FOOD AND DRUG ADMINISTRATION

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OBSTETRICS AND GYNECOLOGY DEVICES PANEL

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SEVENTY-FIRST MEETING

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OPEN SESSION

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Tuesday, March 28, 2006

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The Panel met at 9:00 a.m. in the Ballroom of the Gaithersburg Hilton, Gaithersburg, Maryland, Kenneth Noller, M.D., Chair, presiding.

PRESENT:

KENNETH NOLLER, M.D.	Chair
PAULA HILLARD, M.D.	Voting Member
HUGH MILLER, M.D.	Voting Member
JONATHAN WEEKS, M.D.	Voting Member
MARCELLE I. CEDARS, M.D.	Voting Member
HOWARD SHARP, M.D.	Voting Member
JOSEPH SANFILIPPO, M.D.	Voting Member
DIANA ROMERO, Ph.D.	Consumer Representative
ELISABETH GEORGE	Industry Representative
GERALD SHIRK, M.D.	Consultant
SCOTT EMERSON, M.D., Ph.D.	Consultant
NASSER CHEGINI, Ph.D.	Consultant
NANCY SHARTS-HOPKO, R.N., Ph.D.	Consultant
RUSSELL SNYDER, M.D.	Consultant
MICHAEL T. BAILEY, Ph.D.	Executive Secretary
NANCY C. BROGDON	Division Director

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P R O C E E D I N G S

Time: 9:02 a.m.

CHAIRMAN NOLLER: Good morning. I would like to call this meeting of the Obstetrics and Gynecology Devices Panel to order. My name is Ken Noller. I am the Chairperson of this Obstetrics and Gynecology Devices Panel. I am currently Professor and Chair of the Department of Obstetrics and Gynecology at Tufts University and the Tufts New England Medical Center. I am an obstetrician/gynecologist by trade, a generalist.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors, everyone in attendance.

I am next going to ask the Panel members to introduce themselves. I will ask that each states his or her name, area of expertise, position, and affiliation, and I will start with Dr. Cedars.

DR. CEDARS: Marcelle Cedars. I am a Professor at University of California, San Francisco, and the Division Chief for Reproductive Endocrinology, and Vice Chair for the Department of Obstetrics,

Gynecology and Reproductive Sciences.

DR. SHARP: I am Howard Sharp. I am an Associate Professor of Obstetrics/Gynecology at the University of Utah. I am Division Chief of General OB/GYN and currently serving as Vice Chair for Clinical Affairs.

DR. HILLARD: Paula Hillard, Professor of OB/GYN and Pediatrics, University of Cincinnati, Cincinnati Children's Hospital Medical Center. I do pediatric and adolescent gynecology.

DR. CHEGINI: Nasser Chegini. I am professor at the University of Florida, Department of OB/GYN. I am a PhD, and my research interest is in adhesion and endometriosis, and particularly in molecular biology of fibroids.

DR. WEEKS: My name is Jonathan Weeks. I am a private maternal-fetal medicine physician, Director of Maternal-Fetal Medicine, Norton Health Care in Louisville, Kentucky.

DR. SHIRK: Gerry Shirk. I am in private practice in Cedar Rapids, Iowa, and a clinical Associate Professor at the University of Iowa.

DR. SHARTS-HOPKO: Nancy Sharts-Hopko. My field is maternal, infant and women's health nursing. I am professor and Director of the Ph.D. program in the College of Nursing at Villanova University in Villanova, Pennsylvania.

DR. BAILEY: Mike Bailey, Food and Drug Administration, Executive Secretary of the Panel.

DR. SNYDER: Russ Snyder. I am a general OB/GYN. I also an a gynecologic pathologist. I am the Division Director of Gynecology at the University of Texas Medical Branch at Galveston.

DR. EMERSON: Scott Emerson, a biostatistician and professor of biostatistics at the University of Washington in Seattle.

DR. SANFILIPPO: Joseph Sanfilippo, Professor of Obstetrics and Gynecology and Reproductive Sciences. I am Vice Chairman of the Department of Reproductive Sciences and Director of the Division of Reproductive Endocrinology and Infertility, University of Pittsburgh School of Medicine.

DR. MILLER: Hugh Miller, internal fetal medicine, Associate Professor, private MFN and Medical Director of Obstetrics Practice.

DR. ROMERO: Diana Romero, Assistant Professor of Population and Family Health, Mailman School of Public Health at Columbia University. My research is in reproductive health policies and reproductive related decision making.

