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FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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SIXTY-FOURTH MEETING

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5 Montgomery Village Avenue
Gaithersburg, Maryland
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DR. BLANCO: We will go ahead and begin this morning's open session.

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

Mr. Pollard.

ROOM AIR AND GAS EMBOLI ASSOCIATED WITH OPERATIVE HYSTEROSCOPY

INTRODUCTORY REMARKS

Colin Pollard

MR. POLLARD: Thank you, Dr. Blanco.

Ladies and gentlemen of the panel, distinguished audience: I want to thank all of you for making time on your busy schedules and coming, some of you from quite far, to Gaithersburg, Maryland, for this meeting.

[Slide.]

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

[Slide.]

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

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

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

I would also like to acknowledge the help of Ethicon and many other manufacturers in providing FDA with input to prepare for this meeting. I also recognize that although not all of
you are planning to address the panel during the open public hearing, many of you have a vested interest in the outcome of these discussions.

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

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

[Slide.]

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

First, just in case there is any misperception, we are talking today about adverse events occurring during operative hysteroscopy, not diagnostic hysteroscopy. In diagnostic hysteroscopy, CO2 gas is the preferred distention
medium, and the risks of CO2 emboli are fairly well appreciated.

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

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

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

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

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

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

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

Lastly, you will be hearing about FDA systems for reporting problems. The mandatory
device reporting, the so-called MDR system, and our voluntary MedWatch system. Neither of these are perfect systems, but we will be asking you for ideas that may help or facilitate better reporting, so we can continue to learn.

[Slide.]

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

[Slide.]
As you know, we have got some questions, I am not going to get into them now, so from this point we are going to go to the first presentation. Any questions?

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

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

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

DR. BLANCO: Thank you.

DR. ISENBERG: Good morning. I am Richard Isenberg. I am the Director of Medical Affairs at Ethicon, Inc. I am responsible for the Gynecare Division of Ethicon, our Gynecology Medical Device Product Division.
DR. MUNRO: I am Malcolm Munro. I am a professor in the Department of Ob/Gyn at UCLA. I am a consultant to Gynecare, as well as a number of other companies that may be involved in the discussion today.

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

DR. MUNRO: That's correct.

DR. BLANCO: Thank you.

Presentation by Ethicon

Richard Isenberg, M.D.

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

I will be spending a few minutes this morning recounting the sequence of events that led up to our withdrawal of the device and our reintroduction of the device this winter. Dr. Munro will be speaking to some of the basic science elements and also discussing the recommendations of
the International Scientific Panel which we convened in October.

[Slide.]

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

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

[Slide.]

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

In each of these cases, the patients experienced an abrupt decline in cardiovascular function associated with hypoxemia, and a decrease in end-tidal carbon dioxide. One additional case had been reported to Gynecare, Inc., before we
acquired the device in 1997. On evaluation of that case, it was determined that the event was most likely associated with the use of an argon beam coagulator during a concomitant laparoscopy, and not the hysteroscopic procedure.

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

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

Upon withdrawal of the device, we notified FDA and other regulatory bodies around the world, and began a multi-prong investigation into the role that the procedure may play in these events, the role the devices may play in these events, and into the events themselves in order to better understand them.
This investigation took several approaches. We first performed a search of the worldwide literature, looking at air and gas emboli in surgical subspecialties including gynecology, focusing on operative hysteroscopy.

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

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

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

It was a broad-based questionnaire intended to identify risk factors and to identify
Within three weeks of the withdrawal, Ethicon convened a panel of scientific experts in hysteroscopic surgery, electrosurgery, anesthesia, and cardiopulmonary medicine, and charged them specifically with reviewing the findings of each of the cases, reviewing the literature review, and recommending to Ethicon a research approach that would be valid, reasonable, and sufficient to justify our saying that our device was safe.

Upon evaluation of the seven cases, the panel concluded that of the seven, four were most likely due to air embolism. As Dr. Pollard mentioned, it is important to differentiate between embolism of room air and embolism of gas by activation of the electrosurgical devices. In these cases it was thought that air entered the uterus and entered the uterine vasculature either through air bubbles coming in through the fluid flow lines, pumped in mechanically by pumps, or potentially forced in, in a piston type effect as the hysteroscopic device
was inserted and reinserted into the uterine cavity.

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

[Slide.]

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

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

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

[Slide.] The panel made several recommendations to Ethicon. First, in terms of a research strategy, the panel acknowledging the accepted safety of monopolar devices in hysteroscopy, recommended that Ethicon investigate and compare the performance of
the VersaPoint device to established monopolar
devices with the assumption that if we could
demonstrate comparability, we would be able to
speak of relative safety.

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

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

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

This diagram describes the laboratory
setup. Fresh, morbid bovine cardiac tissue was soaked in a representative solution, either saline or glycine, and over it suspended an inverted filled graduate cylinder, which served as a collection chamber.

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

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

[Slide.]

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

We drove the VersaPoint devices at maximum wattage in order to identify the worst case
scenario in terms of gas production. With the monopolar devices, in some settings we drove them at maximum, in other settings we drove them more closer to the normal usage setting.

[Slide.]

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

[Slide.]

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

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

Highlighted for you here are the chief gases that were produced by activation in this model - 49 to 51 percent hydrogen. Most of the gas produced here was hydrogen followed by carbon monoxide and carbon dioxide with a percentage also oxygen.
It is worth noting that a very small percent, between 1.4 and 2.3 percent were nitrogen. The remainder was composed of a series of hydrocarbon gases.

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

[Slide.]

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

By contrast, with such a small percentage of gas produced by these electrosurgical devices falling in an insoluble category, it may be that these emboli of electrosurgically produced gases would have a less severe clinical consequence.
Taking all these elements of the investigation together, the literature search, the investigation of the individual cases, the recommendations of the panel, the benchtop research, Ethicon determined that no changes were required to the VersaPoint device itself or its waveform, that we did have a responsibility to enhance the warnings and indeed added a section entitled "Warnings Applicable to Air and Gas Emboli Hazards."

At the beginning of February, we returned the VersaPoint device to the market. At this point, I would like to turn the discussion over to Dr. Munro.

Malcolm G. Munro, M.D.

DR. MUNRO: Thank you.

Dr. Blanco, members of the panel, it is an honor to be able to represent a panel of my peers and colleagues, for indeed this was a multidisciplinary effort. The material that was distributed previously has been modified somewhat, so please don't be alarmed if your handout doesn't exactly follow the structure of the presentation,
but in order to make things more clear, we have embellished some of the images to help you and members of the audience have a better understanding of what is going on.

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

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

The differences really relate in part to the location of the second electrode. Bipolar
electrodes—and this is one that might more likely
by seen at laparoscopy—both electrodes are near
the tissue, so the only part of the patient that is
involved is that which is near the electrode.

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

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

[Slide.]
Now, if we look at this graphically, for
those of you who do a little better with graphics,
this is a monopolar/unipolar hysteroscopic system
now, and we have an active electrode, which is up
here, and a dispersive electrode in the red box.
Some people call that a return electrode, but in fact, radiofrequency has no directionality, it goes back forth, it is oscillating, or any alternating current really fits that description.

[Slide.]

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

[Slide.]

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

[Slide.]

This graphic describes the alternating nature of the two poles of an alternating circuit like the one that is powering the lights in this room today, and that creates on an oscilloscope this oscillating image as the polarity moves, and
you can see why there is no directionality to the
current, because it just goes back and forth, and
that speed and radiofrequency is 500 kilohertz or
500,000 times per second.

[Slide.]

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

[Slide.]

Now, let's translate now to tissue. So,
what happens? RF current causes rapid oscillation
of the proteins, all the cations and anions within
the cells, and the kinetic energy that results from
this is converted to heat within the cells, so it
is not an electrode that heats the tissue, it is
the oscillation of the proteins, we believe,
anions, cations in the cell that is converted to
heat, and in that sense it is similar to a laser.

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

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

[Slide.]

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

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

[Slide.]
This is the picture that Dr. Isenberg showed you of collecting gas, and one of the questions asked is how is the vapor pocket—sometimes I call it the steam envelope—formed.

[Slide.]

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

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

[Slide.]

Now, if we now think of this vapor pocket or this vaporization that we showed you on the cellular level, and look at this in a tissue level, what happens is we get vaporization with this multiple-edge density electrode. We get
vaporization over this wide swath of tissue. The resulting gas that is formed then forms this set of bubbles.

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

[Slide.]

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

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

[Slide.]

Now, let's look at this a little bit differently. This is the typical voltage that we throw out. Here is the multiple-edge density electrode that we just showed you in an animated fashion. Here is the loop electrode, the same type of approach. If we look at the tiny little video
clip here of a loop electrode, you can see the gas
being produced as this loop electrode is being
pulled through the tissue.

[Slide.]

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

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

[Slide.]

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

Here is monopolar bulk vaporization. This
is a vaporizing electrode, and this is just a case
that I did not that long ago. You can see the bubbles to the point of even obscuring the field that are being produced.

[Slide.]

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

[Slide.]

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

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

[Slide.]

Now, to come back to this slide, just to look at it a little deeper--and we can spend an enormous amount of time on this slide--but just to
look at it a little deeper, if we now look at those two, the box on the left is a loop electrode at about 100 watts, and the box on the right is one of these multiple-edge density or vaportrodes at 300 watts. The gas production there fits the description that I just gave you.

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

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

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

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

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

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

[Slide.]

So, finally, the panel recommendations--and I have tried to make them a little easier than in the initial PowerPoint summary and categorize them into patient, facility, physician, and intraoperative precautions, and if we start with patients first, we know that the risk of gas
embolism may be greater with the increasing
duration of surgery, with myomas that penetrate the
myometrium maybe because of the greater access to
larger vessels, and for that reason, the surgeon
must be somewhat judicious in counseling and
selecting patients considering all kinds of other
medical and surgical options.

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

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

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

[Slide.]

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

[Slide.]

With respect to physician preparation, the surgeon should be trained in the principles of hysteroscopic surgery, which I think is fairly obvious, and must employ good judgment in patient selection, and this is redundant, but to emphasize size, number, the depth of penetration of a myoma might be factors that might cause one to think of
another approach other than hysteroscopic
approaches or to stage hysteroscopic approaches, so
that it is not all done in one procedure.

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

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

In the surgery, prior to commencing
surgery, the doctor should be sure that the
electrodes are there, that the patient monitoring
and all the issues we talked about are in effect,
that the fluid monitoring system is there and the
staff that are there are trained.
We have talked about the Trendelenburg position. We are not totally sure, all of us, whether that is a major issue, but it is one that we are generally agreeing to minimize, and that the air must be purged from the system before connecting the various tubes to the hysteroscope.

[Slide.]

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

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

[Slide.]

If gas gets into the endometrial cavity, of course, the surgeon often can't see, and also recognizing that this is a normal byproduct, as you saw, of electrosurgical vaporization of fluid. So, if excessive bubbles or pockets of gas are identified, active fluid outflow may aid in purging
them.
One should operate at the lowest
intrauterine pressure required for adequate
visualization of the field.

[Slide.]
If suspected gas embolism occurs, the
surgeon must be prepared to interrupt the
procedure, to deflate the uterus, and if
cardiovascular compromise, to implement appropriate
resuscitative measures.

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

[Slide.]

So, in summary, we felt that all the
evidence that we have been able to determine from
review of the literature and review with peers,
that the hysteroscopy remains a safe procedure.

Air embolism is rare, potentially catastrophic, and
is associated with any procedure involving the
endometrial cavity including Cesarean section and D&C, that gaseous embolisms that are not air,
arising from the products of electrosurgical
vaporization, occur with an unknown frequency, they
seem to be rarely, if ever, associated with
permanent sequelae.
The in vitro evidence suggests that there are no clinically significant differences between monopolar and bipolar systems in the volume or the composition of electrosurgically created gases.

Thank you.

DR. BLANCO: Thank you very much.

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

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

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

DR. MUNRO: With what I call the multiple-edge density electrode, in effect, that is like an array of four or five electrodes sitting beside each other, and you can almost look at them as
independent electrodes. In order to vaporize tissue, in order to generate the power density, a tissue electrode interface sufficient to elevate the intracellular temperature, you need relatively high power, at least initially, at least initially to develop the envelope.

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

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

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

DR. NEUMAN: I would just like to comment. First of all, I would like to compliment the firm for simplifying the biophysics of electrosurgery,
so we can all understand it. On the other hand, I think you left off a few things that perhaps you want to consider in further evaluation of these devices.

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

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

The final comment I would like to make is with regard to the wattage settings on the generators. Indeed, whatever the generator is set at is the power available, but the real question and the real relationship that you want to look at in some of the reports that you provided, you had
gas per unit volume of tissue or mass of tissue.

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

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

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

DR. BLANCO: Thank you.

Any other questions?

[No response.]

DR. BLANCO: I wonder if I could ask one question in terms of the speed with which the gases are dissolved into the liquid. You mentioned that
most of the liquids produced by the procedure are
gases that are fairly easily dissolved in the
liquid, but yet you still were able to measure some
gas production.

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

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

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

DR. BLANCO: Thank you. Michael.

DR. DIAMOND: Just one other comment is
that when these gases are generated, they are not
all necessarily going to go into the circulation in
some mechanisms, and so the issue may not only be
how much is generated, but what happens to it
relative to whether it stays in either cavity,
whether the device or the electrodes, their shape, their configuration alters the amount that might be able to egress back out the cervix or egress out through the fallopian tubes, but the total dissipation of the gas at locations other than just entering the circulation.

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

[No response.]

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

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

Presentation by FDA
Julia Corrado, M.D.

DR. CORRADO: Hi everybody. Good morning. I guess what I would like to do, which is not a part of my slide presentation, is give you all a verbal summary of how the FDA staff reviewed the voluntary withdrawal of the VersaPoint device. The working staff in the Office of Device Evaluation became aware of these events in early November, and we convened a working group among
ourselves, consisting of electrical, chemical, and
biomedical engineers, myself, and an
anesthesiologist.

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

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

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

We looked at the method of distention of
the uterus and specifically, I mean obviously
saline was used at a distending medium, but in some
cases, a blood pressure cuff was placed around the
bag of distending fluid, and the fluid forced into
the uterus, and the pressure was not monitored.

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

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

We concluded that there was a preponderance of certain variables that we felt might have contributed to these events. We looked at the use of the zero degree vaporizing electrode.

I do not have the exact numbers, I believe that in four or five out of the seven cases, that electrode was used exclusively or in conjunction with another electrode.

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

We also looked at the bench testing that the company performed, as you have heard from Dr. Isenberg. We asked the company for additional information on the relative solubility of the gases
generated in the different distending media, and
then we worked with the company on the labeling,
and we will talk about that a little bit at the end
of my talk.

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

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

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

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

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

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

[Slide.]
Pulmonary embolism can evolve from a number of circumstances, physiology is one of them, negative intrathoracic or maybe more properly negative intravenous pressure in the vascular system versus in the uterus, and the vascularity of the particular tissue under treatment.

[Slide.]

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

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

[Slide.]

Electric equipment-related risk factors include the configuration of the electrode, the size and the shape of the electrode, the temperature that is achieved during the treatment, and the extent of vaporization.
When we are performing operative hysteroscopy, the surgeons are usually pretty intent on looking at the tissue, making sure that they see what they are treating and what they are excising.

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

Intraoperatively, there is a combination of anesthesiology maneuvers and surgeon maneuvers to treat a suspected room air or gas embolization. This is not an all-inclusive list, but it includes the following: interrupting the procedure, achieving intubation if the patient is not under general, and assisted ventilation, resuscitation depending on the degree of cardiopulmonary compromise, if necessary, achieving central I.V. access, repositioning a patient into what I believe
is left lateral decubitus position, but Dr. Schroeder can correct me if I am wrong, and considering occluding the cervix and the vagina, at a minimum removing the instruments that are facilitating possible entrainment of room air in the vagina through the cervix and into the uterus.

[Slide.]

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

[Slide.]

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

[Slide.]

This is just a schematic of the direction
of the current in bipolar hysteroscopy. Again, I am a clinician, I am not an engineer. I will certainly try to use the correct terminology.

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

[Slide.]

I am going to give a hypothetical of what FDA staff believes is happening during bipolar tissue treatment. Again, desiccation is not something that we would commonly do using bipolar instrumentation, and I am going to attempt to convince you of why we believe this is the case. Because you must use saline when you do bipolar operative hysteroscopy, you must use saline, it is not option, saline is a conducting medium, and the way we view it is that when we are using saline, we can lose current through the distention medium. Therefore, we are not
effectively delivering energy to the issue in question.

