

1 DR. PERLMUTTER: I would like to go back to the
2 control issue. I feel almost schizophrenic about this. If
3 you are going to do a really good trial you need a control
4 group. But, by the same token, we have a lot of information
5 about contraceptive on the market already. We have a lot of
6 information about these barrier devices in various groups,
7 in various studies, and if you did a study of a new product
8 and it was equivalent to the controls that we already have
9 out there that we know about--I shouldn't use the word
10 control, I guess.

11 DR. BLANCO: Other products.

12 DR. PERLMUTTER: If we take the information we
13 have out there, that would tell us something. Certainly if
14 a new product was much worse, we would know that that is
15 probably not appropriate. But if we are looking for ways in
16 which to try and expedite things, this may be one way.

17 DR. LEVY: I think our issue is when we do a short
18 study with small numbers you can never be sure that your
19 study population is equivalent to the large population of
20 people for whom we have the historical data. Some of the
21 old studies that we have are on thousands and thousands of
22 women, and if we are looking at a study population of, let's
23 say, 200 over 3 months we know that efficacy or
24 effectiveness will vary by parity. Are they parous
25 patients, nulliparous patients? By the age of the patients,

1 sometimes by their location in the country. So, I think the
2 reason that a control arm is necessary with a small study
3 and a short grouping is that we don't know that the study
4 population is equivalent to the population at large for
5 these historical trials. That was the problem that Dr.
6 Trussell was talking to us about this morning. You get the
7 numbers and then you say, well, is this the same population
8 as our historical controls or not?

9 DR. PERLMUTTER: But can't you do some of that in
10 post-surveillance studies?

11 DR. LEVY: You are assuming that we are going to
12 get a number out that says it is relatively equivalent, but
13 what if you don't? You see, you don't know the outcome
14 until you do the study, and if you do the study and you put
15 the manufacturer through that design process and the number
16 you get isn't what you expected, then you don't know why.
17 You don't know if it is different because the device is
18 different, or if it is different because your study
19 population was different. Then you have to go back and
20 redesign and start all over again. So, I think it is
21 cleaner and actually easier for industry and for us to have
22 a control group and a shorter trial so that we will have
23 those answer before we start. I mean, the frustration of
24 doing that trial, getting information that we don't know
25 what to do with is burdensome for industry and it is

1 burdensome for us.

2 DR. DIAMOND: I would just like to echo Dr. Levy's
3 concerns and the need for a control group, and the
4 difficulty after the fact, trying to go back not only for
5 your own study group for retrospective review of articles in
6 the literature to try to get demographics to try to assess
7 how the study groups match up--the data may not even be
8 available in the public domain to be able to begin to
9 initiate that form of analysis.

10 DR. SHARTS-HOPKO: I would speak against the
11 control group requirement because I believe it is going to
12 self-select out very skewed samples. I think, if I take up
13 the study that you presented this morning, Dr. Trussell,
14 about the spermicides, I look at that compared to an 85
15 percent chance of pregnancy with no contraceptive effort in
16 a year. I look at that as a glass three-fourths full, as a
17 matter of fact. But I think if we are forcing people into a
18 condom control study you are going to end up, you know, with
19 graduate students or other highly motivated people that tell
20 you nothing about the real world.

21 DR. BLANCO: I think the point you are making
22 though is, in a way, the same thing that Dr. Levy and Dr.
23 Diamond are making, although you are arguing it the other
24 way. You are saying by trying to find a control group you
25 are going to find people who are not part of the population.

1 Whereas, what they are saying is you have to have people
2 that are out in the population to really know what your data
3 means.

4 DR. DIAMOND: Just one other comment perhaps from
5 a practical point of view. I sat on the panel two or three
6 years ago when we did review the Lea device. As I recall
7 that meeting, in principle many of us were very much in
8 favor of that product but just did not feel that we had
9 enough data that we could vote for approval. Without a good
10 control group, I would be afraid that some of the same
11 members who sat on that panel might have the same problem in
12 the future, or others who come from the same backgrounds,
13 and they were university as well as practitioners. They may
14 have the same concern in this era.

15 DR. BLANCO: Any more comments on that? I think
16 there is some division of opinion but, hopefully, the FDA
17 has got some idea of how different people on the panel
18 think. Any other comments on the issue of the control
19 group?

20 DR. KATZ: Just one. Actually, I would be
21 interested in what Dr. Trussell thinks about the notion of a
22 non-contraceptive control. I don't think you actually spoke
23 to that.

24 DR. TRUSSELL: The paper where this has actually
25 been done is in your green briefing books so you can read

1 it. It did have a design which is one that I would favor,
2 but it had three arms. There was a known device; there was
3 an unknown device--a known device being a condom; an unknown
4 device being spermicide; and no method. So, then you
5 answered both questions at once: How well does it work
6 compared to use of no method? How well does it work
7 compared to a method we think we know something about? Both
8 of those I would find--I would not favor it without three
9 arms.

10 DR. KATZ: I am sort of looking to pragmatism here
11 in terms of an ideal design versus the realities of what we
12 face. Let's say we are constrained to a two-arm design.

13 DR. TRUSSELL: Then I would still rather go with a
14 method that I knew rather than no method. I will tell you
15 why, because we don't have the information for any other
16 method compared to no method compared to no method. I mean,
17 we would need to build up some kind of knowledge about what
18 it meant.

19 DR. BLANCO: But from what I hear women want, if
20 you have a method, if I understand it right, and they know
21 that it is only 30 percent effective but they have control
22 over it, as they have that knowledge, that is what they are
23 looking for to see whether they want to use it. So, I don't
24 want to go back and reinvent the wheel and have to go
25 through new studies for every method, but it seems that the

1 question that needs to be asked is not how does the new
2 barrier compare to condoms, but how does it do in preventing
3 pregnancy, and then deciding, well, is that good enough for
4 me because I have control over it or because I like this
5 method or not?

6 DR. TRUSSELL: Let me put this issue to you then,
7 suppose that you found that this new device compared to
8 nothing reduced the risk of pregnancy by 60 percent, how
9 does that compare with any other contraceptive method? If
10 you are trying to decide among methods A, B, C and D and you
11 have no information except for this one, how is that going
12 to help you make a comparative choice?

13 DR. BLANCO: But I guess the way I would answer
14 that to you would be if we think maybe the question is what
15 should the method be against no method whatsoever, just
16 because every other study in the past 50 years didn't do
17 that, it doesn't mean that we ought to continue plodding
18 along the same way, finding the same data.

19 DR. TRUSSELL: That is fine but then how will we
20 give anybody comparative efficacy information as opposed to
21 absolute?

22 DR. JANIK: Also, I have concerns that if it is a
23 user-dependent instruction following method and you have no
24 real motivation to follow the method, except that you are in
25 the trial, you may be skewing the data to have a higher

1 failure rate than may be indicated in patients who are
2 trying to get pregnant. So, that is another problem I have
3 with it.

4 DR. SHARTS-HOPKO: My comment back to you, Dr.
5 Trussell, was going to be that if--I think we have to go
6 back to Dr. Gollub's presentation this morning. If in
7 reality condoms are highly effective and we have
8 effectiveness data about them, but in reality 75 percent of
9 the time condom-using couples aren't using the condom, how
10 in the world do you make a meaningful comparison about that?

11 DR. TRUSSELL: Well, I will give you the same
12 answer I gave this morning. If in that spermicide trial
13 there had been a condom arm, and the condom had had a
14 failure rate of about 25 percent as well, that would give
15 you an immensely different picture than if in that condom
16 arm the failure rate had been about 3 percent. You would
17 have vastly different amount of information under those two
18 scenarios.

19 DR. BLANCO: And if you had had an arm where no
20 one had used anything and you found that 85 percent of them
21 got pregnant, that tells me a lot too.

22 DR. TRUSSELL: It does, but it doesn't tell you
23 anything--I am just repeating myself--anything comparative.
24 It seems to me that the efficacy information that people
25 want is comparative efficacy information.

1 DR. BLANCO: Why?

2 DR. TRUSSELL: How does this work better than
3 this?

4 DR. LEVY: I don't care about comparative
5 information at all. If I am a woman making a choice I want
6 to know what are my chances of getting pregnant using this
7 device? That is what I want to know. I don't want to know
8 compared to some other device necessarily. The absolute
9 range for this particular device is really good information.

10 MS. PEARSON: I would just say the point that was
11 made earlier, that some women like some sorts of information
12 and some women like others. Some women do want that
13 comparison of if I am interested in a new barrier how does
14 it compare with diaphragm cap? But, unlike James, I think
15 the important comparison for vaginal barrier contraceptives
16 is other women control methods.

17 DR. BLANCO: One more comment and then maybe we
18 will move on to another couple of items.

19 DR. ROY: I think what we are here to help decide
20 is what would be required to be assured that this is safe
21 and effectiveness, not how it compares to anything else. I
22 think what James is saying we, as academicians, as
23 scientists, are fascinated by and would love to know. But
24 that is for Conrad, or NIH or someone else at some point to
25 find and to do, not for us at this point. So, I think the

1 issues about shortening the observation period, expanding
2 the numbers of individuals possibly, doing fewer
3 interventional assessments if we feel confident in the
4 safety and effectiveness would then lead us to enroll people
5 who come from various cohorts and, thereby, represent the
6 population and make it more robust, and get us to the
7 endpoint, which is, is it safe and effectiveness.

8 DR. BLANCO: All right, Dr. Trussell, one more
9 point and then we have to move on.

10 DR. TRUSSELL: I absolutely agree, Dr. Roy, if it
11 weren't for the problem that we then have to put something
12 in the label because then we have to say something about how
13 well does it work, not just that it works.

14 The other point is that the FDA has struggled now
15 for I don't know how many years to come up with uniform
16 labeling that goes across different contraceptives, and it
17 was thought at that point that there was value in having
18 comparative efficacy information that would be available in
19 every single product. Now, it so turns out that as far as
20 devices go, we can forget it. It is not on male condoms.
21 They won't put it in there. It is not in the diaphragm.
22 The only device which has the comparative efficacy
23 information in it is the Reality female condom.

24 DR. BLANCO: Let's move on. The last part of this
25 section talks about over-the-counter versus prescription.

1 Let's open that up again. There didn't seem to be a lot of
2 difference that people would thought would happen in
3 over-the-counter versus prescription. Are there issues of
4 effectiveness that you think are different in
5 over-the-counter than prescription? Cindy?

6 MS. PEARSON: I don't think there need to be any
7 differences in the pivotal trial, whatever that ends up
8 being, but there need to be some differences in the lead-up
9 studies. There need to be specific studies that ask women
10 to read instructions and put the device in and take it out
11 and report on it. Maybe that is something that has already
12 been said or is deep in your green books and we haven't seen
13 it, but I didn't see it here and I think women want that
14 assurance as well as just how effective did it turn out to
15 be in the trial.

16 DR. LEVY: I really agree with that. I think the
17 real issue for us, looking at devices that are intended for
18 OTC use, is that the trial design take that into
19 consideration and that the investigator is not prompting
20 women and teaching women how to use the device because that
21 is clearly not the kind of data we want. So, I think the
22 designs do have to be a little bit different in that for the
23 prescription device you have access to a healthcare provider
24 who is going to teach, in theory, the user how to use the
25 device. I think with an OTC we want to make absolutely sure

1 that our study design only permits use in the same way that
2 it will be used when it comes to market.

3 DR. BLANCO: All right, a lot of agreement on
4 that, it seems, from everyone. So, we will leave it at that
5 and move on.

6 What about the next section, which is premarket
7 versus postmarket analysis? Any thoughts? If we streamline
8 this process should there be some specific postmarket
9 analysis issues that need to go along with the streamlined
10 process?

11 DR. ROY: What would be the purpose?

12 DR. BLANCO: Well, you could look at whether it
13 gives you more ideas of efficacy, safety. That would be the
14 issue. Until a product gets widespread use I don't think
15 you get into those small percentage reactions. But that
16 would be the case in any product.

17 DR. PERLMUTTER: If you are going to go
18 over-the-counter you are going to have a lot of difficulty
19 in coming up with better efficacy figures because you are
20 not going to have any idea of how to calculate those
21 numbers. Are you doing to go by devices sold? Are you
22 going to go by actual usage? You are not going to have
23 those figures. Are you going to go by what occurs in an
24 abortion clinic? I mean, those are the kinds of numbers
25 that are going to be very difficult to come up with

1 post-surveillance if these all go over-the-counter.

2 DR. SHARTS-HOPKO: I would disagree. Federally
3 funded clinics dispense over-the-counter devices all the
4 time, and through those organizations which have financial
5 strings attached to the government you would be able to
6 collect data.

7 DR. PERLMUTTER: No, you would only know what has
8 been dispensed; you would not know what has been used, and
9 that is the difficulty with those numbers. You can go into
10 pharmacies and get the number of items that have been sold
11 but you have no idea what has been used.

12 DR. SHARTS-HOPKO: Well, then it becomes the issue
13 that is true in all data collection, that you are going to
14 have to rely on patient-reported data from those sites of
15 dispensation.

16 DR. DIAMOND: This may be the place to get
17 comparative type data.

18 DR. TRUSSELL: I don't think that you would get
19 data worth having if you didn't design a postmarketing
20 survey the same way that you design the clinical trials that
21 are now done for premarketing clearance. The only
22 difference would be that it was done after it was approved.
23 They are not going to cost any less. They are not going to
24 be any simpler if you really want to get the information
25 that stands up to modern standards of design. They may be

1 of great value in approving the product and then requiring
2 to do a study, or requiring somebody to do a study, but it
3 is not going to be any cheaper, any quicker or anything
4 else.

