It is my bet that probably
13 industry and hospitals know a lot more about that
14 than do clinicians.

15 So, as part of the alerts that you might
16 publish, you might want to include as a component
17 the process of reporting, and you may get
18 information back, not only on this, but on other
19 issues, as well, because my bet is most physicians
20 are not very cognizant of it.

21 DR. SHARTS-HOPKO: This is to dovetail on
22 what Mike said. I am assuming that FDA is not
23 naive, a lot of voluntary reporting doesn't get
24 done because risk managers tell staff not to do it.

25 DR. BLANCO: Any other comments?

1 Let's open it up and see if there are any
2 comments from the audience, anyone who would like
3 to say anything at this time from the audience? No
4 one? Okay.

5 Anyone from the FDA that would like to
6 make a comment at this point?

7 MR. POLLARD: I would just like to thank
8 everybody in the room - the panel especially, but
9 certainly Ethicon and Karl Storz, and the others
10 who offered a lot of valuable input. We got an
11 awful lot of ideas here that we will probably go
12 back to the office and have to sift through, and we
13 might ask one or two of you to help us.

14 I definitely like the idea of if we do go
15 with the public health advisory or some kind of
16 alert, the idea of highlighting the reporting
17 system and maybe taking up the idea of the
18 template, maybe even posting some kind of reporting
19 template, so that people could go to it.

20 A lot of times we get these MDR reports
21 and we are looking at it and realize we are missing
22 half of the information we really want, but at any
23 rate, the bottom line, I really appreciate all the
24 input.

25 DR. BLANCO: Thank you, Colin.

1 I also would like to thank all the panel
2 members for their participation and involvement. I
3 would like to thank the FDA for their excellent
4 work as always, and also the audience, members of
5 industry for their presentations and very
6 interesting information.

7 Thank you all and unless another panel
8 member has something to say, we will call the
9 meeting adjourned. We will be back at 2 o'clock.
10 Thank you.

11 [Whereupon, at 12:50 p.m., the proceedings
12 were recessed, to be resumed at 2:00 p.m., this
13 same day.]

1 AFTERNOON SESSIONS

2 [2:00 p.m.]

3 DR. BLANCO: Why don't we go ahead and
4 call the meeting to order. I think we are going to
5 start on time and try to finish promptly.

6 I am going to go ahead and go through some
7 of the housekeeping chores again, just because we
8 have a slightly different audience this afternoon
9 than we did this morning.

10 I just want to remind everyone that if you
11 do not sign in, in the morning, that there is a
12 sign-up sheet out front, if you would please sign
13 in, so that we know who is in attendance.

14 When we get to the audience comments,
15 please be recognized by the Chair, use the
16 microphones for speaking, and give a full conflict
17 of interest disclosure including any financial
18 issues, travel, per diem, or any relationships with
19 any of the companies that may have any business
20 before the panel.

21 I would like to go ahead and have an
22 introduction of panel addition, and then we will
23 just go around quickly and have everyone state who
24 they are again.

25 DR. WHANG: We are pleased to have joining

1 us for this session this afternoon, Professor Anne
2 Roberts, who is a Professor of Radiology and the
3 Chief of Vascular and Interventional Radiology at
4 UCSD.

5 DR. BLANCO: We can go around the table.

6 MS. BROGDON: Nancy Brogdon, Director of
7 the Division of Reproductive, Abdominal, and
8 Radiological Devices, FDA.

9 DR. NEUMAN: Mike Neuman from the Memphis
10 Joint Program in Biomedical Engineering of the
11 University of Tennessee Health Science Center and
12 the University of Memphis, Tennessee.

13 DR. O'SULLIVAN: Mary Jo O'Sullivan of the
14 University of Miami.

15 DR. ROY: Subir Roy, University of
16 Southern California.

17 DR. SHARTS-HOPKO: Nancy Sharts-Hopko,
18 Villanova University.

19 DR. KATZ: David Katz, Duke University.

20 DR. D'AGOSTINO: Ralph D'Agostino, Boston
21 University.

22 DR. SHIRK: Jerry Shirk, Clinical
23 Associate Professor at University of Iowa and
24 private physician in Cedar Rapids, Iowa.

25 DR. WHANG: Joyce Whang, Executive

1 Secretary of this Ob-Gyn Devices Panel.

2 DR. BLANCO: Jorge George Blanco,
3 perinatologist.

4 DR. LEVY: Barbara Levy, Clinical
5 Gynecologist and Assistant Clinic Professor of Ob-Gyn at
6 University of Washington.

7 DR. DIAMOND: Michael Diamond, Director of
8 the Division of Reproductive Endocrinology and
9 Infertility at Wayne State University.

10 DR. ROBERTS: Anne Roberts. You already
11 heard my bio.

12 MS. MOONEY: Mary Lou Mooney, Industry
13 Rep.

14 MR. REYNOLDS: Stan Reynolds, Consumer
15 Rep.

16 DR. BLANCO: Thank you.

17 Let's go ahead and introduce Mr. Colin
18 Pollard, Chief, Obstetrics and Gynecology Devices
19 Branch of the FDA, who will make some introductory
20 remarks.

21 Uterine Fibroid Embolization (UFE)

22 Introductory Remarks

23 Colin Pollard

24 MR. POLLARD: Thank you, Dr. Blanco,
25 ladies and gentlemen, members of the panel. Today,

1 we will be talking about uterine fibroid
2 embolization, and I would like to go over a number
3 of things just to get things rolling.

4 [Slide.]

5 The last time we met on this topic was
6 October of 1999, when we brought this before our
7 panel. I would also like to talk about some
8 clinical developments with uterine fibroid
9 embolization since then.

10 The Society of Cardiovascular and
11 Interventional Radiology has been working very
12 actively on this and working with us, and I would
13 like to mention a few things that are going on
14 there. They will be following with a more detailed
15 presentation.

16 Since October of 1999, we have approved
17 two clinical trials for uterine fibroid
18 embolization, and we think we are at a good spot
19 where we should be developing a guidance document
20 for clinical trials and the 510(k)'s that would
21 support market clearance, so we are asking the
22 panel for input on that.

23 [Slide.]

24 In October of 1999, we were first looking
25 at uterine fibroid embolization. At that time, we

1 were still grappling with the question of 510(k)
2 versus PMA, and we were sharing that sort of
3 struggle, if you will, or that kind of discussion
4 that was going on within the center.

5 We also heard a very good presentation
6 from the Society of Cardiovascular and
7 Interventional Radiology really introducing the
8 topic to the panel and going over some of the
9 reasons why it was something they wanted to do, and
10 then talking about some of the risks to patients,
11 as well as some of the benefits, and they did go
12 over a couple of the trials that had been
13 published, as well as ones that were in planning
14 stages or ongoing.

15 [Slide.]

16 Since then, there have been quite a few
17 clinical developments in uterine fibroid
18 embolization. The use of it continues to grow in
19 the United States, as well as worldwide. There is
20 more published literature available on it for us to
21 learn from.

22 Last year, ACOG issued a Practice Bulletin
23 No. 16, which is in your background package. That
24 practice bulletin, in fact, states that the College
25 considers it to be investigational.

1 I know there are some ongoing discussions
2 between the College and the Society of
3 Cardiovascular and Interventional Radiology, and
4 there are a number of study proposals that are
5 under consideration at the October 1999 meeting.

6 If you remember the panel or at least some
7 of the panel were recommending, when we asked them
8 the question of what kind of control groups that
9 they were recommending, they had to have
10 randomization between uterine fibroid embolization
11 and myomectomies, and there are some proposals that
12 are under consideration for that.

13 [Slide.]

14 As I mentioned, SCVIR, I will it SCVIR,
15 the Society of Cardiovascular and Interventional
16 Radiology, has been very active since our panel
17 meeting in '99. They established a patient
18 registry, and you will hear more about this.

19 They established standards for reporting
20 data in the published literature on this procedure.
21 You will also hear an update on uterine fibroid
22 embolization in the United States, and they are
23 also going to be presenting some comments on the
24 questions that you have before you.

25 [Slide.]

1 Just very quickly, a regulatory update
2 going over the classification, the market pathway,
3 clinical trials we have looked at, and the
4 development of the guidance document.

5 [Slide.]

6 First of all, the classification of
7 artificial embolizing agents is currently a Class
8 III product. This was originally a preamendments
9 device classified in Class III for neurological
10 indications. It has since then gained other
11 indications, and it is under a general indication
12 of embolization of hypervascular lesions that is
13 currently being done in the U.S.

14 That product or at least certain
15 embolizing agents are on track for reclassification
16 into Class II. In this last 20 years, the center
17 has handled a number of products and a number of
18 new indications for products by 510(k), which we
19 are entitled to do so.

20 I think the reclassification will apply to
21 polyvinyl alcohol particles, coils, and detachable
22 balloons. Those are all on track for
23 reclassification to Class II.

24 For uterine fibroid embolization, most of
25 this is being done with polyvinyl alcohol

1 particles, and really the issue before us is
2 manufacturers' purpose to go from a general
3 indication for a hypervascular lesion to a specific
4 indication, and we are applying the center's
5 guidance document for doing that kind of thing.

6 Since the panel meeting, we made a
7 regulatory decision that we would use 510(k) to
8 handle that, 510(k) premarket notification to
9 handle that kind of market clearance preceded, of
10 course, by a clinical trial to establish that
11 specific indication.

12 [Slide.]

13 As I mentioned, currently, the accepted
14 indications for use for artificial embolization
15 agents are arteriovenous malformations and
16 hypervascular lesions.

17 [Slide.]

18 At this point, we have approved two
19 clinical trials to study artificial embolization
20 agents for uterine fibroid embolization. The
21 discussion questions that you have before you are
22 really a reflection of some of the key elements of
23 those that we wanted to get some panel input as we
24 went ahead and prepared a guidance document.

25 [Slide.]

1 The guidance document, right now we are
2 working on it. We have to follow the good guidance
3 practices that the center uses when it releases
4 guidance documents, so since we haven't actually
5 got it available for public, so we don't have it
6 for you, but we tried to craft our discussion
7 questions in a way that you can get a good sense of
8 what is going on there.

9 It calls for clinical trials and really
10 that is what those discussion questions are all
11 about, and ultimately, the guidance document will
12 also address what needs to be in the 510(k)
13 premarket notification.

14 [Slide.]

15 So, at this point, I would just highlight
16 that we have got some discussion questions before
17 you, and really the main purpose of this meeting
18 this afternoon is really to use those questions to
19 provide us with input that we can take back and
20 help make as good a guidance document as we can.

21 Any questions?

22 [No response.]

23 DR. BLANCO: Thank you, Mr. Pollard.

24 We will move on. The next presentation
25 from the SCVIR will be by Dr. James Spies, I

1 believe, Georgetown University. Please be sure to
2 state any conflict of interest, funding, travel,
3 per diem, honorarium, et cetera.

4 Presentation by Society of Cardiovascular
5 and Interventional Radiology

6 James B. Spies, M.D.

7 DR. SPIES: I don't have any financial
8 relationship with any of the vendors, but I am
9 principal investigator for the multicenter study
10 that is ongoing by BioSphere Medical in
11 Embospheres. I am not an investigator on the
12 Boston Scientific Study, but I am on the Clinical
13 Events Committee, so I do have at least I guess a
14 professional or scientific relationship with both
15 organizations.

16 DR. BLANCO: Thank you.

17 [Slide.]

18 DR. SPIES: What I thought I would do
19 today, I was asked by the SCVIR to make some
20 comments on the questions of the panel, and we
21 thought that what I could start with is just an
22 overview of the current status of this procedure
23 and what we know about it at this stage.

24 [Slide.]

25 So, I would like to talk a little bit

1 about UAE, the rationale for it, and the technique,
2 briefly review the published case series that have
3 been made available in the last few years, review
4 our own experience in a little bit more detail to
5 give you a flavor of some of the analysis that has
6 been done, and then to comment specifically on the
7 questions that the FDA has posed.

8 [Slide.]

9 This was first reported by Ravina in the
10 English literature as the sole therapy for fibroids
11 in 1995. It was an article in Lancet, was a small
12 series, 16 patients. This stimulated Goodwin and
13 Dr. McLucas at UCLA to begin to study this and try
14 this procedure, and Dr. Goodwin reported that first
15 experience in 11 patients in 1997.

16 Despite this very limited experience, it
17 was the subject of considerable interest among
18 other researchers in this area, particularly among
19 the patients.

20 By the beginning of 1999, this therapy was
21 being offered probably in about 20 centers around
22 the country, and there had been numerous small case
23 series reported, and now we are getting into the
24 phase where we have some larger series, longer term
25 follow-up available.

1 [Slide.]

2 One of the things that has always been a
3 question, just the standard approach in this,
4 because there is some discussion or controversy
5 about this is that most patients require a history
6 and physical examination including an examination
7 by a gynecologist, need to have a current Pap
8 smear.

9 For a subset of patients who have really
10 atypical bleeding patterns, an endometrial biopsy
11 or other means of endometrial sampling usually is
12 performed, but is not routinely done. If there has
13 been a history of recent gynecologic infection, we
14 would like to have negative cultures. Most
15 operators will get a CBC, a pregnancy test, and
16 occasionally or at least some operators routinely
17 get an FSH assay.

18 Imaging has to be used to confirm the
19 diagnosis. In our center, we use exclusively MRI
20 with limited charge, but I would say the average
21 operator in this country would use ultrasound.

22 Routine laparoscopy, hysteroscopy,
23 leiomyoma biopsy, deep myometrial biopsy, all those
24 things are generally not done and unnecessary for
25 most patients. There are some centers in which

1 that is done, however.

2 [Slide.]

3 The technique is bilateral embolization of
4 the uterine arteries, and it is a selective uterine
5 artery catheterization, which means that the
6 catheter is placed within the uterine artery. It
7 is not placed within each blood vessel going to
8 each fiber, it is usually placed at the base of the
9 uterus in the cardinal ligament area.

10 A coaxial technique, which is a
11 microcatheter, is frequently needed if there is
12 spasm, and so I would say the typical operator
13 would use that probably half the time.

14 There are a number of different
15 combinations of sizes that can be used of these
16 particles. Polyvinyl alcohol particles, there are
17 two sizes. Most frequently used in this country
18 are 355 to 500, or 500 to 710 micron.

19 Now, embospheres, which are tris-acrl
20 micro-embospheres, are available in a number of
21 sizes, but again almost all the experience today is
22 in these two size ranges.

23 We, at Georgetown, use a bilateral femoral
24 approach, which means we puncture both femoral
25 arteries, which we have found to be a more

1 expeditious way to do this procedure, many
2 operators will use a unilateral approach. Both
3 uterine arteries have to be treated regardless.

4 The goal is to embolize the leiomyoma
5 vascular supply. We do not want to infarct the
6 uterus, we do not want to completely occlude the
7 uterine artery flow. We would like to
8 devascularize the fibroids.

9 In our program, we always try to spare as
10 much of the normal myometrial flow as possible.

11 [Slide.]

12 Why does this work? Well, each leiomyoma--and
13 this is from work from Sampson actually back
14 in 1912, was one of the first, and then there have
15 been others since--each leiomyoma parasitizes
16 normal myometrial branches and converts them
17 essentially to fibroid feeding vessels, and these
18 branches supply only the leiomyoma and are in
19 vessels. They don't have a collateral network.
20 That makes them particularly attractive for
21 embolization because once you block those
22 individual branches, there is no other way for
23 those fibroids to get blood supply.

24 As you all know, the fibroid, as it grows,
25 it tends to compress the normal myometrium adjacent

1 to it, and that normal myometrium continues to
2 derive its blood supply from other branches, and
3 these vessels are an order of magnitude smaller
4 than those that are feeding the leiomyoma, which
5 allows us to embolize the leiomyoma branches while
6 avoiding most of the myometrial branches.

7 There also is a very rich collateral
8 network for those myometrial branches.

9 MRI studies have shown after uterine
10 embolization that the fibroids infarct with
11 preservation of the perfusion of the normal
12 myometrium in almost all cases even if the uterine
13 arteries are completely occluded, which is the
14 approach of some operators still.

15 [Slide.]

16 This is how we do this. This is a digital
17 roadmap of the left hypergastic artery, and you can
18 see the arrow--it is a little difficult to see--but
19 the origin of the uterine artery, the uterine
20 artery usually is very tortuous. This is few
21 minutes later when we are in that patient's artery.

22 We would move the catheter down to about
23 there in order to do the embolization, so it is
24 right before it begins to ascend in the serosa of
25 the uterus, and this is what it looks like.

1 [Slide.]

2 Now, these are Georgetown pictures, which
3 means you are going to see both sides projected
4 simultaneously, which is the way we do this, but
5 you can see there is a left uterine artery here,
6 right here, and these are all these abnormal blood
7 vessels.

8 [Slide.]

9 This is what it looks like after we have
10 done a PVA embolization. We can see some normal
11 myometrial branches here, but essentially, all the
12 fibroid branches, which are the abnormal large
13 branches, are occluded.

14 [Slide.]

15 This is a case using the microspheres.
16 There is a large leiomyoma right here. These are
17 mostly normal myometrial branches.

18 [Slide.]

19 This is what this looks like afterwards.
20 We have normal myometrial flow still here, some
21 here, but the fibroid itself is devascularized, and
22 that is the goal, that is our endpoint that we are
23 looking for.

24 [Slide.]

25 Now, this is an MRI we performed early in

1 our experience in a patient about 48 hours after
2 embolization, because she was having significant
3 pain, and I was concerned that we had actually
4 injured her uterus. I think it was more a matter
5 of pain management in her particular case.

6 Regardless, you can see here in this, what
7 is called a TIW image, there is a slight increase
8 in signal here and here, and that is
9 microhemorrhage within the fibroids. That
10 indicates hemorrhagic infarction.