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

During vaporization, a pocket consisting of water vapor is created around the tip of the electrode. Water vapor is not a good conductor. Therefore, the way we view it is that the bulk of the energy is being delivered to the target tissue. It is then being routed around that vapor pocket, back to the return electrode. We believe that this is how the bipolar instrument is intended to work, that it works more effectively in a vapor pocket than without a vapor pocket, and it is because the property of that vapor pocket is that it is not going to conduct current through it. [Slide.]

Now, I won't spend any time on this. The ground pad is what Dr. Munro referred to as his dispersive electrode, I believe. The current is
delivered to the tissue, into the tissue, routed to the ground, and then the way I have this diagram, back to the generator. Again, the difference is that it is going through the patient to that dispersive electrode.

[Slide.]

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

[Slide.]

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

[Slide.]

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

[Slide.]

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

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

[Slide.]

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

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

Air entrainment was noted in several of the cases of the VersaPoint adverse events. We intended the operators to be advised not to reinsert the instrument unnecessarily, not to exaggerate Trendelenburg, and to avoid the use of nitrous oxide anesthesia although that was only
used in one of the cases of the ones that we evaluated.

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

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

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

I guess I would like to wrap up with an
effort to highlight what FDA staff sees as some of
the important differences and similarities between
these two systems.

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

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

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

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

[Slide.]

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

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

How should we look at decreasing this risk? We think that it may be worthwhile to undertake some research on both types of systems to
again try to quantify some of what I have described as qualitative differences, to beef up the labeling.

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

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

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

I will be happy to answer any questions the panel may have, and I may wish to call on my biomedical engineer depending on the questions.
DR. BLANCO: Thank you very much, Dr. Corrado.

Any questions? Mike.

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

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

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

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

Would that current be large enough to cause vaporization of the saline and produce a
vapor pocket similar to what was shown with the bipolar electrode, and then if that occurs, would the unipolar electrode be just as directional as the bipolar?

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

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

We personally think that the bubble forms because you are heating medium, whether it be a fluid or a tissue, giving a significant amount of energy with the high e-field strength, and that causes the local temperature to actually rise. I guess sort of in concert with what was said before, once the temperature reaches above a certain point, 100 degrees C., you get the
formation of bubbles, so in answer to your question, even though a significant amount of current appears to be going into the saline, because the saline is a fluid and is likely to move, we don't anticipate there being a large gas formation.

DR. NEUMAN: Can I ask one more question?

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

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

DR. BLANCO: Okay. Thank you.

Any other questions at this point?

DR. LEVY: Just from the standpoint of looking at medical errors, however, it would be reasonable to look at those scenarios and look at
the kinds of injuries that could occur when someone
does hang the wrong solution. So, I don't think we
are totally off base in looking at those things,
but we must understand that that is not the way
they are designed to be utilized.

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

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

DR. BLANCO: I think the issue is that as
we get into the discussions, there are clearly two
items or two areas that we need to look at. Some
are going to be procedural issues, reintroduction
of the hysteroscope, et cetera, air in the I.V., in
the tubing, and so forth, that are going to be
applicable to whether you have a unipolar or
bipolar system.

Then, there may be some issues, as well,
in the difference between the unipolar and the
bipolar, so I am just trying to make sure we keep
it and look at it that way, I think that is
probably the most consistent way of looking at it.

Any other questions, comments? If not, we
will have the next speaker.

Sharon Dillard

MS. DILLARD: Mr. Chairman, distinguished
panel members, and ladies and gentlemen of the
audience, I am Sharon Dillard, and I work as a
senior scientist within CDRH's Office of
Surveillance and Biometrics, and today I have the
pleasure of providing you with a brief overview of
both FDA's adverse event reporting program for
medical devices and various postmarket initiatives
and options available to CDRH that help us address
medical device related issues and concerns.

[Slide.]

Patients and caregivers alike rely upon
FDA to provide leadership in addressing medical device-related risks not only in the premarket activities, which you are quite familiar with, but also in the postmarket portion of the medical device life cycle.

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

[Slide.]

FDA's adverse event reporting program consists of both mandatory and voluntary components. Mandatory reporting requirements apply by law to device manufacturers, device importers, and user facilities. These reporting requirements are specified in Title 21 of the Code of Federal Regulations. It is Part 803, and it is entitled, "Medical Device Reporting," and throughout this
presentation, you will hear me say MDR quite a bit, and that is what I mean.

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

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

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

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

[Slide.]

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

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

MS. DILLARD: No problem.

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

That is, when a user facility, a device manufacturer, or an importer becomes aware that such an embolitic event has occurred, even if use error is thought to have contributed to such an
event, they must report in accordance with the
requirements specified in the medical device
reporting regulation.

[Slide.]

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

[Slide.]

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

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

[Slide.]

It is also important to clearly recognize
the limitations of the system, and although MDR is
a powerful signaling tool, for the most part, the
information submitted to the agency consists of
unconfirmed attributions, the reports typically
contain very little information regarding
definitive cause and effect of a given incident,
and it is widely recognized that any passive
surveillance system is subject to substantial
under-reporting.

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

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

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

It also cannot, and should not, be used to
differentiate "good" firms or products from "bad"

firms or products.

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

[Slide.]

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

The search covered the time period from 1996 to the present, and the search included all possible candidate devices, that is, in addition to electrosurgery systems, we looked at hysteroscopes, insufflation systems, and any other type of
endoscopic surgical instrumentation that might be involved in such an incident, and the only reports that met our tech search criteria were associated with bipolar or bipolar type electrosurgical systems.

[Slide.]

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

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

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

Three reports were received in 1999, four reports were received in 2000, and the most recent
report was submitted in April of 2001.

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

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

Drs. Isenberg and Munro have provided detailed information related to the reported events of concern, and Dr. Corrado has talked a bit about some of the internal workings that FDA undertook to address those concerns, but from a more general perspective, the MDR reports have served their signaling function, and they motivate us to consider what factors might explain the differences
in these observed reporting patterns associated
with air or gas embolism in conjunction with
operative hysteroscopy.

[Slide.]

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

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

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

For example, does the observed reporting
pattern suggest that there may be a real difference
between the occurrence of air/gas embolism during
operative hysteroscopy using a fluid insufflation
medium between unipolar and bipolar electrosurgical systems.

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

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

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

Is it possible that clinicians generically consider gas or air emboli formation to be a procedural complication associated with endoscopy, and in this case operative hysteroscopy, rather
than a potential device-related complication, and
as a result, they do not recognize that such events
should be reported to the device manufacturer under
MDR.

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

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

We consider our postmarket authorities to
be a complement to our premarket programs for
medical devices, and with respect to postmarket questions and issues, such as those that have brought us together today, FDA has at its disposal a relatively wide variety of both regulatory, as well as non-regulatory options, that we can use to help us better identify, understand, and address public health concerns in an appropriate manner.

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

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

Based on recognized device-related problems including use error-related concerns, FDA can issue public health notifications, such as
alerts and advisories. We publish information on manufacturer-initiated recalls and safety alerts, and we have a number of educational options at our disposal.

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

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

Most recently, CDRH has received blanket clearance through OMB to conduct what we call a Rapid Response Survey. These are limited surveys of user facilities, professional practice organizations, individual health care professionals, or other targeted groups, and they are designed to help us quickly gather information on postmarket questions without having to go through lengthy survey approval processes.
Panelists, in your package of reference materials, you have some examples of these types of actions that have been taken by FDA with respect to other device issues.

[Slide.]

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

DR. BLANCO: Thank you very much.

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

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

Certainly the laser ablation thing was obviously operator error with the insulation of either carbon dioxide gas or CO2 through coaxial cable into the cavity under high pressures and
rapid volumes, but Don Chapman back in 1986 had a paper about air embolism and two cases that were reported, so these cases obviously extend back beyond 1996.

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

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

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

DR. SHIRK: Another question is are there any literature things in the urological literature that comprise the same thing, since this is borrowed equipment from urology, and urology has been using monopolar and bipolar electrical devices in the bladder for over 50 or 60 years, and are
there any similar problems with air and this type
of technology in the urological field?

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

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

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

I think we need to be careful not to make
the assumption that simply because there have been
no reports with unipolar methodology since the
bipolar methodology was introduced, that that means
that the unipolar methodology does not cause some
similar problems as a possibility.
Am I kind of paraphrasing what you were saying?
DR. SHIRK: Right.
MS. DILLARD: Absolutely, and I hope Dr. Corrado's point was made, as well as mine, that
that is the case.
Dr. Shirk, just from my perspective, when
you said "literature," I was thinking of the
medical literature, not my MDR reports, so my
answer was geared that way, and I just want to
clarify that point.
DR. SHIRK: I was speaking of medical
literature. I mean there are reports in the
medical literature that date back to 1986, when
Chapman put a report in of two cases, so, you
know, there are reports in the medical literature
involving other energy sources and hysteroscopy
that have been associated with air embolism.
DR. BLANCO: Thank you.
In the interest of time, let's go ahead
and proceed.

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

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

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

Please remember to state conflict of interest.

Open Public Hearing

MR. HOUSER: My name is Jay Houser. I am Director of Marketing, Product Development, and Research Development with Karl Storz Endoscopy. Karl Storz Endoscopy is the world leader in durable medical endoscopic products distributing worldwide. My background also is formation from 21 years of experience in endoscopic surgical products
including Conceptus, where I was Director of Marketing and developing their product.

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

[Slide.]

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

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

[Slide.]

One of the benefits I guess and detriments
of being the last speaker on today's schedule is
that I am going to be redundant on a number of
slides, so I will make them quick, at the same
time, hopefully, the previous speakers will have
independently verified some of the things that I am
presenting.

[Slide.]
We have all discussed the complications of
operative hysteroscopy and most of these have all
been well documented in one form or another.

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

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

[Slide.]

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

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

[Slide.]

Bipolar resectoscopes, primarily in devices, the Conceptus ERA bipolar sheath device. There are bipolar electrodes which are being looked at to be distributed independently, which fit onto monopolar systems, which are similar to activity as the Conceptus sheath. They are hybrids. The Gynecare VersaPoint system.
There are differences in the site of current transfer, and we know that the current path now is between the active electrode, through the electrolytic solution and back to the return electrode.

[Slide.]

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

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

[Slide.]

A little bit of history here. First of all, the resectoscope was first used as reported I think in about 1978 with Dr. Robert Neuwirth. Over the years subsequent to that, there were not
reported incidents, and that is the most important part is reported incidents of gas or air emboli was not mentioned in the gynecologic literature on resectoscopic surgery.

[Slide.]

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

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

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

[Slide.]

Laser declined after these reports, and again so did the incidents of reported air emboli or gas emboli, although there were some ancillary reports after that, primarily in anesthesia journals at this point, and some of this may be attributed to some increased vigilance, however, there were no known deaths reported.
In 1997, the ERA Bipolar Resectoscope Sheath was introduced by Conceptus, developed by Dr. Keith Isaacson. During subsequent use with this product, Dr. Isaacson had the hair-rising experience of experiencing a gas or air emboli during a procedure. Things that he noted was that he was using normal saline, there was no monitoring of intrauterine pressure. There was definitely increased bubble volume during the procedure.

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

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

The following comments are directly from Dr. Isaacson on the pilot study. Basically, the use of saline is of benefit over non-electrolytic solutions due to the risk of hyponatremia with those solutions; that the physics of the bipolar
system can be used in saline because it creates the vapor bubble around the electrode. The wattage necessary is really not any different than that of the unipolar system or monopolar system.

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

[Slide.]

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

The exact mechanism for this is still unclear, with two possible causative factors that he reported. One is increased bubbles and unanswered questions as to the intrauterine pressures and what roles they may or may not play in the intravasation of the gas and liquid. This was suggested by Perry in his paper.
In 1998, FemRx/Gynecare also introduces bipolar resectoscope. During this period of time, again we see a rise in air or gas emboli, again the mechanism is unknown. Common factors are bipolar, which creates more bubbles, normal saline distention, and unrecorded or unknown intrauterine pressure recordings.

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

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

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

I would like to show tape number 1 just for about 30 seconds, if we could.
DR. BLANCO: I am sorry, let me interrupt you. Are the tapes simply showing bubble formation?

MR. HOUSER: Yes, that's all.

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

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

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

DR. BLANCO: Any questions of fact?

[No response.]

DR. BLANCO: Okay. Thank you very much.

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

DR. BRILL: I will try to be brief.

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

I am a consultant for Gynecare, and they have accommodated my travel with an honorarium for
I want to share a couple thoughts in listening to this morning's presentations and give what I think is my viewpoint on some of the bigger issues.

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

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

Another issue. We don't have any scientific evidence whether bipolar technology is indeed vaporogenic. You heard from Mack Munro that
we should look at electrosurgery as fundamentally
the same process regardless of whether you have
electrodes close together or some distance apart,
and it is actually the tissue change that creates a
vapor pocket.

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

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

The question is, is this clinically
significant or is it an observation? We don't know
the answer to that question. I think we all have
to accept that whenever you do intrauterine
electrosurgery, you create at least microemboli
through the circulation, and as long as
compensatory measures of the body are sufficient,
there is no clinical sequelae.
Now, the fact is, is that all these cases were stopped because of fear, and that represents prudence, however, we don't know what would happened, and it may be that a number of these observational events are physiologically significant at that moment, but they have no adverse sequelae, especially when you look at the incredible solubility of the combustibles that are created by electrosurgery in the uterus.

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

So, we have a big issue here, and the issue is surface area, a larger surface area, more vaporization, more bubbles. What does that have to do with vaporigenicity of the technology? Nothing. What does it have to do with the observation of monopolar or bipolar necessarily? Not anything. Just the fact that you have different surface area,
different electrode configurations, different
productions of gases based on the amount of tissue
that is vaporized per unit of time.

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

Thanks.

DR. BLANCO: Thank you.

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

[No response.]

Panel Discussion

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

The first discussion question is: What
are the underlying conditions that lead to the formation of room air and gas emboli during operative hysteroscopy with RF unipolar and/or bipolar electrosurgery?

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

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

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

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

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

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

DR. SHIRK: Gas, right, I am talking about a gas, gas of some sort.
DR. LEVY: Okay. Just for the record, I wanted to make sure that that was clear.

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

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

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

The obvious problems comes when the amount is significant enough to cause problems both at the level of pulmonary structures and also in those patients who have significant anatomic variances in their cardiac system where you can have an atrial defect or a ventricular defect where you can shunt gas from the right side of the heart to the left
side of the heart and get catastrophic events by 
air embolism to the brain. It is a very difficult 
situation to look at over time. 

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

DR. BLANCO: Thank you.

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

So, the answer to the first bullet point 
is it is very common, happens in everybody. From 
there then, what can we do to reduce the clinically 
significant risks, and that is what I think we need
So, then, the second bullet, are the risks essentially the same whether using bipolar or unipolar, and I would say are the clinically significant risks the same rather than the amounts of gas, entrainment of gas, you know, what is going on here, and I think we can't answer that question yet.

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

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

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

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

DR. BLANCO: Ralph.

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

DR. LEVY: I think one of the issues is
that if you are doing a patient under general
anesthesia, then, you are monitoring the PACO2, if
you doing it under spinal or local anesthesia, you
are not.

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

DR. BLANCO: Thank you.

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

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

These cases, the MDRs that we have looked at--and I was part of the Gynecare Panel, and I
should disclose that to everybody, so that you know that I have been able to look at those cases—they were not clinically significant in the sense that the patients all did very well. They were significantly different in cases in the literature of deaths being reported, and everything about these patients was different.

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

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

DR. BLANCO: Dr. Diamond.

DR. DIAMOND: I think the last comments that Barbara made are very important, and I think would go a long way to a lot of the issues, but specifically to this question. I am less confident
that we know truly how often gas or air emboli occur. I wouldn't be surprised, based on what I have learned preparing for today's session, that they occur very frequently in almost all cases as others have suggested, but I really don't think we know that factually.

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

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

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

DR. BLANCO: Any comments? Dr. Shirk.
DR. SHIRK: I guess one of my questions would be, you know, would there be any certain patient populations that are at certain risk. Certainly, patients with ASD and BSD might be an exclusion criteria, you know, put out on the labeling as people that should be excluded from use of these products just because of their increased risk of shunting gas from right side of the heart to the left side of the heart, which is a much more serious consequence, and at what point should some studies with echocardiography be done on these patients that are having the procedures done.

DR. BLANCO: Dr. Schroeder.

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

That is an extremely sensitive, extremely sensitive mode for detecting both gas emboli and turbulent flow, and sometimes merely rapid administration of a crystalloid solution, such as the normal saline that you all are infusing into the uterus, can cause what looks like air. It is
in some settings very difficult to tell the

difference between a gas bubble that is from
turbulent flow and a gas bubble that is from actual
introduction of gas.