5 DR. CONNELL: I think that we have to look at this
6 from the point of view of getting things approved, and the
7 no colposcopy and 3-month business is very good I think. I
8 think the companies, if they are going to spend X amount of
9 dollars, they would rather get their product to the market
10 and then participate as one of the investigators in the
11 premarketing surveillance. I think this has been the
12 experience with some of the other products.

13 I remember when we did the female condom which,
14 incidentally I thought had a lot of instructional pictures,
15 we spent a lot of time talking about labeling issues and
16 communication of information, and rates and all of this
17 stuff. But the bottom line was at that time that NIH would
18 pick up the ball and do some additional work.

19 So, there are two avenues to postmarketing. The
20 sooner we can get this out--and you are not going to get
21 good data that early anyway, let the companies put an
22 equivalent amount of money into it and then just make their
23 commitment higher to the postmarket, and then recruit, as we
24 did then, other interested agencies to participate in
25 protocol design and follow-up to diversify where we get

1 data.

2 DR. BLANCO: I guess my view of premarket and
3 postmarket analysis is a little different. You know, I
4 think you have to have enough data in your premarket studies
5 to be able to answer the basic issues of effectiveness and,
6 to some extent, some core issues of safety. Going back
7 again to the example of super absorbent tampons, there may
8 be something that comes out once a million women use it.
9 You can't require a million women on a study for premarket
10 analysis. That is just going to have to happen afterwards.
11 But I think if you have already got the product to market,
12 it just would be very difficult to then, at that point, be
13 looking for efficacy data. That ought to be done before the
14 product ever hits the market. So, I would view it a little
15 differently. I wouldn't be looking for that much postmarket
16 analysis. I think we have to get enough data premarket to
17 feel comfortable that it has some level of effectiveness and
18 a core level of safety, and then the things we would be
19 looking for are the rare events--the woman who leaves it in
20 for a week and doesn't take it out. Hey, I have pulled
21 things out of women's vaginas that have been left there for
22 a week. So I know it happens.

23 DR. LEVY: It stinks.

24 DR. BLANCO: It stinks and causes erosion too.

25 Anybody else have any comments on the premarket-postmarket

1 issue? I guess we will close that discussion.

2 We can move on then to 2.c), should there be a
3 minimal acceptable level of efficacy which vaginal barrier
4 contraceptives need to meet before FDA approval? What
5 should that minimal level be? That is a loaded question.
6 Anybody want to tackle that one to start off with? No
7 takers?

8 I will give you my view. I don't know when I
9 started coming to these meetings--seven years ago or
10 whatever, I would have probably said absolutely. You have
11 to get a minimal number; there must be some magic number
12 that you have to have. Listening to the presentations more
13 and more, I think it is an issue of informing the consumer,
14 and it is an issue of it shows some benefit, and then
15 letting the consumer knowing what the benefit is. That will
16 rustle up some discussion. Go ahead.

17 DR. SHIRK: I guess this is sort of an editorial
18 comment about consumer information. I know some of the
19 panel go back far enough where I go to have a perspective of
20 where obstetrics and gynecology came from, and I understand
21 that there are two reasons why we use contraception. One is
22 social, to not get pregnant. The other is medical because
23 women have significant medical problems from getting
24 pregnant and one of the improvements in women's health care
25 has been through contraception. And, I don't think that the

1 general public understands this any more. Women in the
2 population don't believe that pregnancy can be a fatal
3 disease or a disease at all. So, I don't think that they
4 are informed that way.

5 So, I think that it is important that we put some
6 minimal standards on this thing as to what is efficacy, and
7 that we don't forget that there are two reasons why we are
8 using contraception. So, I think it is a very important
9 issue.

10 DR. BLANCO: So what number would you put?

11 [Laughter]

12 DR. SHIRK: I would say probably around 15
13 percent, which obviously excludes spermatocides.

14 DR. ROY: You would accept a failure rate over a
15 6-month period of only 15 percent to label a product
16 effective. I think that wipes out probably most barrier
17 contraceptives right off the bat.

18 DR. SHIRK: Well, somewhere in there, 15-20
19 percent. I don't know --

20 DR. ROY: Double it.

21 DR. SHIRK: Double it maybe but you have to have
22 some kind of reasonable ballpark figure where the rest of
23 the contraceptives are. We can't have a 50 percent failure
24 rate. Now you are back to where you aren't using anything
25 at all.

1 DR. BLANCO: So we agree 85 is not good --

2 [Laughter]

3 So, somewhere between 15 and 85; 15 is too good; 85
4 is not good enough. Anybody else have any comments?

5 DR. KATZ: What can we learn from other context at
6 FDA in terms of quantitative effectiveness? I mean, this
7 isn't the only part of the body where quantitative standards
8 exist. Suppose a new pill comes out for headaches, how is
9 that deemed effective?

10 DR. BLANCO: Let me go back to what Dr. Shirk said
11 for a minute. He said there are two reasons why women may
12 use contraceptives. You can assume that is right. There
13 are probably more but one is social--you don't want to get
14 pregnant, but if you get pregnant, okay, that is fine or you
15 may deal with that consequence in some way. The other one
16 is medical. I would venture to say that the medical--those
17 women are going to be much more involved with their
18 healthcare provider and are going to be looking at a variety
19 of other methods, not quite what we are talking about here.

20 I guess the point I am trying to make is, you
21 know, what if it is 50 percent? Let's say I don't have a
22 medical reason why I shouldn't be pregnant and I don't
23 particularly want to use birth control pills for whatever,
24 or the injection or whatever, and I am willing to accept
25 that I could get pregnant 50 percent of the time, or however

1 I want to lower that risk. Should we protect the public
2 from that because that method is 50 percent? It has some
3 efficacy, not 100 percent. I don't know what number but I
4 am just trying to stimulate a little discussion and see what
5 we are looking at here.

6 DR. PERLMUTTER: I can agree with whether you said
7 because, in fact, I think that as long as either we can
8 inform the consumers or the consumers can be informed
9 through the labeling what the pregnancy rate is according to
10 the trials that were done, that is their decision as to
11 where they want to take their chances. They may not want to
12 use the pill because of headache, strokes, heart attacks,
13 whatever. They may not want to use the IUD because of
14 infection, and they may decide that a 50 or 60 percent
15 pregnancy rate with a new device is acceptable to them. I
16 think that is their decision.

17 MS. YOUNG: Yes, and that information should be in
18 the patient labeling.

19 DR. LEVY: I really agree. I think the most key
20 issue here is how we present the information, not what the
21 information is, and we have to make absolutely sure that the
22 labeling is understandable by a wide range of people. It is
23 interesting, but when you look at data about what people
24 understand, they don't understand percentages very well at
25 all. In fact, when you look at cancer statistics, people

1 understand one out of ten better than they understand ten
2 percent. So, I think our job really should be guiding the
3 labeling in terms of some probably major changes in how we
4 present this information to the public, and not worry so
5 much about what the absolute number is.

6 DR. SHIRK: Isn't our job to somewhat protect the
7 consumer? We all understand relative risk. We deal with it
8 every day. But how many consumers out there--how many lay
9 people understand the concept of relative risk? Barbara
10 just pointed that out. They have no concept of what
11 relative risk is. So, I think that to a certain extent we
12 have a responsibility to it figure out so the consumer
13 understands what the relative risks are.

14 DR. PERLMUTTER: I don't think you necessarily
15 have to put it only in relative risk. You might want to do
16 it in percentage and relative risks. I think it is the way
17 it is presented, allowing the individual to make up their
18 own mind. I don't think we should be setting those limits.

19 DR. DIAMOND: I agree with your approach as well,
20 George. I think that in view of the variations of patient
21 populations that could be studied and the fact that we may
22 not even know a lot of those important demographics about
23 the patients that are being studied, to have any absolute
24 requirements as far as percentage would be extremely
25 artificial.

1 DR. BLANCO: We want to promote and advise some
2 protection for the public, but that doesn't mean that we
3 have all the answers as to what level of protection
4 everybody should have. You know, we can say, well, you can
5 only have a 20 percent failure rate or else you are not
6 going to go to market. That is being a little too
7 paternalistic for me. I think we need to make sure it is
8 safe, it has some level of effectiveness, and then the
9 labeling--and maybe we ought to go into labeling--needs to
10 be very important about how we convey that level of
11 effectiveness to the public.

12 MS. YOUNG: I think also that, again in the
13 patient labeling, that effectiveness needs to be explained
14 so that the woman knows what we are talking about here and
15 to what extent is it my responsibility as a person using
16 this method to make it effective or not. I think the woman
17 has to understand that with these barrier methods
18 particularly the success rate is very often dependent on how
19 she uses it.

20 DR. BLANCO: Let's go on to labeling. I think we
21 probably did the other one enough. Expound on that a little
22 bit in terms of what you mean in terms of effectiveness.
23 Are you talking about perfect use or typical use?

24 MS. YOUNG: All of those things, but that it is
25 woman controlled, and what does woman controlled mean. So,

1 it has to be very explicit, and I do emphasize I think that
2 the Reality patient insert was considerably better than the
3 other one that we had. The illustrations were much clearer
4 and the words that are used have to be really very, very
5 simple and straightforward. I think that with the changing
6 population in the United States and, you know, just looking
7 in the last ten years, fifteen years at how the populations
8 are changing in specific states, I mean, I don't know
9 whether these patient instructions, for example, are given
10 in Spanish. But if they are not, they should be. I think
11 that those things need to be considered by the companies in
12 terms of marketing.

13 The information that needs to be given does need
14 to be explicit in terms of how the device is inserted and,
15 once inserted, how to check that it has been inserted
16 correctly. I mentioned earlier that if it becomes
17 dislodged, how it could become dislodged and, if it becomes
18 dislodged what does the woman do then, and then finally the
19 instructions about proper removal, a course of the length of
20 time it can be used, that it remains effective when it is in
21 a woman's body. But the whole focus of it is that the woman
22 has control of this device. Therefore, she should be given
23 the maximum information pictorially and in instructions that
24 are understandable to her.

25 DR. SHARTS-HOPKO: This just occurred to me while

1 Diony was talking, I don't know if it is appropriate but
2 perhaps it is appropriate, along with what to do if a device
3 has become dislodged to plug emergency contraception if a
4 woman has reason to believe that she needs it.

5 The other thing that I was going to say is that I
6 would advocate a fourth or fifth grade reading level for
7 materials.

8 DR. BLANCO: Yes, I think the appropriate reading
9 level is very important. I don't know what exact grade
10 level but certainly low enough that everybody can understand
11 it. The other one, the post-coital contraception may be a
12 bit more controversial.

13 DR. CONNELL: It is a great idea but it won't fly.
14 Women don't understand relative risk, but they sure deal
15 with relative risk all day long--how to keep my kid from
16 falling down the stairs and breaking his neck; and this meat
17 looks a little bit bad, do I dare eat it? Relative risk is
18 something that women understand every hour of every day.
19 They don't call it relative risk but they certainly are
20 capable of understanding a comparative situation. I think
21 this is what relative risk using consumer language--it is
22 important to have this in labeling. I think that is the
23 bottom line of what we have all been saying.

24 MS. PEARSON: I think one recommendation that gets
25 made sometimes but not always that we would like to see be

1 consistent is that sponsors do some minimal testing of the
2 patient instructions, whether it be handed out with the
3 prescription device or included over-the-counter. Given
4 that Diony made the point that so much of the effectiveness
5 depends on the women's understanding and ability to use it,
6 I don't think there should be much less at all in a
7 prescription patient handout than an OTC patient handout.
8 They really should be similar in having all the necessary
9 instructions and information, and also having been tested.

10 DR. KATZ: I want to second what Cindy said, and
11 actually ask you, a point that came up at the SRM meeting
12 last week was precisely--well, it related in general to a
13 woman's wants in this area, but specifically here do we have
14 objective cohort information on what sorts of language and
15 pictures are most appropriate? It seems to me that this
16 wouldn't be that hard to get. I wonder whether
17 organizations like yours have any such information.

18 MS. PEARSON: This is one place where my heart
19 just aches for the manufacturers because this is not a white
20 bread country any more, and there is no one cohort that will
21 ever answer anywhere near all the questions that need to be
22 answered. So, we absolutely support getting to a low
23 reading level, getting a lot of pictures in there, having
24 automatic translation to Spanish, but when it goes beyond
25 that it gets harder and harder. There are different

1 dialects spoken in different parts of the country, not to
2 mention all the other languages that are less common. At
3 some point it really gets down to the clinic and community
4 level where they take the basic information and adapted for
5 their community for the women who are coming to their
6 clinic, you know, inner city culture with unique slang. So,
7 it is just tough. I mean, we should get more information
8 about what the average woman prefers in the groups which are
9 common enough to be average, but it won't answer all the
10 questions.

11 MS. YOUNG: I can answer that somewhat. The World
12 Health Organization has many instructional leaflets on
13 reproductive health issues, including use of contraceptives
14 and so on, and a lot of those--in fact, many of the are
15 almost totally pictorial, but certainly the World Health
16 Organization informational material should be examined in
17 this particular area.

18 DR. LEVY: I think as long as we are contemplating
19 controversial things in the new millennium, we had best
20 really take a look at how people learn. In the next
21 generation of people it is not going to be printed word in a
22 printed label and we should begin to look at video sequences
23 because I think they are actually much more instructive, and
24 I am not talking about, you know, a very difficult to
25 produce thing, I am just saying that most of the population

1 has access to a VCR. I just think we need to be looking a
2 little bit more creatively, and if what we are really
3 looking at is a way to get information across, the printed
4 word is probably not the way.

5 MS. DOMECUS: I just want to go back to the
6 suggestion about emergency contraception. I thought it was
7 a good one. Emergency contraception has been approved by
8 the FDA. It is not abortion, and if the goal here is
9 pregnancy prevention, why don't we put in the labeling what
10 a patient should do next if she believes that it broke or
11 was dislodged, or whatever? I think it was a good
12 suggestion.