11 This is a post-contrast image. You can
12 see completely avascular two fibroids. This is the
13 cervix down here, and this is the outline of the
14 myometrium. You can see that the rest of it is
15 normally perfused. This patient, after a few doses
16 of morphine, was fine and was able to be
17 discharged, and she went on without difficulty.

18 This was one of our early experiences in
19 terms of what actually usually happens, and there
20 have been groups that have presented from Mass.
21 General and other places, that have shown that it
22 is very rare to have any significant injury to the
23 normal myometrium. It can happen, but it is
24 unusual.

25 [Slide.]

1 What pathologic changes do we see? There
2 is ischemic infarction of the leiomyomata. In
3 general, the normal myometrium is spared. The
4 leiomyoma shrinks as a result of hyaline
5 degeneration. Degeneration continues for months to
6 years, and as in this particular case, both large
7 and small leiomyomas were infarcted.

8 In this patient, who underwent an elective
9 hysterectomy for other reasons, she was having
10 actually adnexal surgery and elected to have a
11 myomectomy eight months after the procedure.

12 She had a 1 centimeter fibroid, which was
13 infarcted, and she had a 6 centimeter fibroid which
14 was completely infarcted. So, generally, it works
15 on all the leiomyoma that are present.

16 [Slide.]

17 If one were to look at the series that
18 have been published, most of these have been
19 published since the last meeting of the panel. It
20 is impossible to read this, which is why I will
21 summarize it here.

22 This is a nine-case series. They are
23 peer-reviewed publications with a minimum of 40
24 patients excluding duplicate reports, because there
25 are a number of series which report, and then

1 report on subsequent data.

2 So, we have a total of 1,109 patients in
3 those series. There is a mean follow-up of 5 to 29
4 months. Menorrhagia was improved in 79 to 96
5 percent. You can see pelvic pain was improved in a
6 similar percentage.

7 Leiomyoma volume reduction: at initial
8 follow-up, it ranged from 20 to 55 percent. So, 20
9 percent was in a series checked at two months, the
10 60 percent, I think that is the number I can see
11 from across the room, was our own experience where
12 we actually provided free MRIs in a large number of
13 patients at a year in order to assess that.

14 Among those 1,109 patients, there were
15 reported 7 hysterectomies for complications, which
16 is a 0.6 percent rate.

17 [Slide.]

18 This is what happens. This again is some
19 experience from Georgetown, where we showed that
20 the blue is the uterine volume, it's about 50
21 percent reduced to two years on average. The green
22 is the dominant fibroid, the largest fibroid, and
23 it's 43 percent on average at three months, it's
24 about 60 percent here, and it's about 78 percent at
25 two years.

1 Now, this is widely variable, and one of
2 the points I would make is that looking at volume
3 reduction really is a very poor measure of outcome.
4 If we are going to use imaging characteristics, we
5 might want to look at perfusion-related MRI or
6 regions of interest, because there are substantial
7 inter-observer variability associated with the
8 measurement of both uterine volume, particularly in
9 large multi-fibroid uteri and also in the
10 leiomyomas themselves.

11 We have ever had some cases in which, on
12 follow-up studies, the dominant fibroid was
13 misidentified, so we are measuring actually
14 different fibroids occasionally. This is quite
15 easy to do in a large, multi-fibroid uterus. So,
16 it isn't the best means of assessing outcome.

17 [Slide.]

18 In individual cases, however, it certainly
19 is of help. Just some examples of MRIs. These are
20 all lateral views, so in every one you see, the
21 front is here, the back is here, and these are
22 lateral views of the uterus.

23 [Slide.]

24 This is one huge fibroid here. This is
25 three months out, and this is a year out. This is

1 a bit of a close-up, but the top of the uterus used
2 to be up here, and now it is down here, and that
3 fibroid has decreased about 70 percent in volume.

4 [Slide.]

5 Here is a multi-fibroid uterus. You can
6 see multiple fibroids. There is a very large one
7 here in the fundus, multiple fibroids throughout.
8 This is three months, one year, and two years. You
9 can see that the uterus progressively is reducing.

10 Now, two years, you say, well, there is a
11 significant residual fibroid volume there, but it
12 is progressively reducing, and the interesting
13 thing is that you don't have to wait for this
14 volume decrease. Most patient's symptoms are
15 improved at three months after this procedure,
16 which was when most investigators have looked at
17 the outcome.

18 [Slide.]

19 This is one of our early experiences in
20 which we had a large, 7.5 centimeter submucosal
21 fibroid that failed hysteroscopic resection, three
22 months, one year, two years. We actually now have
23 a three-year study in this lady, and her uterus is
24 normal, and that little tiny residual fibroid that
25 was right there is gone.

1 [Slide.]

2 I would like to talk just for a few
3 minutes about our experience. This is going to be
4 published in the July issue of Obstetrics and
5 Gynecology. Part of the reason I would like to
6 present this is it gives a little bit more detail
7 on what most investigators are seeing. I don't
8 think our results are particularly different.

9 We do have 200 patients that are being
10 reported, a minimum follow-up of 12 months and the
11 mean follow-up on this group of patients was 21
12 months, and looking at the percentages of
13 improvement, you can see that in the high 80s or 90
14 percent in terms of percentage that are improved.

15 Patients are satisfied to some degree in
16 over 90 percent of patients. Now, that is in terms
17 of symptom control.

18 [Slide.]

19 Now, if one looks at peri-procedural
20 complications again from the same source, a paper
21 that is going to be published in a month or so, you
22 can see there is a 6.5 percent rate of minor
23 complications, but basically, over half of those
24 are either ER visits or readmission for pain, and
25 probably all those occurred within the first 60 to

1 80 patients we treated, and we have learned a lot
2 more about pain management, and we are much better
3 at it than we used to be. So, we have not really
4 had a patient return for pain management issues in
5 the last 200 or 300 patients we have treated.

6 But if you look at the other
7 complications, certainly, you can always have an
8 injury. This is a minor hematoma at the puncture
9 site, and there are a number of others, urinary
10 retention, one minor I.V. phlebitis. There are
11 complications that required at least a minimum of
12 an office visit, ER visit, or rehospitalization.

13 We did have one pulmonary embolus, which
14 occurred the day after the procedure, actually,
15 after the patient was discharged. She was
16 readmitted, diagnosed, and treated with
17 anticoagulants.

18 The interesting thing about that
19 particular patient is she was on both Aygestin,
20 which is a progesterone agent, and birth control
21 pills because she was essentially exsanguinating
22 when we did the procedure. We did it as an
23 emergency on a Friday afternoon. She was one of
24 the few patients we have seen with clotting
25 complications, and she was on a double dose of

1 hormones.

2 [Slide.]

3 Subsequent hospitalizations and
4 gynecologic interventions. I think this is one of
5 the first series to really look at this particular
6 issue, what happens to these patients down the
7 road.

8 Well, 21 of them needed to have some
9 subsequent intervention over the course of the
10 follow-up, which was again up to, at this stage it
11 was 36 months. The numbers are a little hard to
12 read, but we had repeat embolization or angiogram
13 in two patients, and those both had ovarian supply
14 to their fibroids, which is now a known cause for
15 failure in a small group of patients.

16 Eight of these patients had complications.
17 Usually, it is related to fibroid tissue passage or
18 an infection of the endometrium which occurs
19 associated with that, or recurrent bleeding during
20 fibroid tissue passage. Any of those events might
21 require a D&C, hysteroscopic resection, or
22 hospitalization briefly.

23 We had one patient that went on to a
24 myomectomy because she was dissatisfied with the
25 degree of shrinkage on her fibroid. We did have

1 nine hysterectomies, none for complications. Seven
2 were in patients that failed to improve. If you
3 look back on my original slide, assuming that 90
4 percent roughly are improved, well, obviously, 10
5 percent are not. Roughly half of those patients in
6 this group have gone on to hysterectomy.

7 We did have two incidental hysterectomies
8 that were performed for other gynecologic surgery.

9 [Slide.]

10 We have done a regression analysis, which
11 has been separately submitted for publication,
12 trying to determine what factors would be able to
13 predict how a patient will do.

14 It is interesting that for both uterine
15 and dominant leiomyoma volume change, there are
16 really very few predictors. There are no
17 demographic measures that we were able to see, not
18 age, not race, not anything that would predict the
19 percent volume reduction.

20 Submucosal location was more likely to
21 shrink at three months than a serosal location, but
22 not by 12 months, and so that slight advantage
23 early on with submucosal location went away.

24 Larger leiomyoma volume does predict less
25 volume reduction. If you also look at bleeding

1 improvement, there are no predictors when adjusted
2 for volume at three months, but at 12 months, there
3 is an odds ratio of 0.87 per 100 cc increase in
4 baseline leiomyoma volume of bleeding improvement.

5 Well, what does that mean? It means that
6 by every 100 cc increase, there is a diminished
7 chance, it's 0.87 rather than 1, of bleeding
8 improvement. So, in theory, very large fibroids
9 will be less likely to improve bleeding at that
10 interval than others.

11 Having said that, the difference between
12 them is really not very strong, and I will show
13 that in a minute. There is no difference for women
14 with prior hormone therapy in terms of bleeding
15 improvement, which is one of the panel's questions,
16 and there is a trend toward greater improvement
17 with submucosal location.

18 [Slide.]

19 Now, if you look at the estimated
20 associations, improvement in one symptom does
21 highly correlate with improvement with the other
22 and satisfaction at both 3 and 12 months, of if
23 your bleeding is better, your pressure usually is
24 better, and you are generally satisfied. If you
25 are dissatisfied, obviously, your symptoms are not

1 improving. That is almost self-evident.

2 There is a weak association noted between
3 dominant leiomyoma percent volume reduction and
4 bleeding improvement and satisfaction at three
5 months, but I think it was about 0.17 was the
6 correlation coefficient, so it is really not very
7 strong. Only bleeding improvement maintained this
8 association at 12 months. So, the associations are
9 not strong.

10 So, what they suggest is that size and
11 location have relatively little impact on outcome.

12 [Slide.]

13 Amenorrhea, which is an important topic,
14 after this procedure, it has been reported in most
15 of the series that I mentioned. It ranges from 2
16 to 15 percent at varying time intervals after the
17 procedure.

18 There is only one case series that reports
19 greater than 5 percent, and that was the
20 Northwestern experience, which was at 15 percent
21 overall.

22 Our experience, we have had 11 women out
23 of 200 that had no menstrual period at three
24 months, by three months after this procedure. Of
25 these, all three had resumed menses by six months,

1 and three continued at 12 months. Now, one of
2 those women actually had failed UAE, was one of our
3 few failures. We actually were unable to
4 catheterize her vessels, and she was placed on Depo
5 Provera, which was why she was amenorrheic.

6 One additional woman became amenorrheic
7 six months after the procedure and remained so at
8 12 months, so presumably, she is in menopause. It
9 is a relatively low incidence of this problem in
10 our experience.

11 Now, because of that, we actually asked
12 the question, well, is there a subclinical effect
13 that we are not recognizing on ovarian function in
14 women.

15 So, what we did, although it is not a
16 perfect measure, we did a study looking at basal
17 FSH in a group of patients presenting. We
18 published this in April of this year. We saw that
19 there was no change in basal FSH in women under the
20 age of 45 at three and six months. One patient did
21 go up, but it came back down to her normal range.

22 Over the age of 45, 15 percent of patients
23 had a change from below 20 International Units to
24 above. Presumably, then, they have been moved
25 closer to menopause as a result of the procedure.

1 Again, the youngest woman that we have had other
2 than the lady with Depo Provera that was
3 amenorrheic, was 49 at Georgetown. In almost all
4 cases that were reported are over the age of 45.

5 [Slide.]

6 Another very important issue is radiation
7 dose. I was interested in this early on. Boris
8 Niklik [ph], one of our residents, who is more
9 technically advanced than I, let's put it that way,
10 he was interested in the subject, as well, so we
11 did an initial radiation dose study about three
12 years ago. We measured by using TLDs that were
13 placed in the vagina and also in the skin a mean
14 ovarian dose of 22 centigray or rads, a skin
15 entrance dose of about 162 centigray.

16 Mean fluoroscopy time in that study was 21
17 or almost 22 minutes. This was using an older
18 system, which was non-pulse fluoroscopy, it was
19 when we were using a unilateral embolization
20 approach meaning we would embolize one side first,
21 then the other side.

22 What does this dose mean? Well, it's
23 about 10 times the dose or maybe 15 times the dose
24 depending upon the study of diagnostic pelvic
25 radiograph procedures like barium enemas or other

1 similar procedures. It's 0.1 to 0.006 the dose of
2 therapy for Hodgkin's disease.

3 Well, what does that mean? Well, it is
4 difficult to say, but one can actually calculate a
5 genetically significant dose, which is a measure of
6 the population impact of radiation dose, and using
7 our parameters from this study, we measured, in
8 addition to the medically significant dose of 0.005
9 mSv.

10 This represents a 2.2 percent increase in
11 the medical genetically significant dose at a 0.4
12 percent to the total genetically significant dose.
13 So, those would be the excess fetal abnormalities
14 that would occur as a result of this with broad
15 application in the population. This is a
16 population-based measure, it is not for individual
17 patients.

18 Now, because we are interested in this, we
19 actually did a phantom study and looked at a number
20 of different parameters associated with this, and
21 we were able to show that about 93 percent of the
22 radiation dose associated with this is from
23 fluoroscopy, so the key is to reduce the
24 fluoroscopic dose.

25 By doing that, we were able to, in a

1 subsequent group of patients, measure a mean
2 ovarian dose of 9.5, a skin entrance dose of 47.
3 This is a reduction of about 60 percent of the
4 ovarian dose and over 70 percent in the skin dose.

5 What did we do different? Well, we have a
6 new system with pulse fluoroscopy, which is a huge
7 help. We use a bilateral approach. We
8 simultaneously embolize, two physicians, one on
9 each side embolize, and it significantly reduces
10 the time required.

11 We made a concerted effort to reduce
12 magnification angle 2 position. This basically cut
13 the contribution to the genetically significant
14 dose in half.

15 [Slide.]

16 So, talking specifically to the questions
17 that the FDA posed, I am looking at
18 inclusion/exclusion criteria, women on hormone
19 therapy, there are really four primary uses, and I
20 am probably overstepping my bounds as a radiologist
21 here, but there are four primary uses that we have
22 seen in patient populations for the use of
23 hormones.

24 It includes birth control, control of
25 menorrhagia, hormone replacement therapy, and

1 control of endometriosis. Oral contraceptives and
2 progesterone may impact menstrual bleeding, and we
3 recognize that, and it may affect the measurement
4 of uterine artery embolization treatment effect.
5 If we are trying to control menorrhagia, if oral
6 contraceptives are decreasing the amount of
7 bleeding, then, we might falsely measure in error.

8 However, the error in measurement for
9 using these medications will likely be an
10 underestimate rather than an overestimate of the
11 treatment effect of UAE. If bleeding is being
12 suppressed before, and it is suppressed afterwards,
13 the delta that we will be measuring will be smaller
14 overall.

15 So, I think that if we are going to have
16 an error in the estimate that is going to occur, it
17 is going to be in the conservative direction.

18 If you look at oral contraceptives for
19 birth control in those that are on hormone
20 replacement therapy, patients can continue them
21 before and afterwards, so they can be self-controlled. The
22 treatment effect of UAE is likely
23 to far outshadow the effect of oral contraceptives.

24 Higham scores that have been reported have
25 been decreasing by about 50 percent or more

1 regardless of birth control reviews. As I
2 mentioned in our regression analysis, prior oral
3 contraceptive use did not predict improvement of
4 bleeding or did not affect that prediction.

5 A practical issue is that patients are
6 quite resistant to stopping contraceptives or
7 estrogen replacement therapy, and in this case it
8 would be for months really, because we would have
9 to for a few months before this procedure and then
10 for months afterwards in order to participate in
11 the study, and from my own experience, I can say
12 that does limit the patient's interest in being
13 recruited into studies.

14 [Slide.]

15 For patients that are being treated for
16 menorrhagia, stopping the therapy really sometimes
17 is essentially impossible. They are really barely
18 controlled and they are oftentimes taking two
19 hormones. Eliminating these patients may prevent
20 the assessment of UAE in those that have the most
21 severe symptoms, and there can be quite dramatic
22 effects.

23 If patients stop therapy post-procedure,
24 it will likely again represent an underestimate.
25 If the bleeding is being suppressed before the

1 procedure, and they go off the Provera, they go off
2 the birth control pills afterwards because their
3 bleeding is improved, whatever rebound effect will
4 result in an underestimation of the treatment
5 effect from the UAE, so I think again it is in the
6 conservative direction.

7 [Slide.]

8 One of my specific concerns is if we
9 eliminate patients that are on hormones, we may
10 prevent complete assessment of the safety of
11 uterine embolization. In particular, thrombotic
12 complications may be more likely in those that are
13 on hormones, and that is known from other types of
14 surgery, and obviously, patients that are on
15 hormones are at greater likelihood of
16 thromboembolic disease, and we may be masking the
17 safety of the procedure by eliminating those
18 patients, and I am quite concerned about that.

19 Most published studies of myomectomy and
20 hysterectomy have not restricted the hormone use,
21 so it is a little bit of a false measure to add
22 that in, in this particular procedure.

23 I think that the FDA should, and certainly
24 could, ask for a statistical comparison of users of
25 hormones versus non-users as part of the submission

1 from the companies that are involved in this.

2 [Slide.]

3 In patients being treated for menorrhagia,
4 one of the questions was simple hyperplasia, it was
5 our thought that they should be excluded until
6 there has been resolution of the hyperplasia, and
7 that should be shown on repeat endometrial
8 sampling.

9 Patients with endometrial polyps should
10 also be eliminated until it has been removed.

11 [Slide.]

12 Study endpoints. Leiomyoma, as you all
13 know, cause a variety of symptoms which are very
14 broadly categorized into heavy menstrual bleeding,
15 bulk symptoms, and then the sort of undefined
16 impact they may have on fertility and pregnancy.