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

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

It is also well known that up to 25 to 30
percent of patients have a pro patent foramen
ovale, such that if you do have reversal of
pressure in the right to left atrium, you can have
opening of that shunt, and a patient who doesn't
know they have it and who has never had any type of
embolic phenomenon before, I think those patients
should be remembered.
DR. BLANCO: Let me make some comments, kind of go in a different direction, because I think that it is very commendable and we all like lots of studies and lots of information, but I think it is going to become very difficult again to go back to what is clinically significant and what really is going to give information that is worthwhile.

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

I don't think that medical device reporting or adverse reports is going to do it. Quite frankly, the only experience I have had with this recently is that my wife had a resection--she
will hate going public--and she had a broken little wire loop. That was never reported, I don't think, and it was inside of her.

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

I think that in trying to wrap up the question, I think we need to look at two things, suggestions to FDA, and again it is what I alluded to earlier in terms of as I see this as somebody that doesn't do this, there are two issues. One is the issue of obviously, physicians are doing some things, and operating room personnel are doing some things, that don't sound real good, like having air in the tubing that takes the liquid to the device, et cetera, et cetera, I won't go into that, and I think that means that the labeling for those particular issues really needs to be strengthened to make sure that people realize that just isn't a good idea and not good surgical procedure.
I think some folks have brought forth some things, such as a deep myoma, vascularity of the uterus, length of the procedure, and I don't know what the data is for that and how certain we are of all those different issues, but certainly that should be strengthened in the labeling, so that the physicians who are using, the personnel who are using these are aware that these are issues that may create more complications.

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

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

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

DR. O'SULLIVAN: A couple of issues.
Number one, I know end-tidal CO2 has been monitored for about five or six years and all general anesthesias, so if that is the case and people have been using unipolar techniques, one would think that something would have been picked up that way. That doesn't mean it is going to get reported, I agree with that.

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

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

I have another statement. To say that they may not be clinically meaningful, I think anybody who has these symptoms, who requires to be in the hospital for several hours afterwards, who alerts and throws everybody's heart into a mode
that could clearly cause some of them to have a heart attack, that's clinically significant.

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

DR. O'SULLIVAN: Uh-huh.

DR. BLANCO: Anybody else?

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

I absolutely agree with you in terms of
clinical significance if patients need to stay in
the hospital a lot longer, but I have yet to have a
patient induced with propofol, who doesn't drop her
pressure out for a couple of minutes, and we all
watch that happen, we all watch the systolic
pressure go down to 60 and 70 maybe, you know, we
watch it for a while and it comes right back up,
and we all get a little nervous for a minute or
two, but I think there is a difference between that
and when the whole room stops, everything stops,
and there is something else going with the patient,
she becomes hypotensive and all those other things.
But there has been a spectrum among these
cases, some of which were just simply a very
transient event that did not really cause any
prolonged stay, in fact, the procedure went on, the
patient completed the procedure, and everything was
fine.

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

DR. O'SULLIVAN: All.

DR. LEVY: All.

DR. O'SULLIVAN: Because we don't know
unipolar. I mean it would certainly suggest based
upon the little bit we hear, and I, too, am totally
uninvolved in this, but based upon the little bit
we hear, that if there were unipolar problems, they
were not registered because people were not
monitoring them in the same way.

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

DR. LEVY: No, absolutely not.

DR. O'SULLIVAN: I mean for operative?

DR. SCHROEDER: Actually, if I can address
that for just a moment, there are some places, and
certainly when I trained, spinal anesthesia was the
anesthetic of choice for hysteroscopy for the
reason that mental status is the most sensitive
indicator to check for what we affectionately call
TURP syndrome, which you get from absorption of the
distending medium, be it glycine or whatever it is
that you are using, so the addition of spontaneous
ventilation where a patient could be actually
sucking air, you could have a real negative
pressure in the venous system, makes this risk that
much greater. Some places I know it is still done
that way as a standard. So, certainly, in the
anesthesia community, this is not well known.
The other thing I would add is that the Trendelenburg position, even general anesthesia makes the risk of sucking air into the venous system much greater. I just would add that to your labeling instructions.

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

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

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

DR. O'SULLIVAN: Barbara, don't they occur
even when using unipolar systems?

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

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

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

Any further comments on that?

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

DR. O'SULLIVAN: I think alerts are the
way to go.

DR. LEVY: I agree.

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

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

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

DR. BLANCO: Any other comments on No. 2? Dr. Schroeder, what about on the anesthesia side, I mean do you see some things that could be done for anesthesiologists even if we can't get the ob-gyns to read the label, maybe we get the
anesthesiologists away from reading the newspaper.
Forgive me, I had to throw that in.

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

[Laughter.]

DR. BLANCO: Thank you. Touche.

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

DR. BLANCO: Thank you.

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

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

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

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

DR. D'AGOSTINO: Who is going to do this? I mean I can imagine you sending out educational material, and you will get a flood of cases, and there will be a committee meeting a year from now
saying how serious the problem is, and there will be an expert panel saying all the cases we looked at were negligible.

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

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

DR. BLANCO: Nancy.

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

DR. O'SULLIVAN: I think the other thing is that you definitely will have an increase, there is no question about that, but getting that increase will also get the increase or the presence
of the same problem occurring in the unipolar
system.

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

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

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

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

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

If we are sitting here as a discussion, I
think it is something that we need to look at.

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

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

DR. SHIRK: It is a multifactorial problem.

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

DR. BLANCO: Subir.

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

So, I think what we need is education through all the usual means and persistent, repetitive, repetitive, repetitive, because people get sloppy and they forget. This is a human
problem, not a technological problem.

DR. BLANCO: Michael.

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

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

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

One additional thought perhaps to deal with some of these latter issues we are talking about would be interactions with CREOG and residency training as to expectations of what residents ought to be able to be taught and learn
in that training process including assembling
hysteroscopes, assembling laparoscopes, generators,
basic fundamental information.

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

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

Any other comments?
Let me read 4, so we have read them all.
Are there additional measures that can be
taken by FDA, NIH, relevant professional societies,
et cetera, that will further add to the
understanding of the risks of air and gas emboli
during operative hysteroscopy?

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

DR. LEVY: I would just like to say that
the basic research with the TEE's and all those
things, that probably is the purview of the NIH. I
mean I don't think that that is up to the companies
to have to do that kind of research.

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

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

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

DR. BLANCO: Any other comments from any
of the members of the panel? Yes, Subir.
DR. ROY: Just to reiterate something Michael said. I think it is important to encourage endoscopic laboratories be used, and not only in residency training programs, but for clinicians who are out in the field who need refreshers and things like that, because I think that helps reiterate a lot of the nuts and bolts of the whole process of what is involved in terms of the RF systems, what is involved in terms of the difference between bipolar and unipolar, the use of distending media, things like that, and it gives one a better appreciation than when you go into the clinical setting of all these different factors which are so critically important to the safe performance of these procedures.

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

It is very hard to do a good bench model for hysteroscopy that really teaches the problems that, you know, you don't dilate a cervix in the
wet lab, you don't create much pressure in a pig bladder, so there are a whole bunch of things in those wet labs that are kind of difficult to teach. I think we need to publish more. I think we need to write more about what the problem situations are, and we probably need to publish in some form an analysis of these cases very specifically, so that people can learn from them.

DR. BLANCO: Dr. Diamond.

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

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

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

DR. BLANCO: Any other comments?
Let's open it up and see if there are any comments from the audience, anyone who would like to say anything at this time from the audience? No one? Okay.

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

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

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

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

DR. BLANCO: Thank you, Colin.
I also would like to thank all the panel members for their participation and involvement. I would like to thank the FDA for their excellent work as always, and also the audience, members of industry for their presentations and very interesting information.

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

Thank you.

[Whereupon, at 12:50 p.m., the proceedings were recessed, to be resumed at 2:00 p.m., this same day.]
DR. BLANCO: Why don’t we go ahead and call the meeting to order. I think we are going to start on time and try to finish promptly.

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

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

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

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

DR. WHANG: We are pleased to have joining
us for this session this afternoon, Professor Anne
Roberts, who is a Professor of Radiology and the
Chief of Vascular and Interventional Radiology at
UCSD.

DR. BLANCO: We can go around the table.

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

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

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

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

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

DR. KATZ: David Katz, Duke University.

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

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

DR. WHANG: Joyce Whang, Executive
Secretary of this Ob-Gyn Devices Panel.

DR. BLANCO: Jorge George Blanco, perinatalogist.

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

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

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


DR. BLANCO: Thank you. Let's go ahead and introduce Mr. Colin Pollard, Chief, Obstetrics and Gynecology Devices Branch of the FDA, who will make some introductory remarks.

Uterine Fibroid Embolization (UFE)

Introductory Remarks

Colin Pollard

MR. POLLARD: Thank you, Dr. Blanco, ladies and gentlemen, members of the panel. Today,
we will be talking about uterine fibroid embolization, and I would like to go over a number of things just to get things rolling.

[Slide.]

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

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

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

[Slide.]

In October of 1999, we were first looking at uterine fibroid embolization. At that time, we
were still grappling with the question of 510(k) versus PMA, and we were sharing that sort of struggle, if you will, or that kind of discussion that was going on within the center.

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

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

Last year, ACOG issued a Practice Bulletin No. 16, which is in your background package. That practice bulletin, in fact, states that the College considers it to be investigational.
I know there are some ongoing discussions between the College and the Society of Cardiovascular and Interventional Radiology, and there are a number of study proposals that are under consideration at the October 1999 meeting.

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

[Slide.]

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

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

[Slide.]
Just very quickly, a regulatory update
going over the classification, the market pathway,
clinical trials we have looked at, and the
development of the guidance document.

[Slide.]

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

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

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

For uterine fibroid embolization, most of
this is being done with polyvinyl alcohol
particles, and really the issue before us is manufacturers' purpose to go from a general indication for a hypervascular lesion to a specific indication, and we are applying the center's guidance document for doing that kind of thing. Since the panel meeting, we made a regulatory decision that we would use 510(k) to handle that, 510(k) premarket notification to handle that kind of market clearance preceded, of course, by a clinical trial to establish that specific indication.

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

At this point, we have approved two clinical trials to study artificial embolization agents for uterine fibroid embolization. The discussion questions that you have before you are really a reflection of some of the key elements of those that we wanted to get some panel input as we went ahead and prepared a guidance document.
The guidance document, right now we are working on it. We have to follow the good guidance practices that the center uses when it releases guidance documents, so since we haven't actually got it available for public, so we don't have it for you, but we tried to craft our discussion questions in a way that you can get a good sense of what is going on there.

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

[Slide.]

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

Any questions?

[No response.]

DR. BLANCO: Thank you, Mr. Pollard.

We will move on. The next presentation from the SCVIR will be by Dr. James Spies, I
believe, Georgetown University. Please be sure to state any conflict of interest, funding, travel, per diem, honorarium, et cetera.

Presentation by Society of Cardiovascular and Interventional Radiology

James B. Spies, M.D.

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

DR. BLANCO: Thank you.

[Slide.]

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

[Slide.]

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

[Slide.]

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

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

By the beginning of 1999, this therapy was being offered probably in about 20 centers around the country, and there had been numerous small case series reported, and now we are getting into the phase where we have some larger series, longer term follow-up available.
One of the things that has always been a question, just the standard approach in this, because there is some discussion or controversy about this is that most patients require a history and physical examination including an examination by a gynecologist, need to have a current Pap smear.

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

Imaging has to be used to confirm the diagnosis. In our center, we use exclusively MRI with limited charge, but I would say the average operator in this country would use ultrasound. Routine laparoscopy, hysteroscopy, leiomyoma biopsy, deep myometrial biopsy, all those things are generally not done and unnecessary for most patients. There are some centers in which
that is done, however.

[Slide.]

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

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

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

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

We, at Georgetown, use a bilateral femoral approach, which means we puncture both femoral arteries, which we have found to be a more
expeditious way to do this procedure, many operators will use a unilateral approach. Both uterine arteries have to be treated regardless.

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

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

[Slide.]

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

As you all know, the fibroid, as it grows, it tends to compress the normal myometrium adjacent
to it, and that normal myometrium continues to
derive its blood supply from other branches, and
these vessels are an order of magnitude smaller
than those that are feeding the leiomyoma, which
allows us to embolize the leiomyoma branches while
avoiding most of the myometrial branches.

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

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

[Slide.]

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

We would move the catheter down to about there in order to do the embolization, so it is right before it begins to ascend in the serosa of the uterus, and this is what it looks like.
Now, these are Georgetown pictures, which means you are going to see both sides projected simultaneously, which is the way we do this, but you can see there is a left uterine artery here, right here, and these are all these abnormal blood vessels.

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

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

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

Now, this is an MRI we performed early in
our experience in a patient about 48 hours after embolization, because she was having significant pain, and I was concerned that we had actually injured her uterus. I think it was more a matter of pain management in her particular case.

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

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

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

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

In this patient, who underwent an elective hysterectomy for other reasons, she was having actually adnexal surgery and elected to have a myomectomy eight months after the procedure. She had a 1 centimeter fibroid, which was infarcted, and she had a 6 centimeter fibroid which was completely infarcted. So, generally, it works on all the leiomyoma that are present.

[Slide.]

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

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

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

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

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

[Slide.]

This is what happens. This again is some experience from Georgetown, where we showed that the blue is the uterine volume, it's about 50 percent reduced to two years on average. The green is the dominant fibroid, the largest fibroid, and it's 43 percent on average at three months, it's about 60 percent here, and it's about 78 percent at two years.
Now, this is widely variable, and one of the points I would make is that looking at volume reduction really is a very poor measure of outcome. If we are going to use imaging characteristics, we might want to look at perfusion-related MRI or regions of interest, because there are substantial inter-observer variability associated with the measurement of both uterine volume, particularly in large multi-fibroid uteri and also in the leiomyomas themselves.

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

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

This is one huge fibroid here. This is three months out, and this is a year out. This is
a bit of a close-up, but the top of the uterus used
to be up here, and now it is down here, and that
fibroid has decreased about 70 percent in volume.

[Slide.]

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

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

[Slide.]

This is one of our early experiences in
which we had a large, 7.5 centimeter submucosal
fibroid that failed hysteroscopic resection, three
months, one year, two years. We actually now have
a three-year study in this lady, and her uterus is
normal, and that little tiny residual fibroid that
was right there is gone.
I would like to talk just for a few minutes about our experience. This is going to be published in the July issue of Obstetrics and Gynecology. Part of the reason I would like to present this is it gives a little bit more detail on what most investigators are seeing. I don't think our results are particularly different.

We do have 200 patients that are being reported, a minimum follow-up of 12 months and the mean follow-up on this group of patients was 21 months, and looking at the percentages of improvement, you can see that in the high 80s or 90 percent in terms of percentage that are improved. Patients are satisfied to some degree in over 90 percent of patients. Now, that is in terms of symptom control.

Now, if one looks at peri-procedural complications again from the same source, a paper that is going to be published in a month or so, you can see there is a 6.5 percent rate of minor complications, but basically, over half of those are either ER visits or readmission for pain, and probably all those occurred within the first 60 to
80 patients we treated, and we have learned a lot more about pain management, and we are much better at it than we used to be. So, we have not really had a patient return for pain management issues in the last 200 or 300 patients we have treated.

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

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

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

[Slide.]

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

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

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

We had one patient that went on to a myomectomy because she was dissatisfied with the degree of shrinkage on her fibroid. We did have
nine hysterectomies, none for complications. Seven
were in patients that failed to improve. If you
look back on my original slide, assuming that 90
percent roughly are improved, well, obviously, 10
percent are not. Roughly half of those patients in
this group have gone on to hysterectomy.

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

[Slide.]

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

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

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

Larger leiomyoma volume does predict less
volume reduction. If you also look at bleeding
improvement, there are no predictors when adjusted
for volume at three months, but at 12 months, there
is an odds ratio of 0.87 per 100 cc increase in
baseline leiomyoma volume of bleeding improvement.
Well, what does that mean? It means that
by every 100 cc increase, there is a diminished
chance, it's 0.87 rather than 1, of bleeding
improvement. So, in theory, very large fibroids
will be less likely to improve bleeding at that
interval than others.
Having said that, the difference between
them is really not very strong, and I will show
that in a minute. There is no difference for women
with prior hormone therapy in terms of bleeding
improvement, which is one of the panel's questions,
and there is a trend toward greater improvement
with submucosal location.
[Slide.]
Now, if you look at the estimated
associations, improvement in one symptom does
highly correlate with improvement with the other
and satisfaction at both 3 and 12 months, of if
your bleeding is better, your pressure usually is
better, and you are generally satisfied. If you
are dissatisfied, obviously, your symptoms are not
improving. That is almost self-evident. There is a weak association noted between
dominant leiomyoma percent volume reduction and
bleeding improvement and satisfaction at three
months, but I think it was about 0.17 was the
correlation coefficient, so it is really not very
strong. Only bleeding improvement maintained this
association at 12 months. So, the associations are
not strong.