MS. GEORGE: Elisabeth George, Vice President of Quality and Regulatory at Phillips Medical, and I am the industry rep.

MS. BROGDON: I am Nancy Brogdon. I am not a member of the Panel. I am the Director of FDA's Division of Reproductive, Abdominal and Radiological Devices.

CHAIRMAN NOLLER: Thank you. The FDA press contact is Colin Pollard. Colin, if you would rise. If the press has anyone to talk to, please speak to Colin.

We will try to run a very orderly meeting today. I ask that no one speak unless they have been -- unless I have asked them to do so or indicated in

some way that they are to speak. For those in the audience, when you speak, please approach the podium and, at least the first time, state your name, and we will get through with affiliations later.

We want to run this in an orderly fashion. One of the most important things is that everybody turn off their cell phones.

I am next going to turn the meeting over to Dr. Bailey to read some required documents.

DR. BAILEY: The remaining tentative Panel dates for 2006 are June 5-6, August 28-29 and November 13-14.

I will now read into the record the Conflict of Interest Statement for this meeting.

The Food and Drug Administration is convening today's meeting of the Obstetrics and Gynecology Devices Panel for the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and consultants of the Panel are Special Government Employees or regular

Federal employees from other agencies, and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws under 18 USC 208. Congress has authorized FDA to grant waivers to Special Government Employees who have financial conflicts when it is determined that the agency's needs for a particular individual's services outweighs his or her potential financial conflict of interest.

Members and consultants who are Special Government Employees at today's meeting have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse or minor child, related to discussion at today's meeting. These interests may include investments, consulting,

expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of clinical trial design issues for new devices intended to treat symptomatic uterine fibroids. Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with this meeting.

This conflict of interest statement will be available for review at the registration table during the meeting and will be included as part of the official meeting transcript.

Ms. Elisabeth George is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Phillips Medical Systems.

We would like to remind members and consultants that, if the discussions involve any other product or firms not already on the agenda for which an FDA participant has a personal or imputed financial

interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firm at issue. Thank you.

I should say that transcripts of today's meeting are available from Neal Gross & Company. Information on purchasing videos can be found on the tables outside the door.

Presenters to the Panel who have not already done so should provide FDA with a hard copy and an electronic copy of their remarks, including overheads. Those should go to Karen Oliver. Karen, are you here? To help our transcriptionist, we would like to get a copy of those during our first break.

So, hopefully, all of our speakers are here, but as soon as we have our first break, please identify yourself to Karen Oliver, and we would like to try and get an electronic copies to help our transcriptionist out, and also for posting on the Web at a later date. Thank you.

CHAIRMAN NOLLER: Next, Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch, will make some introductory remarks to the Panel. Mr. Pollard.

MR. POLLARD: Thank you, Dr. Noller. Ladies and gentlemen of the Panel, distinguished audience, I first of all would like to welcome you all to our Panel meeting today in this the 100th year of -- I can't say the FDA's existence, but if you go into the origins of the FDA's existence, we started regulating products like foods, drugs, devices, etcetera, in 1906, and we are celebrating our Centennial this year.

I am very proud of that legacy, and the Panel process itself is an important part of that legacy, so we look forward to a lively and enriching discussion.

Before we move to the main item of today's agenda, I'd like to speak briefly about four products where we have had significant developments since the Panel last met, and this is in the area of condom labeling, the STAN fetal heart monitor, the OxiFirst

fetal pulse oximeter, and the LUMA cervical imaging system.

Regarding condoms, on November 14 of last year, the Center issued a Notice of Proposed Rulemaking accompanied by a draft guidance document. This proposed rule is asking for more specific information on condom labeling about protection against sexually transmitted diseases, and the main upshot of this change is to highlight that the degree of protection afforded by condoms differs, depending on the STD in question. That is, condoms provide STD protection overall, but they work better against STDs like HIV/AIDS and gonorrhea than they do against STDs like herpes or HPV.

The 90-day comment period ended last month, and we received, as you might have guessed, many, many comments. We are reviewing them now, and are developing a plan for response.

The Panel met in June and recommended approval of the PMA for the STAN fetal heart monitor, and no November 1 we approved the PMA. Here is the indication for use: An adjunct to conventional

monitoring to determine whether intervention is warranted when there is increased risk of developing metabolic acidosis. As you can see, it is intended to be used for patients with planned vaginal delivery, greater than 36 weeks completed gestation, singleton fetus, vertex presentation, and ruptured membranes.