17 There has been relatively little study of
18 the outcome measures in this condition, which is
19 one of the things I discovered early on, it is
20 difficult to measure outcome in a woman in whom you
21 leave the uterus in place, and this has been
22 problem dogging some other procedures, as well,
23 particularly myomectomy.

24 So, I think that from my perspective, and
25 I have spent a fair amount of my research time

1 looking at outcome measures from this, I think that
2 we should be using validated symptom and/or QOL,
3 quality of life questionnaires. Validated
4 menstrual pictorial assessment charts are also I
5 think a good way to evaluate this.

6 The volumes we should just forget. I mean
7 they are nice to know, but they really are so
8 subject to inter-observer variability, I think that
9 we are going to mislead ourselves.

10 [Slide.]

11 Pictorial blood loss assessment chart, you
12 are all familiar with Higham scores, and I know it
13 has been used for other gynecologic interventions.
14 It is being used in one of the current studies. I
15 think that these are useful, particularly if one is
16 focusing specifically on menorrhagia.

17 Now, if you are looking at broader
18 symptoms, it is not that helpful. There also is a
19 validated menorrhagia questionnaire, which has also
20 been in use by Ruta, and there are a couple of
21 different ways to go in terms of quality of life.

22 One could use a general health-related
23 quality of life questionnaire, such as the SF-36 or
24 the SF-12. We published some data on a proprietary
25 fibroid specific quality of life questionnaire, and

1 we have just completed a combined symptom and
2 quality of life questionnaire. It is called the
3 UFS-QOL, which we are just submitting now to
4 Obstetrics and Gynecology.

5 Its intent is to be able to be used as a
6 measure of symptom severity, so one could look and
7 compare different procedures, and that was funded
8 by CIRREF, which is a research arm of the SCVIR.

9 [Slide.]

10 This is data from our sort of pilot study,
11 looking at quality of life related to uterine
12 embolization. This was using a proprietary
13 questionnaire which was fibroid specific, and you
14 can see that these are all increased in a
15 statistically significant way at three and six
16 months. The symptoms were even somewhat more
17 dramatic, particularly heavy bleeding was
18 dramatically improved here.

19 All of these were statistically
20 significant except for back pain at six months.

21 [Slide.]

22 Taking the other tack of saying, well,
23 gosh, how sensitive is even a very blunt instrument
24 in measuring outcome, the SF-12 is a 12-question
25 subset of the SF-36, and really is designed for

1 sort of large populations, a quick, two-minute
2 questionnaire, but even using this instrument, we
3 presented this approximately a year ago, there is a
4 statistically significant increase in the physical
5 summary scores at three and six months. The one-year
6 numbers are too small to be able to be
7 interpretable.

8 [Slide.]

9 The UFS-QOL is a new symptom and health
10 related quality of life questionnaire. It has 37
11 questions, 8 symptom and 29 quality of life
12 questions. It provides a symptom score and a
13 summary HRQOL score, as well as 6 subscale scores.

14 We have just completed the validation of
15 it. This was created using focus groups and then
16 we did an expert validation. Then, we went through
17 110 fibroid patients and 30 normal patients, and it
18 has excellent internal and external validity. The
19 cross-sectional validation was very strong with the
20 other measures, and it is the primary outcome
21 measure for the fibroid registry, which you will
22 hear more about later.

23 [Slide.]

24 So, assessing outcome, we believe that
25 patients represent their own controls and each

1 study or company or applicant should set an
2 appropriate clinically relevant level of symptom
3 change measured by validated means.

4 When possible, we think quality of life
5 scores should be included. Comparative surgical
6 and medical therapies should use the same measures.
7 I know that both these studies are comparative
8 studies.

9 It at least gives us an assessment of the
10 relative safety of the two procedures, and also
11 provides some indication of the relative
12 effectiveness, however, as has been demonstrated,
13 if one was to do a randomized trial, the estimate
14 is that this is similar in outcome to myomectomy,
15 and really, we would have to randomize hundreds of
16 patients in order to be able to adequately
17 investigate this.

18 We have actually done some pilot work
19 trying to determine how easy it would be to
20 randomize patients, and it really is quite
21 difficult. Patient resistance is quite high. I
22 think the best alternative to randomized studies,
23 which is what is going on in essence right now, are
24 parallel prospective cohort design of UAE versus
25 some other standard therapy using the same outcome

1 measures contemporaneously.

2 [Slide.]

3 Responding to the question regarding study
4 duration, I do think that six months is an
5 appropriate duration for premarket surveillance.
6 Nearly all the complications that have been seen
7 have occurred in the first six months. Nearly all
8 the secondary events, such as amenorrhea, fibroid
9 expulsion, and early treatment failures occur in
10 the first six months, not every single one, but
11 nearly every one.

12 It is rare to have recurrence in that
13 interval, which is one of the other questions. We
14 have seen a few recurrences. Both of our
15 recurrences were well over a year and in fact, one
16 of the patients was two years after the procedure.

17 It is more important to provide postmarket
18 surveillance for a longer period than one year. We
19 would suggest surveillance for a minimum of two
20 years. The fibroid registry may be a vehicle for
21 that postmarket surveillance, and we are enrolling
22 literally hundreds of patients, and we are hoping
23 to be able to supplement whatever data that each of
24 these companies would provide with that data.

25 [Slide.]

1 Re-treatment. I think re-treatments in
2 the context of these FDA-approved studies should be
3 considered primary failures, although these
4 patients should continued to be followed and look
5 at the subsequent treatments and outcomes. I think
6 it is useful data.

7 Technically unsuccessful procedures should
8 also be considered failures unless the procedure is
9 terminated or postponed for safety or other valid
10 reasons, the patient has some reaction to a
11 medication or something else during the sedation.
12 That really should not be considered a failure,
13 maybe noted, but not a failure.

14 But if we are unable to successfully
15 complete the embolization as intended the first
16 day, with that caveat, those should be considered
17 failures, we think.

18 [Slide.]

19 There was a question regarding labeling
20 elements. Obviously, future fertility is one key
21 issue, and there are some practical issues, which I
22 have discovered over the last four or five years
23 dealing with this group of patients.

24 Many women, even though we think they may
25 have, many women do not really have clear plans for

1 or against future children. Some women are very
2 definite, some women are very vague. You can have
3 a 33-year-old woman who isn't really quite sure
4 what she wants to do, you will have a 48-year-old
5 woman who definitely wants to become pregnant.
6 What do you do with that situation?

7 So, arbitrarily eliminating patients based
8 on a yes or no related to future children is really
9 not practical. The safety of myomectomy for future
10 childbearing varies greatly depending on the
11 surgical skill and the extent of fibroids.
12 Obviously, there is a conversion rate to
13 hysterectomy which is quite low, but certainly it
14 has never really been well studied in terms of its
15 overall safety.

16 Many patients desiring future children
17 have had one or more previous myomectomies, and
18 really are referred to us by infertility
19 specialists saying there is not going to be
20 anything left unless we go forward, so I think we
21 have to have a broader context where we are making
22 these decisions.

23 There have been numerous successful
24 pregnancies after a UAE, but the rate is not known.
25 We are hoping to get that answer from the registry.

1 The fetal wastage rate is also unknown. The role
2 of fibroids and fertility problems is still
3 unclear, it is very difficult to study, and the
4 effectiveness of myomectomy as a infertility
5 operation is not well studied. It has been
6 studied, but they are not large series. They have
7 been relatively poorly controlled. It is a very
8 difficult thing to assess.

9 Many women really resent their choice of
10 therapies being limited without their consent, and
11 would like to make their own decision after
12 obtaining appropriate information.

13 [Slide.]

14 So, the recommendations that we would make
15 are the following: that labeling should contain a
16 warning that the effect that UAE may have on future
17 childbearing is unknown, but that the data to
18 support myomectomy is also limited. This is not a
19 black and white thing in which myomectomy always
20 allows you to have a child and UAE doesn't. It is
21 much, much more difficult than that.

22 Each patient should be carefully assessed
23 to determine which therapy is most likely to
24 preserve the uterus in a functional state and with
25 the least risk of hysterectomy.

1 UAE should not currently be used as an
2 infertility treatment. Determination of the
3 effectiveness of UAE versus myomectomy for
4 infertile women does require I think a randomized
5 trial, and this is the one area I think we actually
6 could get patients to allow themselves to be
7 randomized because it is a very clear legitimate
8 question, and we will eventually have to answer
9 that question.

10 [Slide.]

11 So, I would conclude by saying that while
12 the current published experience suggests that UAE
13 is effective in controlling symptoms and improving
14 health-related quality of life, these comparative
15 studies that the FDA has approved are really a
16 major step forward in the assessment of this
17 therapy.

18 These are well designed studies. They are
19 being monitored in a very appropriate way, and I
20 think that this is a big help in the evaluation of
21 this treatment.

22 The role of the FDA is important, but
23 other efforts including those of the fibroid
24 registry and the adoption of uniform validated
25 means of measuring outcome are also critical, and

1 we are very strong proponents of physician
2 education and training standards to ensure that
3 this is done safely in a broader practice.

4 Thank you.

5 DR. BLANCO: Thank you, Dr. Spies.

6 Any questions of fact at this point? We
7 are running a bit late.

8 DR. D'AGOSTINO: In the quality of life
9 scale, the UFS quality of life, you said it was
10 validated. What was it validated against?

11 DR. SPIES: First of all, we started, as I
12 said, with focus groups, and then we had expert
13 review by gynecologists, and then we went through
14 an iterative process, so it is validated against
15 internally consistent, but externally validated
16 against the SF-36, against the Ruta menorrhagia
17 questionnaire, against the Revicki Wu sexual
18 functioning scale. I think those are the three.

19 DR. D'AGOSTINO: So, it is not validated
20 against some physical activity or measurement, and
21 so forth, it is other quality of life--

22 DR. SPIES: It has not been measured
23 against, for example, severity of menstrual
24 bleeding. It has also, I am sorry, been validated
25 against physician and patient self-assessment of

1 severity of symptoms.

2 DR. D'AGOSTINO: Part of it is symptoms
3 and part of it is quality of life.

4 DR. SPIES: Eight questions are symptoms,
5 29 are quality of life.

6 DR. D'AGOSTINO: When you say it is
7 validated, are you talking about the whole thing?

8 DR. SPIES: The whole thing is validated.

9 DR. D'AGOSTINO: Do you know what drives
10 the validation? I mean is it the symptoms or the
11 quality of life?

12 DR. SPIES: Well, it reliably
13 distinguishes the scores, reliably distinguishes
14 the severity of symptoms and the severity of the
15 impact on quality of life. It reliably
16 distinguishes fibroid patients from normals, and it
17 reliably distinguishes patients with severe
18 symptoms by self-assessment of these other measures
19 from those with milder symptoms. This will be
20 submitted to Obstetrics and Gynecology actually
21 this week, it is just being mailed out.

22 So, there will be an opportunity to review
23 this at greater length. This was done with Med Tap
24 International as our consultant, and they designed
25 the study.

1 DR. D'AGOSTINO: Just one other question.
2 What triggers the re-treatment? I am trying to
3 sort out why they are failures.

4 DR. SPIES: Well, it is not clearly known.
5 In other words, we haven't restudied every single
6 patient that fails to improve. I think there are a
7 number of possibilities. One is misdiagnosis, the
8 patient may have an endometrial polyp that might be
9 missed, and that may be the cause of their
10 bleeding, so you have to assess patients carefully.

11 There may be incomplete embolization, the
12 fibroid may not infarct, and we have shown that if
13 you don't infarct the fibroid, you are unlikely to
14 get improvement.

15 One of the primary reasons that happens is
16 collateral flow from the ovarian arteries, and we
17 have seen that in 2, 3, 4 percent of patients.

18 DR. D'AGOSTINO: What I am wondering, is
19 it the procedure or do the physicians do something
20 wrong?

21 DR. SPIES: No, many times it is related
22 to anatomic variation of patients. It may also be
23 due to the embolic material used or the way it was
24 delivered. It could be a combination of either,
25 but there are some anatomic factors which will

1 cause you to fail.

2 If a substantial portion of the uterus or
3 the fibroids are supplied by the ovarian arteries,
4 it will fail unless you embolize the ovarian
5 arteries, which no one regularly advocates in any
6 way. So, there are reasons to fail on this, and
7 the two that we re-angio'd, both had significant
8 supply from the ovarian arteries, which was
9 undetected at the initial study.

10 DR. BLANCO: Let me go ahead and interrupt
11 because we are really going to run late, and let's
12 introduce our other speaker, and hopefully, we will
13 go ahead and try to catch up on time.

14 Thank you very much, Dr. Spies.

15 The next speaker is Dr. Matthew Mauro from
16 the University of North Carolina, I believe also
17 representing the Society of Cardiovascular and
18 Interventional Radiology.

19 Matthew Mauro, M.D.

20 DR. MAURO: Thank you. We certainly
21 appreciate the opportunity to address this
22 committee, and I ask your indulgence for several
23 more minutes.

24 DR. BLANCO: I am sorry, introduce
25 conflict of interest.

1 DR. MAURO: No conflict of interest.

2 My purpose is really to highlight the
3 major efforts of the Society regarding its
4 activities, and that really leads us to the Uterine
5 Artery Embolization Fibroid Registry.

6 [Slide.]

7 To date, we estimate that worldwide there
8 has been 10,000 to probably more like 15,000
9 procedures done, the majority of which have been
10 done in the United States although the procedure
11 was begun in Europe. Approximately, 40 major
12 complications have been reported, one death in the
13 United States, two other deaths reported in Europe.

14 Typically, at the beginning these
15 procedures have been performed in high-volume
16 institutions, but recently we have noted that it
17 has been migrated out into the community and
18 community hospitals.

19 [Slide.]

20 You can see here that the growth has been
21 relatively impressive over 1999, where
22 approximately 4,000 cases have been done, to an
23 aggregate total U.S. procedures of 8,600 in the
24 year 2000.

25 [Slide.]

1 In April of 1999, the SCVIR developed a
2 task force to investigate and evaluate the uterine
3 artery embolization procedure. We developed a
4 multifaceted approach which looked at standards,
5 research initiatives, physician education, and
6 other activities.

7 [Slide.]

8 Training standards was an important part
9 of this multifaceted approach. In January of 2001,
10 the SCVIR published in the JVIR training standards
11 for physicians and also equipment relating to this
12 procedure.

13 The physicians must be very highly
14 educated and trained in this technically skilled
15 procedure. Embolotherapy is probably one of the
16 most challenging procedures that interventional
17 radiologists perform, and most interventional
18 radiologists perform this from head to toe on a
19 daily basis.

20 [Slide.]

21 In addition to the training skills,
22 optimal equipment is required as highlighted by the
23 marked reduction in radiation dose from antiquated
24 equipment, which uses continuous high-dose
25 fluoroscopy to the more standard used state-of-the-art

1 equipment, which uses pulse fluoroscopy, and
2 give you an idea of what the significance is by
3 using continuous fluoroscopy that utilizes
4 radiation at 60 pulses per second where we now can
5 use routinely 7.5 pulses per second using this
6 pulse-dosed, which is a reduction of 7/8ths of the
7 dose, so it is a very important aspect of the
8 performance of this procedure.

9 In conjunction with that radiation safety
10 training, which is a part of all radiologists'
11 training, it is an important requirement when using
12 radiation-producing equipment.

13 [Slide.]

14 Reporting standards has also been
15 developed and will be published soon, and this is
16 intended to serve as a guideline for investigators,
17 not only interventional radiologists, but perhaps
18 for all other investigators in the treatment of
19 fibroids.

20 [Slide.]

21 Research initiatives have been developed
22 in conjunction with the Rand Health Service, where
23 a multidisciplinary expert panel was convened in
24 June of 1999, and this panel identified several key
25 outcome measures to be investigated and recommended

1 four areas of research.

2 The first was a prospective registry,
3 which I will comment on further. The second was a
4 disease-specific QOL instrument, which has been
5 accomplished.

6 The third recommendation was a randomized
7 clinical trial. Two attempts were made to date for
8 a randomized clinical trial. One was UAE versus
9 hormonal therapy, and UAE versus myomectomy. Both
10 projects failed to receive adequate rating to be
11 funded. The fourth area of research was a cost
12 study.

13 The CIRREF, which is the research arm of
14 the SCVIR, has already funded five research grants
15 dealing with ovarian function, the quality of life
16 instrument, and the effect on the endometrium.

17 [Slide.]

18 The registry is an ongoing effort which we
19 are very proud of. It is sponsored jointly by the
20 SCVIR and its research arm CIRREF. It has a
21 registry steering committee. The principal
22 investigator of the committee is Evan Myers, who is
23 an obstetrical gynecologist from Duke, of the Duke
24 Clinical Research Institute. The DCRI is the body
25 that we are working with in order to conduct this

1 clinical survey, a very reputable research
2 institute.

3 All IRs with subspecialty training are
4 performing these procedures, and we do have
5 industry sponsors.

6 [Slide.]

7 The primary objective of the registry is
8 really to collect very high quality information
9 regarding patient safety and effectiveness for this
10 procedure. We would like to assess the durability
11 of the embolization, its impact on fertility, as
12 well as the quality of life in general.

13 The secondary objectives would be to
14 assess and benchmark for clinical practice
15 patterns, and to evaluate the utilization for
16 patients undergoing this procedure.

17 [Slide.]

18 This is an observational database, and our
19 intent was to collect consecutive patients
20 undergoing this procedure, and we would emphasize
21 to our members participating in this registry that
22 we would like to capture every case performed.

23 We estimate that our sample size would
24 include 3,000 patients per year, and for our
25 prolonged longitudinal follow-up study,

1 approximately 900 patients per year.

2 [Slide.]

3 All patients enrolled will have baseline
4 data, as well as procedural data, 30-day data
5 entered into a web-based form. There will be
6 patients enrolled at 24 core sites, which will be
7 considered for follow-up study at 6, 12, and 24
8 months. This constitutes our longitudinal study.