13 DR. BLANCO: I don't think anyone disagrees with
14 you that it is a good suggestion. I think it goes a little
15 beyond what a manufacturer may want to do, and I guess it is
16 somewhat more controversial, although we are talking about
17 contraception as you mentioned. I guess I would hate to
18 make the suggestion of that as a requirement. I mean, I
19 think maybe if somebody wants to do that, or if you want to
20 put it in the product information that there are other
21 options if this product fails, or something--I don't know.
22 Help me out here.

23 DR. SHARTS-HOPKO: I need to extend my comment and
24 say when I reread the Reality instructions I thought it was
25 ludicrous that the instruction says when you notice the

1 device is dislodged stop what you are doing.

2 [Laughter]

3 They are not going to notice until afterwards.
4 Probably nobody is going to stop what they are doing if they
5 do notice. I mean, it is crazy.

6 MS. DOMECUS: Actually, I wasn't suggesting that
7 it be a requirement because even FDA's uniform contraception
8 labeling isn't a requirement either; it is a suggestion to
9 manufacturers. So, I think it should be offered as another
10 suggestion if we are really trying to address a public
11 health issue.

12 MS. YOUNG: I will get back to personal
13 experience. My cervical cap became dislodged, and I
14 thought, "yikes, what do I do now?" And, I wasn't quite
15 sure whether I should put a whole lot of spermicide jelly
16 into it, shove it back on--I mean, I didn't know. This was
17 a long time ago but, I mean, I am talking about something as
18 basic as that. You know, I felt it in my vagina afterwards
19 and really wasn't quite sure about whether I should take it
20 all the way out and, as I say, put some jelly and put it
21 back on again, or what I should do.

22 DR. BLANCO: So, you are suggesting that maybe it
23 is a good idea to put some options --

24 MS. YOUNG: Yes, I said that earlier. Yes, right.

25 DR. BLANCO: All right.

1 DR. ROY: The manufacturers will, and should, take
2 that into account but their legal departments will probably
3 dictate whether they will include it or not because of the
4 obvious repercussions.

5 DR. BLANCO: Any other comments?

6 DR. CONNELL: I would like to suggest that if
7 there is a healthcare provider in the scenario I would hope
8 that emergency contraception would be listed. On the other
9 hand, I think to saddle a process that we are trying to move
10 forward quickly with something which would raise all kinds
11 of hassles is not in our best interest.

12 DR. BLANCO: All right. We have sort of discussed
13 most of the questions on labeling. Are there any other
14 issues? We addressed the issue of over-the-counter versus
15 prescription and estimates or ranges of effectiveness. I
16 think you had a comment, Dr. Connell.

17 DR. CONNELL: I hate to bring this up but do we
18 have to have an STD disclaimer on this, like everybody else,
19 since we are not talking about STDs today? Is there a need
20 from the FDA's point of view because we put labeling
21 disclaimers on all kinds of things? Will it be necessary?
22 I don't know the answer.

23 DR. CONNELL: I am just raising this as an issue,
24 as to whether an STD disclaimer would be demanded,
25 warranted, indicated, whatever.

1 DR. BLANCO: You certainly couldn't make the claim
2 that it prevented STDs unless you brought forth data. There
3 is a lot of silence around that room. That is unusual.

4 DR. KATZ: I just wanted to follow up on Subi's
5 comment regarding--if no one has a response on the STD
6 question.

7 DR. BLANCO: There is a lot of conferencing over
8 there.

9 DR. SCHULTZ: Did you have a comment?

10 MS. PEARSON: No; we are waiting for you.

11 DR. SCHULTZ: My understanding is that it is not
12 required at this particular time. But I think, certainly,
13 if the panel wanted to make a recommendation that some type
14 of statement regarding either the presence of positive
15 information or the absence of information should be required
16 or strongly suggested in labeling, that that is something
17 that we would certainly take under advisement.

18 MS. PEARSON: From the consumer perspective, you
19 saw I couldn't even give the formal comments without talking
20 about STDs because women associate barrier contraceptives
21 with protection against disease.

22 If it could be so finely crafted, as he has just
23 said, that, on some methods, it would say, accurately,
24 "there is no evidence at all whether or not this device
25 protects against STDs." Then, on some other methods, it

1 could say, "There is some evidence that indicates." But
2 didn't we go down that path three years ago and spend three
3 days straight here and couldn't come up with what that
4 finely crafted sentence would be?

5 So, in the absence of being able to finely craft
6 it, I think it might be better just to leave it blank in all
7 these barrier contraceptives.

8 MS. DOMECUS: But I think FDA's current guidelines
9 do have suggested wording for the different categories of
10 barrier devices, for the male condom, the female condom and
11 diaphragm and cervical caps. So there is suggestion on how
12 strongly you can word the STD prevention or lack thereof.

13 DR. BLANCO: Any other comments on the STD issue?
14 Dr. Katz?

15 DR. KATZ: I just wanted to return to the
16 dislodgement issue because presumably this is a factor in
17 the effectiveness and lack thereof of these methods. I think
18 you were saying that it is a legal quagmire to include
19 suggestions on the label of what to do you if you discover
20 that the device has become dislodged.

21 DR. ROY: If you have a device and you mention a
22 drug, then, to what extent, do you incur the liabilities
23 that may be construed by some to be associated by the use of
24 that drug. That was what I was referring to.

25 DR. KATZ: Let's suppose we eliminate emergency

1 contraception, per se, and just talk about Diony's question
2 which is, "What do I do?"

3 DR. BLANCO: Before you do that one, I think you
4 could word the emergency contraception in a way that you
5 wouldn't take on the drug. I think you might word it
6 somewhat like this, to say, "if the method is not used
7 appropriately or the barrier was dislodged, you may not be
8 protected from pregnancy and you may want to seek medical
9 attention for possible pregnancy prevention."

10 DR. LEVY: Within twenty-four hours.

11 DR. BLANCO: Thank you; within twenty-four hours.

12 DR. PERLMUTTER: And not at 3:00 in the morning.

13 DR. BLANCO: I won't go that specific, but
14 something to that effect. I don't think there would be a
15 lot of legal problems with that kind of issue.

16 MS. DOMECUS: I don't think you have to
17 necessarily mention a specific drug. You could just say,
18 "Contact your local physician for information about
19 emergency contraception."

20 MS. YOUNG: I need the information much earlier
21 than that.

22 DR. BLANCO: No, no; now we are going to back to
23 the other issue, what do you do with--

24 MS. YOUNG: Oh; we are going back to dislodgement.
25 What to do? What happens if it becomes dislodged, right

1 now.

2 DR. BLANCO: Now we are going to that.

3 DR. KATZ: I can tell you that, biologically, the
4 damage is likely to be done in the sense that we know that
5 sperm enter the cervix pretty quickly after ejaculation. My
6 personal view would be get a soluble spermicidal material
7 into your fornix and, preferably, on your os as quickly as
8 you can.

9 But it is too late. That is the point. But the
10 point is that you are splitting hairs because it is probably
11 too late.

12 DR. BLANCO: Not only that. Do we have any proof
13 that that works?

14 DR. KATZ: No. What I am saying is we don't. We
15 have very limited knowledge of the time interval during
16 which the fertilizing sperm enter the cervix. All we know
17 is they enter the cervix as quickly as we can possibly look
18 for it which is 90 seconds.

19 DR. BLANCO: To me, quite frankly, I am not so
20 sure what I would put in there other than I would be
21 concerned about trauma or those kinds of issues because, in
22 terms of pregnancy, I think you would have to look at the
23 individual device.

24 We have got one device that, if it works by
25 preventing contact with sperm going up--it has got a hole in

1 it. So we don't know how these things work.

2 DR. KATZ: We can't generalize.

3 DR. BLANCO: From a pregnancy prevention point of
4 view, I think all you can say is, "Go see a healthcare
5 professional to do something about reducing your chances or
6 getting pregnant."

7 DR. KATZ: That's right. That is the sort of
8 thing that even the product reps could be mindful of when
9 they are selling their product.

10 DR. BLANCO: I thought where you were going was
11 something to do with trauma if you continue with this or
12 somewhere in that ballpark. But I think they would probably
13 figure it out and stop. That might cause them to stop.

14 I am glad everybody is having such a good time.
15 Always glad to put on a good show.

16 Any other issues? Anything else the FDA would
17 like for us to discuss? We have a little bit of time left
18 over and we seem to have gone through all the questions.

19 MS. PEARSON: Could you ask the FDA to talk about
20 their time line for the follow up. Dr. Connell opened up
21 with how nice it is that there is consensus. I agree. But
22 we had a similar meeting in 1990 with a lot of consensus and
23 a guideline that followed, and it didn't really move things
24 forward super-quickly. So maybe you could ask them, they
25 who are sitting so quietly, what kind of time line we might

1 be looking at.

2 DR. BLANCO: Does anyone care to address that
3 issue?

4 MS. YOUNG: What would hold things up?

5 DR. SCHULTZ: What would hold things up in terms
6 of coming out with a new guideline? I think, basically,
7 what we need to do, after this meeting, is go back and
8 analyze what you have said to us today and, hopefully, come
9 away with some fairly clear directives.

10 I think I would sort of put it back that the
11 extent to which the recommendations are clear and allow us
12 to make some meaningful changes is the extent to which the
13 time with the process is going to take.

14 I think, obviously, the fact that we are holding
15 this meeting means that we are committed to making those
16 kinds of changes that are reasonable and that are in the
17 public health. We are going to do it as quickly as we
18 possibly can.

19 DR. BLANCO: I think we need to remember that the
20 idea is not we are, all of a sudden, not going to be very
21 stringent or not use good science in how we are evaluating
22 products brought before the FDA.

23 I think the issue has been one of let's come
24 together with a specific detailed plan that, when fulfilled,
25 will hop through all the different hoops that it needs to go

1 through without someone putting in and saying, "Oh; wait a
2 minute. I want to see this other data. Go back and do
3 another study."

4 I think that is where the FDA is going. It is not
5 that we want to not be any less stringent. We just want to
6 make sure industry knows what the requirements would be and,
7 if they meet those requirements, that the process should be
8 smooth.

9 Am I overstating what the feeling is?

10 MR. POLLARD: No. I think you are stating it
11 well. I guess the one thing I would add, as I mentioned at
12 the end of my opening remarks, is that there is nothing that
13 prevents a sponsor from approaching FDA today and saying,
14 "Hey; I heard a lot of good discussion at the panel meeting.
15 Here is the plan I am talking about."

16 So a lot of this, really--we can put together what
17 you all are calling a consensus--actually, I heard a lot of
18 different ideas. Putting that into a guidance document may
19 be a bit of work. I think we can do that, but I think the
20 real rubber hitting the road is going to be when sponsors
21 look at what is going on and say, "That is attractive to me.
22 I am going to come to FDA with my plan and we are going to
23 talk," and actually put pen on paper and get it down.

24 We are encouraging companies to do that. I think
25 that is my last point.

1 DR. BLANCO: I would encourage companies to make
2 highly effective products that women can control.

3 MS. YOUNG: I have a question. How do you
4 encourage companies to get onto marketing something or doing
5 something or starting something? You said that you are
6 encouraging companies. How do you do that? How can the
7 results of today's meeting be got out quickly to the
8 companies that might be interested?

9 DR. SCHULTZ: First of all, let me just say that I
10 think the fact that we are having this meeting to begin
11 with, I would dare say that there are a fair number of
12 representatives that are here right now and that the word
13 will get out, both through the industry press and through
14 the lay press, as well, that, in fact, FDA is holding a
15 meeting, that we are interested in looking at new ideas for
16 barrier-contraceptive devices.

17 I think you are absolutely right. We can't change
18 the economics. We can't change the fact that there is
19 a--whatever the market share was--2 percent or whatever, in
20 terms of the earnings potential. But what we can say and,
21 hopefully, what this meeting has said loud and clear is the
22 fact that we have been using certain guidelines over the
23 last few years.

24 We think that, based on the information that we
25 have today in 1999, it is, perhaps, time to rethink what we

1 have required or asked of manufacturers in the past, that,
2 number one, we are going to be preparing a new set of
3 guidelines for distribution.

4 But I think, as Colin said, and I think the point
5 needs to be reemphasized that, as of today or tomorrow, if
6 someone were to come in and say, "I heard about your
7 meeting. You used to require a year's study. We are
8 hearing that maybe a three-month study is okay. We have a
9 good design, not just a three-month study. We have what we
10 believe is a design that, based on a three-month study that
11 will provide you with the valid scientific evidence you need
12 to show safety and effectiveness, that we would be willing
13 and receptive to look at that, as of tomorrow."

14 So I guess that is about as quick as you can get.

15 DR. BLANCO: Diony, I would tell you, and I would
16 do this also as a challenge to many of the women's groups
17 who presented, I think one of the things that manufacturers
18 want to look at is something that is bigger than 1.2 percent
19 of the market.

20 If somebody went out there and did a study and
21 said, "If I had a barrier product that did this, and did
22 this and did this," and showed that 10 percent or 15 percent
23 of American women would use it, I think there would be a lot
24 of manufacturers knocking of FDA's door to get some products
25 approved.

1 DR. ROY: Could I turn things around just a little
2 bit. I think what we have been discussing is one part of
3 the issue. The other part is compounds and devices that,
4 perhaps, had been attempted in years past but, for whatever
5 reason, were sort of put on the back burner and never taken
6 forward, is there any way that that information, which may
7 still be in the archives or someplace, be made available as
8 a source of information so that we could re-look some of
9 things.