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

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

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

Our experience, we have had 11 women out
of 200 that had no menstrual period at three
months, by three months after this procedure. Of
these, all three had resumed menses by six months,
and three continued at 12 months. Now, one of
those women actually had failed UAE, was one of our
few failures. We actually were unable to
catheterize her vessels, and she was placed on Depo
Provera, which was why she was amenorrheic.

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

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

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

Over the age of 45, 15 percent of patients
had a change from below 20 International Units to
above. Presumably, then, they have been moved
closer to menopause as a result of the procedure.
Again, the youngest woman that we have had other than the lady with Depo Provera that was amenorrheic, was 49 at Georgetown. In almost all cases that were reported are over the age of 45.

[Slide.]

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

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

What does this dose mean? Well, it's about 10 times the dose or maybe 15 times the dose depending upon the study of diagnostic pelvic radiograph procedures like barium enemas or other
similar procedures. It's 0.1 to 0.006 the dose of therapy for Hodgkin's disease.

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

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

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

By doing that, we were able to, in a
subsequent group of patients, measure a mean ovarian dose of 9.5, a skin entrance dose of 47. This is a reduction of about 60 percent of the ovarian dose and over 70 percent in the skin dose.

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

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

[Slide.]

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

It includes birth control, control of menorrhagia, hormone replacement therapy, and
control of endometriosis. Oral contraceptives and progesterone may impact menstrual bleeding, and we recognize that, and it may affect the measurement of uterine artery embolization treatment effect. If we are trying to control menorrhagia, if oral contraceptives are decreasing the amount of bleeding, then, we might falsely measure in error. However, the error in measurement for using these medications will likely be an underestimate rather than an overestimate of the treatment effect of UAE. If bleeding is being suppressed before, and it is suppressed afterwards, the delta that we will be measuring will be smaller overall.

So, I think that if we are going to have an error in the estimate that is going to occur, it is going to be in the conservative direction. If you look at oral contraceptives for birth control in those that are on hormone replacement therapy, patients can continue them before and afterwards, so they can be self-controlled. The treatment effect of UAE is likely to far outshadow the effect of oral contraceptives. Higham scores that have been reported have been decreasing by about 50 percent or more.
regardless of birth control reviews. As I mentioned in our regression analysis, prior oral contraceptive use did not predict improvement of bleeding or did not affect that prediction.

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

[Slide.]

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

If patients stop therapy post-procedure, it will likely again represent an underestimate.

If the bleeding is being suppressed before the
procedure, and they go off the Provera, they go off
the birth control pills afterwards because their
bleeding is improved, whatever rebound effect will
result in an underestimation of the treatment
effect from the UAE, so I think again it is in the
conservative direction.

[Slide.]

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

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

I think that the FDA should, and certainly
could, ask for a statistical comparison of users of
hormones versus non-users as part of the submission
from the companies that are involved in this.

[Slide.]

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

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

[Slide.]

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

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

So, I think that from my perspective, and I have spent a fair amount of my research time
looking at outcome measures from this, I think that we should be using validated symptom and/or QOL, quality of life questionnaires. Validated menstrual pictorial assessment charts are also I think a good way to evaluate this.

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

[Slide.]

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

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

One could use a general health-related quality of life questionnaire, such as the SF-36 or the SF-12. We published some data on a proprietary fibroid specific quality of life questionnaire, and
we have just completed a combined symptom and
quality of life questionnaire. It is called the
UFS-QOL, which we are just submitting now to
Obstetrics and Gynecology.

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

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

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

Taking the other tack of saying, well,
gosh, how sensitive is even a very blunt instrument
in measuring outcome, the SF-12 is a 12-question
subset of the SF-36, and really is designed for
sort of large populations, a quick, two-minute questionnaire, but even using this instrument, we presented this approximately a year ago, there is a statistically significant increase in the physical summary scores at three and six months. The one-year numbers are too small to be able to be interpretative.

[Slide.]

The UFS-QOL is a new symptom and health related quality of life questionnaire. It has 37 questions, 8 symptom and 29 quality of life questions. It provides a symptom score and a summary HRQOL score, as well as 6 subscale scores. We have just completed the validation of it. This was created using focus groups and then we did an expert validation. Then, we went through 110 fibroid patients and 30 normal patients, and it has excellent internal and external validity. The cross-sectional validation was very strong with the other measures, and it is the primary outcome measure for the fibroid registry, which you will hear more about later.

[Slide.]

So, assessing outcome, we believe that patients represent their own controls and each
study or company or applicant should set an
appropriate clinically relevant level of symptom
change measured by validated means.

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

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

We have actually done some pilot work
trying to determine how easy it would be to
randomize patients, and it really is quite
difficult. Patient resistance is quite high. I
think the best alternative to randomized studies,
which is what is going on in essence right now, are
parallel prospective cohort design of UAE versus
some other standard therapy using the same outcome
Responding to the question regarding study duration, I do think that six months is an appropriate duration for premarket surveillance. Nearly all the complications that have been seen have occurred in the first six months. Nearly all the secondary events, such as amenorrhea, fibroid expulsion, and early treatment failures occur in the first six months, not every single one, but nearly every one.

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

It is more important to provide postmarket surveillance for a longer period than one year. We would suggest surveillance for a minimum of two years. The fibroid registry may be a vehicle for that postmarket surveillance, and we are enrolling literally hundreds of patients, and we are hoping to be able to supplement whatever data that each of these companies would provide with that data.
Re-treatment. I think re-treatments in the context of these FDA-approved studies should be considered primary failures, although these patients should continue to be followed and look at the subsequent treatments and outcomes. I think it is useful data.

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

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

[Slide.]

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

Many women, even though we think they may have, many women do not really have clear plans for
or against future children. Some women are very
definite, some women are very vague. You can have
a 33-year-old woman who isn't really quite sure
what she wants to do, you will have a 48-year-old
woman who definitely wants to become pregnant.

What do you do with that situation?

So, arbitrarily eliminating patients based
on a yes or no related to future children is really
not practical. The safety of myomectomy for future
childbearing varies greatly depending on the
surgical skill and the extent of fibroids.

Obviously, there is a conversion rate to
hysterectomy which is quite low, but certainly it
has never really been well studied in terms of its
overall safety.

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

There have been numerous successful
pregnancies after a UAE, but the rate is not known.

We are hoping to get that answer from the registry.
The fetal wastage rate is also unknown. The role of fibroids and fertility problems is still unclear, it is very difficult to study, and the effectiveness of myomectomy as a infertility operation is not well studied. It has been studied, but they are not large series. They have been relatively poorly controlled. It is a very difficult thing to assess.

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

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

Each patient should be carefully assessed to determine which therapy is most likely to preserve the uterus in a functional state and with the least risk of hysterectomy.
UAE should not currently be used as an infertility treatment. Determination of the effectiveness of UAE versus myomectomy for infertile women does require I think a randomized trial, and this is the one area I think we actually could get patients to allow themselves to be randomized because it is a very clear legitimate question, and we will eventually have to answer that question.

[Slide.]

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

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

The role of the FDA is important, but other efforts including those of the fibroid registry and the adoption of uniform validated means of measuring outcome are also critical, and
we are very strong proponents of physician education and training standards to ensure that this is done safely in a broader practice.

Thank you.

DR. BLANCO: Thank you, Dr. Spies.

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

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

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

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

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

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

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

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

DR. SPIES: The whole thing is validated.

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

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

So, there will be an opportunity to review this at greater length. This was done with Med Tap International as our consultant, and they designed the study.
DR. D'AGOSTINO: Just one other question.

What triggers the re-treatment? I am trying to sort out why they are failures.

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

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

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

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

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

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

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

Thank you very much, Dr. Spies.

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

Matthew Mauro, M.D.

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

DR. BLANCO: I am sorry, introduce conflict of interest.
DR. MAURO: No conflict of interest.

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

[Slide.]

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

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

[Slide.]

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

[Slide.]
In April of 1999, the SCVIR developed a task force to investigate and evaluate the uterine artery embolization procedure. We developed a multifaceted approach which looked at standards, research initiatives, physician education, and other activities.

[Slide.]

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

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

[Slide.]

In addition to the training skills, optimal equipment is required as highlighted by the marked reduction in radiation dose from antiquated equipment, which uses continuous high-dose fluoroscopy to the more standard used state-of-the-art
equipment, which uses pulse fluoroscopy, and
give you an idea of what the significance is by
using continuous fluoroscopy that utilizes
radiation at 60 pulses per second where we now can
use routinely 7.5 pulses per second using this
pulse-dosed, which is a reduction of 7/8ths of the
dose, so it is a very important aspect of the
performance of this procedure.

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

[Slide.]

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

[Slide.]

Research initiatives have been developed
in conjunction with the Rand Health Service, where
a multidisciplinary expert panel was convened in
June of 1999, and this panel identified several key
outcome measures to be investigated and recommended
four areas of research.

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

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

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

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

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

[Slide.]

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

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

[Slide.]

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

We estimate that our sample size would include 3,000 patients per year, and for our prolonged longitudinal follow-up study,
approximately 900 patients per year.

All patients enrolled will have baseline data, as well as procedural data, 30-day data entered into a web-based form. There will be patients enrolled at 24 core sites, which will be considered for follow-up study at 6, 12, and 24 months. This constitutes our longitudinal study. They will be randomly sampled and undergo a quality of life instrument evaluating patient satisfaction. All patients intending subsequent pregnancy will be involved in this longitudinal study.

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

We have several short term outcomes that are being measured. Baseline data is relatively exhaustive, and that is one of the principal
purposes of this registry, is to obtain consistent
and important data regarding the procedure, as well
as procedural data and the variety of adverse
events that may occur.

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

[Slide.]

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

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

Thank you very much.

DR. BLANCO: Thank you very much, Dr.

Mauro.
Are there any questions of fact?

[No response.]

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

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

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

DR. HUFNAGEL: Yes, I am.

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

Go right ahead. We are here listening.

Open Public Hearing

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

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

DR. HUFNAGEL: The general destruction of
normal uterine tissue is the result of uterine artery embolization. To hear in this meeting that after the fact, 10,000 cases have already been performed and now a registry is going to occur is extremely distressing to myself and to many women who would hear this, but this is typical of the types of evaluations of procedures that goes on. I think this is partially from our culturalization that the uterus is an organ which we can eliminate easily. You need to look at your social concepts when you think about the uterus. The uterus has physiological function that include sexual response, creation of hormones, substances, inhibin, relaxin, prostacyclins. It is also an organ of placement in the pelvis.

In speaking out, I will be attacked in presenting a case that I recently did of Achieng Wamabo, who is, by the way, one of 10 patients that I selected to bring to you today, 10 patients who all had very bad outcomes with uterine artery embolization, 10 patients who were never reported to the FDA, 10 patients who were never followed up. Achieng Wamabo described her uterine artery embolization in one word, "fast." She was seen at one of the major sites in which this was
being performed. In 1998, she had a Lupron injection. Ten days after that injection, she had an emboli shower in her lungs and nearly died from the pulmonary emboli. That was 1998.

She was told that the Lupron would be helpful in her procedure for her embolization later on. In 1999, she had her embolization. That embolization operative report is very contradictory. That operative report says that both arteries were embolized. Then, it says only one artery was embolized.

Her physicians who handled her pulmonary emboli refused to give her her medical records. The physicians who saw her, both the radiologist and gynecologist, were well known to this committee. Both made no notations whatsoever in her medical workup that this woman already suffered a significant pulmonary emboli in 1998. There actually was relatively little workup, and she was pushed in one day from the gynecologist to the radiologist to have this procedure done.

This is consistent with 10 cases that I have reviewed recently. What is of major importance is that there is a lack of workup, a lack of informed consent. All the negatives for
uterine artery embolization are not--let me repeat--are not
being discussed with the patients. Women
are not told that they may not be able to have a
myomectomy in the future.

Having been able to actually see the
tissue results as a surgeon, I was able to see that
the resulting myometrium, normal myometrium is
severely affected by uterine artery embolization,
and selection of patients who have very, very large
uteruses, which you know the reduction is not going
to be down to a normal size uterus, and the woman
is going to be still left with a large mass, makes
these poor candidates. Yet, these women are still
having uterine artery embolizations.

There was no dissection line in the
removal of Achieng's fibroid. There was no
capsule. What occurs is microabscess formation,
histiocytic clumping, fibrosis, and other tissue
reactions, which actually removed the capsule.

The hallmark for a myomectomy is the
ability to distinguish between normal and abnormal
tissue during your dissection. This is gone with
uterine artery embolization, and women are not
being told this.

I have great concerns over the lack of
adequate informed consent. I have great concerns that there is so much silence on this. Why was this case not presented? Why did the FDA not get any reports on it? Ten women have now reported major complications that have never been reported to the FDA.

Women need to have surgical options, as well. Myomectomy needs to come out of the dark ages, and we need to approve it. Uterine artery embolization probably has a place, however, the widespread entrepreneurial selling of this procedure when women are scared and frightened, are told they have no other option other than a hysterectomy, just sending them in to get an embolization without full knowledge of all the problems that can happen.

Radiation exposure still an issue, I believe. Toxin exposure, another issue. The lack of follow-up. Every one of the women who have come and reported have never even had an ultrasound after their uterine artery embolization. Their uterus just shrunk, they were sent on their way, and no follow-up. These are clinical crisis.

Achieng Wamabo will be sending her report in. She will be leaving the hospital next week,
having had more than 50 fibroid tumors removed. It was a difficult surgery, and this is my expertise. I do more myomectomies than anyone I have ever met, and I had a difficult time doing it.

Would we embolize a neoplasia on the testes? I doubt it. What are we thinking about when we are promoting these kinds of processes without looking at all the issues and providing them to the women?

This is being sold to women, it is being marketed. There are actual contracts between women who are writing books and working for university hospitals, and are getting funding for their web sites. None of these web sites have any advocacy section. None of these web sites have any area except for one, one web site has an area to report problems with AUE.

The marketing aspect of this is enormous, and it is doing well, obviously, by looking at the graphs and the data. The problem is that some women have suffered, and others will continue to suffer because of the fact that this is so fast, there is a lack of procedural protocol, and the response to the tissue of the myometrial normal tissue and its destruction is not being adequately
provided to the women prior to this procedure.

I do not like this procedure and the way in which it has evolved whatsoever, and I conclude.

DR. BLANCO: Thank you, Dr. Hufnagel.

The next individual who has requested time for public comment is Carla Dione—I apologize if that is not right—Executive Director, National Uterine Fibroids Foundation.

Again, please state any conflict of interest and limit your remarks to five minutes.

[No response.]

DR. BLANCO: It appears that she is not here.

The last one that I have or that we will open it to the audience if there is anyone else is Nora W. Coffey, President, Hysterectomy Educational Resources and Services Foundation (HERS).

MS. COFFEY: Good afternoon. I am Nora Coffey, President of the Hysterectomy Educational Resources and Services Foundation, a national nonprofit women's health education organization. HERS is also the repository of thousands of reports from women regarding the treatment they receive and have had suggested to them by physicians.

I am going to truncate what I intended to
say today in the interest of time, but I am still
going to I guess rush through.

Research of the medical literature
revealed that UAE was a surgery that had been
performed on a small number of women for postpartum
hemorrhage initially and at risk of death. It is
now being performed on women notably absent from
any danger to life and often even lacking the
minimal symptoms for which any treatment might
rationally be suggested.

Since UAE first emerged, the pool of so-called
qualified UAE candidates has shrunk as the
obvious dangers of performing it in certain women
has become apparent, but the number and seriousness
of adverse effects has mounted and now sits well
outside the promised no complications, and from the
hint that there might be pain as a result for a
very short time requiring the possibility of
hospital admission for treatment, we now know that
many or most do have pain and others have
persistent, some severe pain for months and even
years later as a permanent complication.

All this has been learned, not from
laboratory science before exposing large numbers of
women, but from the ill effects suffered by women
who expected that this was an easy and trouble-free
solution to the problems that some, but not the
majority, of women encounter from fibroids.

Our office continues to receive calls from
women unsuspecting of these facts including one who
doctor told her that he would perform the procedure
on her. When she asked how many UAE he had
performed, he said he hadn't performed any, but he
had read about it, and he was sure that he could do
it.