9 They will be randomly sampled and undergo
10 a quality of life instrument evaluating patient
11 satisfaction. All patients intending subsequent
12 pregnancy will be involved in this longitudinal
13 study.

14 [Slide.]

15 As I said, it is being coordinated by the
16 DCRI. We intend to have relatively broad inclusion
17 criteria as this is an observational database and
18 therefore patients choosing to participate and have
19 signed an informed consent has symptomatic fibroids
20 documented by an imaging study, and obviously is 21
21 years or older.

22 [Slide.]

23 We have several short term outcomes that
24 are being measured. Baseline data is relatively
25 exhaustive, and that is one of the principal

1 purposes of this registry, is to obtain consistent
2 and important data regarding the procedure, as well
3 as procedural data and the variety of adverse
4 events that may occur.

5 Thirty-day follow-up will be required from
6 all registrants, and the long-term outcomes again
7 will be in a group hopefully numbering 900 patients
8 per year. This will be a relatively intense review
9 for long-term outcomes and currently we have
10 funding that will lead to a 24-month follow-up.

11 [Slide.]

12 In conclusion, this has been a large
13 effort from the Society, and the registry will
14 provide long-term data on the use of this procedure
15 for the treatment of fibroids including evidence of
16 safety, efficacy, and durability, the impact on
17 uterine and ovarian function, fertility, and
18 quality of life.

19 We anticipate having a full 24 months at
20 the current level of funding of approximately 450
21 patients and 12-month follow-up data for
22 approximately 1,350 patients.

23 Thank you very much.

24 DR. BLANCO: Thank you very much, Dr.

25 Mauro.

1 Are there any questions of fact?

2 [No response.]

3 DR. BLANCO: Thank you very much for
4 concentrating your presentation. We appreciate.

5 Now we come to the open public forum. We
6 have some folks that have asked to speak.

7 We will with Dr. Vicki Hufnagel from
8 Studio City, California. I believe she is on the
9 speaker phone, is that correct? Dr. Hufnagel, are
10 you there?

11 DR. HUFNAGEL: Yes, I am.

12 DR. BLANCO: We would ask you to go ahead
13 and state your name and any conflict of interest,
14 and also, please limit your remarks to five
15 minutes.

16 Go right ahead. We are here listening.

17 Open Public Hearing

18 DR. HUFNAGEL: (By telephone) Number one,
19 there is no financial relationship. There is a
20 conflict of interest in that I am an extremely
21 biased and extremely opinionated individual, so
22 that the panel will know that.

23 DR. BLANCO: Thank you for advising us of
24 that.

25 DR. HUFNAGEL: The general destruction of

1 normal uterine tissue is the result of uterine
2 artery embolization. To hear in this meeting that
3 after the fact, 10,000 cases have already been
4 performed and now a registry is going to occur is
5 extremely distressing to myself and to many women
6 who would hear this, but this is typical of the
7 types of evaluations of procedures that goes on.

8 I think this is partially from our
9 culturalization that the uterus is an organ which
10 we can eliminate easily. You need to look at your
11 social concepts when you think about the uterus.
12 The uterus has physiological function that include
13 sexual response, creation of hormones, substances,
14 inhibin, relaxin, prostacyclins. It is also an
15 organ of placement in the pelvis.

16 In speaking out, I will be attacked in
17 presenting a case that I recently did of Achieng
18 Wamabo, who is, by the way, one of 10 patients that
19 I selected to bring to you today, 10 patients who
20 all had very bad outcomes with uterine artery
21 embolization, 10 patients who were never reported
22 to the FDA, 10 patients who were never followed up.

23 Achieng Wamabo described her uterine
24 artery embolization in one word, "fast." She was
25 seen at one of the major sites in which this was

1 being performed. In 1998, she had a Lupron
2 injection. Ten days after that injection, she had
3 an emboli shower in her lungs and nearly died from
4 the pulmonary emboli. That was 1998.

5 She was told that the Lupron would be
6 helpful in her procedure for her embolization later
7 on. In 1999, she had her embolization. That
8 embolization operative report is very
9 contradictory. That operative report says that
10 both arteries were embolized. Then, it says only
11 one artery was embolized.

12 Her physicians who handled her pulmonary
13 emboli refused to give her her medical records.
14 The physicians who saw her, both the radiologist
15 and gynecologist, were well known to this
16 committee. Both made no notations whatsoever in
17 her medical workup that this woman already suffered
18 a significant pulmonary emboli in 1998. There
19 actually was relatively little workup, and she was
20 pushed in one day from the gynecologist to the
21 radiologist to have this procedure done.

22 This is consistent with 10 cases that I
23 have reviewed recently. What is of major
24 importance is that there is a lack of workup, a
25 lack of informed consent. All the negatives for

1 uterine artery embolization are not--let me repeat--are not
2 being discussed with the patients. Women
3 are not told that they may not be able to have a
4 myomectomy in the future.

5 Having been able to actually see the
6 tissue results as a surgeon, I was able to see that
7 the resulting myometrium, normal myometrium is
8 severely affected by uterine artery embolization,
9 and selection of patients who have very, very large
10 uteruses, which you know the reduction is not going
11 to be down to a normal size uterus, and the woman
12 is going to be still left with a large mass, makes
13 these poor candidates. Yet, these women are still
14 having uterine artery embolizations.

15 There was no dissection line in the
16 removal of Achieng's fibroid. There was no
17 capsule. What occurs is microabscess formation,
18 histiocytic clumping, fibrosis, and other tissue
19 reactions, which actually removed the capsule.

20 The hallmark for a myomectomy is the
21 ability to distinguish between normal and abnormal
22 tissue during your dissection. This is gone with
23 uterine artery embolization, and women are not
24 being told this.

25 I have great concerns over the lack of

1 adequate informed consent. I have great concerns
2 that there is so much silence on this. Why was
3 this case not presented? Why did the FDA not get
4 any reports on it? Ten women have now reported
5 major complications that have never been reported
6 to the FDA.

7 Women need to have surgical options, as
8 well. Myomectomy needs to come out of the dark
9 ages, and we need to approve it. Uterine artery
10 embolization probably has a place, however, the
11 widespread entrepreneurial selling of this
12 procedure when women are scared and frightened, are
13 told they have no other option other than a
14 hysterectomy, just sending them in to get an
15 embolization without full knowledge of all the
16 problems that can happen.

17 Radiation exposure still an issue, I
18 believe. Toxin exposure, another issue. The lack
19 of follow-up. Every one of the women who have come
20 and reported have never even had an ultrasound
21 after their uterine artery embolization. Their
22 uterus just shrunk, they were sent on their way,
23 and no follow-up. These are clinical crisis.

24 Achieng Wamabo will be sending her report
25 in. She will be leaving the hospital next week,

1 having had more than 50 fibroid tumors removed. It
2 was a difficult surgery, and this is my expertise.
3 I do more myomectomies than anyone I have ever met,
4 and I had a difficult time doing it.

5 Would we embolize a neoplasia on the
6 testes? I doubt it. What are we thinking about
7 when we are promoting these kinds of processes
8 without looking at all the issues and providing
9 them to the women?

10 This is being sold to women, it is being
11 marketed. There are actual contracts between women
12 who are writing books and working for university
13 hospitals, and are getting funding for their web
14 sites. None of these web sites have any advocacy
15 section. None of these web sites have any area
16 except for one, one web site has an area to report
17 problems with AUE.

18 The marketing aspect of this is enormous,
19 and it is doing well, obviously, by looking at the
20 graphs and the data. The problem is that some
21 women have suffered, and others will continue to
22 suffer because of the fact that this is so fast,
23 there is a lack of procedural protocol, and the
24 response to the tissue of the myometrial normal
25 tissue and its destruction is not being adequately

1 provided to the women prior to this procedure.

2 I do not like this procedure and the way
3 in which it has evolved whatsoever, and I conclude.

4 DR. BLANCO: Thank you, Dr. Hufnagel.

5 The next individual who has requested time
6 for public comment is Carla Dione--I apologize if
7 that is not right--Executive Director, National
8 Uterine Fibroids Foundation.

9 Again, please state any conflict of
10 interest and limit your remarks to five minutes.

11 [No response.]

12 DR. BLANCO: It appears that she is not
13 here.

14 The last one that I have or that we will
15 open it to the audience if there is anyone else is
16 Nora W. Coffey, President, Hysterectomy Educational
17 Resources and Services Foundation (HERS).

18 MS. COFFEY: Good afternoon. I am Nora
19 Coffey, President of the Hysterectomy Educational
20 Resources and Services Foundation, a national
21 nonprofit women's health education organization.
22 HERS is also the repository of thousands of reports
23 from women regarding the treatment they receive and
24 have had suggested to them by physicians.

25 I am going to truncate what I intended to

1 say today in the interest of time, but I am still
2 going to I guess rush through.

3 Research of the medical literature
4 revealed that UAE was a surgery that had been
5 performed on a small number of women for postpartum
6 hemorrhage initially and at risk of death. It is
7 now being performed on women notably absent from
8 any danger to life and often even lacking the
9 minimal symptoms for which any treatment might
10 rationally be suggested.

11 Since UAE first emerged, the pool of so-called
12 qualified UAE candidates has shrunk as the
13 obvious dangers of performing it in certain women
14 has become apparent, but the number and seriousness
15 of adverse effects has mounted and now sits well
16 outside the promised no complications, and from the
17 hint that there might be pain as a result for a
18 very short time requiring the possibility of
19 hospital admission for treatment, we now know that
20 many or most do have pain and others have
21 persistent, some severe pain for months and even
22 years later as a permanent complication.

23 All this has been learned, not from
24 laboratory science before exposing large numbers of
25 women, but from the ill effects suffered by women

1 who expected that this was an easy and trouble-free
2 solution to the problems that some, but not the
3 majority, of women encounter from fibroids.

4 Our office continues to receive calls from
5 women unsuspecting of these facts including one who
6 doctor told her that he would perform the procedure
7 on her. When she asked how many UAE he had
8 performed, he said he hadn't performed any, but he
9 had read about it, and he was sure that he could do
10 it.

11 Another woman who underwent UAE reported
12 that she had developed a foul vaginal odor,
13 obviously not only to herself, but to others. She
14 had an infection. When it was exposed at surgery,
15 had appeared to simmer for months, and had caused
16 adhesion of the bowel to the uterus and other
17 organs, requiring that a specialist come in mid-operating
18 procedure, and there are many other
19 reports. I am going to skip over the women's
20 reports, although I think they are really
21 important, and I wish I had time to show them.

22 You all know of similar problems which
23 have not yet appeared in the journals, although
24 none of us know how large the total numbers are or
25 will become from this experimental misadventure.

1 Uterine artery embolization has already
2 caused deaths, hysterectomies, infections,
3 cessation of menstrual periods, rehospitalization,
4 and other damage that was unexpected by women, all
5 in a scant few years.

6 This leads to the expectation that there
7 is more in terms of numbers and additional
8 consequences not yet identified. We ask then of
9 the FDA the following:

10 If you have the authority to confer
11 approval on a surgical procedure, and thus confer
12 its legitimacy, although there are no standards
13 that exist for doctors, materials, or other
14 instrumentation, and no uniform procedure to
15 assess, that you exercise your authority and
16 responsibility to require that vendors, doctors,
17 and other proponents for widespread use of UAE curb
18 advertising and publicity which makes it appear
19 that all the answers are in and that they are
20 uniformly positive.

21 There is a public health danger posed by
22 the self-promoting websites and publicity in media
23 generated by doctors and other commercial
24 interests, such as the manufacturers, inventors of
25 devices who advocate for UAE.

1 Unfortunately, the biological sequela
2 arising as a result of this procedure will be
3 learned on the bodies of women, many of whom, as in
4 the case with hysterectomy, have no medical need
5 for any treatment whatsoever, and the argument that
6 hysterectomy is worse does not make UAE better,
7 only different in its dangers, which are as yet
8 largely unknown.

9 What are the lifetime sequela of the long-term
10 effects on ovarian function, endocrine
11 function, and the implications for vascular and the
12 immune systems?

13 If the permanence of artery occlusion
14 causes concerns, there are equal concerns lest the
15 blockade degrade or partially separate and drift.

16 What women need is a return to laboratory
17 science in order to identify the reasons women
18 develop fibroids, so that their arteries, uteri,
19 and other organs not be targets of interference and
20 demolition.

21 A name change, changing from uterine
22 artery embolization to UFE, uterine fibroid
23 embolization, will not serve women well. In fact,
24 it raises more questions about the problems we have
25 not yet read about in the journals and those yet to

1 come.

2 Calling it fibroid embolization rather
3 than artery embolization is an evasion and
4 ultimately misleading to women because it is, in
5 fact, the arteries that are embolized.

6 If clinical trials do proceed, and
7 apparently they are already in progress, we suggest
8 that women be provided with the following: Full
9 written disclosure of the known risks and adverse
10 consequences of UAE. An opportunity to ask
11 questions in writing, which doctors will respond to
12 in writing, and signed and date.

13 An adverse events reporting form should be
14 provided to the woman undergoing embolization, in
15 triplicate, with a copy to go to her doctor, a copy
16 to go to the FDA, and a copy for the patient.

17 Disclosure should include deaths,
18 sterility, radiation to the ovaries, infection,
19 loss of menstruation, hematoma, allergy to contrast
20 material, failure to shrink fibroids or resolve
21 symptoms, regrowth of fibroids, growth of new
22 fibroids, post-embolization syndrome, damage to
23 nerves, embolization of the wrong arteries, damage
24 to the blood supply to the ovaries, and loss of
25 libido, loss of sexual feeling.

1 Women should be told of all of the
2 alternatives to hysterectomy including no treatment
3 at all, myomectomy, and hysteroscopic resection of
4 submucosal fibroids.

5 Currently, a large number of doctors tell
6 women that the only option they have available to
7 them is hysterectomy or UAEE, which is certainly
8 not the case.

9 Thank you.

10 DR. BLANCO: Thank you very much.

11 Is there anyone else in the audience that
12 would like to address the panel before we begin our
13 deliberations?

14 I am sorry, who is this?

15 MS. BOOKER: (By telephone) My name is
16 Susan Booker.

17 DR. BLANCO: Okay. Please state any
18 conflict of interest statement and limit your
19 remarks to five minutes, please.

20 MS. BOOKER: I don't believe there is a
21 financial conflict of interest. I am not, I guess
22 you would say, pro uterine artery embolism. I am
23 surprised that the name is being changed to uterine
24 fibroid embolism or occlusion.

25 The surgery is going to be known as a

1 barbaric surgery in 20 years when doctors look back
2 on the damage that is going to happen to women, and
3 if the numbers of women being victimized by this
4 surgery, if it was the same numbers of men, the FDA
5 would take an immediate stance and halt until a
6 follow-up is done on the women who have already
7 gone through uterine artery embolism.

8 A complete, full follow-up on the women
9 who have had uterine artery embolism needs to be
10 done now immediately.

11 I have great concerns on the number who
12 have been injured, and I understand that a similar
13 situation took place years ago with the ova block,
14 which has never been fully recalled, women still
15 have not been informed, and that is an unresolved
16 issue in its own.

17 I conclude.

18 DR. BLANCO: Before you conclude, may we
19 ask you, are you speaking as an individual or do
20 you represent an organization or have an
21 affiliation with an organization?

22 MS. BOOKER: At the moment I am speaking
23 on my own, as an individual. I am a member of NOW.
24 I work on health right issues, and I am a house
25 advocate.

1 DR. BLANCO: Thank you very much.

2 Anyone else in the audience?

3 [No response.]

4 DR. BLANCO: We will then begin the panel
5 discussion, and I would like to go ahead and have
6 Dr. Levy address some issues, and then we will go
7 through the discussion questions.

8 Panel Discussion

9 DR. LEVY: First of all, I would like to
10 congratulate the Society of Cardiovascular and
11 Interventional Radiology for putting forth this
12 huge amount of effort in trying to study the
13 science of this procedure.

14 I think that you have gone far beyond what
15 most medical organizations and societies have done
16 in the efforts to try to learn something about this
17 procedure and to put some of the comments in
18 context.

19 I really say congratulations. There is a
20 huge amount of effort here, and there is an effort
21 to study a new procedure, far beyond what we, in
22 medical science, have done with any of the
23 operative procedures that we have currently in
24 place for women, so congratulations, and I think
25 every effort is being made to study this as

1 scientifically as possible, and I am in absolute
2 agreement with you.

3 I must say that I agree with most of the
4 speakers' comments in terms of the FDA questions.
5 I agree with consistent use of hormones pre-procedure, post-
6 procedure. I don't think we should
7 exclude patients who are on hormones, but I think
8 that we should keep them consistent across the time
9 that we are studying, so that we don't get shifts
10 and differences that we can't attribute to the
11 interventional procedure. I think that is very
12 important.

13 I think that quality of life
14 questionnaires should be done early on if we are
15 really going to be able to use these data to inform
16 women. Then, we need to be able to compare uterine
17 artery embolization with myomectomy, with
18 hysterectomy, and that means the quality of life in
19 the first day, second day, the first seven days,
20 two weeks, three weeks, and a month, two months
21 later.

22 I don't know if that can be done within
23 the context of some of the studies or as a substudy
24 of some of what you are doing, but as a practicing
25 gynecologist who tries to give informed consent to

1 patients, I know there is a lot of pain with
2 uterine artery embolization, there is certainly a
3 lot of pain with surgery initially, and I don't
4 know how to compare the two.

5 I think it would be very valuable to have
6 some of these quality of life surveys done at 24
7 hours, 48 hours, perhaps from there to a week post-op, so
8 that we have some sense of when the return
9 to function really occurs, not in retrospect, but
10 on a prospective basis. That would be very useful
11 information to me.