One important thing we did after the Panel meeting was craft language describing the principle of action, and I would like to thank some of the Panel members who helped us in that regard.

Briefly, the STAN monitor provides intrapartum information about two aspects of fetal myocardial physiology, myocardial glycogenolysis and myocardial function relating to perfusion and contractile performance.

In short, when these changes occur, together with nonreassuring fetal heart rate patterns during labor, the clinician has additional information about the working conditions of the fetal heart, much like stress testing in the adult for coronary insufficiency. The monitor helps the clinician to determine when the stress of labor on a fetus has

progressed to a point where intervention is warranted.

The Panel recommended post-approval studies to look at the effect of this new technology, and suggested several key outcomes of interest, such as caesarian delivery rates, perinatal outcomes, etcetera. However, in the end after considering the Plymouth RCT, the Swedish RCT, results from the European Centers of Excellence, and the U.S. bridging studies, we did not believe there was a compelling clinical reason to impose the burden of new post-approval studies on the manufacturer, and did not attach this as a condition of approval.

That being said, many of the questions posted by the Panel are real, and we want answers, if and when this technology is adopted. We intend to fully utilize the various post-market methods in our regulatory toolbox to track its performance, and this will include signal detection using our MDR Adverse Event Reporting System, as well as enhanced surveillance using our MedSen Network of 350 participating hospitals.

We intend to exercise rigorous

epidemiologic review of the published literature, and explore other databases external to FDA that may contain additional useful medical device related data; and depending on our findings, labeling changes or training may be required.

We also plan to engage with our colleagues at NIH and professional organizations like SMFM and ACOG to explore ways of tracking this technology as it makes its way, if it makes its way, into clinical practice. We plan to involve them and other major stakeholders in the public health questions that this new technology poses, possibly leading to studies very much like the ones recommended by the Panel.

Neoventa, as you know, is based in Sweden, and they are currently working to line up a marketing partner. We expect their market launch to occur shortly, and we will update the Panel periodically on this.

Turning next to the OxiFirst fetal oxygen saturation monitoring system: Some of you may remember that six years ago in May of 2000 we approved a PMA for this device, a first of a kind. Shortly

after that, we approved two additional PMAs for manufacturers who licensed the same technology.

Even as we gave permission to market this monitor, there remained serious questions about its impact if and when the technology was adopted. We attached a condition to the approval, requiring a manufacturer to either conduct or cooperate in the conduct of clinical studies addressing those questions.

The manufacturer supported the first two studies, a general use study and one looking specifically at distortion. They were both completed sometime ago. The last was a large randomized study sponsored by NIH called the FOX trial, a randomized trial involving more than 5,000 patients.

The manufacturer provided technical support for this study, and FDA actually provided some additional technical help from Sandy Weininger, a software engineer in our Office of Science and Engineering Labs. This study has now been completed. The results were presented a few weeks ago as the number one paper at this year's SMFM meeting.

The FOX trial failed to show an impact of the technology on Caesarian delivery rates for both the overall population as well as the indicated population of labors with a nonreassuring fetal heart rate.

The manufacturer has voluntarily stopped marketing the monitor, although it will continue to provide technical support to customers still using the monitor with remaining disposable centers at hand. The firm will also continue to fulfill other PMA requirements, such as annual reports, adverse event reporting, etcetera.

We are now studying the results of the FOX trial to see if key information from the study needs to be included in the labeling for clinicians who still use the monitor, even as we recognize that its use is waning.

The LUMA Surgical Imaging System is indicated as an adjunct to colposcopy for the detection of cervical cancer precursors. Last May the Panel recommended that this PMA be disapproved, and I want to briefly review why we decided to approve this

device after all.

There were two major clinical studies supporting this PMA. Pivotal Study I was a randomized study comparing concurrent use of colposcopy and LUMA to colposcopy alone. Pivotal Study II was a single arm study looking at the incremental contribution of LUMA at the patient level when used in sequence after colposcopy.

PSI involved a little under 2200 women referred with an abnormal PAP smear, randomized to either colpo or colpo plus LUMA. As you know, the study showed no difference overall between the two arms, but we did see an encouraging trend in the ASC and LSIL subgroups.

Because we wanted to be able to see the individual contribution of the new technology on top of colposcopy on a per patient basis, we convinced the firm to do Pivotal Study 2, PSII. This study had two co-primary outcome measures, the true positive increment and the false positive increment, with a separate hypothesis for each, as you can see on the slide. The confidence interval for a true positive

increment needed to be above two percent. The confidence interval for the false positive increment needed to be below 15 percent.