Another woman who underwent UAE reported
that she had developed a foul vaginal odor,
obviously not only to herself, but to others. She
had an infection. When it was exposed at surgery,
had appeared to simmer for months, and had caused
adhesion of the bowel to the uterus and other
organs, requiring that a specialist come in mid-operating
procedure, and there are many other
reports. I am going to skip over the women's
reports, although I think they are really
important, and I wish I had time to show them.

You all know of similar problems which
have not yet appeared in the journals, although
none of us know how large the total numbers are or
will become from this experimental misadventure.
Uterine artery embolization has already caused deaths, hysterectomies, infections, cessation of menstrual periods, rehospitalization, and other damage that was unexpected by women, all in a scant few years.

This leads to the expectation that there is more in terms of numbers and additional consequences not yet identified. We ask then of the FDA the following:

If you have the authority to confer approval on a surgical procedure, and thus confer its legitimacy, although there are no standards that exist for doctors, materials, or other instrumentation, and no uniform procedure to assess, that you exercise your authority and responsibility to require that vendors, doctors, and other proponents for widespread use of UAE curb advertising and publicity which makes it appear that all the answers are in and that they are uniformly positive.

There is a public health danger posed by the self-promoting web sites and publicity in media generated by doctors and other commercial interests, such as the manufacturers, inventors of devices who advocate for UAE.
Unfortunately, the biological sequela arising as a result of this procedure will be learned on the bodies of women, many of whom, as in the case with hysterectomy, have no medical need for any treatment whatsoever, and the argument that hysterectomy is worse does not make UAE better, only different in its dangers, which are as yet largely unknown.

What are the lifetime sequela of the long-term effects on ovarian function, endocrine function, and the implications for vascular and the immune systems?

If the permanence of artery occlusion causes concerns, there are equal concerns lest the blockade degrade or partially separate and drift.

What women need is a return to laboratory science in order to identify the reasons women develop fibroids, so that their arteries, uteri, and other organs not be targets of interference and demolition.

A name change, changing from uterine artery embolization to UFE, uterine fibroid embolization, will not serve women well. In fact, it raises more questions about the problems we have not yet read about in the journals and those yet to
Calling it fibroid embolization rather than artery embolization is an evasion and ultimately misleading to women because it is, in fact, the arteries that are embolized.

If clinical trials do proceed, and apparently they are already in progress, we suggest that women be provided with the following: Full written disclosure of the known risks and adverse consequences of UAE. An opportunity to ask questions in writing, which doctors will respond to in writing, and signed and date.

An adverse events reporting form should be provided to the woman undergoing embolization, in triplicate, with a copy to go to her doctor, a copy to go to the FDA, and a copy for the patient. Disclosure should include deaths, sterility, radiation to the ovaries, infection, loss of menstruation, hematoma, allergy to contrast material, failure to shrink fibroids or resolve symptoms, regrowth of fibroids, growth of new fibroids, post-embolization syndrome, damage to nerves, embolization of the wrong arteries, damage to the blood supply to the ovaries, and loss of libido, loss of sexual feeling.
Women should be told of all of the alternatives to hysterectomy including no treatment at all, myomectomy, and hysteroscopic resection of submucosal fibroids.

Currently, a large number of doctors tell women that the only option they have available to them is hysterectomy or UAEE, which is certainly not the case.

Thank you.

DR. BLANCO: Thank you very much.

Is there anyone else in the audience that would like to address the panel before we begin our deliberations?

I am sorry, who is this?

MS. BOOKER: (By telephone) My name is Susan Booker.

DR. BLANCO: Okay. Please state any conflict of interest statement and limit your remarks to five minutes, please.

MS. BOOKER: I don't believe there is a financial conflict of interest. I am not, I guess you would say, pro uterine artery embolism. I am surprised that the name is being changed to uterine fibroid embolism or occlusion.

The surgery is going to be known as a
barbaric surgery in 20 years when doctors look back on the damage that is going to happen to women, and if the numbers of women being victimized by this surgery, if it was the same numbers of men, the FDA would take an immediate stance and halt until a follow-up is done on the women who have already gone through uterine artery embolism.

A complete, full follow-up on the women who have had uterine artery embolism needs to be done now immediately.

I have great concerns on the number who have been injured, and I understand that a similar situation took place years ago with the ova block, which has never been fully recalled, women still have not been informed, and that is an unresolved issue in its own.

I conclude.

DR. BLANCO: Before you conclude, may we ask you, are you speaking as an individual or do you represent an organization or have an affiliation with an organization?

MS. BOOKER: At the moment I am speaking on my own, as an individual. I am a member of NOW. I work on health right issues, and I am a house advocate.
DR. BLANCO: Thank you very much.
Anyone else in the audience?
[No response.]
DR. BLANCO: We will then begin the panel discussion, and I would like to go ahead and have Dr. Levy address some issues, and then we will go through the discussion questions.

Panel Discussion

DR. LEVY: First of all, I would like to congratulate the Society of Cardiovascular and Interventional Radiology for putting forth this huge amount of effort in trying to study the science of this procedure.

I think that you have gone far beyond what most medical organizations and societies have done in the efforts to try to learn something about this procedure and to put some of the comments in context.

I really say congratulations. There is a huge amount of effort here, and there is an effort to study a new procedure, far beyond what we, in medical science, have done with any of the operative procedures that we have currently in place for women, so congratulations, and I think every effort is being made to study this as
scientifically as possible, and I am in absolute agreement with you.

I must say that I agree with most of the speakers' comments in terms of the FDA questions. I agree with consistent use of hormones pre-procedure, post-procedure. I don't think we should exclude patients who are on hormones, but I think that we should keep them consistent across the time that we are studying, so that we don't get shifts and differences that we can't attribute to the interventional procedure. I think that is very important.

I think that quality of life questionnaires should be done early on if we are really going to be able to use these data to inform women. Then, we need to be able to compare uterine artery embolization with myomectomy, with hysterectomy, and that means the quality of life in the first day, second day, the first seven days, two weeks, three weeks, and a month, two months later.

I don't know if that can be done within the context of some of the studies or as a substudy of some of what you are doing, but as a practicing gynecologist who tries to give informed consent to
patients, I know there is a lot of pain with
uterine artery embolization, there is certainly a
lot of pain with surgery initially, and I don't
know how to compare the two.

I think it would be very valuable to have
some of these quality of life surveys done at 24
hours, 48 hours, perhaps from there to a week post-op, so
that we have some sense of when the return
to function really occurs, not in retrospect, but
on a prospective basis. That would be very useful
information to me.

I agree with doing a six-month study and
then continuing surveillance for two years. I
think two years is a very short period of time, and
there is a lot of information I personally, as a
woman, and as a gynecologist giving informed
consent would want to have about this procedure
long term.

Whether we can persist with a registry
after the two years, I don't know, but it is
something that would be of interest. Many of these
patients will not become pregnant within two years.

Some of them may become pregnant five
years out or 10 years out, and whether there is an
opportunity for us to take the study and continue
an ongoing registry where patients could just log on and be able to give us further information, I think that would be very useful.

The things that concern me are things like radiation exposure to the ovaries in a young woman, are we going to precipitate premature menopause in these women, not immediately, but five years down the road. You know, are we impairing ovarian function with the amount of radiation that we are using, are we going to generate cancers, other things with the amount of radiation.

I think certainly in the radiological literature, you have enough data on things like barium enemas and other things to give us some reassurance about that, but these are situations in which we are electively using radiation, so I want to make sure, and I think in your effort to go really quickly, I think I saw it go by really fast, that are you collecting the amount of radiation exposure in every patient, is that correct?

DR. MAURO: Fluoroscopic time.

DR. LEVY: Fluoroscopic time? But I would like to see us if we can collect radiation exposure. I know that you at Georgetown are making every effort. Can't do it? Okay.
DR. MAURO: Right now it's fluoroscopic time plus numbers of images.

DR. BLANCO: Please identify yourself for the record.

DR. MAURO: Matt Mauro from the Society of Cardiovascular and Interventional Radiology.

As part of the registry, as part of the database, we are collecting fluoroscopic time, as well as number of images obtained.

DR. LEVY: But we are really not collecting, whether it is a single surgeon, two surgeons, just total time in fluoroscopy, number of images. Is that a surrogate, can we march that out in some way to look at outcomes?

DR. SPIES: Dr. Spies from Georgetown.

The problem with these studies is you actually have to place what are called TLDs in the patient's vagina and on her skin, which is mildly invasive although most patients have no objection, but it is very elaborate, and the reading is very elaborate, and it takes a lot of time, so what we are hoping to do is look at some of these studies as pilots and then be able to extrapolate that data to a population based on the fluoro times that are used for this. It is not exact science, but it
will give us a better idea of the population load of excess radiation or excess cancers.

The cancers are probably not going to be an issue. All the radiobiologists we have talked to do not think that this is anywhere near the range in which we would be instigating cancer. The bigger issue is, is there an effect on a woman's ability to have a normal child.

If you look at the studies that have been done for Hodgkin's, which have roughly 100 to 500 times the dose, their rate of having abnormal children, genetically abnormal children or any kind of malformation is about the same.

DR. LEVY: Actually, my concern is not genetically abnormal children, my concern is taking a 29-year-old or a 30-year-old and creating, not premature menopause, but subtle alterations in hormonal function, follicular function to the point where we have significantly impaired their fertility.

DR. SPIES: I think to be able to estimate, it is very difficult. Actually, there is very little literature on the effect of radiation on the ovary. It is a difficult thing to study partly because we have not been in the situation
before.

DR. LEVY: Which is why I just want to collect as much data as we can with this wonderful tool that you have started. I think it is critical.

The only other comments that I would like to make, there are some things rolling around in the literature about use of Lupron pre-surgery. I think you might want to separate use of hormones. As I understand it now, it is not recommended that Lupron be used for some particular reasons, but when you say hormones, Lupron could be construed in some way to be a hormone, so we probably just want to clarify what we mean when we say hormones, do we mean oral contraceptives, do we mean progestational agents, do we mean--what specifically do we mean, so that you are excluding GnRH agonists perhaps.

I am just saying that as we are answering these questions and we are saying should we exclude patients on hormones, we want to clarify which ones we are talking about and what dosages we are talking about.

DR. SPIES: We basically are separating the patients into three groups, and those are
patients on oral contraceptives, a progestational agent, or GnRH agonists, and the agonists, in general, most people exclude, and the studies that are currently at present exclude, so patients should not have an active agonist at the time they have this procedure.

So, if it is a three-month dose, they should not have this procedure within three months, and that is pretty much standard practice now, and I think that that ought to be the recommendation of our group.

What I was actually speaking to was the birth control pills, and in a case of a women that have heavy bleeding, the use of progesterone agents.

DR. LEVY: I think that is fine. In summary, I agree with some of the consumer people that have spoken, that a written informed consent is obviously something we do with all studies. I think it is absolutely critical. I think that women need to understand that we do not have long-term follow-up for these procedures.

I think that is fairly well established in your things and the things that you have done. You cannot be held responsible for what other people
out there are doing, as I very well understand.
But as a vehicle and as FDA, we probably do have
some responsibility to create in our guidance
document some sort of informed consent, some
written document that discusses these things in
general for the public, and I think that is very,
very important.

DR. BLANCO: Thank you.

MR. POLLARD: I would just add to the
point that you made about the informed consent.
Clearly or hopefully, obviously, when we looked at
these IDE applications, we did look carefully at
the informed consent, and we are also working with
the Society on identifying a more standardized list
of the risks and explanations of those that would
be incorporated into the guidance document, as
well.

DR. BLANCO: Thank you.

Let's go ahead and begin with the
discussion questions. The first discussion
question is quite lengthy. Let me try to read it
for you.

FDA is currently drafting an IDE/510(k)
guidance document to help in the preparation of
such submissions to the agency. Response to these
1. Currently, the inclusion and exclusion criteria for UFE performed in FDA-approved clinical studies of UFE are generally as follows:


Use or non-use of hormonal contraception must be maintained uniformly from 3 months pre-treatment through study completion. Willingness to consent and complete follow-up requirements of study.

Exclusion Criteria. Pregnancy or desire for pregnancy. Gynecologic malignancy or pre-malignancy. Adenomyosis. Candidate for hysteroscopic or laparoscopic myomectomy. Any drug treatment for uterine fibroids within 3 months pre-treatment. Active pelvic infection or history or pelvic inflammatory disease. Any acute or chronic infection. Undiagnosed pelvic mass outside of the uterus. Coagulopathy. History of pelvic irradiation. ASA score greater than or equal to IV. Uterine arterio-venous fistula. Allergy to the I.V. contrast media.
Let me go ahead and open it up to the panel for discussion. Any comments of any of these inclusion or exclusion criteria? Go ahead, Dr. Levy.

DR. LEVY: I am not sure that I would exclude patients who are candidates for hysteroscopic or laparoscopic procedures. I think this is a choice as you have eloquently stated, patients want to have choices, they don't want to be randomized. There are patients who don't want to have surgery and are symptomatic.

I think that we are making a value judgment when we are excluding patients who are candidates for laparoscopic or hysteroscopic procedure. I think they need to be given informed consent that these are procedures that could be done as an outpatient basis, that there may be a little bit more data specifically on hysteroscopic resection. I think you probably have as much data as we have on laparoscopic resection of myomas, but I am not sure that I would exclude those patients as much as I would just give them informed consent that they have other options. Some of the other patients may not have that option, but in listing the options that patients have, they would be given
that choice.

DR. BLANCO: Dr. Diamond.

DR. DIAMOND: I would agree with most of the inclusion and exclusion criteria here. The couple that I would want to emphasize, that I do agree with, is that at this point in time, I don't think we ought to be recommending the inclusion of women with known or suspected by gynecologic malignancies and even endometrial hyperplasia, certainly, at this point, I think ought to be excluded.

Without a large amount of data about subsequent pregnancy outcomes of these individuals, for research trial's purposes, for new agents that will be coming before FDA, I would also recommend, as is stated here, that individuals who desire future pregnancy be excluded from those trials until we can get additional information.

I would disagree a little bit with Barbara, but for a different reason, about patients who are candidates for hysteroscopic myomectomies or perhaps--we talk about laparoscopic potential, you are talking about pedunculated fibroids--just about the hysteroscopic, while I agree that we should be giving patients choice, the question is
are those fibroids going to respond differently
than others that are intramural, and if so, would
including them in the database potentially alter
the result or make it more difficult to interpret
the results.

   The one inclusion criteria that I think I
would disagree with is the issue of women who are
currently on hormonal contraceptives, and I would
agree that if individuals were on them, and would
stay on them afterwards, that that would probably
be less of an issue, but I don't think that the
sponsors are going to have any control over whether
women stay on their hormones or not after their
procedures, and I think that also would potentially
introduce a bias if the women are on them
initially, have the procedure, and then go off
them, particularly if there are short follow-up
periods where stress-related amenorrhea from the
procedures may affect subsequent bleeding rates, as
well.

   But I think that potentially introduces an
additional factor which may influence the outcome
by the woman coming off the birth control pills or
just starting that themselves, and then having
alterations in their bleeding histories which would
have to be interpolated into the results in order to draw conclusions of the studies.

DR. BLANCO: Dr. Shirk, you had some comments?

DR. SHIRK: I guess I have got one comment, and that is, one of the exclusion criteria was dropped out from our initial inclusion/exclusion criteria, from the initial draft, we got the second draft, and that is on pedunculated fibroids. Since the two deaths in Europe, and I am not sure about the death in the United States, were associated with pedunculated fibroids, either intrauterine or subserosal, do we want to consider that as part of the exclusion criteria?

DR. BLANCO: Any comments?

DR. O'SULLIVAN: The question I would have is if you have a pedunculated submucous fibroid, and you then go ahead and embolize that, are you not exposing the patient to a greater risk of infection as a result of that pedunculated fibroid, that you are causing degeneration to, which is sitting free in the uterine cavity, which is not sterile?

DR. LEVY: I would think if the only myoma
a patient had were a submucous pedunculated
fibroid, that we would not be considering these
kinds of procedures. We are really looking at, in
these procedures, women who have 14, 16, 18-week
size uteri with multiple fibroids. They may have a
submucous fibroid, and I don't think they should be
excluded from consideration if they do.

We know that if they do have submucous
fibroids that are on a pedicle, that they
frequently slough, they pass them, these are the
small percentage of people that sometimes need
hysteroscopic resection or D&C to get rid of that
necrotic tissue.

DR. ROBERTS: I have a number of concerns
about some of these inclusion and exclusion
criteria, and I will just sort of go through them
in order.

One is regular menstrual cycles. Many of
the women that we treat do not have normal cycles.
They may have bleeding in between their cycles.
They may bleed for two weeks, stop for a week and a
half, and bleed for another two weeks. So, I think
normal menstrual cycles is probably not a
reasonable inclusion criteria.