12 I agree with doing a six-month study and
13 then continuing surveillance for two years. I
14 think two years is a very short period of time, and
15 there is a lot of information I personally, as a
16 woman, and as a gynecologist giving informed
17 consent would want to have about this procedure
18 long term.

19 Whether we can persist with a registry
20 after the two years, I don't know, but it is
21 something that would be of interest. Many of these
22 patients will not become pregnant within two years.

23 Some of them may become pregnant five
24 years out or 10 years out, and whether there is an
25 opportunity for us to take the study and continue

1 an ongoing registry where patients could just log
2 on and be able to give us further information, I
3 think that would be very useful.

4 The things that concern me are things like
5 radiation exposure to the ovaries in a young woman,
6 are we going to precipitate premature menopause in
7 these women, not immediately, but five years down
8 the road. You know, are we impairing ovarian
9 function with the amount of radiation that we are
10 using, are we going to generate cancers, other
11 things with the amount of radiation.

12 I think certainly in the radiological
13 literature, you have enough data on things like
14 barium enemas and other things to give us some
15 reassurance about that, but these are situations in
16 which we are electively using radiation, so I want
17 to make sure, and I think in your effort to go
18 really quickly, I think I saw it go by really fast,
19 that are you collecting the amount of radiation
20 exposure in every patient, is that correct?

21 DR. MAURO: Fluoroscopic time.

22 DR. LEVY: Fluoroscopic time? But I would
23 like to see us if we can collect radiation
24 exposure. I know that you at Georgetown are making
25 every effort. Can't do it? Okay.

1 DR. MAURO: Right now it's fluoroscopic
2 time plus numbers of images.

3 DR. BLANCO: Please identify yourself for
4 the record.

5 DR. MAURO: Matt Mauro from the Society of
6 Cardiovascular and Interventional Radiology.

7 As part of the registry, as part of the
8 database, we are collecting fluoroscopic time, as
9 well as number of images obtained.

10 DR. LEVY: But we are really not
11 collecting, whether it is a single surgeon, two
12 surgeons, just total time in fluoroscopy, number of
13 images. Is that a surrogate, can we march that out
14 in some way to look at outcomes?

15 DR. SPIES: Dr. Spies from Georgetown.

16 The problem with these studies is you
17 actually have to place what are called TLDs in the
18 patient's vagina and on her skin, which is mildly
19 invasive although most patients have no objection,
20 but it is very elaborate, and the reading is very
21 elaborate, and it takes a lot of time, so what we
22 are hoping to do is look at some of these studies
23 as pilots and then be able to extrapolate that data
24 to a population based on the fluoro times that are
25 used for this. It is not exact science, but it

1 will give us a better idea of the population load
2 of excess radiation or excess cancers.

3 The cancers are probably not going to be
4 an issue. All the radiobiologists we have talked
5 to do not think that this is anywhere near the
6 range in which we would be instigating cancer. The
7 bigger issue is, is there an effect on a woman's
8 ability to have a normal child.

9 If you look at the studies that have been
10 done for Hodgkin's, which have roughly 100 to 500
11 times the dose, their rate of having abnormal
12 children, genetically abnormal children or any kind
13 of malformation is about the same.

14 DR. LEVY: Actually, my concern is not
15 genetically abnormal children, my concern is taking
16 a 29-year-old or a 30-year-old and creating, not
17 premature menopause, but subtle alterations in
18 hormonal function, follicular function to the point
19 where we have significantly impaired their
20 fertility.

21 DR. SPIES: I think to be able to
22 estimate, it is very difficult. Actually, there is
23 very little literature on the effect of radiation
24 on the ovary. It is a difficult thing to study
25 partly because we have not been in the situation

1 before.

2 DR. LEVY: Which is why I just want to
3 collect as much data as we can with this wonderful
4 tool that you have started. I think it is
5 critical.

6 The only other comments that I would like
7 to make, there are some things rolling around in
8 the literature about use of Lupron pre-surgery. I
9 think you might want to separate use of hormones.

10 As I understand it now, it is not
11 recommended that Lupron be used for some particular
12 reasons, but when you say hormones, Lupron could be
13 construed in some way to be a hormone, so we
14 probably just want to clarify what we mean when we
15 say hormones, do we mean oral contraceptives, do we
16 mean progestational agents, do we mean--what
17 specifically do we mean, so that you are excluding
18 GnRH agonists perhaps.

19 I am just saying that as we are answering
20 these questions and we are saying should we exclude
21 patients on hormones, we want to clarify which ones
22 we are talking about and what dosages we are
23 talking about.

24 DR. SPIES: We basically are separating
25 the patients into three groups, and those are

1 patients on oral contraceptives, a progestational
2 agent, or GnRH agonists, and the agonists, in
3 general, most people exclude, and the studies that
4 are currently at present exclude, so patients
5 should not have an active agonist at the time they
6 have this procedure.

7 So, if it is a three-month dose, they
8 should not have this procedure within three months,
9 and that is pretty much standard practice now, and
10 I think that that ought to be the recommendation of
11 our group.

12 What I was actually speaking to was the
13 birth control pills, and in a case of a women that
14 have heavy bleeding, the use of progesterone
15 agents.

16 DR. LEVY: I think that is fine. In
17 summary, I agree with some of the consumer people
18 that have spoken, that a written informed consent
19 is obviously something we do with all studies. I
20 think it is absolutely critical. I think that
21 women need to understand that we do not have long-term
22 follow-up for these procedures.

23 I think that is fairly well established in
24 your things and the things that you have done. You
25 cannot be held responsible for what other people

1 out there are doing, as I very well understand.
2 But as a vehicle and as FDA, we probably do have
3 some responsibility to create in our guidance
4 document some sort of informed consent, some
5 written document that discusses these things in
6 general for the public, and I think that is very,
7 very important.

8 DR. BLANCO: Thank you.

9 MR. POLLARD: I would just add to the
10 point that you made about the informed consent.
11 Clearly or hopefully, obviously, when we looked at
12 these IDE applications, we did look carefully at
13 the informed consent, and we are also working with
14 the Society on identifying a more standardized list
15 of the risks and explanations of those that would
16 be incorporated into the guidance document, as
17 well.

18 DR. BLANCO: Thank you.

19 Let's go ahead and begin with the
20 discussion questions. The first discussion
21 question is quite lengthy. Let me try to read it
22 for you.

23 FDA is currently drafting an IDE/510(k)
24 guidance document to help in the preparation of
25 such submissions to the agency. Response to these

1 discussion questions will help with the development
2 of this guidance document.

3 1. Currently, the inclusion and exclusion
4 criteria for UFE performed in FDA-approved clinical
5 studies of UFE are generally as follows:

6 Inclusion Criteria. Symptomatic uterine
7 myomata. Premenopausal, but over 30 to 35 years of
8 age. Normal Pap smears in the last 12 months.
9 Regular menstrual cycles. Normal kidney function.
10 Use or non-use of hormonal contraception must be
11 maintained uniformly from 3 months pre-treatment
12 through study completion. Willingness to consent
13 and complete follow-up requirements of study.

14 Exclusion Criteria. Pregnancy or desire
15 for pregnancy. Gynecologic malignancy or pre-malignancy.
16 Adenomyosis. Candidate for
17 hysteroscopic or laparoscopic myomectomy. Any drug
18 treatment for uterine fibroids within 3 months pre-
19 treatment. Active pelvic infection or history of
20 pelvic inflammatory disease. Any acute or chronic
21 infection. Undiagnosed pelvic mass outside of the
22 uterus. Coagulopathy. History of pelvic
23 irradiation. ASA score greater than or equal to
24 IV. Uterine arterio-venous fistula. Allergy to
25 the I.V. contrast media.

1 Let me go ahead and open it up to the
2 panel for discussion. Any comments of any of these
3 inclusion or exclusion criteria? Go ahead, Dr.
4 Levy.

5 DR. LEVY: I am not sure that I would
6 exclude patients who are candidates for
7 hysteroscopic or laparoscopic procedures. I think
8 this is a choice as you have eloquently stated,
9 patients want to have choices, they don't want to
10 be randomized. There are patients who don't want
11 to have surgery and are symptomatic.

12 I think that we are making a value
13 judgment when we are excluding patients who are
14 candidates for laparoscopic or hysteroscopic
15 procedure. I think they need to be given informed
16 consent that these are procedures that could be
17 done as a outpatient basis, that there may be a
18 little bit more data specifically on hysteroscopic
19 resection. I think you probably have as much data
20 as we have on laparoscopic resection of myomas, but
21 I am not sure that I would exclude those patients
22 as much as I would just give them informed consent
23 that they have other options. Some of the other
24 patients may not have that option, but in listing
25 the options that patients have, they would be given

1 that choice.

2 DR. BLANCO: Dr. Diamond.

3 DR. DIAMOND: I would agree with most of
4 the inclusion and exclusion criteria here. The
5 couple that I would want to emphasize, that I do
6 agree with, is that at this point in time, I don't
7 think we ought to be recommending the inclusion of
8 women with known or suspected by gynecologic
9 malignancies and even endometrial hyperplasia,
10 certainly, at this point, I think ought to be
11 excluded.

12 Without a large amount of data about
13 subsequent pregnancy outcomes of these individuals,
14 for research trial's purposes, for new agents that
15 will be coming before FDA, I would also recommend,
16 as is stated here, that individuals who desire
17 future pregnancy be excluded from those trials
18 until we can get additional information.

19 I would disagree a little bit with
20 Barbara, but for a different reason, about patients
21 who are candidates for hysteroscopic myomectomies
22 or perhaps--we talk about laparoscopic potential,
23 you are talking about pedunculated fibroids--just
24 about the hysteroscopic, while I agree that we
25 should be giving patients choice, the question is

1 are those fibroids going to respond differently
2 than others that are intramural, and if so, would
3 including them in the database potentially alter
4 the result or make it more difficult to interpret
5 the results.

6 The one inclusion criteria that I think I
7 would disagree with is the issue of women who are
8 currently on hormonal contraceptives, and I would
9 agree that if individuals were on them, and would
10 stay on them afterwards, that that would probably
11 be less of an issue, but I don't think that the
12 sponsors are going to have any control over whether
13 women stay on their hormones or not after their
14 procedures, and I think that also would potentially
15 introduce a bias if the women are on them
16 initially, have the procedure, and then go off
17 them, particularly if there are short follow-up
18 periods where stress-related amenorrhea from the
19 procedures may affect subsequent bleeding rates, as
20 well.

21 But I think that potentially introduces an
22 additional factor which may influence the outcome
23 by the woman coming off the birth control pills or
24 just starting that themselves, and then having
25 alterations in their bleeding histories which would

1 have to be interpolated into the results in order
2 to draw conclusions of the studies.

3 DR. BLANCO: Dr. Shirk, you had some
4 comments?

5 DR. SHIRK: I guess I have got one
6 comment, and that is, one of the exclusion criteria
7 was dropped out from our initial
8 inclusion/exclusion criteria, from the initial
9 draft, we got the second draft, and that is on
10 pedunculated fibroids. Since the two deaths in
11 Europe, and I am not sure about the death in the
12 United States, were associated with pedunculated
13 fibroids, either intrauterine or subserosal, do we
14 want to consider that as part of the exclusion
15 criteria?

16 DR. BLANCO: Any comments?

17 DR. O'SULLIVAN: The question I would have
18 is if you have a pedunculated submucous fibroid,
19 and you then go ahead and embolize that, are you
20 not exposing the patient to a greater risk of
21 infection as a result of that pedunculated fibroid,
22 that you are causing degeneration to, which is
23 sitting free in the uterine cavity, which is not
24 sterile?

25 DR. LEVY: I would think if the only myoma

1 a patient had were a submucous pedunculated
2 fibroid, that we would not be considering these
3 kinds of procedures. We are really looking at, in
4 these procedures, women who have 14, 16, 18-week
5 size uteri with multiple fibroids. They may have a
6 submucous fibroid, and I don't think they should be
7 excluded from consideration if they do.

8 We know that if they do have submucous
9 fibroids that are on a pedicle, that they
10 frequently slough, they pass them, these are the
11 small percentage of people that sometimes need
12 hysteroscopic resection or D&C to get rid of that
13 necrotic tissue.

14 DR. ROBERTS: I have a number of concerns
15 about some of these inclusion and exclusion
16 criteria, and I will just sort of go through them
17 in order.

18 One is regular menstrual cycles. Many of
19 the women that we treat do not have normal cycles.
20 They may have bleeding in between their cycles.
21 They may bleed for two weeks, stop for a week and a
22 half, and bleed for another two weeks. So, I think
23 normal menstrual cycles is probably not a
24 reasonable inclusion criteria.

25 Normal kidney function. I think if you

1 had someone who is on dialysis and is bleeding, and
2 may not be a good candidate certainly for surgery,
3 certainly, that person who is on dialysis should,
4 in fact, not be excluded from this.

5 I think I would agree that if someone has
6 borderline renal function, that is something
7 different, but if they are already on dialysis,
8 then, there is no reason. You know, contrast is
9 not going to hurt their kidneys.

10 My concern about the hormonal
11 contraceptives is that I think it needs to be how
12 it is defined. If it is just simply hormones for
13 contraceptives, I agree, I think it is going to be
14 hard to legislate to patients whether or not they
15 are going to remain on contraceptives or whether
16 they are going to want to start contraceptives now
17 that they are not bleeding so much. Maybe they
18 figure they will have sex, so they would like to be
19 on contraceptives because they don't want to have
20 children.

21 In terms of the exclusion criteria, I
22 guess in terms of a research study, pregnancy, I
23 think that is a question we really want to answer,
24 and it may be, in fact, that pregnancy is something
25 we want to leave, you know, we don't want to

1 exclude, but I think that perhaps there is enough
2 question about that, that we at least ought to
3 think about that.

4 Certainly, anyone with a malignancy or
5 pre-malignancy shouldn't be treated. I don't know
6 that adenomyosis should be on the exclusion
7 criteria. We know that some patients with
8 adenomyosis seem to respond to this. We don't
9 really understand what is going on with
10 adenomyosis.

11 Some patients, where they have done
12 hysterectomies, they found that some of those
13 patients have adenomyosis, but in other patients
14 that they know have adenomyosis, they have a good
15 response.

16 I would say that it shouldn't be an
17 exclusion criteria, but probably should be perhaps
18 in a subset, if someone is going to study it, it is
19 going to be in a subset.

20 I think in terms of any drug treatment for
21 uterine fibroids, that is not a reasonable
22 exclusion criteria because I get a lot of patients
23 who come in, who are taking, you know, who have
24 been put on double dose hormones, double dose
25 contraceptives to try and control their bleeding,

1 and that is their control for right now until
2 something else can be done.

3 I will tell you a lot of these patients
4 aren't just taking double dose, they are taking
5 four times because they find out, they are told to
6 be taking twice as much, and then they find it is
7 not really working, so they are taking four times,
8 and obviously, those patients I don't think should
9 be excluded from this.

10 I think in terms of the allergy to
11 contrast media, I think it is important to say an
12 untreatable allergy to contrast media because many
13 patients have hives to contrast, you give them a
14 little SoluMedrol or you give them a little
15 benedryl, and they are going to be just fine. So,
16 I think it should be an untreated allergy to
17 contrast media.

18 So, I will stop with those.

19 DR. BLANCO: Any other comments?

20 Let me comment on a couple of things that
21 you said. I think the way that it is written, you
22 are going to exclude a lot of patients if you want
23 regular menstrual cycles when you are dealing with
24 patients with symptomatic uterine fibroids.

25 DR. LEVY: Maybe we could say normal

1 ovarian function.

2 DR. BLANCO: I think as far as the
3 hormones, the contraception, the three months, I
4 think you are going to face that problem either way
5 the decision is made because just like you are
6 likely to have women who will come off the oral
7 contraceptives after the procedure, you are going
8 to have some that will go back on it, as you
9 alluded to.

10 So, I think essentially, whatever study
11 gets designed, you are going to have to presuppose
12 that those are going to happen and take into
13 account numbers that you may have to analyze
14 separately or analyze differently in terms of how
15 big you plan for the study to be in order to prove
16 what you want to prove.

17 I would be interested in other folks'
18 comments, but I think pregnancy is a big issue, and
19 until we know more information--and I recognize a
20 lot of women may say now they don't want to get
21 pregnant, they may want to in five years from now
22 and vice versa--until we know a little bit more of
23 what it does, and we will.

24 I mean some of these women that are going
25 to say that they don't want to be pregnant, will

1 eventually become pregnant, and until we find out a
2 little bit more, it is probably better to leave
3 those folks out.

4 Any questions?

5 DR. O'SULLIVAN: I am just going to make a
6 comment. I mean we do have some information albeit
7 a slightly different situation, in which we have
8 had women with postpartum hemorrhages, and in an
9 attempt to conserve the uterus, have done both
10 bilateral uterine artery and ovarian artery
11 ligations, and they have subsequently gotten
12 pregnant. But it is starting out as a different
13 situation with a huge collateral blood supply that
14 probably wouldn't be the case here.

15 One of the questions I have--could we go
16 back to the last slide that you just took off? I
17 see the contraindication, uterine arterio-venous
18 fistula, why is that a contraindication? As an
19 exclusion criteria I mean, why would that be
20 exclusion?

21 DR. ROBERTS: I am not sure that it should
22 be, but the problem, if you have a really large
23 arterio-venous fistula, is that you are treating a
24 fistula, not fibroids. I am assuming that they
25 mean with this that they don't have fibroids, they,

1 in fact, have an arterio-venous fistula, and then
2 you can have the particles move through the fistula
3 into the lungs. So, that is considered bad form.

4 If it was simply an arterio-venous
5 fistula, you would have to treat the fistula
6 differently than you would the fibroids, and then
7 you could presumably treat it, so I am assuming
8 that that is the reason, because your treatment for
9 the fistula would be very different than with the
10 fibroids.