The firm stopped PSII early for financial reasons, not influenced by any early peak, and this is what we saw: 193 subjects. Colposcopy and LUMA each led to an average of about one biopsy per patient. On the true positive side, colposcopy ID'ed 41 women with true positive disease, and LUMA added another nine. on the false positive side, colposcopy led to 141 patients being biopsied, about three-quarters of the population; and on a subject level, there were 100 false positives, giving a 51 percent false positive rate. LUMA added an additional 35 patients, giving an 18 percent false positive increment.

So remembering the hypothesis, you can see that the confidence interval for the true positive is above the two percent mark. However, the observed increment in false positives, 18 percent, upper bound of 24 percent. That is above the 15 percent mark. so the study missed on this.

In short, it met one mark and not the

other, and this is pretty much where things were when we met in May when the Panel recommended disapproval. The main reason given was simply the biostatistical failure of the study to meet one of the two targets.

After the meeting, as we continued our review of the PMA, we looked at these two endpoints together as an overall measure of diagnostic performance. We know these two endpoints are not independent and, really, we came to believe that they should be evaluated as a ratio.

When you do that, it leads to the finding of the subject level that LUMA used results in about four women biopsied unnecessarily for each woman detected with true disease that colposcopy missed.

When we looked at the results this way, we felt the four to one tradeoff really wasn't that far from what we hoped; and when we considered how low the risk an extra biopsy really was, we felt that clinically these results were meaningful and positive.

That was a big step for us toward coming to view this device as approvable, not quite as good as hoped going into the study, but not that bad

either. But we wanted to be sure the LUMA technology itself really was doing something that led to these additional true positives.

To tackle this, we asked MediSpectra to look at the relationship between the LUMA score generated at the biopsy site in PSII and the corresponding pathology result on that biopsy. Clinicians don't see these numbers, but the LUMA scores are generated by the system algorithm and used to create the false color image of the cervix that the colposcopist actually does see.

From this analysis, the firm was able to show that the LUMA score has a direct and significant relationship to the probability of a CIN II/III biopsy with a higher LUMA score, indicating a higher likelihood that the biopsy will be positive.

The analysis also looked at this finding as a function of whether the biopsy was taken because of colposcopy or because of LUMA, and our analysis showed a large interaction effect, indicating that the previously described relationship was even larger in the LUMA phase than in the colpo phase.

One way of looking at these findings represented with this slide is that, for every 25 percent increase in the LUMA score, for instance, the odds of a positive biopsy is estimated to increase 2.6 during the LUMA procedure, compared to an increase of half that much when taken during the colposcopy phase. This large effect difference in the LUMA phase led us to believe that the LUMA is effective as a valuable adjunct to colposcopy.

Now there was one other question we considered as part of the continuing review of this PMA after the Panel meeting, namely: Would simply taking an extra biopsy have led to the same result?

This was not a reason cited by the panelists, but we felt it was a reasonable question to ask. Only that morning we heard data from the ALTS trial to the effect that, not too surprising when you think about it, the more biopsies you take with colposcopy, the better the sensitivity.

How do we know that we are not looking at such an effect when we look at true positive increment from the LUMA technology in PSII? The simple answer

is we don't know. From the beginning, PSII wasn't designed to answer that question. Even if the study had been completely successful and the results led to rejection of the LUMA for both endpoints, we still would not know the answer to that question.

In the end, we felt that it wasn't fair for a PMA approval to turn on this question, because it was not, and still is not, the standard of care for colposcopy.

My understanding is that ASCCP is currently exploring whether and how colposcopic practice and training should be changed to account for these new findings, but it wasn't clear to us just how this would be done, or should have been done, in a clinical trial of a new adjunctive technology without introducing selection bias or how such results should be interpreted.

We decided that this point could be adequately mitigated by information provided in the professional labeling.

I would also like to touch on four other issues voiced by the Panel. Some panel members

expressed concern that results from PSI and PSII only represents that attainable by the most highly experienced colpolscopists. What happens when LUMA is used by less experienced clinicians?

In fact -- and this information was not presented at the Panel -- the 50 or so clinicians who used colposcopy and LUMA in PSI and II represented a wide range of colposcopy experience fairly equally divided.

Some of the Panel thought the data should have differentiated between CIN II and CIN III, but per the 2001 consensus guidelines in effect when the study was designed, and even today, CIN II/III -- even today, to our understanding, CIN II/III is managed the same way, and biologically CIN II is more like CIN III, and because of this many path labs no longer separate CIN II from CIN III, and most have moved to a two-tier terminology.