Normal kidney function. I think if you
had someone who is on dialysis and is bleeding, and
may not be a good candidate certainly for surgery,
certainly, that person who is on dialysis should,
in fact, not be excluded from this.
I think I would agree that if someone has
borderline renal function, that is something
different, but if they are already on dialysis,
then, there is no reason. You know, contrast is
not going to hurt their kidneys.
My concern about the hormonal
contraceptives is that I think it needs to be how
it is defined. If it is just simply hormones for
contraceptives, I agree, I think it is going to be
hard to legislate to patients whether or not they
are going to remain on contraceptives or whether
they are going to want to start contraceptives now
that they are not bleeding so much. Maybe they
figure they will have sex, so they would like to be
on contraceptives because they don't want to have
children.
In terms of the exclusion criteria, I
guess in terms of a research study, pregnancy, I
think that is a question we really want to answer,
and it may be, in fact, that pregnancy is something
we want to leave, you know, we don't want to
exclude, but I think that perhaps there is enough
question about that, that we at least ought to
think about that.

    Certainly, anyone with a malignancy or
pre-malignancy shouldn't be treated. I don't know
that adenomyosis should be on the exclusion
criteria. We know that some patients with
adenomyosis seem to respond to this. We don't
really understand what is going on with
adenomyosis.

    Some patients, where they have done
hysterectomies, they found that some of those
patients have adenomyosis, but in other patients
that they know have adenomyosis, they have a good
response.

    I would say that it shouldn't be an
exclusion criteria, but probably should be perhaps
in a subset, if someone is going to study it, it is
going to be in a subset.

    I think in terms of any drug treatment for
uterine fibroids, that is not a reasonable
exclusion criteria because I get a lot of patients
who come in, who are taking, you know, who have
been put on double dose hormones, double dose
contraceptives to try and control their bleeding,
and that is their control for right now until
something else can be done.

I will tell you a lot of these patients
aren't just taking double dose, they are taking
four times because they find out, they are told to
be taking twice as much, and then they find it is
not really working, so they are taking four times,
and obviously, those patients I don't think should
be excluded from this.

I think in terms of the allergy to
contrast media, I think it is important to say an
untreatable allergy to contrast media because many
patients have hives to contrast, you give them a
little SoluMedrol or you give them a little
benedryl, and they are going to be just fine. So,
I think it should be an untreated allergy to
contrast media.

So, I will stop with those.

DR. BLANCO: Any other comments?

Let me comment on a couple of things that
you said. I think the way that it is written, you
are going to exclude a lot of patients if you want
regular menstrual cycles when you are dealing with
patients with symptomatic uterine fibroids.

DR. LEVY: Maybe we could say normal
ovarian function.

DR. BLANCO: I think as far as the hormones, the contraception, the three months, I think you are going to face that problem either way the decision is made because just like you are likely to have women who will come off the oral contraceptives after the procedure, you are going to have some that will go back on it, as you alluded to.

So, I think essentially, whatever study gets designed, you are going to have to presuppose that those are going to happen and take into account numbers that you may have to analyze separately or analyze differently in terms of how big you plan for the study to be in order to prove what you want to prove.

I would be interested in other folks' comments, but I think pregnancy is a big issue, and until we know more information--and I recognize a lot of women may say now they don't want to get pregnant, they may want to in five years from now and vice versa--until we know a little bit more of what it does, and we will.

I mean some of these women that are going to say that they don't want to be pregnant, will
eventually become pregnant, and until we find out a
little bit more, it is probably better to leave
those folks out.

Any questions?

DR. O'SULLIVAN: I am just going to make a
comment. I mean we do have some information albeit
a slightly different situation, in which we have
had women with postpartum hemorrhages, and in an
attempt to conserve the uterus, have done both
bilateral uterine artery and ovarian artery
ligations, and they have subsequently gotten
pregnant. But it is starting out as a different
situation with a huge collateral blood supply that
probably wouldn't be the case here.

One of the questions I have--could we go
back to the last slide that you just took off? I
see the contraindication, uterine arterio-venous
fistula, why is that a contraindication? As an
exclusion criteria I mean, why would that be
exclusion?

DR. ROBERTS: I am not sure that it should
be, but the problem, if you have a really large
arterio-venous fistula, is that you are treating a
fistula, not fibroids. I am assuming that they
mean with this that they don't have fibroids, they,
in fact, have an arterio-venous fistula, and then you can have the particles move through the fistula into the lungs. So, that is considered bad form. If it was simply an arterio-venous fistula, you would have to treat the fistula differently than you would the fibroids, and then you could presumably treat it, so I am assuming that that is the reason, because your treatment for the fistula would be very different than with the fibroids.

DR. ROY: The second inclusion criteria, premenopausal; more than 30, 35 years of age, by implication excludes people younger than that. I was surprised that no one has yet mentioned that there are women who have completed their childbearing younger than that, who have myomata uteri, who are symptomatic.

DR. BLANCO: You are going to want premenopausal, but what you are basically saying is you may not need that 30 to 35.

DR. ROY: Right.

DR. BLANCO: Colin.

MR. POLLARD: I just wanted to highlight, so that it is clear to everyone what we are looking at. What we are looking at is sort of a synopsis,
which is why in that opening sentence, it says "generally" of the two clinical trials that we have approved.

This is not necessarily exactly what is going to go into the guidance document, but it is sort of something that we thought would be very helpful for the panel to work from, so in the context of where did these come from, they came from clinical trials we looked at.

The other thing was Dr. Roberts went through a number of exclusions that she had some question about, and we are hoping that the panel might sort of engage on those, do they agree, do they not agree, are there qualifiers, that sort of thing.

DR. BLANCO: Thank you.

Let's hear from Dr. Spies. He wanted to say something.

DR. SPIES: I am sorry, I don't mean to interject, but the issue of hormones, I think is quite important. I am actually more concerned about the safety of this procedure than having a truly accurate assessment.

So, if I had to choose between a truly accurate assessment of the treatment effect of this
procedure versus the safety of the procedure, we
should go with safety.

Now, we have treated 425 patients at
Georgetown. We have had three thrombotic
complications – the PE I showed you, we had an
arterial thrombosis, and we had a very minor DVT
that didn't require any specific therapy. All
three women were on hormones.

The two with the worst complications were
on both Provera, double-dose Provera, or Aygestin,
and birth control pills. Now, we are just about to
start a study looking at prothrombotic states as a
result of this procedure, so that it is quite
likely that women become prothrombotic as a result
of this, just as they do with neurosurgery and hip
surgery, and other kinds of things.

The question is are they made more
prothrombotic by this, so I would ask the panelists
to seriously think about it before they exclude
these patients because this really is a significant
safety issue.

DR. O'SULLIVAN: First of all, in the
white population, the incidence of thrombophilia,
especially Factor V Leiden, is somewhere in the
range of 3 to 4.5 percent, and their risk of
developing thromboemboli on any of these drugs is increased, and I agree with you, that would be a concern, and I was rather surprised that in the first 200 patients, you didn't have any, which is kind of why I kept my mouth shut.

I do think that that is an issue. I think that perhaps one of the ways around the issue could be to do—and that is going to be expensive, though—is to do a thrombophilia screen, certainly for Factor V Leiden, which is the most common one by far.

DR. SPIES: I have no doubt that we have treated Factor V Leiden patients. I, in fact, am V Leiden positive, I mean it is everywhere. I imagine we have, and I imagine that those people have gone through without a problem.

I expect that what we are going to do with this group of patients is look at fragment 1, fragment 2, platelet dependent factor, thrombin/antithrombin complex, a whole variety of different thrombotic—and we are working with Dr. Kessler with Georgetown on this—to look at a group of 20 patients in a row, let's do 5, 6 samples. We will look at the curve and see what happens.

In most studies surgical interventions
double those, and if they double those, then, we need to look at the subset perhaps that are on hormones and look at that specific issue. That is $1,000 worth of lab tests.

You may be right, that Factor V Leiden is a predisposer, but I have no doubt we have treated some of those. None of the patients that we have done so far with those thrombotic complications have had actually any—we have done genetic screening afterwards—the only risk factors were hormones in that group of women that we can identify.

DR. ROY: I think it is important to remember that norethindrone acetate is a prodrug. One milligram gets converted to, on average, 5 micrograms of ethinyl estradiol. Let's suppose just for sake of argument that it stays the same. You give 10 milligrams, you get 50 micrograms of ethinyl estradiol, and you said you gave double the dose, you were potentially giving 100 microgram dose.

DR. LEVY: We didn't give it.

DR. ROY: Well, the patient was receiving it. Okay? All I am suggesting is that that more than the possibility of Leiden, although I think in
Caucasians it is a very important issue to consider because of the link with the hormone therapy, as Dr. O'Sullivan said, markedly increases their risk of clotting.

DR. LEVY: I think we need to get back to the practicality of who are these patients that we are taking care of and who are these patients that are candidates for the procedure. Young women with symptomatic fibroids at times are bleeding horrendously, and in order to keep them out of constant transfusion and get them ready, they will be treated with hormones. I think we should include those patients, stratify for them. I completely agree, we just need to see what are they taking, which ones are at risk.

We may learn, for example, that 20 milligrams a day of norethindrone acetate is absolutely contraindicated. Clinically, we don't really know that right now. We give them as much as it takes to get them not to bleed until we get them to the operating room or get them to the lab for UAE.

But in practical terms, those are the patients we are targeting for this procedure, and I think they must be included. I think we just need
to stratify for them. We will need to know who
they are and how much they are taking, and for how
long, so that we can take a look at safety, as well
as effectiveness in the long run, and just keep the
registry growing, but I think to exclude all those
patients is going to be a miserable thing for us to
try to do.

DR. BLANCO: Actually, that is probably
one of the deficiencies in looking at this is a
longitudinal study as opposed to a comparison
study, because it may be that the incidence of
pulmonary embolus or thrombophlebitis is actually
worse in these patients that are highly loaded on
hormones when they undergo a myomectomy or
hysterectomy, and it may not be that it is
necessarily the procedure that is doing it, but
it's the prettiest position of the hormones, the
high level of hormones, and then having them sit
around for any type of procedure for a while.

Do you want to say something about the
hormones?

DR. DIAMOND: Something about what Colin
wanted and one thing about the hormones both.

DR. BLANCO: Go.

DR. DIAMOND: With regard to Dr. Roberts'
comments about adenomyosis, adenomyosis as a coexisting disorder with fibroids, I don't think should be an exclusion criteria, but someone whose entire pathology is thought to be adenomyosis as opposed to fibroids is not someone who I would recommend including because then we are treating different disorders.

With regard to the hormone issue, you just need to keep in mind also that there are at least two different types of studies that are probably going to be ongoing for uterine artery embolizations.

One may be of the sort at Georgetown that you all are doing, the multicenter studies that you are conducting, which very well might include individuals who are on hormones, because those are very key questions because we so often do put our patients on them.

But the guidance document would not necessarily be for that population. That may be for companies that are coming in with devices they would like to be able to be utilized for these purposes, and for the purpose of those trials where there is going to be potentially some sort of comparison, then, to have them included and with
possible changes in the hormones, hormonal therapy, I think will complicate the interpretations.

DR. LEVY: I will agree with Dr. Roberts that patients on dialysis should be included, but patients with renal failure, who are not on dialysis, should be excluded.

DR. ROBERTS: The other thing is, also on the exclusion criteria, I would also say that uncorrectable coagulopathy would be an exclusion, but not coagulopathy in general.

DR. BLANCO: I don't know. Do you really want folks who are having coagulopathy to be part of a research protocol? It is the same thing sort of as someone who has an allergy. Even if you think you can treat it with a little SoluMedrol, I mean that may be what happened last time, but maybe won't happen this time.

I think as part of a research protocol, it is probably better to exclude folks that you know are going to have some other added complications than include them because you may get somebody who was controlled okay before, but is not, so I have some concerns.

I would probably keep both the allergy and the coagulopathy as it is, it would seem to me.
MR. REYNOLDS: I just have one question since we had some consumer groups who seemed to be terribly concerned about informed consent.

On that informed consent form that the people are going to fill out, is it going to say anything on there about alternative procedures?

DR. BLANCO: IRB forms routinely have as one of their components alternative therapies.

DR. ROBERTS: Quite frankly, as someone who does these procedures, I mean I can't speak for every practitioner, just as I am sure the Ob-Gyn's here would not want to speak for every Ob-Gyn, but I would say that, by and large, these patients, first of all, are educated in terms of what it is that we know and what we don't know by the large majority of people.

I will speak for myself in saying that all of the patients that I see are told that there are a lot of things that we don't know about this, this is what we do know, these are what all of your options are, hormones, doing nothing, myomectomy, hysterectomy, all of these are options for you, and the other thing that I think is very important is to realize that, by and large, these are a very educated group of women that are coming in for this
study or this proposed treatment.

I mean they have been on the Internet, they have been contacting different doctors. They, by and large, are not sort of, you know, lambs being led to the slaughter on this, I will tell you, and I, quite frankly, will speak publicly to say that I violently disagree with some of the public speakers that were here today.

DR. BLANCO: Let me just say that I think part of the rationale why we are here is that we would like to be able to derive through research projects, publications, education, and guidance documents to the type of things that need to be available by folks who may not be doing it under such strict protocols, so that people can be aware of what really is required.

Neither the FDA nor us can be out there policing every single doctor that may use a procedure that may not quite do it in the appropriate way. So, I think the best that we can do is try to make sure we get the appropriate data, so that the appropriate information is available and can be promulgated, and without a doubt, inform women appropriately with the best data available as to what the options are and what the different
procedures are, and what might be the results of
those or at least what we know.

Having said that, anything else on the
inclusion/exclusion criteria? If not, we are going
to move on.

DR. CORRADO: Dr. Blanco, it is Julia Corrado from FDA staff.

I just wanted to I guess beat this issue
of hormonal contraception one more time, because we
have had some concerns that I just want to make
sure the panel is aware of, so that we can
definitively come to closure on this, because I
sense that there is still some disagreement among
the members of the panel, as well as among the
staff and the sponsors on this issue.

What we are anticipating is getting a data
set that we want to be able to interpret
statistically and for labeling as straightforwardly
as possible, and we have been concerned that if
some of the patients, an unspecified percentage of
patients are on uniform hormonal contraception
prior to and during the study, and that their data
is pooled with the data of women who are not on any
kind of hormonal medication including
contraception, that they might not be poolable and
that we won't be able to adequately represent who
the patient population in the study was in terms of
presenting the data.

So, that is one of our concerns. We, in
general, I think would agree that we like the
cleanest data set that we can get.

I would also like to point out that to my
way of thinking, there is analogy between these
studies and the endometrial ablation studies that
we have been entertaining, and in those studies,
women were excluded if they desired to be on any
kind of hormonal contraception for any period
during the study evaluation, and that didn't limit
those sponsors from enrolling patients in their
studies. It didn't appear to be a problem.

Dr. Levy?

DR. LEVY: Actually, it did significantly
impair our ability to enroll patients in those
trials. I think there was a significant problem,
but I also think that the quality and the amount of
bleeding that some of these patients with fibroids
do is substantial, and it is substantially
different than what we were dealing with, with the
endometrial ablation protocols.

I don't disagree that the cleanest data is
the best, but I think that in order to look at all populations for whom this procedure may be indicated, what we probably need to have is the data stratified. We should not pool the data, but I think we should not exclude those patients who require hormonal treatment for the management of their bleeding until they can get into the appropriate intervention.

So, what you might want to say is we might even stratify it further and say we want to exclude those patients who are just taking oral contraceptives for birth control, not for management of bleeding, but allow those patients in the trial who are on some sort of hormonal management for their active problem.

I would actually like to see the data on all of the patients, I would just like to see it stratified rather than pooled.

DR. BLANCO: I think Dr. Spies actually made a very good argument why probably the hormonally-treated patients should be included, and that is an issue that is a major issue, and that is the issue of safety.

If you do this and you exclude all the hormonally-treated patients, and somehow the
combination of hormone treatment and this procedure really predisposes significantly the thrombophlebitis of pulmonary emboli, you know, I think everybody would like to figure that out pretty early in the game, and not once this is all approved and being widely used, and all of a sudden we find that there is significant numbers of these safety issues going on.

So, I think that while you may not be able to use the data, Dr. Levy's suggestion about stratification is important, it is probably good early on in the game to look specifically at the safety issue in that combination.

DR. ROBERTS: And I think it is very important that what you need to do is to do, as Dr. Spies said, which is to remember that you have got patients that are on an estrogen preparation, you have got patients that are on a progesterone preparation, you have got patients who are on Lupron or anti-estrogen preparation.