11 DR. ROY: The second inclusion criteria,
12 premenopausal; more than 30, 35 years of age, by
13 implication excludes people younger than that. I
14 was surprised that no one has yet mentioned that
15 there are women who have completed their
16 childbearing younger than that, who have myomata
17 uteri, who are symptomatic.

18 DR. BLANCO: You are going to want
19 premenopausal, but what you are basically saying is
20 you may not need that 30 to 35.

21 DR. ROY: Right.

22 DR. BLANCO: Colin.

23 MR. POLLARD: I just wanted to highlight,
24 so that it is clear to everyone what we are looking
25 at. What we are looking at is sort of a synopsis,

1 which is why in that opening sentence, it says
2 "generally" of the two clinical trials that we have
3 approved.

4 This is not necessarily exactly what is
5 going to go into the guidance document, but it is
6 sort of something that we thought would be very
7 helpful for the panel to work from, so in the
8 context of where did these come from, they came
9 from clinical trials we looked at.

10 The other thing was Dr. Roberts went
11 through a number of exclusions that she had some
12 question about, and we are hoping that the panel
13 might sort of engage on those, do they agree, do
14 they not agree, are there qualifiers, that sort of
15 thing.

16 DR. BLANCO: Thank you.

17 Let's hear from Dr. Spies. He wanted to
18 say something.

19 DR. SPIES: I am sorry, I don't mean to
20 interject, but the issue of hormones, I think is
21 quite important. I am actually more concerned
22 about the safety of this procedure than having a
23 truly accurate assessment.

24 So, if I had to choose between a truly
25 accurate assessment of the treatment effect of this

1 procedure versus the safety of the procedure, we
2 should go with safety.

3 Now, we have treated 425 patients at
4 Georgetown. We have had three thrombotic
5 complications - the PE I showed you, we had an
6 arterial thrombosis, and we had a very minor DVT
7 that didn't require any specific therapy. All
8 three women were on hormones.

9 The two with the worst complications were
10 on both Provera, double-dose Provera, or Aygestin,
11 and birth control pills. Now, we are just about to
12 start a study looking at prothrombotic states as a
13 result of this procedure, so that it is quite
14 likely that women become prothrombotic as a result
15 of this, just as they do with neurosurgery and hip
16 surgery, and other kinds of things.

17 The question is are they made more
18 prothrombotic by this, so I would ask the panelists
19 to seriously think about it before they exclude
20 these patients because this really is a significant
21 safety issue.

22 DR. O'SULLIVAN: First of all, in the
23 white population, the incidence of thrombophilia,
24 especially Factor V Leiden, is somewhere in the
25 range of 3 to 4.5 percent, and their risk of

1 developing thromboemboli on any of these drugs is
2 increased, and I agree with you, that would be a
3 concern, and I was rather surprised that in the
4 first 200 patients, you didn't have any, which is
5 kind of why I kept my mouth shut.

6 I do think that that is an issue. I think
7 that perhaps one of the ways around the issue could
8 be to do--and that is going to be expensive,
9 though--is to do a thrombophilia screen, certainly
10 for Factor V Leiden, which is the most common one
11 by far.

12 DR. SPIES: I have no doubt that we have
13 treated Factor V Leiden patients. I, in fact, are
14 V Leiden positive, I mean it is everywhere. I
15 imagine we have, and I imagine that those people
16 have gone through without a problem.

17 I expect that what we are going to do with
18 this group of patients is look at fragment 1,
19 fragment 2, platelet dependent factor,
20 thrombin/antithrombin complex, a whole variety of
21 different thrombotic--and we are working with Dr.
22 Kessler with Georgetown on this--to look at a group
23 of 20 patients in a row, let's do 5, 6 samples. We
24 will look at the curve and see what happens.

25 In most studies surgical interventions

1 double those, and if they double those, then, we
2 need to look at the subset perhaps that are on
3 hormones and look at that specific issue. That is
4 \$1,000 worth of lab tests.

5 You may be right, that Factor V Leiden is
6 a predisposer, but I have no doubt we have treated
7 some of those. None of the patients that we have
8 done so far with those thrombotic complications
9 have had actually any--we have done genetic
10 screening afterwards--the only risk factors were
11 hormones in that group of women that we can
12 identify.

13 DR. ROY: I think it is important to
14 remember that norethindrone acetate is a prodrug.
15 One milligram gets converted to, on average, 5
16 micrograms of ethinyl estradiol. Let's suppose
17 just for sake of argument that it stays the same.
18 You give 10 milligrams, you get 50 micrograms of
19 ethinyl estradiol, and you said you gave double the
20 dose, you were potentially giving 100 microgram
21 dose.

22 DR. LEVY: We didn't give it.

23 DR. ROY: Well, the patient was receiving
24 it. Okay? All I am suggesting is that that more
25 than the possibility of Leiden, although I think in

1 Caucasians it is a very important issue to consider
2 because of the link with the hormone therapy, as
3 Dr. O'Sullivan said, markedly increases their risk
4 of clotting.

5 DR. LEVY: I think we need to get back to
6 the practicality of who are these patients that we
7 are taking care of and who are these patients that
8 are candidates for the procedure.

9 Young women with symptomatic fibroids at
10 times are bleeding horrendously, and in order to
11 keep them out of constant transfusion and get them
12 ready, they will be treated with hormones. I think
13 we should include those patients, stratify for
14 them. I completely agree, we just need to see what
15 are they taking, which ones are at risk.

16 We may learn, for example, that 20
17 milligrams a day of norethindrone acetate is
18 absolutely contraindicated. Clinically, we don't
19 really know that right now. We give them as much
20 as it takes to get them not to bleed until we get
21 them to the operating room or get them to the lab
22 for UAE.

23 But in practical terms, those are the
24 patients we are targeting for this procedure, and I
25 think they must be included. I think we just need

1 to stratify for them. We will need to know who
2 they are and how much they are taking, and for how
3 long, so that we can take a look at safety, as well
4 as effectiveness in the long run, and just keep the
5 registry growing, but I think to exclude all those
6 patients is going to be a miserable thing for us to
7 try to do.

8 DR. BLANCO: Actually, that is probably
9 one of the deficiencies in looking at this is a
10 longitudinal study as opposed to a comparison
11 study, because it may be that the incidence of
12 pulmonary embolus or thrombophlebitis is actually
13 worse in these patients that are highly loaded on
14 hormones when they undergo a myomectomy or
15 hysterectomy, and it may not be that it is
16 necessarily the procedure that is doing it, but
17 it's the prettiest position of the hormones, the
18 high level of hormones, and then having them sit
19 around for any type of procedure for a while.

20 Do you want to say something about the
21 hormones?

22 DR. DIAMOND: Something about what Colin
23 wanted and one thing about the hormones both.

24 DR. BLANCO: Go.

25 DR. DIAMOND: With regard to Dr. Roberts'

1 comments about adenomyosis, adenomyosis as a
2 coexisting disorder with fibroids, I don't think
3 should be an exclusion criteria, but someone whose
4 entire pathology is thought to be adenomyosis as
5 opposed to fibroids is not someone who I would
6 recommend including because then we are treating
7 different disorders.

8 With regard to the hormone issue, you just
9 need to keep in mind also that there are at least
10 two different types of studies that are probably
11 going to be ongoing for uterine artery
12 embolizations.

13 One may be of the sort at Georgetown that
14 you all are doing, the multicenter studies that you
15 are conducting, which very well might include
16 individuals who are on hormones, because those are
17 very key questions because we so often do put our
18 patients on them.

19 But the guidance document would not
20 necessarily be for that population. That may be
21 for companies that are coming in with devices they
22 would like to be able to be utilized for these
23 purposes, and for the purpose of those trials where
24 there is going to be potentially some sort of
25 comparison, then, to have them included and with

1 possible changes in the hormones, hormonal therapy,
2 I think will complicate the interpretations.

3 DR. LEVY: I will agree with Dr. Roberts
4 that patients on dialysis should be included, but
5 patients with renal failure, who are not on
6 dialysis, should be excluded.

7 DR. ROBERTS: The other thing is, also on
8 the exclusion criteria, I would also say that
9 uncorrectable coagulopathy would be an exclusion,
10 but not coagulopathy in general.

11 DR. BLANCO: I don't know. Do you really
12 want folks who are having coagulopathy to be part
13 of a research protocol? It is the same thing sort
14 of as someone who has an allergy. Even if you
15 think you can treat it with a little SoluMedrol, I
16 mean that may be what happened last time, but maybe
17 won't happen this time.

18 I think as part of a research protocol, it
19 is probably better to exclude folks that you know
20 are going to have some other added complications
21 than include them because you may get somebody who
22 was controlled okay before, but is not, so I have
23 some concerns.

24 I would probably keep both the allergy and
25 the coagulopathy as it is, it would seem to me.

1 MR. REYNOLDS: I just have one question
2 since we had some consumer groups who seemed to be
3 terribly concerned about informed consent.

4 On that informed consent form that the
5 people are going to fill out, is it going to say
6 anything on there about alternative procedures?

7 DR. BLANCO: IRB forms routinely have as
8 one of their components alternative therapies.

9 DR. ROBERTS: Quite frankly, as someone
10 who does these procedures, I mean I can't speak for
11 every practitioner, just as I am sure the Ob-Gyn's
12 here would not want to speak for every Ob-Gyn, but
13 I would say that, by and large, these patients,
14 first of all, are educated in terms of what it is
15 that we know and what we don't know by the large
16 majority of people.

17 I will speak for myself in saying that all
18 of the patients that I see are told that there are
19 a lot of things that we don't know about this, this
20 is what we do know, these are what all of your
21 options are, hormones, doing nothing, myomectomy,
22 hysterectomy, all of these are options for you, and
23 the other thing that I think is very important is
24 to realize that, by and large, these are a very
25 educated group of women that are coming in for this

1 study or this proposed treatment.

2 I mean they have been on the Internet,
3 they have been contacting different doctors. They,
4 by and large, are not sort of, you know, lambs
5 being led to the slaughter on this, I will tell
6 you, and I, quite frankly, will speak publicly to
7 say that I violently disagree with some of the
8 public speakers that were here today.

9 DR. BLANCO: Let me just say that I think
10 part of the rationale why we are here is that we
11 would like to be able to derive through research
12 projects, publications, education, and guidance
13 documents to the type of things that need to be
14 available by folks who may not be doing it under
15 such strict protocols, so that people can be aware
16 of what really is required.

17 Neither the FDA nor us can be out there
18 policing every single doctor that may use a
19 procedure that may not quite do it in the
20 appropriate way. So, I think the best that we can
21 do is try to make sure we get the appropriate data,
22 so that the appropriate information is available
23 and can be promulgated, and without a doubt, inform
24 women appropriately with the best data available as
25 to what the options are and what the different

1 procedures are, and what might be the results of
2 those or at least what we know.

3 Having said that, anything else on the
4 inclusion/exclusion criteria? If not, we are going
5 to move on.

6 DR. CORRADO: Dr. Blanco, it is Julia
7 Corrado from FDA staff.

8 I just wanted to I guess beat this issue
9 of hormonal contraception one more time, because we
10 have had some concerns that I just want to make
11 sure the panel is aware of, so that we can
12 definitively come to closure on this, because I
13 sense that there is still some disagreement among
14 the members of the panel, as well as among the
15 staff and the sponsors on this issue.

16 What we are anticipating is getting a data
17 set that we want to be able to interpret
18 statistically and for labeling as straightforwardly
19 as possible, and we have been concerned that if
20 some of the patients, an unspecified percentage of
21 patients are on uniform hormonal contraception
22 prior to and during the study, and that their data
23 is pooled with the data of women who are not on any
24 kind of hormonal medication including
25 contraception, that they might not be poolable and

1 that we won't be able to adequately represent who
2 the patient population in the study was in terms of
3 presenting the data.

4 So, that is one of our concerns. We, in
5 general, I think would agree that we like the
6 cleanest data set that we can get.

7 I would also like to point out that to my
8 way of thinking, there is analogy between these
9 studies and the endometrial ablation studies that
10 we have been entertaining, and in those studies,
11 women were excluded if they desired to be on any
12 kind of hormonal contraception for any period
13 during the study evaluation, and that didn't limit
14 those sponsors from enrolling patients in their
15 studies. It didn't appear to be a problem.

16 Dr. Levy?

17 DR. LEVY: Actually, it did significantly
18 impair our ability to enroll patients in those
19 trials. I think there was a significant problem,
20 but I also think that the quality and the amount of
21 bleeding that some of these patients with fibroids
22 do is substantial, and it is substantially
23 different than what we were dealing with, with the
24 endometrial ablation protocols.

25 I don't disagree that the cleanest data is

1 the best, but I think that in order to look at all
2 populations for whom this procedure may be
3 indicated, what we probably need to have is the
4 data stratified. We should not pool the data, but
5 I think we should not exclude those patients who
6 require hormonal treatment for the management of
7 their bleeding until they can get into the
8 appropriate intervention.

9 So, what you might want to say is we might
10 even stratify it further and say we want to exclude
11 those patients who are just taking oral
12 contraceptives for birth control, not for
13 management of bleeding, but allow those patients in
14 the trial who are on some sort of hormonal
15 management for their active problem.

16 I would actually like to see the data on
17 all of the patients, I would just like to see it
18 stratified rather than pooled.

19 DR. BLANCO: I think Dr. Spies actually
20 made a very good argument why probably the
21 hormonally-treated patients should be included, and
22 that is an issue that is a major issue, and that is
23 the issue of safety.

24 If you do this and you exclude all the
25 hormonally-treated patients, and somehow the

1 combination of hormone treatment and this procedure
2 really predisposes significantly the
3 thrombophlebitis of pulmonary emboli, you know, I
4 think everybody would like to figure that out
5 pretty early in the game, and not once this is all
6 approved and being widely used, and all of a sudden
7 we find that there is significant numbers of these
8 safety issues going on.

9 So, I think that while you may not be able
10 to use the data, Dr. Levy's suggestion about
11 stratification is important, it is probably good
12 early on in the game to look specifically at the
13 safety issue in that combination.

14 DR. ROBERTS: And I think it is very
15 important that what you need to do is to do, as Dr.
16 Spies said, which is to remember that you have got
17 patients that are on an estrogen preparation, you
18 have got patients that are on a progesterone
19 preparation, you have got patients who are on
20 Lupron or anti-estrogen preparation.

21 I would say that the patients who are on
22 Lupron should be off that Lupron for three months
23 before you treat them with embolization because
24 there is no question that the arteries are very
25 different in size, and your embolization result is

1 probably quite different, so I would say in terms
2 of that particular type of drug, that those
3 patients ought to be off that.

4 But in terms of the other, I think you do
5 need to separate out, I mean stratify and think of
6 a little bit differently those patients who are on
7 birth control pills that are on a standard dose and
8 they are being used simply for contraceptives, and
9 the patients who are on these high doses of birth
10 control pills to try and control their bleeding.

11 It is a whole different way of treating
12 those patients and thinking of those patients.
13 They are very different.

14 DR. CORRADO: I think that the idea of
15 stratification is probably the best compromise
16 here. I think that will enable us to produce a
17 data set that is understandable and interpretable
18 by people.

19 I would just say that if part of the
20 philosophy of including these patients is to find
21 out what the morbidity of the treatment is in
22 patients who are on hormonal contraceptives, for
23 example, that that needs to be real clear in the
24 informed consent, that there is the possibility
25 that there will be increased morbidity if I

1 understand correctly that last argument, and maybe
2 Dr. Spies wants to comment on that.

3 DR. ROBERTS: I am sorry. Run that by me
4 again.

5 DR. CORRADO: Well, maybe I am
6 misunderstanding, but I am hearing an argument that
7 we ought to leave these patients in the study, that
8 is, we ought to leave patients who are on hormonal
9 contraception in the study, so that we will then
10 know whether or not they have an increased risk of
11 thrombotic morbidity.

12 DR. ROBERTS: But even more importantly,
13 it is these patients that are on these heavy-duty
14 birth control pills, in other words, they are
15 taking two or three times the normal dosage, those
16 are the ones that are probably really at risk, and
17 those, you know, I think you do that because you
18 are trying to control their other problem, which is
19 their bleeding.

20 DR. CORRADO: That wasn't clear from the
21 discussion. I was not hearing the women at the
22 high end of the hormone treatment, I was hearing we
23 want to know if these women on hormonal
24 contraception are going to be at increased risk of
25 DVT, because of the treatment, and that is the

1 point that I just want to make sure that I
2 understand clearly, that that is not the purpose of
3 this.

4 DR. ROBERTS: That was why I said it that
5 way, because I thought you were confused about the
6 fact that we are looking at the ones that are
7 really having a lot of hormones. Now, it doesn't
8 mean that the ones who are on regular
9 contraceptives, when you do this procedure, and
10 they are bed rest, you know, 12 hours or whatever,
11 maybe are at higher risk, as well, and that would
12 be something that we would certainly want to know,
13 but I don't think anybody has a good feeling about
14 that.

15 DR. SPIES: If I could just comment, we
16 probably have treated 75 or 80 patients that have
17 been on either birth control pills or Provera or
18 one of the other, and actually a number that have
19 been on high dose, so this is obvious and very
20 clear public health menace, it is a concern. We
21 have had a whole spectrum, but really, it is that
22 subset that we have seen the problem in, so I think
23 parsing it out the way Dr. Roberts suggested is
24 probably what we ought to try to do.

25 Early in these studies, we have an Adverse

1 Events Committee, that is what they are there for,
2 to be able to identify these things. These things
3 need to be reported to the FDA, and if a study
4 needs to be stopped or altered because of a clear
5 recognizable danger to patients, it ought to happen
6 immediately. We don't have that data right now.

7 DR. BLANCO: I apologize for having to
8 step out for a minute. I also wanted to support
9 what you said, Dr. Roberts, I think it is very
10 important, and we talked about that we need to
11 really define, and not use the term "hormonal" in
12 such a broad sense.