10 The reason I bring this up is twenty-five years
11 ago, or something, I was working with Dan Michel in the
12 Population Council. We studied all kinds of different
13 suppositories and things. Some of them produced reactions
14 which caused us not to go forward but I bet if we re-looked
15 some of those compounds at certain concentrations or
16 different ways of delivery, that, perhaps, that would be
17 another whole pool of information that could be culled to
18 possible develop new products.

19 DR. BLANCO: Again, the impetus for that, though,
20 has to come from industry to generate those--

21 DR. ROY: Well, I know that. But if industry
22 doesn't even know about it--why is it that FDA would
23 necessarily, absent some legal prohibition, if time has gone
24 past and it is able to be made available through freedom of
25 information, can that be asked of FDA?

1 DR. KATZ: I would argue, if we are distinguishing
2 devices from delivery systems, I think industry does know a
3 fair amount about that. There is a lot of work now on new
4 bioactive molecules, microbicides, for example, not so much
5 work on their delivery systems.

6 But my sense is that industry knows what is known
7 and is starting to 'fess up to what is not known.

8 DR. BLANCO: I think that is a good statement to
9 end on. We will begin the afternoon session, for those of
10 you who are here, promptly at 1:30.

11 [Whereupon, at 12:30 p.m., the proceedings were
12 recessed to be resumed at 1:30 p.m.]

A F T E R N O O N S E S S I O N

[1:30 p.m.]

DR. BLANCO: Let's go ahead and call the meeting to order. I want to remind everyone that there is a sign-in sheet in the back, if you would please sign in so that we have an accurate idea of who was here for the meeting.

Let me remind the audience that you must be recognized by the chair. We will have a chance for the public to speak. We want you to come forward and use the microphone. After stating your name, if you would please give out any disclosure of any conflict of interest including any involvement with any of the companies that might have business before the FDA, including any travel, per diem or any other relationship with any of the companies.

As we did this morning, we have some different panel members and we would like to go ahead and have introductions from that panel. If we could go ahead and start from this side, if everyone would state their name and their affiliation.

MS. DOMECUS: Cindy Domecus, Senior Vice President of Clinical Research, Regulatory Affairs and Quality Assurance for Conceptus. I am the industry representative on the panel.

MS. YOUNG: Diony Young, Editor of the Birth

1 Journal. I am the consumer representative on the panel.

2 DR. ROY: Subir Roy, Professor, OB-GYN, USC School
3 of Medicine.

4 DR. PERLMUTTER: Johanna Perlmutter, Assistant
5 Professor, OB-GYN at Harvard. I am on the staff of Beth
6 Israel Deaconess Hospital in Boston.

7 DR. KATZ: David Katz, Professor, Biomedical
8 Engineering and Obstetrics and Gynecology, Duke University.

9 DR. HARVEY: Elisa Harvey in the Obstetrics and
10 Gynecology Devices Branch. I am the executive secretary for
11 the panel.

12 DR. BLANCO: Jorge "George" Blanco. I am a
13 Professor at the University of Florida, Department of
14 OB-GYN.

15 DR. LEVY: Barbara Levy, a practicing gynecologist
16 and Assistant Clinical Professor of Obstetrics and
17 Gynecology at the University of Washington in Seattle and
18 Yale University.

19 DR. DIAMOND: Michael Diamond, Professor of
20 Obstetrics and Gynecology, Wayne State University, Detroit,
21 Michigan.

22 DR. JANIK: Grace Janik, Reproductive
23 Endocrinologist, Medical College of Wisconsin, Associate
24 Clinical Professor.

25 DR. SHIRK: Gerald Shirk. I am a practicing

1 gynecologist and a Clinical Associate Professor, University
2 of Iowa.

3 DR. SHARTS-HOPKO: Nancy Sharts-Hopko, Professor
4 of Women's Health, College of Nursing, Villanova University.
5 I am the nurse rep on the panel.

6 DR. SCHULTZ: I am Dan Schultz. I am the Acting
7 Director of the Division of Reproductive, Abdominal and
8 Radiological Devices. I am still here representing FDA.

9 DR. PENTECOST: I am Mike Pentecost. I am
10 Professor and Chairman of Radiology at Georgetown.

11 DR. ROBERTS: Anne Roberts, Professor of Radiology
12 and Chief of Vascular and Interventional Radiology at UCSD.

13 DR. HARVEY: There are a couple of other
14 announcements. The FDA press contact for this afternoon is
15 Dr. Schultz. We do have a real full agenda so we will want
16 to try and keep comments as brief and concise as possible.

17 If you would like transcripts or videos, you can
18 get flyers at the back for those. Any presenters to the
19 panel who have not done so should provide a copy to FDA of
20 their remarks including overheads. Mike will take those if
21 you have those for us.

22 I want to just announce again the dates for the
23 Year 2000 for this panel that we decided on this morning.
24 They are all Monday and Tuesday dates; January 24 and 25,
25 April 10 and 11, July 24 and 25 and October 9 and 10.

1 I also just want to direct the panel to their
2 folder contents. They should have copies of the
3 presentations that are going to be given by Dr. Mitchell,
4 Dr. Vogelzang and several of the open public hearing
5 participants.

6 **Study Requirements for Devices**

7 **Used to Treat Uterine Fibroids**

8 DR. BLANCO: We will have Dr. Diane Mitchell, now,
9 medical officer from the Obstetrics and Gynecology Devices
10 Branch, Office of Device Evaluation, make some introductory
11 comments about the topic for this afternoon.

12 **Introductory Comments**

13 DR. MITCHELL: Good afternoon, ladies and
14 gentlemen of the panel.

15 [Slide.]

16 This afternoon, our topic is nonextirpated methods
17 of fibroid treatment. Specifically, we will be listening to
18 you discuss the appropriate study design for these types of
19 procedures. Our goal is to use this discussion, additional
20 research and ongoing conversations with interested groups to
21 develop a guidance document for these studies.

22 But, first, I hope to give you a brief
23 introduction to the issue and its implications in the United
24 States.

25 [Slide.]

1 Each year, in the United States, there are 175,000
2 hysterectomies. Approximately one-third of the
3 hysterectomies and 17,000 myomectomies are performed for
4 fibroids. Hysterectomies are done on women who have
5 completed childbearing and myomectomies are done primarily
6 on women who are still interested in childbearing.

7 Laparoscopic and hysteroscopic myomectomies are
8 also performed. However, these techniques are often
9 reserved for pedunculated or submucosal leiomyomas. The
10 majority of fibroids do not fit into these categories and,
11 therefore, most women undergoing surgery for fibroids have
12 open procedures.

13 This means that the hospital stay and recovery are
14 long and the risks of hemorrhage, infection and death are
15 real.

16 [Slide.]

17 Fibroids are benign, smooth-muscle tumors that
18 arise from the uterine myometria. Approximately 50 percent
19 of women at their death have fibroids. They can occur in
20 any age group. However, they are most common after the
21 middle age. They are also more common in some races than
22 others. Fibroids can grow very large in size and women can
23 have single or multiple fibroids.

24 Fibroids are responsive to hormones and have been
25 known to shrink at menopause and increase in size under the

1 stimulation of pregnancy, oral contraceptives or
2 post-menopausal hormone-replacement therapy.

3 [Slide.]

4 In general, the core of a fibroid has outgrown its
5 blood supply and the center of the fibroid is hypovascular
6 and hyalinized. This is particularly true in large
7 fibroids. The periphery of the fibroid contains the blood
8 supply. The arterial supply consists of one or two feeder
9 vessels. The venous supply is rich and anastomotic.

10 Overall, when comparing the blood flow of a normal
11 uterus to a myomatous uterus, the supply is greater in the
12 myomatous uterus but, in reality, the blood flow per volume
13 is actually less.

14 [Slide.]

15 The majority of fibroids are asymptomatic. Only
16 20 to 30 percent of fibroids actually cause symptoms. The
17 symptoms fibroids cause include pain, heavy and irregular
18 menstrual bleeding, pressure and pressure symptoms such as
19 incontinence, and occasionally infertility.

20 Rarely, fibroids degenerate into cancer.
21 Sarcomatous change only in about 0.3 to 0.7 percent of
22 fibroids.

23 [Slide.]

24 Currently, the medical literature recommends the
25 removal of fibroids when they cause symptoms. The diagnosis

1 of the fibroid as the cause of symptom is one of exclusion
2 since they can also be present and asymptomatic. In the
3 not-too-distant past, removal of a fibroid uterus was also
4 recommended if it got beyond a certain size, usually
5 14 weeks gestation.

6 The rationale for this was that the enlarged
7 uterus would obscure the palpation of the ovaries at the
8 time of the annual examination. With our current imaging
9 techniques, this logic is not as popular as it once was.

10 When performing myomectomy, there is a risk of
11 recurrence. The amount of recurrence is varied. More
12 recent literature reports recurrence rates up to 61 percent
13 is which is much higher than previously believed. The
14 increase is felt to be because of better imaging techniques
15 to detect fibroids.

16 The reoperative rate for recurrent fibroids has
17 been reported to be around 6.8 percent. Of note, most
18 recurrences occurred more than three years after the initial
19 procedure.

20 Within the last twenty years, several other
21 alternatives have become available. GnRH agonists can be
22 used to treat fibroids. They cause the fibroids to shrink
23 by creating an artificial menopause and, so, reducing the
24 hormonal supply to the fibroid. When add-back hormonal
25 replacement therapy is added, the patient can continue on

1 the regimen for a prolonged period of time.

2 In addition, other technologies have been adapted
3 to treat fibroids. The phrase myolysis has been used to
4 describe these techniques. They can be done through the
5 laparoscope or hysteroscope. This greatly reduces patient
6 hospital stays.

7 ND ag, KTP ag, and diode lasers have been used to
8 destroy fibroids without actually removing them. Bipolar
9 cautery needles can also be used to treat uterine fibroids
10 through the laparoscope. Follow up lasting not more than
11 three years for these treatment modalities has shown a
12 reduction in fibroid size as well as an improvement in
13 symptoms with no recurrences noted.

14 The adverse events, and, again, this depends on
15 the technology, have included hemorrhage, leiomyoma,
16 degeneration and pain, pelvic abscess, bacteremia and severe
17 post-operative adhesive disease.

18 More recently, the use of freezing temperatures is
19 being proposed as a treatment for uterine fibroids. This
20 technique, known as cryomyolysis, also has promising early
21 results. The most obvious advantage is that fewer puncture
22 sites are needed to freeze the entire fibroid. This should
23 reduce the incidence of adhesive disease seen caused by some
24 of the other technologies.

25 Another recent technique--well, it is an old

1 technique but recently available--is uterine-artery
2 embolization. This technique is different for many reasons.
3 First, the procedure involves embolizing the uterine
4 arteries bilaterally.

5 This means that the entire uterus could be
6 subjected to the there and not just the fibroids. Secondly,
7 the complications are different, or some of them are
8 different. The most obvious one is premature menopause
9 secondary to unintentional embolization of the ovaries.

10 [Slide.]

11 Our goal today is to begin the process of
12 developing a guidance to industry as to how to conduct
13 studies that will lead to approval of these varying
14 technologies for the treatment of fibroids. To do that, we
15 will listen to a discussion from the panel about various
16 aspects of clinical studies for these devices.

17 The remainder of my talk will highlight the points
18 to consider when designing a study for nonextirpated methods
19 of fibroid treatment.

20 One of the issues is whether or not studies should
21 have an active control. We have heard concerns voiced that
22 women will not want to enter studies if their choices are by
23 surgery and no surgery. This would make recruitment
24 extremely difficult.

25 If we do opt for actively controlled studies, then

1 we should consider whether or not we should allow for
2 self-selection in the study. In addition, we need to decide
3 what type of treatment for fibroids would be the best one
4 for our control group.

5 Advantages to using hysterectomy include the fact
6 that it is currently the most common method of treatment for
7 fibroids. A significant disadvantage is that it may be
8 difficult to get patients to agree to randomization.

9 Another option is myomectomy. This would leave
10 the uterus intact as with these newer procedures.
11 Unfortunately, it is not the most common method of treating
12 fibroids. In some circles, it is felt that it is a more
13 morbid procedure and, again, it may be difficult to get
14 patients to agree to being randomized.

15 GnRH-agonist therapy could also be used as a
16 control group. The advantages are that it does not require
17 surgery so patients may be more willing to enter the study
18 and be randomized. The disadvantages are that, because it
19 is only a temporizing measure, patients may not be willing
20 to be randomized. It is not traditional therapy for
21 fibroids and it may also be required as a pretreatment of
22 patients who undergo nonextirpated methods of fibroid
23 destruction.

24 There may be other options as well.

25 [Slide.]

1 The next point we will ask the panel to consider
2 is the study objective; what, exactly, should be measured in
3 order to determine that the use of the device in treating
4 fibroids has been a success.

5 Clinical endpoints are measurements of the signs
6 and symptoms a patient has that cause her to visit the
7 doctor. By measuring clinical endpoints, we would know that
8 the procedure actually eliminated or reduced the signs and
9 symptoms the patient had.

10 The difficulty with clinical endpoints is that
11 they are often difficult to quantitate. The measurable
12 clinical endpoints from the treatment of fibroids are:
13 bleeding, which is quantifiable; pain, which is a subjective
14 evaluation; and pressure and its symptoms. There may be
15 other as well.

16 Surrogate endpoints are endpoints that are easily
17 quantifiable and easy to measure but do not directly report
18 on the condition of the patient. Once surrogate endpoint
19 for nonextirpative methods of treating uterine fibroids
20 would be reduction in fibroid or uterine size. The problem
21 is that this reduction in fibroid or uterine size is not
22 well wedded to clinical endpoints since, in the past, the
23 fibroids have been removed.

24 Other objectives for a study might have to do with
25 the training required of the physician prior to beginning

1 the procedure. Should the training be well-thought-out and
2 proven successful before the device is marketed for fibroid
3 treatment? Finally, we are open to any other suggestions or
4 comments about objectives.