I would say that the patients who are on Lupron should be off that Lupron for three months before you treat them with embolization because there is no question that the arteries are very different in size, and your embolization result is
probably quite different, so I would say in terms of that particular type of drug, that those patients ought to be off that.

But in terms of the other, I think you do need to separate out, I mean stratify and think of a little bit differently those patients who are on birth control pills that are on a standard dose and they are being used simply for contraceptives, and the patients who are on these high doses of birth control pills to try and control their bleeding.

It is a whole different way of treating those patients and thinking of those patients.

DR. CORRADO: I think that the idea of stratification is probably the best compromise here. I think that will enable us to produce a data set that is understandable and interpretable by people.

I would just say that if part of the philosophy of including these patients is to find out what the morbidity of the treatment is in patients who are on hormonal contraceptives, for example, that that needs to be real clear in the informed consent, that there is the possibility that there will be increased morbidity if I
understand correctly that last argument, and maybe Dr. Spies wants to comment on that.

DR. ROBERTS: I am sorry. Run that by me again.

DR. CORRADO: Well, maybe I am misunderstanding, but I am hearing an argument that we ought to leave these patients in the study, that is, we ought to leave patients who are on hormonal contraception in the study, so that we will then know whether or not they have an increased risk of thrombotic morbidity.

DR. ROBERTS: But even more importantly, it is these patients that are on these heavy-duty birth control pills, in other words, they are taking two or three times the normal dosage, those are the ones that are probably really at risk, and those, you know, I think you do that because you are trying to control their other problem, which is their bleeding.

DR. CORRADO: That wasn't clear from the discussion. I was not hearing the women at the high end of the hormone treatment, I was hearing we want to know if these women on hormonal contraception are going to be at increased risk of DVT, because of the treatment, and that is the
point that I just want to make sure that I
understand clearly, that that is not the purpose of
this.

    DR. ROBERTS: That was why I said it that
way, because I thought you were confused about the
fact that we are looking at the ones that are
really having a lot of hormones. Now, it doesn't
mean that the ones who are on regular
contraceptives, when you do this procedure, and
they are bed rest, you know, 12 hours or whatever,
maybe are at higher risk, as well, and that would
be something that we would certainly want to know,
but I don't think anybody has a good feeling about
that.

    DR. SPIES: If I could just comment, we
probably have treated 75 or 80 patients that have
been on either birth control pills or Provera or
one of the other, and actually a number that have
been on high dose, so this is obvious and very
clear public health menace, it is a concern. We
have had a whole spectrum, but really, it is that
subset that we have seen the problem in, so I think
parsing it out the way Dr. Roberts suggested is
probably what we ought to try to do.

    Early in these studies, we have an Adverse
Events Committee, that is what they are there for, to be able to identify these things. These things need to be reported to the FDA, and if a study needs to be stopped or altered because of a clear recognizable danger to patients, it ought to happen immediately. We don't have that data right now.

DR. BLANCO: I apologize for having to step out for a minute. I also wanted to support what you said, Dr. Roberts, I think it is very important, and we talked about that we need to really define, and not use the term "hormonal" in such a broad sense.

I think it needs to be very specific whether you are talking about oral contraceptives, whether you are talking about progestational therapy, and your talking about Lupron or any of these type drugs, and it be looked at that way rather than it is such a hormonal issue is a broad issue.

Anything else in the inclusion of exclusion criteria?

[No response.]

DR. BLANCO: All right. Anything else on the hormone, which is the next little dot?

DR. ROBERTS: I think we have beat that
one into the ground.

DR. BLANCO: Beat that horse to death, okay. Any comments?

All right. How about exclusion criteria already include gynecologic malignancy or pre-malignancy, should simple endometrial hyperplasia be considered a pre-malignant condition? Any comments on that?

DR. DIAMOND: As I said before, yes, I think it should.

DR. BLANCO: I think we would agree, and Dr. Levy left me a note saying yes, that really should. At this time, in a research protocol, it probably should be included as an exclusion criteria.

All right. If there is no other comments, let move on to No. 2.

2. As the primary study endpoint, FDA-approved studies currently use either a quality of life instrument validated for uterine fibroids or a validated uterine bleeding scoring instrument coupled with a QOL instrument.

Secondary endpoints include adverse events, fibroid and uterine size, time to return to normal activities, and comparisons to the controls.
Primarily, patients are serving as their own controls, with secondary comparisons to patients in non-randomized arms (either control subjects undergoing myomectomy or hysterectomy).

Please comment on interpretation of these studies when completed.

Does anybody want to open up discussion?

DR. D'AGOSTINO: First, I should say I think the quality of life instrument generated is really quite superb, it is very impressive, and it does have a nice set of questions, which I can see why you did have reasonably good validation.

In terms of responding to the question, in other settings, in many settings, and I think probably here also, some of these quality of life instruments tend to be too much of an aggregate, too much of a composite, and it is oftentimes components of it that really are the main item even with the SF-36, quite often it's the physical function as opposed to the mental that shows changes with different conditions and sort of tracks what is going on.

I would suggest, and I would like to put on the table that something like bleeding seems to have come up over and over again, that maybe this
idea of bleeding and then a quality of life
instrument is a very sensible way to go in terms of
primary variables.

I think that global quality of life may
work, but I think that once you have that, you are
going to be compelled to say, well, what was it
that was significant, and then you rush to
bleeding, so why not put it right on the table to
begin with.

DR. BLANCO: Dr. Sharts-Hopko.

DR. SHARTS-HOPKO: I would agree that the
instrument you guys have provided for our review is
very fine. I think that menorrhagia is kind of
like pain, it is a problem when the woman says it
is a problem, and it is alleviated when the woman
says it is alleviated with the addition of you can
always look at hematocrit and hemoglobin, which
anemia is an undiagnosed problem in this population
in a lot of cases.

I agree that you are going to want to use
a visual bleeding assessment tool. I also think
that pain per se might be a specific thing that you
would want to assess. I am not sure that that is a
big item or not.

DR. BLANCO: I think that that is one of
the known factors that go along with this procedure, I think as Dr. D'Agostino was saying, you might as well just say it upfront and go look for the information in terms of pain, narcotic use, that kind of thing, and have that information available.

DR. SHARTS-HOPKO: I think that these secondary endpoints are appropriate. I think that the radiologic people's long-term database will answer the other question that we have talked about, which is fertility. I don't think that a shorter term study can really deal with that.

DR. BLANCO: Jerry.

DR. SHIRK: I guess I just have a question, and partly it is for our statisticians, and that is basically, obviously, with our endometrial ablation studies, we had a nice, clean double-blinded kind of study with a nice, neat mathematical endpoint, and using one basic measurement as a primary measurement, that is, a PBAC Score.

This obviously is fairly complex with using both a PBAC score and a quality of life instrument as a thing with no other controlled study, when you get to reviewing a PMA, how do you
look at this from a statistical standpoint as to
how you are going to evaluate this over time.

DR. BLANCO: Do you want to tackle that
one, Ralph?

DR. D'AGOSTINO: I think that you don't
want a lot of endpoints that you are calling
primary, you may have a lot of secondary, and what
I was trying to do, and I think what Nancy was also
doing, is to pull out a couple that you think, like
bleeding, maybe pain, that you think are really big
ones, and this amorphous, global quality of life,
and you go for that, and that is three endpoints,
three primary endpoints, it is not hard to control
the type 1 error, the alpha error on the three
endpoints, and the FDA can argue or discuss with
the sponsor do you have to win on all three or how
is that going to be worked out, but that is not
asking an awful lot.

I think that if you just did the quality
of life, and you sort of win on it, then, you start
splitting it up, and you get into all these
arguments on what is it that you want to look at if
you say right upfront bleeding is important, pain
is important, and the global quality of life is
important, you can do that.
One of the things that is I think interesting and problematic is the before or after that comes down later on, but that is a much rougher question to deal with.

DR. DIAMOND: We are being asked to comment here on how is the interpretation of studies using patients as their own controls going to be able to be interpreted, and I am going to have to make the sort of comments I made back in October of '99, that I think it is very difficult. There are potential major placebo type effects. The mind is also a very powerful thing. There is now evidence over the last six months, actually, evidence for about 10 years, but evidence that has come out over the last six months, reported that women that talk about their infertility and are open and express about it, will have a higher success rate of conceiving than women that don't. There are theories about the biological correlates that go along with it, but nonetheless, there is now good data to support that. So, a study that does not have a control group or that tries to use historical controls from different patient populations, different surgeons,
different technologies, I think is extremely difficult to interpret.

The argument against requiring studies evaluating uterine artery embolization to have a control, it is only going to be a subpopulation of the patients that are going to be able to be included because some patients are having life-threatening hemorrhage of other women are not willing to participate, but in the six or seven years that I have sat on this committee, we continually have clinical trials that come before us in obstetrics and gynecology where it is subsets of the populations with certain types of pathologies who are being evaluated, and those results subsequently interpreted and extrapolated to other populations, sometimes with additional studies.

But to answer the question, interpretation of studies, longitudinal studies with each patient as their own control, I think are very difficult to accurately interpret.

DR. D'AGOSTINO: What did the FDA accept, there were two controlled trials or two products that they accepted, were they before or after studies?
DR. ROBERTS: They probably can't answer that.

DR. BLANCO: While they are thinking over how they are going to answer that, let's have Dr. Roberts--

DR. ROBERTS: One of the things that I was wondering, and you may not be able to answer, you probably can't answer this either, but the other issue is that there were supposed to be, it sounds like anyway, there was some talk about having concurrent controls of patients with myomectomy or hysterectomy, and I would, of course, assume and encourage, if I can't assume, that those patients would be undergoing this same quality of life with bleeding scoring and secondary endpoints, that the patients undergoing embolization would be doing.

DR. D'AGOSTINO: But it says non-randomized.

DR. ROBERTS: But it could be concurrent controls. I mean they are not randomized, but you are looking for a group of patients that are having a hysterectomy or a myomectomy, and judging them, you know, they are concurrent, at least they are not historical, they are going on in the same--

DR. D'AGOSTINO: But you could argue that
a person's own control might be better than a non-related
group, and so forth, in terms of symptoms
and conditions.

DR. ROBERTS: Yes, but at least it sounds—I mean
I am reading this that there are both
things going on, that there is both the internal
control and then also a concurrent non-randomized
concurrent control group, but I don't know.

DR. BLANCO: Mike, what do you think of
that, I mean Dr. Roberts' idea, since you brought
it up?

DR. DIAMOND: I think a concurrent non-randomized
control is better than a historical
control, because it controls for time and
technology. I still think there are many potential
biases as to why individual patients choose one
modality versus another. If you are comparing
different physicians, you might be able to do
myomectomies better than I do, and so depending on
whether your patients get the myomectomies or mine
get the myomectomies, that could influence the
result.

It is a step in the right direction, but I
don't think it is all the way that I think it
should be.
DR. BLANCO: Jerry.

DR. SHIRK: I guess it comes back to the question I asked, and Mike obviously stated it in a much more eloquent way than I did initially.

My question was if we take three different parameters that the patient has as far as quality of life, PBAC, and pain, and use all three of those, and use the patients as control, is there a good statistical way, using enough variables to basically get significant data or, as Mike suggested, are we still over a barrel as far as to have some control that is basically either randomized or non-randomized that we compare to.

DR. D'AGOSTINO: By not having a randomized control, you can do all of these different strategies, but what you are looking at may turn out to be statistically significant, but not relate to the procedure. The randomization gives you the procedure.

I think all of these different ways, you know, they are in a bind, I think, that you just can't do or I am assuming from the context that you can't do a randomized control, so the more ways you can look at the data, the more ways you can get data for comparison, the better, but none of these
non-randomized controls or the before or after really address the question.

We are not talking about historical controls at all, isn't it either before or after, or non-randomized was what I gather, and I think that both of those are suboptimal, but two suboptimals don't equal an optimal.

DR. BLANCO: Any other comments on that?

Dr. Levy left me a comment. I think it was an important issue for her, and I think it probably is an important issue going back to the radiation. She put it here, although I am not sure why. This was the issue she brought up before about the radiation exposure, and it may be because we are ob-gyns, and so we don't deal with radiation exposure a lot of the times, so I will defer to that, but I guess I would echo here an encourage that some sort of estimation or attempt, maybe with a subgroup of patients, to get a fair amount of information.

I mean we would hate to do all these studies and have this widely spread, and 10 or 15 years from now, start getting into all kinds of problems from the radiation exposure of the ovary, and maybe it is, as I said, an overconcern, because
I don't deal with radiation all the time, but I will just throw that out.

DR. ROBERTS: I think it is important, and I think I would assume and hope that whoever was doing this kind of study, that at the minimum that one should account for the amount of radiation time that one uses in the examination and also for the number of images that one obtains.

The problem is that what you would really like to do is to know exactly what the dose to a particular patient is, and unfortunately, most of the equipment that is available today does not give you that kind of information, because it depends on where the patient is with regards to the x-ray tube, are they close to the x-ray tube, are they far away from the x-ray tube, is the x-ray tube angled.

All of these kinds of things go into what the radiation exposure is, and so as Dr. Spies said, it is a difficult thing to get, but I certainly would agree that in terms of the amount of fluoro time and the number of images that are obtained should be part of the data collection for this.

DR. BLANCO: Any other comments on
Question 2? That side has been kind of quiet.

DR. ROY: You have been preempting us.

DR. BLANCO: Oh, well, I will try to look over there more then.

[Laughter.]

DR. BLANCO: Let's go on to No. 3 then.

FDA currently asks for a six-month follow up (premarket) with an additional six-month follow up (postmarket) for a total of a one-year follow up. Is this an appropriate follow-up regime?

Nancy.

DR. SHARTS-HOPKO: I think because we know that the database is being established and is going to go out 24 months, I think it makes 6 months before and after, combined 12 months, I think it makes that okay.

I would like to say at this point that I thank the consumer groups who made their concerns known to us. The MedWatch form is on the FDA's web site, and informing consumers that it is there and they should use it would be a good thing to do, and I don't know if there is some possible tie-in to the database that is being developed with that.

DR. BLANCO: Dr. Spies.

DR. SPIES: There is, in fact. This is a
web-based interface, and what happens is there is a
registry form, and when you get down, if you log
in, and there is an adverse event which appears to
be device related, you automatically have a link to
the MedWatch, and basically, there is a warning
there saying this must be reported to MedWatch.
So, that is there, and we recognize it. We
actually had FDA put in that when we designed the
registry.

Also, I should just add about the
registry, is that we clearly have the intention to
try to get federal funding to continue this
registry ideally out to five years or even longer.
This is a very, very expensive undertaking, so we
have two years to see if we can get some federal
funds to keep it going.

DR. ROBERTS: One thing I guess I might
bring up in terms of the six-month follow up, it is
not that I think it's unrealistic, but quite
frankly, I think the sponsors may be sorry if they
only take it to six months, because I will say that
from my own patients, that a number of them are
doing much better at six months, but at 12 months,
they are really doing a lot better, and some of
them have said, you know, it has taken me sort of
10 months or 9 months to really get--but now, you know, it's great.

So, they actually may find that they are sorry they didn't make it 12-month data.

DR. DIAMOND: Some of the data that Dr. Spies showed us before, as far as uterine volume and size of fibroids, showed continuing changes from 6 months to 12 months, and I think for the clinical trials, that will be done under the auspices of the FDA for the purposes of approval, I would think a 12-month approval followed by another 6 or 12 months would be more appropriate than 6 and 6.

DR. O'SULLIVAN: I would agree with that.
The other question I have is relative to the registry. How sure are we that patients are going to be reported to the registry or that the patients themselves will report themselves to the registry? I mean this is one of the things about registries. You can have them, but that doesn't mean they are going to be used.

DR. BLANCO: Again, this goes back to the issue of you can't control what the physician does. I am sure members of the Society, since the Society has been so instrumental in doing all these things,
will likely report that, but, I don't know, folks
are out there probably that are not members of the
Society, are likely doing this, I would suspect,
and it may not get there, so yes, that is a problem
with registries.

Again, you know, I guess I would go back
to the issues of well done studies that identify
the safety issues and the long-term effects, so
that there is more education for the physicians and
the public and everyone else to know what the real
issues are, what the real complications, problems,
and answers are.

DR. SPIES: The registry is divided into
two groups, and there is a core group of about 25
sites that admittedly are high-volume sites, but
first of all, they have their IRB--everyone one has
to get IRB approval for this, and you have to sign
an agreement which says that every patient will be
entered.

So, if you take the patient into the
angiographic suite to attempt this procedure, and
you don't complete it, or you fail, and the patient
has a complication, death, or whatever else, at
least in writing you have obligated yourself to
report that. We really don't have any way to
enforce it.