13 I think it needs to be very specific
14 whether you are talking about oral contraceptives,
15 whether you are talking about progestational
16 therapy, and your talking about Lupron or any of
17 these type drugs, and it be looked at that way
18 rather than it is such a hormonal issue is a broad
19 issue.

20 Anything else in the inclusion of
21 exclusion criteria?

22 [No response.]

23 DR. BLANCO: All right. Anything else on
24 the hormone, which is the next little dot?

25 DR. ROBERTS: I think we have beat that

1 one into the ground.

2 DR. BLANCO: Beat that horse to death,
3 okay. Any comments?

4 All right. How about exclusion criteria
5 already include gynecologic malignancy or pre-malignancy,
6 should simple endometrial hyperplasia
7 be considered a pre-malignant condition? Any
8 comments on that?

9 DR. DIAMOND: As I said before, yes, I
10 think it should.

11 DR. BLANCO: I think we would agree, and
12 Dr. Levy left me a note saying yes, that really
13 should. At this time, in a research protocol, it
14 probably should be included as an exclusion
15 criteria.

16 All right. If there is no other comments,
17 let move on to No. 2.

18 2. As the primary study endpoint, FDA-approved
19 studies currently use either a quality of
20 life instrument validated for uterine fibroids or a
21 validated uterine bleeding scoring instrument
22 coupled with a QOL instrument.

23 Secondary endpoints include adverse
24 events, fibroid and uterine size, time to return to
25 normal activities, and comparisons to the controls.

1 Primarily, patients are serving as their own
2 controls, with secondary comparisons to patients in
3 non-randomized arms (either control subjects
4 undergoing myomectomy or hysterectomy).

5 Please comment on interpretation of these
6 studies when completed.

7 Does anybody want to open up discussion?

8 DR. D'AGOSTINO: First, I should say I
9 think the quality of life instrument generated is
10 really quite superb, it is very impressive, and it
11 does have a nice set of questions, which I can see
12 why you did have reasonably good validation.

13 In terms of responding to the question, in
14 other settings, in many settings, and I think
15 probably here also, some of these quality of life
16 instruments tend to be too much of an aggregate,
17 too much of a composite, and it is oftentimes
18 components of it that really are the main item even
19 with the SF-36, quite often it's the physical
20 function as opposed to the mental that shows
21 changes with different conditions and sort of
22 tracks what is going on.

23 I would suggest, and I would like to put
24 on the table that something like bleeding seems to
25 have come up over and over again, that maybe this

1 idea of bleeding and then a quality of life
2 instrument is a very sensible way to go in terms of
3 primary variables.

4 I think that global quality of life may
5 work, but I think that once you have that, you are
6 going to be compelled to say, well, what was it
7 that was significant, and then you rush to
8 bleeding, so why not put it right on the table to
9 begin with.

10 DR. BLANCO: Dr. Sharts-Hopko.

11 DR. SHARTS-HOPKO: I would agree that the
12 instrument you guys have provided for our review is
13 very fine. I think that menorrhagia is kind of
14 like pain, it is a problem when the woman says it
15 is a problem, and it is alleviated when the woman
16 says it is alleviated with the addition of you can
17 always look at hematocrit and hemoglobin, which
18 anemia is an undiagnosed problem in this population
19 in a lot of cases.

20 I agree that you are going to want to use
21 a visual bleeding assessment tool. I also think
22 that pain per se might be a specific thing that you
23 would want to assess. I am not sure that that is a
24 big item or not.

25 DR. BLANCO: I think that that is one of

1 the known factors that go along with this
2 procedure, I think as Dr. D'Agostino was saying,
3 you might as well just say it upfront and go look
4 for the information in terms of pain, narcotic use,
5 that kind of thing, and have that information
6 available.

7 DR. SHARTS-HOPKO: I think that these
8 secondary endpoints are appropriate. I think that
9 the radiologic people's long-term database will
10 answer the other question that we have talked
11 about, which is fertility. I don't think that a
12 shorter term study can really deal with that.

13 DR. BLANCO: Jerry.

14 DR. SHIRK: I guess I just have a
15 question, and partly it is for our statisticians,
16 and that is basically, obviously, with our
17 endometrial ablation studies, we had a nice, clean
18 double-blinded kind of study with a nice, neat
19 mathematical endpoint, and using one basic
20 measurement as a primary measurement, that is, a
21 PBAC Score.

22 This obviously is fairly complex with
23 using both a PBAC score and a quality of life
24 instrument as a thing with no other controlled
25 study, when you get to reviewing a PMA, how do you

1 look at this from a statistical standpoint as to
2 how you are going to evaluate this over time.

3 DR. BLANCO: Do you want to tackle that
4 one, Ralph?

5 DR. D'AGOSTINO: I think that you don't
6 want a lot of endpoints that you are calling
7 primary, you may have a lot of secondary, and what
8 I was trying to do, and I think what Nancy was also
9 doing, is to pull out a couple that you think, like
10 bleeding, maybe pain, that you think are really big
11 ones, and this amorphous, global quality of life,
12 and you go for that, and that is three endpoints,
13 three primary endpoints, it is not hard to control
14 the type 1 error, the alpha error on the three
15 endpoints, and the FDA can argue or discuss with
16 the sponsor do you have to win on all three or how
17 is that going to be worked out, but that is not
18 asking an awful lot.

19 I think that if you just did the quality
20 of life, and you sort of win on it, then, you start
21 splitting it up, and you get into all these
22 arguments on what is it that you want to look at if
23 you say right upfront bleeding is important, pain
24 is important, and the global quality of life is
25 important, you can do that.

1 One of the things that is I think
2 interesting and problematic is the before or after
3 that comes down later on, but that is a much
4 rougher question to deal with.

5 DR. DIAMOND: We are being asked to
6 comment here on how is the interpretation of
7 studies using patients as their own controls going
8 to be able to be interpreted, and I am going to
9 have to make the sort of comments I made back in
10 October of '99, that I think it is very difficult.

11 There are potential major placebo type
12 effects. The mind is also a very powerful thing.
13 There is now evidence over the last six months,
14 actually, evidence for about 10 years, but evidence
15 that has come out over the last six months,
16 reported that women that talk about their
17 infertility and are open and express about it, will
18 have a higher success rate of conceiving than women
19 that don't.

20 There are theories about the biological
21 correlates that go along with it, but nonetheless,
22 there is now good data to support that.

23 So, a study that does not have a control
24 group or that tries to use historical controls from
25 different patient populations, different surgeons,

1 different technologies, I think is extremely
2 difficult to interpret.

3 The argument against requiring studies
4 evaluating uterine artery embolization to have a
5 control, it is only going to be a subpopulation of
6 the patients that are going to be able to be
7 included because some patients are having life-threatening
8 hemorrhage of other women are not
9 willing to participate, but in the six or seven
10 years that I have sat on this committee, we
11 continually have clinical trials that come before
12 us in obstetrics and gynecology where it is subsets
13 of the populations with certain types of
14 pathologies who are being evaluated, and those
15 results subsequently interpreted and extrapolated
16 to other populations, sometimes with additional
17 studies.

18 But to answer the question, interpretation
19 of studies, longitudinal studies with each patient
20 as their own control, I think are very difficult to
21 accurately interpret.

22 DR. D'AGOSTINO: What did the FDA accept,
23 there were two controlled trials or two products
24 that they accepted, were they before or after
25 studies?

1 DR. ROBERTS: They probably can't answer
2 that.

3 DR. BLANCO: While they are thinking over
4 how they are going to answer that, let's have Dr.
5 Roberts--

6 DR. ROBERTS: One of the things that I was
7 wondering, and you may not be able to answer, you
8 probably can't answer this either, but the other
9 issue is that there were supposed to be, it sounds
10 like anyway, there was some talk about having
11 concurrent controls of patients with myomectomy or
12 hysterectomy, and I would, of course, assume and
13 encourage, if I can't assume, that those patients
14 would be undergoing this same quality of life with
15 bleeding scoring and secondary endpoints, that the
16 patients undergoing embolization would be doing.

17 DR. D'AGOSTINO: But it says non-randomized.

18 DR. ROBERTS: But it could be concurrent
19 controls. I mean they are not randomized, but you
20 are looking for a group of patients that are having
21 a hysterectomy or a myomectomy, and judging them,
22 you know, they are concurrent, at least they are
23 not historical, they are going on in the same--

24 DR. D'AGOSTINO: But you could argue that

1 a person's own control might be better than a non-related
2 group, and so forth, in terms of symptoms
3 and conditions.

4 DR. ROBERTS: Yes, but at least it sounds--I mean
5 I am reading this that there are both
6 things going on, that there is both the internal
7 control and then also a concurrent non-randomized
8 concurrent control group, but I don't know.

9 DR. BLANCO: Mike, what do you think of
10 that, I mean Dr. Roberts' idea, since you brought
11 it up?

12 DR. DIAMOND: I think a concurrent non-randomized
13 control is better than a historical
14 control, because it controls for time and
15 technology. I still think there are many potential
16 biases as to why individual patients choose one
17 modality versus another. If you are comparing
18 different physicians, you might be able to do
19 myomectomies better than I do, and so depending on
20 whether your patients get the myomectomies or mine
21 get the myomectomies, that could influence the
22 result.

23 It is a step in the right direction, but I
24 don't think it is all the way that I think it
25 should be.

1 DR. BLANCO: Jerry.

2 DR. SHIRK: I guess it comes back to the
3 question I asked, and Mike obviously stated it in a
4 much more eloquent way than I did initially.

5 My question was if we take three different
6 parameters that the patient has as far as quality
7 of life, PBAC, and pain, and use all three of
8 those, and use the patients as control, is there a
9 good statistical way, using enough variables to
10 basically get significant data or, as Mike
11 suggested, are we still over a barrel as far as to
12 have some control that is basically either
13 randomized or non-randomized that we compare to.

14 DR. D'AGOSTINO: By not having a
15 randomized control, you can do all of these
16 different strategies, but what you are looking at
17 may turn out to be statistically significant, but
18 not relate to the procedure. The randomization
19 gives you the procedure.

20 I think all of these different ways, you
21 know, they are in a bind, I think, that you just
22 can't do or I am assuming from the context that you
23 can't do a randomized control, so the more ways you
24 can look at the data, the more ways you can get
25 data for comparison, the better, but none of these

1 non-randomized controls or the before or after
2 really address the question.

3 We are not talking about historical
4 controls at all, isn't it either before or after,
5 or non-randomized was what I gather, and I think
6 that both of those are suboptimal, but two
7 suboptimals don't equal an optimal.

8 DR. BLANCO: Any other comments on that?

9 Dr. Levy left me a comment. I think it
10 was an important issue for her, and I think it
11 probably is an important issue going back to the
12 radiation. She put it here, although I am not sure
13 why. This was the issue she brought up before
14 about the radiation exposure, and it may be because
15 we are ob-gyns, and so we don't deal with radiation
16 exposure a lot of the times, so I will defer to
17 that, but I guess I would echo here an encourage
18 that some sort of estimation or attempt, maybe with
19 a subgroup of patients, to get a fair amount of
20 information.

21 I mean we would hate to do all these
22 studies and have this widely spread, and 10 or 15
23 years from now, start getting into all kinds of
24 problems from the radiation exposure of the ovary,
25 and maybe it is, as I said, an overconcern, because

1 I don't deal with radiation all the time, but I
2 will just throw that out.

3 DR. ROBERTS: I think it is important, and
4 I think I would assume and hope that whoever was
5 doing this kind of study, that at the minimum that
6 one should account for the amount of radiation time
7 that one uses in the examination and also for the
8 number of images that one obtains.

9 The problem is that what you would really
10 like to do is to know exactly what the dose to a
11 particular patient is, and unfortunately, most of
12 the equipment that is available today does not give
13 you that kind of information, because it depends on
14 where the patient is with regards to the x-ray
15 tube, are they close to the x-ray tube, are they
16 far away from the x-ray tube, is the x-ray tube
17 angled.

18 All of these kinds of things go into what
19 the radiation exposure is, and so as Dr. Spies
20 said, it is a difficult thing to get, but I
21 certainly would agree that in terms of the amount
22 of fluoro time and the number of images that are
23 obtained should be part of the data collection for
24 this.

25 DR. BLANCO: Any other comments on

1 Question 2? That side has been kind of quiet.

2 DR. ROY: You have been preempting us.

3 DR. BLANCO: Oh, well, I will try to look
4 over there more then.

5 [Laughter.]

6 DR. BLANCO: Let's go on to No. 3 then.

7 FDA currently asks for a six-month follow
8 up (premarket) with an additional six-month follow
9 up (postmarket) for a total of a one-year follow
10 up. Is this an appropriate follow-up regime?

11 Nancy.

12 DR. SHARTS-HOPKO: I think because we know
13 that the database is being established and is going
14 to go out 24 months, I think it makes 6 months
15 before and after, combined 12 months, I think it
16 makes that okay.

17 I would like to say at this point that I
18 thank the consumer groups who made their concerns
19 known to us. The MedWatch form is on the FDA's web
20 site, and informing consumers that it is there and
21 they should use it would be a good thing to do, and
22 I don't know if there is some possible tie-in to
23 the database that is being developed with that.

24 DR. BLANCO: Dr. Spies.

25 DR. SPIES: There is, in fact. This is a

1 web-based interface, and what happens is there is a
2 registry form, and when you get down, if you log
3 in, and there is an adverse event which appears to
4 be device related, you automatically have a link to
5 the MedWatch, and basically, there is a warning
6 there saying this must be reported to MedWatch.
7 So, that is there, and we recognize it. We
8 actually had FDA put in that when we designed the
9 registry.

10 Also, I should just add about the
11 registry, is that we clearly have the intention to
12 try to get federal funding to continue this
13 registry ideally out to five years or even longer.
14 This is a very, very expensive undertaking, so we
15 have two years to see if we can get some federal
16 funds to keep it going.

17 DR. ROBERTS: One thing I guess I might
18 bring up in terms of the six-month follow up, it is
19 not that I think it's unrealistic, but quite
20 frankly, I think the sponsors may be sorry if they
21 only take it to six months, because I will say that
22 from my own patients, that a number of them are
23 doing much better at six months, but at 12 months,
24 they are really doing a lot better, and some of
25 them have said, you know, it has taken me sort of

1 10 months or 9 months to really get--but now, you
2 know, it's great.

3 So, they actually may find that they are
4 sorry they didn't make it 12-month data.

5 DR. DIAMOND: Some of the data that Dr.
6 Spies showed us before, as far as uterine volume
7 and size of fibroids, showed continuing changes
8 from 6 months to 12 months, and I think for the
9 clinical trials, that will be done under the
10 auspices of the FDA for the purposes of approval, I
11 would think a 12-month approval followed by another
12 6 or 12 months would be more appropriate than 6 and
13 6.

14 DR. O'SULLIVAN: I would agree with that.
15 The other question I have is relative to the
16 registry. How sure are we that patients are going
17 to be reported to the registry or that the patients
18 themselves will report themselves to the registry?
19 I mean this is one of the things about registries.
20 You can have them, but that doesn't mean they are
21 going to be used.

22 DR. BLANCO: Again, this goes back to the
23 issue of you can't control what the physician does.
24 I am sure members of the Society, since the Society
25 has been so instrumental in doing all these things,

1 will likely report that, but, I don't know, folks
2 are out there probably that are not members of the
3 Society, are likely doing this, I would suspect,
4 and it may not get there, so yes, that is a problem
5 with registries.

6 Again, you know, I guess I would go back
7 to the issues of well done studies that identify
8 the safety issues and the long-term effects, so
9 that there is more education for the physicians and
10 the public and everyone else to know what the real
11 issues are, what the real complications, problems,
12 and answers are.

13 DR. SPIES: The registry is divided into
14 two groups, and there is a core group of about 25
15 sites that admittedly are high-volume sites, but
16 first of all, they have their IRB--everyone one has
17 to get IRB approval for this, and you have to sign
18 an agreement which says that every patient will be
19 entered.

20 So, if you take the patient into the
21 angiographic suite to attempt this procedure, and
22 you don't complete it, or you fail, and the patient
23 has a complication, death, or whatever else, at
24 least in writing you have obligated yourself to
25 report that. We really don't have any way to

1 enforce it.

2 We are a pretty cohesive group of people,
3 we have done projects together before, and we are
4 not a huge group of physicians either, there is
5 only a couple of thousand of us. So, we hope that
6 by peer pressure and positive reinforcement, we
7 will be able to do that, but there is no guarantee.

8 DR. ROBERTS: I guess, you know, as much
9 as the registry can be a problem, quite frankly,
10 having just sat on another panel a couple of weeks
11 ago, a randomized controlled study can have the
12 same problems.

13 DR. BLANCO: Any other comments on No. 3?

14 MS. MOONEY: One point to make since it
15 seems like the data were consistent and showing
16 that six-month follow up addressed any safety
17 issues and identified those that were going to
18 occur, it may be more prudent to give sponsors the
19 option for six month versus 12-month follow up with
20 the caveat that Dr. Roberts and others have
21 mentioned, that it may theoretically reduce your
22 ability to show effectiveness, but I think that we
23 heard safety was addressed in the six months, and
24 that may be what we should focus on.

25 DR. BLANCO: Any comments?

1 DR. ROBERTS: This is what I was kind of
2 saying is that I don't really have a problem with
3 six months, I just think that the industry might
4 find that, in fact, if they did 12 months, it would
5 actually a bigger delta and might be happier in the
6 long run.

7 DR. BLANCO: I think we are ready to move
8 on.

9 No. 4. Preliminary results have shown
10 that some subjects require re-treatment with UFE.

11 Should there be specific study
12 requirements regarding re-treatment? How should
13 the clinical study design account for this? Should
14 these subjects be handled as primary treatment
15 failures? Can these data provide additional
16 information on the success of UFE re-treatment?