5 [Slide.]

6 Appropriate exclusion and inclusion criteria is
7 another area we are looking for guidance on. Important
8 issues include the women's interest in childbearing, what
9 type of prior treatment and evaluation the patient has had,
10 the size and the number of fibroids present, the menopausal
11 status of a patient, the presence of adenomyosis, can we
12 truly diagnose this with MRI and should we ask the
13 investigators to do this, and the presence of cancer or
14 infection.

15 [Slide.]

16 The final issue we will ask you to consider is the
17 duration of the study. There will be short-range issues
18 such as infection and post-operative pain, but there will
19 also be long-term issues such as recurrence, pregnancy and
20 cancer. Some of these questions can be answered during
21 postmarket surveillance while others should be well
22 understood before the devices are approved.

23 This concludes my presentation. I just want to
24 take a minute in advance to thank the panel for all the hard
25 work they are about to do.

1 DR. BLANCO: Thank you, Dr. Mitchell.

2 **Open Public Hearing**

3 It is now time to start the open public hearing.
4 Let me remind the speakers to identify themselves and any
5 possible conflict of interest. Also, let's try to keep it
6 as brief as possible. We normally give five minutes per
7 speaker, but we have more speakers than the time allotted.
8 So if you could make it a little less than that, we would
9 all be appreciative.

10 The first speaker is Patricia Cole, Yale
11 University Society of Cardiovascular and Interventional
12 Radiology.

13 DR. COLE: Thank you. I have no conflicts of
14 interest. I am going to using some overheads.

15 [Slide.]

16 The Society of Cardiovascular and Interventional
17 Radiology has pursued a multifaceted approach to activities
18 involving uterine-artery embolization. These include
19 research initiatives, education, standards development and
20 public information.

21 [Slide.]

22 In terms of research initiatives, a grant from the
23 Serif Foundation, which is our research foundation, funded a
24 multidisciplinary expert panel which was run by RAND Health.
25 This was for a research development meeting. This panel

1 identified key outcome measures in studying the treatment of
2 uterine fibroids. The Delphi process was used for
3 identifying those outcome measures.

4 The multiexpert panel came up with four
5 recommendations. They recommended a prospective registry.
6 They recommended development of a disease-specific
7 quality-of-life instrument for treatment of uterine fibroids
8 and a randomized controlled trial with other trial designs
9 as well, with uterine-artery embolization being compared
10 with surgical methods.

11 They also recommended a cost study.

12 [Slide.]

13 In terms of the research that the society, itself,
14 has been doing, an SCVIR registry, prospective registry, is
15 currently under development and design. The implementation
16 of that registry should start in the first quarter of 2000.
17 The registry is meant to capture adverse events and follow
18 up going out to five years using, obviously, both the
19 short-term follow-up issues and long-term follow-up issues,
20 in particular those delineated from the critical issues
21 identified at the RAND meeting and a quality-of-life
22 instrument will also be used for that.

23 [Slide.]

24 In addition to that, there are member-initiated
25 research programs that are started and ongoing. There is

1 now a nationally funded prospective, multicenter study to
2 develop and validate disease-specific quality-of-life
3 instrument for uterine fibroids treatments, not just
4 uterine-artery embolization but all treatments, a general
5 quality-of-life instrument.

6 There is an NIH grant that will be resubmitted for
7 a multicenter randomized controlled trial comparing UAE to
8 surgical therapies. This was initially submitted for UAE
9 versus drug therapy and NIH requested resubmission with
10 surgical therapies.

11 [Slide.]

12 In terms of education and standards, we have in
13 place reporting standards, a reporting standards body and a
14 standards-of-practice body. Standards are being developed
15 for uterine-fibroid embolization. Educationally, we are
16 holding a national conference on uterine-artery embolization
17 that will be held in about two weeks at Tysons Corners. We
18 have symposia at our annual meeting on uterine-artery
19 embolization and we also have a web page which provides the
20 current state of information and literature references.

21 [Slide.]

22 In the public-information forum, the SCVIR has
23 issued a policy statement which has been made available to
24 members of the panel indicating the status of the procedure
25 as we see it. There is also information available on our

1 webset about the procedure and its status of development.

2 Thank you.

3 DR. BLANCO: Thank you.

4 The next speaker is Jay Cooper, Women's Health
5 Research, on behalf of Biosphere Medical.

6 DR. COOPER: I am Jay Cooper. I am in private
7 practice in obstetrics and gynecology in Phoenix, Arizona.
8 I am a clinical assistant professor at the University of
9 Arizona in Tucson. I have, in the past, served as a
10 clinical investigator in the randomized controlled trials of
11 several different endometrial-ablation technologies and
12 continue to serve in that capacity.

13 I am here today at the request of Biosphere
14 Medical. I have no financial interest in the company.

15 I will significantly truncate my remarks as Dr.
16 Mitchell did an excellent job, I think, in preparing all of
17 us for the significance of the impact of uterine fibroids.
18 It is clear that there is increasing pressure on healthcare
19 providers to offer women alternatives to hysterectomy. This
20 is coming not only from major health plans and insurance
21 companies but from customers, or consumers, I should say,
22 who are ready targets for legitimate and not so legitimate
23 advertising and promotional schemes.

24 Although there has been significant progress made
25 in advancing uterine-sparing procedures such as myomectomy,

1 myolysis, operative hysteroscopy, in many cases, these are
2 procedures that have a rather limited application to a
3 specific clinical situation.

4 Despite the remarkable advances and enabling
5 technology, particularly in the field of operative
6 hysteroscopy, still a relatively small number of
7 gynecologists have adopted operative hysteroscopy into their
8 clinical practices.

9 Consequently, into this mix of alternatives to
10 hysterectomy, we now face uterine-artery embolization.
11 Clearly not without potential risks or failure,
12 uterine-artery embolization, if more readily available and
13 expertly performed, could fill a void amongst therapeutic
14 options for women with fibroids.

15 Early studies of uterine-artery embolization
16 demonstrates that short-term results compare favorably with
17 myomectomy where 90 percent of patients experience
18 symptomatic improvement. Major and minor risks of UAE
19 appear similar to traditional procedures such as myomectomy
20 and hysterectomy.

21 Although promising, the data, essentially, are
22 case lists without control groups making it difficult, if
23 not impossible, to actively determine whether UAE risks and
24 benefits truly equate with traditional gynecologic
25 therapies. Therefore, conventional wisdom would dictate

1 that a properly designed, randomized controlled trial would
2 be essential.

3 Although such an effort is clearly desirable and
4 ethical, its feasibility must be seriously questioned. The
5 first, and most obvious, question was raised by Dr.
6 Mitchell; what would be the appropriate control group. If
7 hysterectomy or myomectomy is the control group, how many
8 women meeting appropriate inclusion and exclusion criteria
9 would be willing to participate in such a randomized study.

10 As a clinical investigator of various global
11 endometrial-ablation technologies, I have had first-hand
12 experience with difficulties in patient enrollment and
13 compliance. The nationwide multicenter trial entitled
14 STOP-DUB intended to compare safety, efficacy, durability
15 and patient satisfaction between endometrial ablation and
16 hysterectomy continues to drag on hampered by a painfully
17 slow enrollment, this despite the fact that the protocol
18 allows any form of traditional or global ablation procedure
19 in the investigational arm of the study.

20 I am concerned that the prospects for a randomized
21 clinical trial of uterine-artery embolization versus
22 hysterectomy or myomectomy would have a similar fate, drag
23 on and on. As many more interventional radiologists are
24 available to do these procedures outside of a protocol, I
25 think enrollment would be quite difficult.

1 Consequently, I have proposed what I think is a
2 reasonable proposal for the clinical study and market
3 clearance of embolization agents for uterine-fibroid
4 embolization. It is included in my handout.

5 Basically, I would propose that each company who
6 proposed the marketed device for UAE would submit a 510(k)
7 with data from a prospectively designed premarket study with
8 short-term results, six months to one year. FDA clearance
9 would be conditional on participation in and submission of
10 results from a postmarket surveillance study or patient
11 registry which would provide for long-term monitoring of
12 patients' safety.

13 The premarket clinical study would be multicenter,
14 nonrandomized. Controls would be case controls or
15 historical data. Size, at least 100 patients for each
16 embolization agent. Patients would not be pregnant, have no
17 desire for future pregnancy unless myomectomy or
18 hysterectomy was the only alternative, no pelvic malignancy.

19 Key inclusion criteria; symptomatic fibroids and
20 an enlarged uterus. Key endpoints; symptomatic relief of
21 bleeding, pain and discomfort and reduction in size of the
22 uterus and fibroids and quality-of-life data.

23 As to the postmarket study for each embolization
24 product, the company would agree to provide long-term, as
25 much as five-years, follow-up results from a postmarket

1 surveillance study. The company could either sponsor their
2 own study or participate in a third-party registry.

3 Finally, if the agency insists that there be a
4 control group, an option to a randomized trial would be to
5 develop one common control group of surgical patients from
6 several clinical sites, either prospectively or
7 retrospectively that could be used by all companies with UAE
8 products. This could be sponsored by a third party such as
9 SCVIR with support from industry.

10 Results from the control group can be made
11 available to each company for use in clearance of its
12 product.

13 Thank you for your attention.

14 DR. BLANCO: Thank you.

15 The next speaker will be Fannie Fonseca-Becker
16 from Baltimore, Maryland

17 MS. FONSECA-BECKER: Good afternoon and thank you
18 very much for giving me the opportunity to come here and
19 share my experience as a patient with fibroids and my
20 experience with uterine-artery embolization.

21 Five years ago, I was diagnosed with uterine
22 fibroids during a regular GYN exam. I had two fibroids at
23 the time. They were small in size. Over the years, they
24 grew and more fibroids appeared until last year I had five
25 fibroids, total. The largest one was 13 by 10 by

1 11 centimeters.

2 The volume of my uterus was about 900 cc's. I
3 think a normal uterus is about 150 cc's volume. So it was
4 very large. I had just started hemorrhaging and that really
5 scared me. I could take the pain and I could take the
6 pressure but not the hemorrhaging.

7 So, at the time, my GYN--my ex-GYN--recommended as
8 the only procedure to do a hysterectomy, not only a
9 hysterectomy but a radical hysterectomy. My ovaries and my
10 cervix were good and healthy. He thought that that will be
11 a preventive measure so I would never have to worry about
12 the spectrum of cancer in the future.

13 I am sorry to say to a panel that is represented
14 by many OB-GYNs, that when I asked him why this was the only
15 procedure that he was recommending, he said, "Well, why do
16 you want to keep a useless bag?" That, to me, was very
17 upsetting.

18 This gave me the energy to start looking around
19 for alternatives. Thankfully, I have access to the Welch
20 Medical Library at Hopkins. I found some articles on
21 uterine-artery embolization and found out that there were
22 some people actually doing this in the area.

23 I met with Dr. Vembrooks, Tony Vembrooks, at Johns
24 Hopkins Hospital. I decided, after having read all the
25 literature and having asked him many questions about his

1 expertise with this kind of procedure, and he has more than
2 a thousand embolizations--not of uterine myoma--I cannot say
3 it anyway--of fibroids but other kinds of embolizations.

4 Being comforted by the fact that he had all this
5 experience, I underwent the embolization. I was given
6 conscious sedation. I did not feel anything during the
7 procedure. I stayed overnight in the hospital, went home
8 and was given some pain killers. I did have pain and the
9 pain peaked around the third day after the procedure.

10 But, with time, it decreased. As I understand
11 with the hysterectomy, pain lasts longer and I would have
12 had to stay in the hospital much longer which not only would
13 have been very bad psychologically but, also, from the cost
14 point of view.

15 I now, at this point, after having gone through
16 the procedure fourteen months ago, have only two fibroids
17 left. They are very small. They are like 5 centimeters.
18 My uterus is almost a normal size--not totally, because I
19 have these two small fibroids. I don't have any more
20 hemorrhaging. I have regular menstrual periods which last
21 about three days.

22 I don't have any pressure. I don't have any
23 symptoms. So I would recommend the uterine-artery
24 embolization to even women with large fibroids like mine. I
25 would ask the panel that putting differences aside from

1 different practitioners, that you look at the well-being of
2 the woman and really give a good look at this type of
3 procedure because, for us women, if we have the information
4 and the choice, I think a lot of us will choose to have this
5 kind of procedure instead of a hysterectomy.

6 Thank you.

7 DR. BLANCO: Thank you. I'm sorry; do you have
8 any conflict of interest? You didn't make the statement.

9 MS. FONSECA-BECKER: I don't think so; no.

10 DR. BLANCO: Thank you.

11 The next speaker will be Elizabeth Pedicini from
12 Laurel, Maryland.

13 MS. PEDICINI: Good afternoon. My name is
14 Elizabeth Pedicini. I have no conflict of interest. I am a
15 patient of Dr. Spies and my uterine-artery embolization on
16 June 1 of this year, so three months ago.

17 I had a fibroid larger than a grapefruit and it
18 kept getting larger. I had a uterus about the size of a
19 woman who was five-months pregnant. I had chronic back
20 pain. I had to stop running. I couldn't wear some of my
21 clothes. I had constant pelvic pressure and frequency and
22 did not like the options of a hysterectomy or myomectomy
23 because, as a single person, could not afford to take all
24 that time off from work for recovery and, also, did not want
25 major abdominal surgery.

1 So I put it off and kept putting it off. My
2 symptoms got worse and got more constant. Then I got heavy
3 bleeding which really started to scare me. So I was very
4 fortunate to work with, and have a friend that I worked
5 with, that was a patient of Dr. Spies that told me of the
6 UAE procedure which I did not know of.