We are a pretty cohesive group of people, we have done projects together before, and we are not a huge group of physicians either, there is only a couple of thousand of us. So, we hope that by peer pressure and positive reinforcement, we will be able to do that, but there is no guarantee.

DR. ROBERTS: I guess, you know, as much as the registry can be a problem, quite frankly, having just sat on another panel a couple of weeks ago, a randomized controlled study can have the same problems.

DR. BLANCO: Any other comments on No. 3?

MS. MOONEY: One point to make since it seems like the data were consistent and showing that six-month follow up addressed any safety issues and identified those that were going to occur, it may be more prudent to give sponsors the option for six month versus 12-month follow up with the caveat that Dr. Roberts and others have mentioned, that it may theoretically reduce your ability to show effectiveness, but I think that we heard safety was addressed in the six months, and that may be what we should focus on.

DR. BLANCO: Any comments?
DR. ROBERTS: This is what I was kind of saying is that I don't really have a problem with six months, I just think that the industry might find that, in fact, if they did 12 months, it would actually a bigger delta and might be happier in the long run.

DR. BLANCO: I think we are ready to move on.

No. 4. Preliminary results have shown that some subjects require re-treatment with UFE. Should there be specific study requirements regarding re-treatment? How should the clinical study design account for this? Should these subjects be handled as primary treatment failures? Can these data provide additional information on the success of UFE re-treatment?

Would anybody care to address those?

DR. DIAMOND: If no one else wants to, I will try.

I think patients that feel their first UFE should be considered failures, however, at the discretion of the sponsor and the physician and the patient, I think they should be given the option of a repeat treatment. I think there are things that can be learned from those patients. Hopefully, the
devices that are being tested work, there will be
not a large number of these individuals, but if it
does turn out that there are, we may learn
important things about specific patient
demographics, history, physical findings, hybrid
size, location, which will allow us to predict
which patients they will work well and which ones
they won't.

DR. D'AGOSTINO: The idea of re-treatment
is--and the reason I was sort of hesitant to jump
up--it is not a simple question, because if you
take cardiac procedures, and you have a CABG, and
the individual develops a problem, and you give
another one, there is a real failure that the
procedure didn't work. If you have analgesic
studies, and somebody has a headache, they take the
treatment, and it doesn't work, and they go on a
rescue medication, it really didn't work.

But if you flip over to, say, like liver
transplantations, liver transplantations, the NIH
consensus, when you make the commitment that you
are going to transplant the liver, if the first one
fails, you get another one. That person keeps
going until either they die or it takes. So, re-treatment
has different modalities in terms of what
When you say re-treatment, the question I was asking when the speaker was up there, why a re-treatment, was there something wrong with the procedure or did the body not react appropriately, somehow or other that it is a real failure, then, everything we are talking about, and the easy way out is just to call it a failure and obviously get information, but if it is something that there is a procedure that was given, and it somehow or other didn't work, and you go at it again, is it a re-treatment or is it just following that individual until they get the right treatment. You introduce a much more complicated whole sequence of activities if you take the latter approach.

DR. ROBERTS: First of all, I agree with Dr. Diamond that if someone has a procedure, and assuming it was done to completion, I guess one would say, so you said, okay, I have done my study, and it fails, and the patient's symptoms recur, then, I think it should, number one, be counted as a failure.

The issue I think that becomes should the patient be restudied to see what might have happened, and I certainly would encourage the fact
that the patients be restudied. I think what the
problem becomes then is, is that what I suspect we
will find is what Dr. Spies brought up, was the
fact that many of these patients or the patients
that fail, may, in fact develop large uterine
arteries that weren't really present, at least you
didn't see before in terms of being present, and,
in fact, if you are going to re-treat the patient,
you are going to need to treat them via those
ovarian arteries.

Now, at that point, you might say wait a
minute, now I am concerned about ovarian failure,
and I think that now it becomes an issue in terms
of working with the physician, referring physician
and the patient, about whether or not one should go
ahead and treat that, and so that is where I think,
you know, it gets a little murky, and it may be
better to say, you know, they failed, and now they
failed and now you can go on and do whatever it is
that seems to be appropriate to do, but we are
going to count that patient as a failure, and then
we will follow that patient in terms of getting
safety data or getting more information, but we
will just count it as a failure.

DR. BLANCO: I think that is the issue for
the research project portion, that has to be counted as a failure, but what happens to that patient afterwards, it is kind of outside of the research protocol is what I am hearing you say.

DR. ROBERTS: I think so.

DR. ROY: Except that it would be preferable to capture as much data as possible.

DR. ROBERTS: Oh, I think the patient should continue in the study, but in terms of the procedure is counted as a failure. Now, like I say, you would want to go on and perhaps collect data, you know, maybe you are going to embolize the ovarian arteries, you know, which might put them into ovarian failure, or maybe they are going to go on and have a hysterectomy or a myomectomy or something else, but the main thing is, is that you would continue to follow them, but they are counted as a failure in terms of the study.

DR. D'AGOSTINO: There is something artificial about that, though. I mean you call them a failure. Say you do that, and all of them take a second and they do well on it, and then you are in the dilemma of—it makes the analysis so much simpler just to say call them a failure, and then my analysis, and they have no quality of life,
and so you get zero quality of life, and so forth, and it generates a bizarre analysis, but what do you do the second time with those individuals, how do you look at that data?

DR. ROBERTS: I don't think you necessarily do look at it.

DR. D'AGOSTINO: You analyze it separately, but what do you do with it?

DR. ROBERTS: Probably nothing unless there are a whole lot of them, and then you would want to know that there is a whole lot of people that are coming back for whatever their problem is. I mean that is what you want to capture. It is not just that the failed, but hopefully, what was it that caused them to fail.

DR. D'AGOSTINO: That is the question I was raising, is it a real failure. I mean if they are real failures, the procedure, you know, you brought it to completion. What we mean by a failure, I still don't know what your definition of a failure is. I know if they need another cardiac procedure, if they need another liver, if they need a rescue medicine, I don't know really what a failure is here, so how to respond to it.

DR. ROBERTS: You mean how is it defined a
failure?

DR. D'AGOSTINO: How is it defined.

DR. DIAMOND: Probably another surgical procedure.

DR. BLANCO: Wait a minute. You are measuring bleeding and quality of life, so your failure is going to be because you have no change in the bleeding or quality of life, so you are not going to get quality of life scores of zero, and all that. I mean it is not because you are going to have another surgery. You are going to have another surgery because you didn't change either the bleeding or the quality of life issues. That is what is going to make the failure, right, or am I wrong on that?

DR. ROBERTS: No, that is what I would think.

DR. BLANCO: I mean I would think that that would be what a failure is.

MR. REYNOLDS: There is no reason to have another procedure. The quality of life issues are all answered, and if you are not bleeding and you are not in pain, you are not going to have another procedure.

DR. BLANCO: And you are a success.
MS. BROGDON: May I ask a follow-up question? Are there any special informed consent considerations for patients who would be re-treated in a study?

DR. BLANCO: Well, let me ask the question before that one. How soon would someone be re-treated typically? Unfortunately, Dr. Spies has walked out, I was going to ask him that. But, Dr. Roberts, could you give us some idea? I mean is this something that happens and they get re-treated right away, or, you know, you wait six or eight months, or a year, or how does that work?

DR. ROBERTS: I haven't had one yet. I think that what you would have is it would not be somebody that you would do immediately unless they were hemorrhaging or something, and they didn't stop hemorrhaging, and then presumably you would re-look at them right away, but by and large, it would be patients that have had the procedure.

You would probably wait at least a couple of months to see whether or not their menstrual cycle sort of stabilized out, whether or not they are bleeding, because sometimes they can have, you know, usually not as heavy bleeding the first cycle, but it may be still fairly heavy, and then
the next one is lighter and it gets progressively better.

I think it would be several months later and that they had not improved, and they were still bleeding, and their quality of life presumably at that point is essentially the same as it was before, and then that is when you would discuss with them re-looking at things and possibly re-treating.

I think in terms of concerns with that and complications with that, because many of those patients are going to be patients that have large ovarian arteries, I think the issue at that point is that if you are going to embolize, if those ovarian arteries are supplying the fibroid, and you are going to need to embolize that, then, I think you have to discuss much more seriously—not that it wasn't serious before—but with a lot more expectations that you may, in fact, have ovarian failure if you are going to embolize that ovarian artery.

That is why I am saying, by and large, what I have told patients is if they have a large ovarian artery at the time, I don't embolize it, but I tell the patient they may not do as well, and
if they don't do as well, and we need to think
about re-treating them, then, they have to really
decide that they are willing to risk ovarian
failure.

MS. BROGDON: Thank you.

DR. BLANCO: Anyone else care to comment
on the issue of informed consent for the re-treatments?
Okay.

I think we have probably answered No. 4.

Any other comments or any other subsections of 4?
Let move on to No. 5 then.

No. 5. Labeling for new UFE indication.

What are the key elements that should be covered in
the professional labeling of embolizing agents that
are cleared for UFE?

How should labeling handle the issue of
women who desire a future pregnancy? Should
bleeding results be stratified by use and non-use
of hormonal contraception? Any other specific
questions?

I think we have kind of addressed both of
those a fair amount, but I open it up for
discussion. Anyone care to add anything else to
what we said? Jerry.

DR. SHIRK: I had one other question. I
guess this goes to more post-study type of thing.
There is a literature about this procedure. Some of the authors have suggested that there is a decreased risk of fibroid recurrence over time, that one of the problems with myomectomy is obviously that there is a significant recurrence rate in this patient population.

Certainly, the literature, he has basically suggested that this would prevent long-term recurrence rates of fibroids. Is that something that we should consider studying over the post-treatment time frame as we look at this over the long haul, or is this not really an issue and something that the literature is basically advocating?

DR. ROY: That is premature, isn't it? I mean that is why we are doing the study, and hopefully, they will have five years of extended federal support for this registry, so that we can capture that sort of information. I think this labeling issue and that issue are all premature. We would have to wait and see what the study shows.

DR. ROBERTS: Well, I think that the problem is going to be, as this said, I mean you
look at the patients who have recurrence of fibroids, and maybe they are going to recur and that you are going to know about it in five years, but maybe you are not.

I think in terms of the FDA study, I think to think that you are going to know what happens in terms of recurrence or new fibroids developing or anything, I mean I think that is going to be way beyond the scope of the FDA studies, not that you wouldn't want to know that, it would be great, but I don't think the time frame is going to be right. Certainly not at their six-month follow up and another six months maybe to see what goes on.

MR. POLLARD: I think maybe that is kind of really where this question is coming from. We are going to see this data, six-month data. We will have some data from the registry. We will have to see what we have got then, but really, the question that is coming from the point of view of what do we put in the labeling, what do we tell clinicians who have to inform their patients about what we know about it, especially with respect to longer term effectiveness and recurrence.

DR. ROY: You can only tell them what you know, and if you don't know beyond six months or a
year, you say the data is limited, just like we do
for everything else.

DR. ROBERTS: Yes. I think the same thing
goes with pregnancy. I mean we are not studying
pregnancy here, so all we can say is we don't know
about pregnancy.

You know, you can refer them to whatever
there is to refer to, but if we are going to
exclude them, then, we are not going to know, and
so if we don't know, we are not going to be able to
say anything about it.

I think the same thing comes with the
regrowth of fibroids. I think you say that the
long-term efficacy of the procedure is not yet
clear.

DR. SHIRK: I agree there. I asked the
question because the literature sort of suggests
that this is a long-term geared for fibroids is
basically what the study should say.

DR. BLANCO: Let me throw something out.
It is not an FDA question, but I would be
interested to hear what the panel thinks. The
presentations alluded to the fact that uterine size
was not that important.

That is an issue if you have got a big
fibroid, it could mask other processes going on, the size of it. Does the fact that right now we haven't said anything about uterine size or fibroid size. Is that acceptable to everybody on the panel, or would they like some information on that?

DR. ROBERTS: It is in the secondary endpoints. I mean it is still there. I don't know whether the thought was to not make it a primary endpoint. I think you would probably still want it as a secondary endpoint because it does impact, I mean at least to some degree it impacts on the quality of life for those patients who have bulk symptoms.

I mean they are the ones that are really uncomfortable with having that big fibroid, so I think it correlates to some degree, maybe just not as much as we thought we did in terms of symptoms.

DR. BLANCO: You are recommending is not make that a primary endpoint, but do collect the data on size, so that you know what is happening to the size of the fibroid.

MR. REYNOLDS: I think that is something that physicians might want to have for future reference. In other words, if we know that this procedure just doesn't work well for fibroids over
a certain size, you know, if the data shows that,
the patient comes in with a fibroid over a certain
size, you say, well, you are really not a candidate
for this procedure, but right now we don't have
that information, but there is no reason why you
can't gather it.

DR. D'AGOSTINO: But if they feel good, we
are saying they are a success, what does it mean by
a failure? What it does it mean by a failure, that
somehow or other you think that the size, if it is
very big, that they won't be bleeding?

MR. REYNOLDS: No. What I am saying if
you have a woman, let's say, who has got a 15
centimeter fibroid, let's say--I just throw that
out as an example--and everyone that has had one
over 15 centimeters, they come back three months
later and say I am still bleeding, I am still in
pain, to me that is a failure. I will call that a
failure.

DR. D'AGOSTINO: That is the definition of
a failure.

Maybe I can clarify it. You know, you may
want to look at the patients by size of fibroid and
some sort of stratification, not as a part of the
overall project, but just to know, if a large
fibroid, you know, beyond a certain size, seem to fail more often, or something to that extent, or maybe its positioning, where there is subserosal or submucosal, intramural, or whatever, I mean those are all issues that you don't want to make primary endpoints, but that would be great information to have, to be able to narrow down who is a good candidate for this procedure and who is not a good candidate for this procedure. Is that fair enough?

MR. REYNOLDS: That is very fair.

DR. ROBERTS: But I think that your point is a good one, too, and that is that just because there is still a large fibroid, if the woman feels good and quality of life is good, and whatever it is that was causing her problems is better, that also is important information. I think that is why to make it a secondary endpoint rather than a primary.

DR. D'AGOSTINO: If it works the way being suggested, that they have bad outcomes, then, it is great, you say large corresponds to bad outcomes, but what I was raising, what if large still carries with it lots of good outcomes.

MR. REYNOLDS: Then, fine.

DR. BLANCO: Any other points?
DR. DIAMOND: Just to follow up this last line of thought, I think it would be the other way around, it might be the small fibroids which are treated, which wouldn't have a big success rate, because for some of the smaller fibroids, that may not truly be the issue for the pathology. It may be a finding on ultrasound, but it may not be the cause of the pelvic pain or the discomfort the individual is experiencing, plus we heard earlier that fibroids have larger vessels than the rest of the uterus, the myometrium, and actually I didn't know that. There are more recent references than Sampson.

But if that is the case, if it is a small fibroid, there may not be large vessels, and so in that case it may not be efficacious.

DR. BLANCO: I will just go around the table. Anything else that anyone would like to say?

[No response.]

DR. BLANCO: If not, it looks like we are coming to the end of the afternoon session. I would like, as I am sure the FDA would like, to thank all of the folks that came before us and presented and spoke to us.
I personally would like to thank all the panel members for all of their participation and their excellent input and devoting fractions of their time from a day and a half, two days, to half a day, to participate in this.

I guess we will have some comments, if anyone from the audience wants to make any comment at this point? No? End of chance.

Anyone from FDA wants to make any?

[No response.]

SPEAKER: Dr. Hufnagel would like to make a comment.

DR. BLANCO: All right. Please go ahead.

DR. HUFNAGEL: (By telephone) Yes. I think that the dismissal of the comments we made in the negative aspects are not being discussed at all other than to [inaudible] them is really unethical and not called for.

The concerns that were provided are legitimate concerns. The case of Achieng Wamabo is not an isolated incident. It is the case of a woman at one of your studies, and that is why I provided the actual documents to you, so that you will have them.

I would have hoped that you would have
addressed these concerns publicly, so the public
could hear them, but I guess the train must go on.
But there will be robbers to stop those trains if
they are transporting and handling things, such as
this meeting has continued.
You did not really listen and you did not
respond in the appropriate way in which I think
most people would generally accept. But that's the
way it goes.
DR. BLANCO: Thank you, Dr. Hufnagel.
FDA, any comments?
MS. BROGDON: We would just like to thank
the panel for your preparation and your excellent
input. Thank you very much.
DR. BLANCO: Thank you, everyone.
This panel meeting is adjourned.
[Whereupon, at 4:46 p.m., the panel
meeting was adjourned.]