17 Would anybody care to address those?

18 DR. DIAMOND: If no one else wants to, I
19 will try.

20 I think patients that feel their first UFE
21 should be considered failures, however, at the
22 discretion of the sponsor and the physician and the
23 patient, I think they should be given the option of
24 a repeat treatment. I think there are things that
25 can be learned from those patients. Hopefully, the

1 devices that are being tested work, there will be
2 not a large number of these individuals, but if it
3 does turn out that there are, we may learn
4 important things about specific patient
5 demographics, history, physical findings, hybrid
6 size, location, which will allow us to predict
7 which patients they will work well and which ones
8 they won't.

9 DR. D'AGOSTINO: The idea of re-treatment
10 is--and the reason I was sort of hesitant to jump
11 up--it is not a simple question, because if you
12 take cardiac procedures, and you have a CABG, and
13 the individual develops a problem, and you give
14 another one, there is a real failure that the
15 procedure didn't work. If you have analgesic
16 studies, and somebody has a headache, they take the
17 treatment, and it doesn't work, and they go on a
18 rescue medication, it really didn't work.

19 But if you flip over to, say, like liver
20 transplantations, liver transplantations, the NIH
21 consensus, when you make the commitment that you
22 are going to transplant the liver, if the first one
23 fails, you get another one. That person keeps
24 going until either they die or it takes. So, re-treatment
25 has different modalities in terms of what

1 you mean here.

2 When you say re-treatment, the question I
3 was asking when the speaker was up there, why a re-
4 treatment, was there something wrong with the
5 procedure or did the body not react appropriately,
6 somehow or other that it is a real failure, then,
7 everything we are talking about, and the easy way
8 out is just to call it a failure and obviously get
9 information, but if it is something that there is a
10 procedure that was given, and it somehow or other
11 didn't work, and you go at it again, is it a re-treatment or
12 is it just following that individual
13 until they get the right treatment. You introduce
14 a much more complicated whole sequence of
15 activities if you take the latter approach.

16 DR. ROBERTS: First of all, I agree with
17 Dr. Diamond that if someone has a procedure, and
18 assuming it was done to completion, I guess one
19 would say, so you said, okay, I have done my study,
20 and it fails, and the patient's symptoms recur,
21 then, I think it should, number one, be counted as
22 a failure.

23 The issue I think that becomes should the
24 patient be restudied to see what might have
25 happened, and I certainly would encourage the fact

1 that the patients be restudied. I think what the
2 problem becomes then is, is that what I suspect we
3 will find is what Dr. Spies brought up, was the
4 fact that many of these patients or the patients
5 that fail, may, in fact develop large uterine
6 arteries that weren't really present, at least you
7 didn't see before in terms of being present, and,
8 in fact, if you are going to re-treat the patient,
9 you are going to need to treat them via those
10 ovarian arteries.

11 Now, at that point, you might say wait a
12 minute, now I am concerned about ovarian failure,
13 and I think that now it becomes an issue in terms
14 of working with the physician, referring physician
15 and the patient, about whether or not one should go
16 ahead and treat that, and so that is where I think,
17 you know, it gets a little murky, and it may be
18 better to say, you know, they failed, and now they
19 failed and now you can go on and do whatever it is
20 that seems to be appropriate to do, but we are
21 going to count that patient as a failure, and then
22 we will follow that patient in terms of getting
23 safety data or getting more information, but we
24 will just count it as a failure.

25 DR. BLANCO: I think that is the issue for

1 the research project portion, that has to be
2 counted as a failure, but what happens to that
3 patient afterwards, it is kind of outside of the
4 research protocol is what I am hearing you say.

5 DR. ROBERTS: I think so.

6 DR. ROY: Except that it would be
7 preferable to capture as much data as possible.

8 DR. ROBERTS: Oh, I think the patient
9 should continue in the study, but in terms of the
10 procedure is counted as a failure. Now, like I
11 say, you would want to go on and perhaps collect
12 data, you know, maybe you are going to embolize the
13 ovarian arteries, you know, which might put them
14 into ovarian failure, or maybe they are going to go
15 on and have a hysterectomy or a myomectomy or
16 something else, but the main thing is, is that you
17 would continue to follow them, but they are counted
18 as a failure in terms of the study.

19 DR. D'AGOSTINO: There is something
20 artificial about that, though. I mean you call
21 them a failure. Say you do that, and all of them
22 take a second and they do well on it, and then you
23 are in the dilemma of--it makes the analysis so
24 much simpler just to say call them a failure, and
25 then my analysis, and they have no quality of life,

1 and so you get zero quality of life, and so forth,
2 and it generates a bizarre analysis, but what do
3 you do the second time with those individuals, how
4 do you look at that data?

5 DR. ROBERTS: I don't think you
6 necessarily do look at it.

7 DR. D'AGOSTINO: You analyze it
8 separately, but what do you do with it?

9 DR. ROBERTS: Probably nothing unless
10 there are a whole lot of them, and then you would
11 want to know that there is a whole lot of people
12 that are coming back for whatever their problem is.
13 I mean that is what you want to capture. It is not
14 just that the failed, but hopefully, what was it
15 that caused them to fail.

16 DR. D'AGOSTINO: That is the question I
17 was raising, is it a real failure. I mean if they
18 are real failures, the procedure, you know, you
19 brought it to completion. What we mean by a
20 failure, I still don't know what your definition of
21 a failure is. I know if they need another cardiac
22 procedure, if they need another liver, if they need
23 a rescue medicine, I don't know really what a
24 failure is here, so how to respond to it.

25 DR. ROBERTS: You mean how is it defined a

1 failure?

2 DR. D'AGOSTINO: How is it defined.

3 DR. DIAMOND: Probably another surgical
4 procedure.

5 DR. BLANCO: Wait a minute. You are
6 measuring bleeding and quality of life, so your
7 failure is going to be because you have no change
8 in the bleeding or quality of life, so you are not
9 going to get quality of life scores of zero, and
10 all that. I mean it is not because you are going
11 to have another surgery. You are going to have
12 another surgery because you didn't change either
13 the bleeding or the quality of life issues. That
14 is what is going to make the failure, right, or am
15 I wrong on that?

16 DR. ROBERTS: No, that is what I would
17 think.

18 DR. BLANCO: I mean I would think that
19 that would be what a failure is.

20 MR. REYNOLDS: There is no reason to have
21 another procedure. The quality of life issues are
22 all answered, and if you are not bleeding and you
23 are not in pain, you are not going to have another
24 procedure.

25 DR. BLANCO: And you are a success.

1 MS. BROGDON: May I ask a follow-up
2 question? Are there any special informed consent
3 considerations for patients who would be re-treated
4 in a study?

5 DR. BLANCO: Well, let me ask the question
6 before that one. How soon would someone be re-treated
7 typically? Unfortunately, Dr. Spies has
8 walked out, I was going to ask him that. But, Dr.
9 Roberts, could you give us some idea? I mean is
10 this something that happens and they get re-treated
11 right away, or, you know, you wait six or eight
12 months, or a year, or how does that work?

13 DR. ROBERTS: I haven't had one yet. I
14 think that what you would have is it would not be
15 somebody that you would do immediately unless they
16 were hemorrhaging or something, and they didn't
17 stop hemorrhaging, and then presumably you would
18 re-look at them right away, but by and large, it
19 would be patients that have had the procedure.

20 You would probably wait at least a couple
21 of months to see whether or not their menstrual
22 cycle sort of stabilized out, whether or not they
23 are bleeding, because sometimes they can have, you
24 know, usually not as heavy bleeding the first
25 cycle, but it may be still fairly heavy, and then

1 the next one is lighter and it gets progressively
2 better.

3 I think it would be several months later
4 and that they had not improved, and they were still
5 bleeding, and their quality of life presumably at
6 that point is essentially the same as it was
7 before, and then that is when you would discuss
8 with them re-looking at things and possibly re-treating.

9 I think in terms of concerns with that and
10 complications with that, because many of those
11 patients are going to be patients that have large
12 ovarian arteries, I think the issue at that point
13 is that if you are going to embolize, if those
14 ovarian arteries are supplying the fibroid, and you
15 are going to need to embolize that, then, I think
16 you have to discuss much more seriously--not that
17 it wasn't serious before--but with a lot more
18 expectations that you may, in fact, have ovarian
19 failure if you are going to embolize that ovarian
20 artery.

21 That is why I am saying, by and large,
22 what I have told patients is if they have a large
23 ovarian artery at the time, I don't embolize it,
24 but I tell the patient they may not do as well, and

1 if they don't do as well, and we need to think
2 about re-treating them, then, they have to really
3 decide that they are willing to risk ovarian
4 failure.

5 MS. BROGDON: Thank you.

6 DR. BLANCO: Anyone else care to comment
7 on the issue of informed consent for the re-treatments?
8 Okay.

9 I think we have probably answered No. 4.
10 Any other comments or any other subsections of 4?

11 Let move on to No. 5 then.

12 No. 5. Labeling for new UFE indication.
13 What are the key elements that should be covered in
14 the professional labeling of embolizing agents that
15 are cleared for UFE?

16 How should labeling handle the issue of
17 women who desire a future pregnancy? Should
18 bleeding results be stratified by use and non-use
19 of hormonal contraception? Any other specific
20 questions?

21 I think we have kind of addressed both of
22 those a fair amount, but I open it up for
23 discussion. Anyone care to add anything else to
24 what we said? Jerry.

25 DR. SHIRK: I had one other question. I

1 guess this goes to more post-study type of thing.
2 There is a literature about this procedure. Some
3 of the authors have suggested that there is a
4 decreased risk of fibroid recurrence over time,
5 that one of the problems with myomectomy is
6 obviously that there is a significant recurrence
7 rate in this patient population.

8 Certainly, the literature, he has
9 basically suggested that this would prevent long-term
10 recurrence rates of fibroids. Is that
11 something that we should consider studying over the
12 post-treatment time frame as we look at this over
13 the long haul, or is this not really an issue and
14 something that the literature is basically
15 advocating?

16 DR. ROY: That is premature, isn't it? I
17 mean that is why we are doing the study, and
18 hopefully, they will have five years of extended
19 federal support for this registry, so that we can
20 capture that sort of information.

21 I think this labeling issue and that issue
22 are all premature. We would have to wait and see
23 what the study shows.

24 DR. ROBERTS: Well, I think that the
25 problem is going to be, as this said, I mean you

1 look at the patients who have recurrence of
2 fibroids, and maybe they are going to recur and
3 that you are going to know about it in five years,
4 but maybe you are not.

5 I think in terms of the FDA study, I think
6 to think that you are going to know what happens in
7 terms of recurrence or new fibroids developing or
8 anything, I mean I think that is going to be way
9 beyond the scope of the FDA studies, not that you
10 wouldn't want to know that, it would be great, but
11 I don't think the time frame is going to be right.
12 Certainly not at their six-month follow up and
13 another six months maybe to see what goes on.

14 MR. POLLARD: I think maybe that is kind
15 of really where this question is coming from. We
16 are going to see this data, six-month data. We
17 will have some data from the registry. We will
18 have to see what we have got then, but really, the
19 question that is coming from the point of view of
20 what do we put in the labeling, what do we tell
21 clinicians who have to inform their patients about
22 what we know about it, especially with respect to
23 longer term effectiveness and recurrence.

24 DR. ROY: You can only tell them what you
25 know, and if you don't know beyond six months or a

1 year, you say the data is limited, just like we do
2 for everything else.

3 DR. ROBERTS: Yes. I think the same thing
4 goes with pregnancy. I mean we are not studying
5 pregnancy here, so all we can say is we don't know
6 about pregnancy.

7 You know, you can refer them to whatever
8 there is to refer to, but if we are going to
9 exclude them, then, we are not going to know, and
10 so if we don't know, we are not going to be able to
11 say anything about it.

12 I think the same thing comes with the
13 regrowth of fibroids. I think you say that the
14 long-term efficacy of the procedure is not yet
15 clear.

16 DR. SHIRK: I agree there. I asked the
17 question because the literature sort of suggests
18 that this is a long-term geared for fibroids is
19 basically what the study should say.

20 DR. BLANCO: Let me throw something out.
21 It is not an FDA question, but I would be
22 interested to hear what the panel thinks. The
23 presentations alluded to the fact that uterine size
24 was not that important.

25 That is an issue if you have got a big

1 fibroid, it could mask other processes going on,
2 the size of it. Does the fact that right now we
3 haven't said anything about uterine size or fibroid
4 size. Is that acceptable to everybody on the
5 panel, or would they like some information on that?

6 DR. ROBERTS: It is in the secondary
7 endpoints. I mean it is still there. I don't know
8 whether the thought was to not make it a primary
9 endpoint. I think you would probably still want it
10 as a secondary endpoint because it does impact, I
11 mean at least to some degree it impacts on the
12 quality of life for those patients who have bulk
13 symptoms.

14 I mean they are the ones that are really
15 uncomfortable with having that big fibroid, so I
16 think it correlates to some degree, maybe just not
17 as much as we thought we did in terms of symptoms.

18 DR. BLANCO: You are recommending is not
19 make that a primary endpoint, but do collect the
20 data on size, so that you know what is happening to
21 the size of the fibroid.

22 MR. REYNOLDS: I think that is something
23 that physicians might want to have for future
24 reference. In other words, if we know that this
25 procedure just doesn't work well for fibroids over

1 a certain size, you know, if the data shows that,
2 the patient comes in with a fibroid over a certain
3 size, you say, well, you are really not a candidate
4 for this procedure, but right now we don't have
5 that information, but there is no reason why you
6 can't gather it.

7 DR. D'AGOSTINO: But if they feel good, we
8 are saying they are a success, what does it mean by
9 a failure? What it does it mean by a failure, that
10 somehow or other you think that the size, if it is
11 very big, that they won't be bleeding?

12 MR. REYNOLDS: No. What I am saying if
13 you have a woman, let's say, who has got a 15
14 centimeter fibroid, let's say--I just throw that
15 out as an example--and everyone that has had one
16 over 15 centimeters, they come back three months
17 later and say I am still bleeding, I am still in
18 pain, to me that is a failure. I will call that a
19 failure.

20 DR. D'AGOSTINO: That is the definition of
21 a failure.

22 Maybe I can clarify it. You know, you may
23 want to look at the patients by size of fibroid and
24 some sort of stratification, not as a part of the
25 overall project, but just to know, if a large

1 fibroid, you know, beyond a certain size, seem to
2 fail more often, or something to that extent, or
3 maybe its positioning, where there is subserosal or
4 submucosal, intramural, or whatever, I mean those
5 are all issues that you don't want to make primary
6 endpoints, but that would be great information to
7 have, to be able to narrow down who is a good
8 candidate for this procedure and who is not a good
9 candidate for this procedure. Is that fair enough?

10 MR. REYNOLDS: That is very fair.

11 DR. ROBERTS: But I think that your point
12 is a good one, too, and that is that just because
13 there is still a large fibroid, if the woman feels
14 good and quality of life is good, and whatever it
15 is that was causing her problems is better, that
16 also is important information. I think that is why
17 to make it a secondary endpoint rather than a
18 primary.

19 DR. D'AGOSTINO: If it works the way being
20 suggested, that they have bad outcomes, then, it is
21 great, you say large corresponds to bad outcomes,
22 but what I was raising, what if large still carries
23 with it lots of good outcomes.

24 MR. REYNOLDS: Then, fine.

25 DR. BLANCO: Any other points?

1 DR. DIAMOND: Just to follow up this last
2 line of thought, I think it would be the other way
3 around, it might be the small fibroids which are
4 treated, which wouldn't have a big success rate,
5 because for some of the smaller fibroids, that may
6 not truly be the issue for the pathology. It may
7 be a finding on ultrasound, but it may not be the
8 cause of the pelvic pain or the discomfort the
9 individual is experiencing, plus we heard earlier
10 that fibroids have larger vessels than the rest of
11 the uterus, the myometrium, and actually I didn't
12 know that. There are more recent references than
13 Sampson.

14 But if that is the case, if it is a small
15 fibroid, there may not be large vessels, and so in
16 that case it may not be efficacious.

17 DR. BLANCO: I will just go around the
18 table. Anything else that anyone would like to
19 say?

20 [No response.]

21 DR. BLANCO: If not, it looks like we are
22 coming to the end of the afternoon session. I
23 would like, as I am sure the FDA would like, to
24 thank all of the folks that came before us and
25 presented and spoke to us.

1 I personally would like to thank all the
2 panel members for all of their participation and
3 their excellent input and devoting fractions of
4 their time from a day and a half, two days, to half
5 a day, to participate in this.

6 I guess we will have some comments, if
7 anyone from the audience wants to make any comment
8 at this point? No? End of chance.

9 Anyone from FDA wants to make any?

10 [No response.]

11 SPEAKER: Dr. Hufnagel would like to make
12 a comment.

13 DR. BLANCO: All right. Please go ahead.

14 DR. HUFNAGEL: (By telephone) Yes. I
15 think that the dismissal of the comments we made in
16 the negative aspects are not being discussed at all
17 other than to [inaudible] them is really unethical
18 and not called for.

19 The concerns that were provided are
20 legitimate concerns. The case of Achieng Wamabo is
21 not an isolated incident. It is the case of a
22 woman at one of your studies, and that is why I
23 provided the actual documents to you, so that you
24 will have them.

25 I would have hoped that you would have

1 addressed these concerns publicly, so the public
2 could hear them, but I guess the train must go on.
3 But there will be robbers to stop those trains if
4 they are transporting and handling things, such as
5 this meeting has continued.

6 You did not really listen and you did not
7 respond in the appropriate way in which I think
8 most people would generally accept. But that's the
9 way it goes.

10 DR. BLANCO: Thank you, Dr. Hufnagel.

11 FDA, any comments?

12 MS. BROGDON: We would just like to thank
13 the panel for your preparation and your excellent
14 input. Thank you very much.

15 DR. BLANCO: Thank you, everyone.

16 This panel meeting is adjourned.

17 [Whereupon, at 4:46 p.m., the panel
18 meeting was adjourned.]