7 It seemed to meet all my needs because it was a
8 quick recovery time and not as long a procedure. So I had
9 my procedure on June 1 and, within two weeks, saw relief of
10 symptoms. I have no back pain whatsoever. I am back to
11 running and my periods have gotten much better. I have seen
12 things decrease dramatically, dramatically.

13 I just went back for my three-month MRI and I have
14 had considerable shrinkage. I am very pleased with the
15 results and know in a year, when I go to my next follow-up
16 MRI, I will continue to see progress. So I was very pleased
17 with that.

18 It was a wonderful experience for me. There was
19 pain in the first two days, but they very openly give you
20 the good and the bad and the ugly and all your options and
21 say this is the reality. I had enough pain medication to be
22 fine with that.

23 I was back at work within a week.

24 Are there any questions?

25 DR. BLANCO: Thank you.

1 The next speaker is Robert Rosen, New York
2 University, Society of Cardiovascular and Interventional
3 Radiology.

4 DR. ROSEN: Good afternoon. My name is Dr. Robert
5 Rosen. I am Director of Interventional Radiology at New
6 York University Medical Center, a member of SCVIR, and I
7 have no conflicts of interest regarding UAE.

8 I have been asked to just say a fairly rapid-fire
9 overview of embolization procedures because they may not be
10 familiar to everybody.

11 [Slide.]

12 Basically, the four areas that I just wanted to
13 touch on were the history of the procedure, the indications
14 currently for the procedure, risks involved and training
15 issues.

16 [Slide.]

17 I am not going to get into the details of the
18 history except to make the point that this is not a new
19 technology. The concept of embolization has been around for
20 nearly 100 years. In practical terms, really, it was in the
21 late '60's and early '70's that embolization began to be
22 used routinely on a clinical basis.

23 The early work was in head and neck tumors and
24 bleeding problems, then moved to treating pelvic trauma, GI
25 bleeding, other types of hemorrhage and kidney tumors. In

1 the '80's, the indications began to be expanded to other
2 types of lesions and, basically, throughout this period from
3 1975 until now, there has been a steady progress, both in
4 delivery systems for embolic agents and in the agents,
5 themselves.

6 In the early '70's, Gelfoam was really the
7 mainstream available material. Coils were introduced in the
8 mid '70's and finally the coils became more sophisticated
9 and miniaturized. Detachable balloons and various liquid
10 agents were then developed in the late '70's and early
11 '80's.

12 [Slide.]

13 The later '80's saw the introduction of platinum
14 microcoils and more sophisticated detachable coils.

15 [Slide.]

16 At this point in our history, we have a wide range
17 of embolic materials available to us. Some of them are
18 temporary and biodegradable which include the biologics
19 which are rarely used these days. Gelfoam, I mentioned.
20 Particles, I will talk a little bit more about. And a
21 variety of other more specialized agents.

22 [Slide.]

23 The first main area where embolization was used
24 and continues to be a very major indication is in the
25 treatment of hemorrhage. Pelvic trauma, gastrointestinal

1 and GU bleeding and life-threatening hemoptysis.

2 [Slide.]

3 Just an example of a patient with a massive pelvic
4 fracture following a motorcycle accident. It doesn't really
5 project very well with the lights on, but there is an area
6 of extravasation from the posterior division of the
7 hypogastric artery which would often be a lethal type of
8 injury. These are almost impossible to control surgically
9 and it basically can be managed very quickly and safely with
10 embolization therapy.

11 [Slide.]

12 These types of procedures are usually done with
13 fairly simple mechanical devices such as Gianturco coils.

14 [Slide.]

15 Embolization for hemorrhage can be done in many
16 organ systems. This is an example of a mesenteric angiogram
17 showing GI bleeding which is now commonly controlled with
18 embolization.

19 [Slide.]

20 Bronchial embolization which is performed for
21 life-threatening hemoptysis seen in association with many
22 serious diseases like cystic fibrosis and tuberculosis.

23 [Slide.]

24 Moving away from hemorrhage, abnormal
25 arterial-venous communications are very difficult to manage

1 using surgical or other standard types of therapy. They are
2 pretty ideally suited to embolization therapy with an
3 endoluminal approach. This would include arteriovenous
4 fistulas, congenital vascular malformations and primary
5 venous lesions.

6 [Slide.]

7 Just a fairly simple example of a traumatic
8 arteriovenous fistula because the subclavian artery branch
9 and the subclavian vein.

10 [Slide.]

11 This can be treated using these more specialized
12 miniature platinum microcoils.

13 [Slide.]

14 This is a post-embolization study showing these
15 coils in place which are occluding the site of the fistula,
16 itself. And this is definitive therapy. No further surgery
17 needs to be done.

18 [Slide.]

19 More specialized types of AV communication are
20 sometimes seen in otherwise healthy patients with pulmonary
21 arteriovenous malformations.

22 [Slide.]

23 This is a site where something as exotic as
24 detachable balloons is very useful because they can be
25 flow-guided and very precisely positioned here at the site

1 of the malformation.

2 [Slide.]

3 Again, this is a curative procedure. No major
4 lung resection is required.

5 [Slide.]

6 When we get in to pelvic arteriovenous
7 malformations and other more complex lesions, they are more
8 difficult to treat and much more difficult to cure.

9 [Slide.]

10 This is another pelvic AVM. This one actually
11 happens to be located in the body of the uterus.

12 [Slide.]

13 These have been treated with a great deal of
14 success for many years using embolization procedures. Here
15 we have to look at very specific characteristics of the
16 embolic agents including agents that are permanent, that are
17 safe, non-toxic and have a long enough track record that we
18 could use them in young patients.

19 [Slide.]

20 As in many of these settings, the idea is not to
21 do the equivalent of a ligation which, really, is just
22 associated with rapid recurrence.

23 [Slide.]

24 We are used to seeing these kinds of problems.
25 This is a child that had an AVM on his back, resected

1 surgically. You can see it very quickly recurred. Big scar
2 and obviously recurrent malformation.

3 [Slide.]

4 Worst-case scenario; a young woman who started out
5 with a small AVM on her foot and ended up with a high-thigh
6 amputation from ill-advised surgery.

7 [Slide.]

8 So the experience with these types of problems has
9 led to a lot of work with various penetrating embolic agents
10 that go more distally than the coils and the Gelfoam.

11 [Slide.]

12 Probably PVA or IVALON is one of the commonest
13 agents in clinical use at this point.

14 [Slide.]

15 Most research has shown that the particles larger
16 than 50 microns will be safe in terms of avoiding tissue
17 ischemia.

18 [Slide.]

19 It is just one of several commercially available
20 preparations of PVA particles that are currently in clinical
21 use. The advantage of the material is that it is permanent,
22 it has very low tissue toxicity which has been shown over
23 many years of experience, good long-term safety, fairly easy
24 to use. It is injected as a suspension in various graded
25 particle sizes and it is readily available.

1 [Slide.]

2 The best applications are either for preoperative
3 embolization or definitive treatment using the particles to
4 penetrate the small-vessel nidus of AVMs. Tumor
5 embolization, both benign and malignant, is a very heavily
6 used application. Bronchial embolization, we already
7 mentioned.

8 [Slide.]

9 I am not going to get into liquid embolic agents
10 in this discussion.

11 [Slide.]

12 When we are talking about uterine-fibroid
13 embolization, I think it is important to realize that this
14 is not the only benign tumor that is treated with
15 embolization therapy. There are several other hypervascular
16 benign tumors included renal angiomyolipomas, hepatic
17 adenomas and other lesions which are benign but have a
18 tendency to either enlarge or bleed which can have
19 definitive treatment using embolization techniques. These
20 have been done for many years.

21 [Slide.]

22 In terms of malignant tumors, this is an area of
23 very extensive clinical research right now, both as a
24 palliative or an emergent procedure to control bleeding, but
25 also as a treatment using a combination of embolization

1 techniques and chemotherapeutic agents.

2 [Slide.]

3 Just an example of a preoperative embolization, a
4 very large retroperitoneal liposarcoma. You can see in this
5 patient, which looks somewhat vascular on this angiogram.

6 [Slide.]

7 If you do a selective angiogram, you could see
8 that it actually is wildly vascular and it would be
9 virtually impossible to resect with unacceptable blood loss
10 without embolization beforehand.

11 [Slide.]

12 Finally, a lot of work is being done in the
13 treatment of focal solid organ malignancies now such as
14 hepatoma. An example of a hepatoma in the liver.

15 [Slide.]

16 And using embolization techniques, we can guide
17 microcatheters directly to the blood vessels supplying the
18 tumor and inject a combination of embolic agent and
19 chemotherapy at a very high concentration with quite
20 promising clinical results.

21 [Slide.]

22 What are the risks of embolization? Really, the
23 two major risks are non-target embolization, meaning the
24 embolic particles, materials, go someplace you don't want
25 them to go which, these days, is actually quite uncommon

1 with the delivery systems and the imaging that we have
2 available.

3 Ischemia and also post-embolization syndrome,
4 which isn't really a complication but a manifestation of
5 devascularizing a significant volume of tissue. Tissue
6 toxicity due to the embolic agent. This is generally only
7 seen with certain agents such as alcohol and very fine
8 particles which penetrate very distally.

9 Migration, even though it is a concern of many
10 people that first hear about the technique is actually quite
11 rare and the long-term effects have been remarkably few in
12 the literature.

13 [Slide.]

14 Finally, training issues. Embolization techniques
15 are a standard part of interventional fellowship training.
16 They are extensively covered in the certificate of adequate
17 qualification examination. With over 3500 members with this
18 fellowship training in the SCVIR, virtually all
19 tertiary-care hospitals and most significant-sized hospitals
20 now have interventional radiology available.

21 [Slide.]

22 Really, these are procedures that are done widely
23 in many hospitals including, as we saw, trauma, bleeding and
24 tumor embolization. These are probably the commonest
25 agents used; Gelfoam, coils and PVA or IVALON.

1 [Slide.]

2 To conclude, just making the points that
3 embolization is not a new procedure. It has been around for
4 almost 25 years. All intervention radiologists are trained
5 and experienced in these techniques. It is already a
6 first-line option in managing many types of clinical
7 problems including bleeding and many benign and malignant
8 tumors. Most of the agents that are currently used,
9 including Gelfoam, PVA and coils, have been in use for
10 almost twenty-five years with a very low complication rate,
11 and no reports of agent-related long-term adverse effects.

12 Thank you.

13 DR. BLANCO: Thank you very much.

14 The next speaker is Tony Shiley of Georgetown
15 University on behalf of Boston Scientific.

16 DR. SHILEY: Thank you. I am Tony Shiley. I am a
17 professor of OB-GYN at Georgetown University Medical Center.
18 Boston Scientific asked me to come. To my knowledge, they
19 are not paying me. I also paid for my own gas to get up
20 here from Georgetown.

21 I do, actually, have what might be considered a
22 conflict of interest in that I have researched for Tap
23 Holdings which, to my knowledge, does not have an
24 application before the FDA. But this research project
25 involving the use of GnRH agonists for the long-term

1 measurement of fibroids.

2 I thought Dr. Mitchell's presentation was
3 excellent and up to the minute as far as published studies
4 but she failed to read my unpublished study because I just
5 mailed it in to the journal. So what I would like to do is
6 just mention what my experience has been although certainly
7 I do not intend to propose it as being clearly of benefit,
8 and that is to use GnRH agonists intermittently six months
9 at a time.

10 What is interesting is that we have found rather
11 sustained results in controlling symptoms from fibroids. I
12 agree with Dr. Mitchell that size of the tumors is no longer
13 an issue and that we are really concerned about symptoms.
14 So I think we may see the day when this pharmacologic class
15 is used for more prolonged management without the idea that
16 you need to keep women on it month after month,
17 indefinitely.

18 However, my main reason for coming to the
19 microphone is that I have been privileged to work with Jim
20 Spies in the embolization program at Georgetown and have
21 been singularly impressed with the effectiveness and
22 acceptability of this technique.

23 Really, the only reservation I have is that my
24 patients soon fall in love in Jim and I lose their affection
25 because he does such good things for them.

1 My comment for the panel, though, is a suggestion
2 that hysterectomy not be regarded as any sort of gold
3 standard and although a previous speaker pointed out that it
4 can be logistically difficult to use an active control--that
5 is, a surgery control--to me, it is also philosophically
6 objectionable. Hysterectomy has never been subjected, to my
7 knowledge, to any sort of trial to establish safety and
8 effectiveness.

9 In fact, although we know it is effective in
10 stopping bleeding, we also know that it is not particularly
11 safe or pleasant. In addition to the usual surgical
12 problems with which the gynecologists on the panel are very
13 familiar, we also have the concern that there may be a
14 decrease in ovarian function even if the ovaries are
15 retained.

16 You would be correct to wonder whether that occurs
17 after uterine-artery embolization. Jim is certainly
18 collecting data on this point. So, while I think it is a
19 very good idea to come up with criteria for evaluating the
20 safety and effectiveness of this new technique, I would make
21 a plea, really, not to hold major surgical therapy as any
22 sort of reliable comparator.

23 Thank you.

24 DR. BLANCO: Thank you very much.

25 The panel will note that it has two letters in its

1 folder, one from Vin Cutarelli, Endocare, Incorporated, and
2 another from April Lavender, Cook Incorporated.

3 Does anyone else wish to speak from the public?

4 MS. PEARSON: I just wanted to make a brief
5 remark. Thank you. My name is Cindy Pearson. I am the
6 Director of the National Women's Health Network and we have
7 no conflict of interest.

8 As you heard from the patients who spoke today,
9 this is a big issue for women. Fibroids and alternative
10 treatments for fibroids are one of the areas that we are
11 asked the most questions about. Unfortunately, gynecologist
12 education and change-of-practice patterns hasn't happened as
13 quickly as some of the researchers and regulators believe it
14 should have.

15 We still talk to women who are recommended to have
16 a hysterectomy even with no symptoms. We still talk to
17 women who are recommended to have a hysterectomy merely on
18 size, alone. And women feel very frustrated.

19 So the need is there. We understand that you
20 realize that because you are having this hearing today. But
21 what do women need to know? Women need to know some of the
22 things that the patients who spoke today told you.

23 They need to know a good idea of how long the
24 procedure will take, what are the risks of complications
25 while the procedure is being done or immediately afterward,

1 how much pain is associated with it, those sorts of things.

2 They also need to know, in the sort of medium
3 term, "How likely am I to be happy with the results?" I
4 found it interesting that one of the women who spoke said,
5 "I have had my three-month checkup. It's great. And I
6 know, at my year checkup, it will be good, too."

7 Well, I know positive attitude about health
8 outcomes is important so I am glad and I hope I feel that
9 way when I have important procedures done, but I have to
10 think, based on what we have heard today, that no one can
11 really tell any patient what to expect at a year because
12 those data haven't been collected yet.

13 Because the interference that fibroid pain and
14 heavy bleeding caused by fibroids can cause, I think that is
15 something that women really want to know. We do know, even
16 though hysterectomy is never subjected to a rigorous trial
17 and it is very overused in the United States, we do know
18 that it stops bleeding.

19 We also know the immediate serious short-term
20 risks associated with it. I think, to the extent that FDA
21 is involved in regulating this procedure which I doubt is
22 fully, I have to say what, exactly, you are about to
23 regulate here. Is it the catheter, the coil, the whatever?
24 But I know you are not regulating doctors' procedures.

25 So you are sort of dancing around here trying to

1 find a way to make sure that women get the information they
2 need. To the extent that you have some ability to influence
3 this, I think that women would like to know how effective is
4 this procedure in the short term and sort of the medium term
5 and how likely are they to get the results that they want.

6 So it is really exciting to see that there is
7 already some funding for the development of a
8 quality-of-life questionnaire because it is women's
9 definition of what is the most troublesome part of fibroids.
10 That is the important thing to cure with an intervention.

11 I am also excited to see that there has been a
12 submission for a multicenter trial because we are all too
13 familiar with results that are achievable only in the hands
14 of a fabulous surgeon.

15 I am sure there are people out there who do a
16 great job with this procedure but, as a health activist
17 following lots of things that have come down the pike, I am
18 not sure how well that will translate out into the general
19 world. And women need to know that because they will be
20 getting it all over.

21 So those are our thoughts on this issue. Thanks.

22 DR. BLANCO: Thank you.

23 Anyone else? If not, we will proceed with the
24 introduction of our guest speaker.

25 I would like to introduce now Dr. Robert

1 Vogelzang, Northwestern University Society for
2 Cardiovascular and Interventional Radiologists. He will
3 present to us of ~~symptomatic uterine artery embolization~~ ~~fibroids~~ for treatment

4 **Guest Speaker**

5 **Uterine Artery Embolization for Treatment of**
6 **Symptomatic Uterine Fibroids.**

7 DR. VOGELZANG: Thank you very much. It is a
8 pleasure to be here.

9 [Slide.]

10 I was asked to talk about uterine-artery
11 embolization for the treatment of fibroids. Some of the
12 material has been handled before. You will be pleased to
13 know that--I bought this laser pointer a few days ago--it
14 meets FDA standards.

15 [Slide.]

16 Interventional radiology, as you have heard, is
17 the application of percutaneous techniques to a wide variety
18 of conditions including ablation of tumors and other types
19 of things.

20 [Slide.]

21 All these percutaneous techniques are based on
22 catheter/guidewire techniques which were invented by Dr.
23 Seldinger in 1953 which involved needle puncture of a target
24 artery, guidewire passage and placement of a catheter, all
25 of which purpose is to do, in this case, embolotherapy. As

1 Dr. Rosen pointed out, there have been a number of
2 applications of embolotherapy in obstetrics and gynecology
3 including predominantly postpartum hemorrhage, vascular
4 malformations and some venous embolotherapy.

5 [Slide.]

6 The current indications that I would point out
7 that are commonly used for obstetrics and gynecology include
8 the post-Caesarian bleeding, ectopic pregnancy, mostly
9 post-surgical or post-birth problems, pelvic trauma and
10 arteriovenous malformations.

11 There has been advocacy and some difficult
12 obstetric cases of prophylactic embolotherapy as well.

13 [Slide.]

14 All these have reported very high success rates
15 with few complications. There is a fairly extensive and
16 well-documented experience with these procedures in pelvic
17 trauma, success rates of 85 to 100 percent. I think an
18 important point is that surgical options in these matters
19 are almost always preserved.

20 [Slide.]

21 What we are talking about there, from an
22 angiographic or anatomic perspective, is the internal iliac
23 artery with which you may be familiar. It has a posterior
24 division which essentially supplies the gluteal vessels.
25 This is a catheter angiogram of a right internal iliac

1 artery.

2 The anterior division, which supplies the uterus
3 as well as other structures, gives off the uterine artery
4 which you see here in its characteristic course arising off
5 the anterior division of the internal iliac artery.

6 Similarly, and of course, is a bilateral process,
7 this uterine artery, catheterized here off the anterior
8 division, which is here, of the internal iliac artery,
9 posterior division. This is the external iliac artery, to
10 give you a complete picture of the pelvic anatomy that we
11 are trying to catheterize.

12 [Slide.]

13 As I said, it is a branch of the anterior
14 division. It is variable in its origin which accounts for
15 the skill and catheterization equipment necessary to do it.
16 It has a characteristic appearance of spiral endometrial
17 arteries that we look for on a regular basis.

18 [Slide.]

19 This is a diagrammatic picture. It is a little
20 small. But it points out the major issue that I wanted to
21 discuss here which is that the uterus is supplied by a two,
22 or several, sources of vascular supply, not only the uterine
23 artery, itself, but branches via anastomoses from the
24 ovarian artery as well as cervical branches and vaginal
25 branches.

1 [Slide.]

2 This is a subselective catheterization and
3 catheter angiogram of the uterine artery. Notice that we
4 placed a 4 French catheter here into the right uterine
5 artery. It follows this characteristic course, gives off
6 some branches to the cervix.

7 There are anastomotic branches here, not
8 visualized to the ovarian arteries.

9 [Slide.]

10 Uterine leiomyoma have been well characterized, I
11 thought, gone over very nicely by Dr. Mitchell. That is in
12 your pamphlet or handouts.

13 [Slide.]

14 To reiterate again, the first report of
15 embolization for the treatment of uterine myomata was in
16 1995 by the French group headed by Ravina et al. in which
17 sixteen patients with symptomatic fibroids were treated with
18 good effects. Decreased tumor size of 20 to 80 percent was
19 seen in twelve of sixteen. Clearly, this meant the
20 indication was that we should go on with further research
21 and clinical observations which has been the case.

22 [Slide.]

23 The point about uterine-artery embolization that I
24 think is so fascinating is that we are producing a select
25 effect on fibroids via a non-selective embolization meaning

1 the entire uterine vascular supply is embolized. We believe
2 that sparing of the uterus is related predominantly to the
3 collateral arterial supply which I indicated here, via the
4 ovarian artery and from vaginal and lower cervical branches.
5 Endometrial and other supply obviously have prevented
6 uterine infarction while the peculiar blood supply of the
7 uterine myomata produces necrosis in that structure.

8 [Slide.]

9 Uterine-artery embolization is an interventional
10 procedure. It involves angiographic and catheter skills
11 which I thought Dr. Rosen alluded to, experience and
12 training, then, is required in patient evaluation. Basic
13 angiographic technique and anatomy, superselective
14 catheterization, methods and techniques including
15 alternatives to be used in the management of
16 postembolization events, all of which are present in trained
17 interventional radiologists.

18 [Slide.]

19 The technique of uterine-artery embolization,
20 which I will show a brief videotape about, is conventional
21 in the sense that it is via unilateral femoral access,
22 usually which is sufficient to catheterize both of the
23 uterine arteries.

24 Some workers prefer bilateral access. Most of us
25 use 4 to 5 French diameter catheters and coaxial

1 microcatheters used as necessary.

2 [Slide.]

3 The embolization agent of choice currently has
4 been polyvinyl foam, alcohol foam particles, ranging from
5 300 to 700 microns in diameter. Some workers have preferred
6 the 300 to 500 diameter, others the larger. Bilateral
7 embolization to near or complete stasis is generally the
8 accepted methodology for this particular treatment.

9 [Slide.]

10 Here is an example of such a case. Again, the
11 anatomy here, internal iliac artery, posterior division,
12 anterior division. Notice arising here in an anterior
13 course is the uterine artery here supplying a very large
14 uterine fibroid.

15 [Slide.]

16 A subselective catheterization shows the
17 hypervascular supply of the uterus predominantly here
18 produced by the uterine leiomyomata. After embolization, a
19 few small branches preserved, but essentially, the entire
20 uterine artery is occluded.

21 [Slide.]

22 The reason this procedure works, or we believe it
23 works and produces necrosis is, we think, related to the
24 specific blood supply of uterine myomata which were
25 originally described in 1912 by Sampson by specimen

1 injection. He noted that in men, and I am quoting now,
2 "only one nutrient artery was found, in others two or three
3 with one predominating." He also indicated that there was
4 extensive angiomatous transformation of the myoma.

5 It appears to me that many of these single feeding
6 vessels are responsible not only for the phenomenon that
7 gynecologists have observed for years of twisting or
8 spontaneous infarction but also relate to the benefit that
9 we produce here.

10 [Slide.]

11 Specimens from the Sampson article.

12 [Slide.]

13 Injection specimens which, now, 80 years later,
14 still look fresh and up-to-date. Here a vascular supply to
15 a pedunculated fibroid indicating, I think, fairly clearly
16 the single vascular stalk that often supplies these tumors
17 and is responsible for the necrosis we see.

18 [Slide.]

19 Again, another appearance here of a uterine-artery
20 embolization before.

21 [Slide.]

22 Another case before. Note that each one looks
23 different depending on the vascularity. But here we see
24 quite a bit of hypervascularity here.

25 [Slide.]

1 The effect of uterine-artery embolization is quite
2 significant. As the patients in the public-comment session
3 testified, the results have been consistently good. These
4 are two paired MRIs of a patient before and after
5 uterine-artery embolization for fibroid. This is an axial
6 MRI demonstrating a very large uterus related, of course, to
7 at least one of these fibroids.

8 [Slide.]

9 And, at three-month follow up, significant
10 decrease in the overall size of the uterine.

11 [Slide.]

12 Notice the protuberance of the anterior abdomen
13 here on the pre-MRI

14 [Slide.]

15 And with considerable decrease in production of
16 low intensity, indicating necrosis of the uterine fibroid.

17 [Slide.]

18 Post procedurally, uterine-artery embolization for
19 fibroids consists of aggressive management of pain, nausea
20 and vomiting experience. In our experience, these peak at
21 about 8 to 12 hours. Nausea and vomiting is treated with
22 Decadron and Zofran in our hands and pain, generally, is
23 best handled, in our hands, by morphine delivered by a
24 patient-controlled analgesia pump overnight with conversion
25 to oral agents and/or oral narcotics as necessary.

1 Generally, we have found this to be very well
2 tolerated. Our average patient returns to work in 4.3 days.
3 An average time to complete recovery--that is, free of all
4 symptoms related to the procedure--about 13 days.

5 [Slide.]

6 The complications can and should be expected to be
7 those of angiography and ischemic complications
8 predominantly, if they occur, related to non-target
9 embolization, for example, and/or target-organ ischemia.
10 Infectious complications can also be of concern and have
11 been in some situations.

12 [Slide.]

13 So, with that in mind, I would like to just go
14 over briefly here what we know and don't know about
15 uterine-fibroid embolization and uterine-artery embolization
16 for the treatment of fibroids.

17 We know that all published reports, and there are
18 emerging reports on a very regular basis, show similar
19 results with 90 percent control of those patients' symptoms,
20 predominantly pain and bleeding. 50 percent mean reduction
21 in uterine volume has generally been seen at about six
22 months to one year and 70 to 80 percent improvement in
23 bulk-related symptoms. Those would be pressure, pain,
24 constipation, urinary frequency and the like.

25 We believe, and the evidence shows, that it is

1 safe with a low rate of hysterectomy to date and very few
2 adverse, or no adverse, sequelae from non-target
3 embolization.

4 [Slide.]

5 I tried to summarize the current literature as we
6 have it now. This is a moving target, but, as best we can
7 tell, we have about 515 patients reported in referee
8 journals, level-3 data; that is, uncontrolled case series.
9 1500 total cases have been reported, to the best of my
10 knowledge, at abstracts, meeting presentations and the like.

11 Technical success has ranged in the high 90s;
12 menorrhagia resolution, 86 to 96 percent; complications
13 requiring a repeat procedure or rehospitalization such as
14 for pain, fever and the like, 4 to 8 percent; hysterectomy
15 postembolization has been reported at 1 to 2 percent and the
16 ovarian failure rate, or induction of premature ovarian
17 failure, at 1 to 2 percent. That is a question mark,
18 however, as I will point out.

19 [Slide.]

20 Uterine size reduction on average is 48 percent at
21 3 to 6 months. Volumes of one-third to one-half reduction
22 in volume with, at one year, in the limited series
23 available, median dominant fibroid reduction of 80 percent.
24 So the procedure, obviously, is working at producing the
25 endpoints that are measured here which is uterine fibroid

1 reduction and uterine volume reduction.

2 [Slide.]

3 Here is an example of another patient with a very,
4 very large fibroid uterus. You can see on this sagittal MR,
5 we have the uterus extending all the way up to L2, a very
6 large uterus. At three months after treatment, the uterus
7 is down here. It is significantly smaller--this is the
8 lumbosacral junction--and production reduction in the
9 uterine fibroid size.

10 [Slide.]

11 To my eye, and from the literature summary, the
12 risks of serious and minor risks appear to be similar to
13 more established procedures. We know of two deaths in about
14 1500 reported cases for uterine-artery embolization probably
15 related to sepsis as opposed to hysterectomy with about
16 eleven deaths per 10,000 in one report.

17 [Slide.]

18 What don't we know? Importantly, I think, and
19 number one on the list, is the effect of the uterine-artery
20 embolization on future fertility. Endometrial effects may
21 be responsible, maybe production of ischemia. We know that
22 there are probably ovarian effects, embolization via these
23 uterine ovarian anastomoses.

24 Therefore, we do not currently recommend this
25 procedure for women who have not begun or completed their

1 families. We do not absolutely know, at this point, the
2 utility of uterine-artery embolization in simple reduction
3 in bulk or size. We know that there is some data on that.
4 However, the efficacy of this procedure just to reduce
5 uterine size is still unknown at this point.

6 [Slide.]

7 We also don't know the long-term durability of the
8 effect. Follow up to a year is very limited at this point.
9 We do not know the fibroid recurrence rate. We believe it
10 will be lower because of the global treatment of fibroids.
11 And others which I include in here; what complications will
12 or can be seen as a large population is treated by a large
13 group of physicians.

14 We just have two deaths in about 1500 procedures
15 reported to date which is, as I said, in line with other
16 series for other procedures.

17 [Slide.]

18 So, in summary, embolization for uterine fibroids,
19 I think, may well take its place alongside other therapies
20 which have been, up until now, the methods of choice for
21 treating these particular tumors.

22 I have about a minute-and-a-half videotape of the
23 procedure, itself, if you wish.

24 [Video.]

25 This is basically a videotape compiled from an

1 institution and illustrates the technique of the procedure,
2 not results so much. This is catheterization from the right
3 femoral artery over across the bifurcation. The procedure
4 is performed in a sterile environment.

5 This is the angiographic image that the operators
6 are looking at looking for the uterine artery here on a
7 selective internal iliac-artery injection from the left over
8 to the right.

9 Another example; the uterine artery demonstrated
10 here in this projection moving anteriorly. Following
11 catheterization, the embolic particles are mixed, usually in
12 a solution of contrast so they are visible, and mixed to a
13 uniform suspension to prevent clogging of the catheter and
14 to make sure that a uniform effect is achieved.

15 This is through a microcatheter so a small syringe
16 is being injected. Aliquots are given. What the operator
17 sees and watches is--here is the tip of the catheter. You
18 can see small amounts of dark material going out there.
19 This is the opacified particles going into the uterine
20 artery.

21 Ultimately, what we look for is stasis or flow
22 arrest in the uterine artery, generally seen both
23 fluoroscopically and on spot films. An angiogram is done to
24 ascertain that that is the case.

25 Another depiction. -Then the catheter is

1 withdrawn, as you can see here from static contrast. The
2 catheter is pushed up to the aortic bifurcation and, at
3 least in this methodology, is redirected down the right side
4 to recatheterize the right uterine artery.

5 That's it. Thank you very much.

6 DR. BLANCO: Thank you.

7 I think there are some questions from the panel if
8 you would not mind. Why don't you come join the panel.

9 DR. LEVY: What is the radiation exposure to the
10 ovaries and the pelvis with the procedure?

11 DR. VOGELZANG: It is currently being measured,
12 but my understanding is it is on the order of 20 rads; that
13 is, the exposure would be equivalent to barium enemas and CT
14 scans, in that range.

15 DR. BLANCO: We also have another video on
16 cryomyolysis.

17 Laparoscopic Cryomyolysis

18 [Video]

19 DR. KRESCH: Uterine myomas are the most common
20 benign neoplasm in the female pelvis. Approximately
21 25 percent of women over the age of thirty are affected.
22 Most fibroids are asymptomatic and require no treatment.
23 However, if symptoms such as menorrhagia, anemia, pelvic
24 pain, pelvic pressure, urinary and bowel symptoms as well as
25 infertility are related to the fibroids, clearly, treatment

1 is indicated.

2 A number of conservative procedures are used for
3 the treatment of uterine fibroids. Most commonly utilized
4 is the abdominal myomectomy, the procedure that provides the
5 surgeon with excellent control, good hemostasis and known
6 efficacy.

7 However, the required laparotomy can result in
8 extended recovery time, significant adhesion formation and
9 substantial cost. Women are becoming more educated with the
10 alternatives and are beginning to request less invasive
11 treatments without removal of the entire uterus.

12 Laparoscopic myomectomy offers a less invasive
13 approach over laparotomy. However, the laparoscopic
14 myomectomy has its own disadvantages such as the requirement
15 of great laparoscopic skill for tissue resection, removal
16 and hemostasis. Uterine closures typically require
17 multilayer uterine closure with advanced laparoscopic
18 suturing skills. Laparoscopic myolysis is yet another less
19 invasive approach for uterine-fibroid treatment requiring
20 less laparoscopic skill. However, it carries a high risk of
21 adhesion formation and destruction of the normal myometrium
22 may be considerable.

23 Recently, a new method has been introduced.
24 Uterine-artery embolization which devitalizes the uterine
25 and fibroid tumor by embolizing arterial blood flow.

1 Although this method is new with limited results, associated
2 risks are present.

3 Another modality recently applied to surgical
4 tumor management is cryogenic technology. Cryosurgery has
5 been utilized to treat prostate disease and hepatic tumors
6 with great success. Recently, it is currently under
7 evaluation for endometrial ablation.

8 Another application of cryosurgery called
9 cryomyolysis is the treatment of uterine fibroids. This
10 offers a number of potential advantages. The procedure can
11 be performed laparoscopically, thus providing a short
12 procedure time, a short recovery time and low cost.
13 Technically, the procedure offers little difficulty for the
14 experienced laparoscopist as few instruments are required.

15 Finally, a limited number of entry points into the
16 fibroid might potentially lead to less serosal damage and,
17 therefore, less adhesion formation.

18 Cellular destruction with the application of cold
19 temperatures, or cryotherapy, depends upon each component of
20 the freeze-thaw cycle. In the frozen state, extracellular
21 and intracellular freezing should occur in a rapid fashion
22 with temperatures reaching negative 20 degrees Celsius or
23 colder. The cells become dehydrated and hypotonic setting
24 the stage for membrane rupture to occur during the thaw.

25 The thawed state warms the tissue slowly,

1 passively allowing the cell to become diluted with extra
2 fluid volume leading to membrane rupture. The effects of
3 cryotherapy continues for days to weeks following treatment
4 for complete necrosis.

5 The standard setup for operative laparoscopy is
6 required including videocamera and monitor, high-flow
7 insufflator, an irrigation aspiration system and
8 electrosurgical instrumentation.

9 The cryoprobe is 8 millimeters in diameter with a
10 sharp tip for tissue penetration. A 4-centimeter active
11 freeze zone allows ice-ball formation at the distal end.
12 The cryoprobe is inscribed with centimeter markers for easy
13 identification of insertion depth.

14 For the procedure, three to four trocar sites are
15 required, one large port for the laparoscope, another port
16 for the cryoprobe and another port for the
17 irrigator-aspirator. The placement of the trocars is
18 dependent upon the location of the fibroids. The port to
19 hold the cryoprobe is generally placed just above the
20 fibroid and angled to penetrate along the long axis of the
21 tumor. The irrigator-aspirator is positioned within the
22 reach of the surgical site but in a different plane from the
23 cryoprobe port.

24 This patient has a history of hypermenorrhea and
25 presents with an 18-week uterus and a 6-centimeter fundal

1 subserosal fibroid. Pretreatment with GnRH analogue therapy
2 and Provera was conducted.

3 The cryoprobe is positioned through the anterior
4 surface of the fibroid for nine minutes of cryotherapy.
5 Cutresin in a 1 to 100 dilution is injected into the tumor
6 at the site of the insertion of the cryoprobe to minimize
7 bleeding.

8 The insertion track for the cryoprobe is initiated
9 by drilling a small hole through the uterine serosa with an
10 electrosurgical instrument. The hole is extended into the
11 superficial aspect of the uterine fibroid. The cryoprobe is
12 then advanced through the track using steady pressure in a
13 twisting motion.

14 The goal is to advance the cryoprobe to within
15 1 centimeter of the opposite side of the fibroid. Care must
16 be taken to advance the cryoprobe through the center of the
17 fibroid and not along the side of the fibroid.

18 Once the placement of the cryoprobe is acceptable,
19 freezing begins. The temperature ultimately reaches
20 approximately negative 110 degrees celsius. A freeze of
21 five to ten minutes is generally required and can be
22 monitored by palpation. Larger fibroids may require freezes
23 as long as fifteen minutes or can be treated with a second
24 cryoprobe placement.

25 Warm irrigation is routinely used to protect

1 surrounding tissues within the pelvis from inadvertent
2 freezing. If the fibroid is less than 5 centimeters, a
3 portion of the freeze zone may be outside the fibroid. If
4 this occurs, copious irrigation throughout the freeze cycle
5 would prevent the lateral spread of serosal surface
6 freezing.

7 When the ice ball has encompassed the entire
8 fibroid, the freeze is discontinued. This is determined by
9 palpating a rock-hard fibroid just below the serosal
10 surface. As the ice ball expands through the fibroid, the
11 blood supply is compromised and tissue blanching is seen in
12 the serosa.

13 The fine function is activated and the temperature
14 of the cryoprobe begins to warm. The cryoprobe is removed
15 with the temperature warms to zero degrees with a gentle,
16 twisting motion. A hollow track remains through the frozen
17 fibroid. It is important to quickly provide hemostasis
18 along the track as blood supply slowly returns to the
19 thawing tissue.

20 This can be achieved by plugging the track with
21 several small pieces of oxidized, regenerated cellulose
22 called SurgiCell. Once hemostasis is achieved, an
23 adhesion-prevention barrier such as Intercede may be
24 positioned over the entry site to reduce the incidence of
25 postoperative adhesion formation.

1 Ultrasound is not necessary in all cases but is
2 required in some situations. These include transvaginal
3 monitoring for an anterior fibroid pressing against the
4 bladder to prevent inadvertent freezing of the bladder,
5 transvaginal monitoring for a patient wishing to maintain
6 fertility to prevent freezing of the endometrium,
7 transrectal monitoring for a posterior fibroid to insure
8 that no rectal involvement of the ice ball occurs.

9 A preliminary feasibility and efficacy study of
10 cryomyolysis was conducted by my colleague, Dr. David Olive,
11 and his associates at Yale University School of Medicine.
12 Fourteen women requesting conservative surgery for uterine
13 fibroids were recruited. Their ages ranged from
14 twenty-seven to forty-six years old. Their symptoms
15 consisted of heavy menstrual flow, pelvic pressure and/or
16 pain, dysmenorrhea and irregular bleeding.

17 All patients received two preoperative injections
18 of a GnRH analogue to shrink the total uterine and fibroid
19 volume. Of the fourteen women, two were lost to follow up.
20 The remaining twelve were evaluated for up to 17 months
21 after the procedure. Eight women experienced continued
22 improvement up to 17 months postoperatively.

23 Three women who had mild to moderate improvement
24 after GnRH therapy experienced no additional improvement in
25 the symptoms after surgery. One patient who reported

1 subjective improvement had recurrence of irregular bleeding
2 nine months after the procedure. No complications occurred
3 in any of the patients.

4 Two MRI scans were performed, the first scan,
5 after the first GnRH analogue therapy and just prior to
6 cryomyolysis. The second MRI scan was performed four months
7 after surgery when regrowth of the uterus to its original
8 size would have been expected.

9 The results indicate that from the first to the
10 second MRI scan, the uterus enlarged by 40 percent as
11 expected indicating reversal effect of the GnRH analogue.
12 However, the mean fibroid volume reduction was 6 percent
13 with several patients showing a decrease of over 50 percent
14 up to 87 percent.

15 The second-look laparoscopy in six women at 7 to
16 14 days postoperatively revealed two patients with no
17 adhesions, two patients with mild filmy adhesions, one
18 patient with moderate adhesions and one patient with severe
19 adhesions from multiple probe sites.

20 The reduction of fibroid size by GnRH agonist can
21 be enhanced by cryomyolysis. Pure puncture sites to the
22 uterine serosa with cryomyolysis offers a decreased risk of
23 adhesion formation. Cryomyolysis represents an alternative
24 to the currently available minimally invasive treatments of
25 uterine fibroids.

1 discussing why we are here this afternoon. We are not here
2 because FDA decided it was going to go out and investigate
3 this. We are here because companies have come to us
4 requesting that the specific indication of uterine-artery
5 embolization be added to their product labeling.

6 If it weren't for that fact, we would not be
7 having this meeting today. Let me just differentiate that
8 very, very clearly and unambiguously, I hope, from the
9 practice of medicine where you, as physicians, can, using
10 legally marketed devices, mostly legally marketed devices,
11 with general indications, can basically go out and do
12 whatever is within your guidelines as far as good practice
13 of medicine.

14 So there are two very different issues but the
15 reason that we are here today is a sponsor-driven request or
16 interest to add this to the labeling. That is why we are
17 involved. That is why our panel is involved. So,
18 hopefully, that is clear and now we can get on with the
19 discussion.

20 Thanks.

21 DR. BLANCO: Thank you, Dr. Schultz.

22 For this afternoon's discussion session, Dr.
23 Michael Diamond will act as discussion leader. So I will
24 turn it over to him. And Dr. Vogelzang is a guest on our
25 panel.