A couple of panelists were concerned that use of LUMA will lead to more LEEPs in younger women and, frankly, we saw this point as the practice of medicine -- that is, what do GYNs do when they get a

particular diagnosis back from the path lab? -- not a consequence of use of this device.

Then and now, GYNs want to know the true disease status of their patients, and they get that as pathology results from the biopsies. What they do with that information is practice of medicine.

Finally, some of the Panel was concerned that clinicians won't follow the always/never rule, namely always do colposcopy thoroughly first, select your sites and never subtract them based on the adjunct technology.

We did not see this as a reason not to approve the PMA, but we did ask MediSpectra to implement some screen annotation software to facilitate and encourage physicians to use the technology appropriately, and training also underscores this approach.

So to wrap up the question of why we approved this PMA, I just want to say that we understand our decision was based on post hoc analyses, not pre-specified in the study design, and we understand what that means about its biostatistical

underpinnings -- that is, observational findings supported by descriptive statistics versus probabilistic inferences; and we appreciate that some of these analyses were ones that the Panel did not have access to at the time. We did not believe it appropriate to bring the PMA back to the Panel.

It was not an easy decision, but one taken in its totality. We found the data to be persuasive. That is, the LUMA system identified areas on the cervix with higher probability of true disease, and more importantly, when viewed as a tradeoff between false positives and true positives, use of this technology led to detection of more true positives at an acceptable cost of about one extra biopsy per patient.

Finally, I want to briefly summarize a few of the key elements of the PMA approval itself. Labeling, clearly and unequivocally, defines use of the technology as a thorough colposcopy first with commitment to biopsy sites, followed by evaluation of the LUMA image and identification of any additional biopsy sites, without subtracting any committed to by

colposcopy. And as I mentioned, MediSpectra has implemented new software that facilitates this device use sequence, something we call the "always/never rule." That is, screen prompts essentially require the colposcopist to mark his or her biopsy sites from the colposcopy exam before proceeding on to the LUMA procedure.

Labeling and training make it clear that colposcopy catches some disease that LUMA misses, and vice versa. The labeling also clearly indicates that use of the LUMA technology will inevitably lead to additional biopsies, and that it is unknown whether additional colposcopically directed biopsies would yield comparable results.

As I mentioned, training was implemented to underscore these aspects of the device use. Finally, a major condition attached to approval of this PMA is the requirement to conduct a post-market study to help answer some of the remaining questions about this technology.

The study will enroll nearly 1,000 subjects to ensure 800 evaluables when finished, and

it will address reader variability, the effect of age, colposcopy experience and HPV status on diagnostic performance, and it will also provide diagnostic information again with larger numbers and a tighter confidence interval.

I would like to next move on to today's agenda, and that is the topic of symptomatic uterine fibroids, new treatment technologies and clinical trial design.

I don't intend this to be very long. I want to give just a brief overview of the problem, give a quick snapshot of the kinds of technologies we are looking at, a few aspects of the problems that we encounter when we look at clinical trial design, and what we are really asking the Panel to do; and we also have scheduled immediately after this an open public hearing where we will hear from a number of the developers and other stakeholders in this question.

We will not be talking about a more regulatory type question of whether different devices should go 510(k) or PMA. That is really not the topic at hand.

So very briefly, as you are far more aware than I am, symptomatic uterine fibroids are a major problem in the U.S., complex symptomatology and a leading indication for the more than 600,000 hysterectomies in this country every year. They have a complex constellation of anatomical manifestation as well as symptomology. The biology is not that well understood, and how to evaluate treatment success is not well established.

I have listed here a variety of the technologies that we are now encountering. Many of these you have seen in the published literature already: Radiofrequency RF myolysis performed laparoscopically; cryomyolysis, typically performed laparoscopically; and interventional radiology over the last five-plus years has actively engaged in the area of treating uterine fibroids, most notably in the aspect of uterine artery embolization but also with focused ultrasound, cryomyolysis, and RF. Finally, we are also looking at devices for vascular clamping or uterine artery ligature.

I am highlighting a few points that I am

sure are going to come out in your discussion, but some of the things that make the problem more difficult is the fact that fibroids vary quite a bit in terms of the number of fibroids an individual patient has, where they are located, the size of each of those fibroids, and that in turn leads to a multiplicity of symptoms and then begs the question, what are the study endpoints that should be chosen for a given clinical trial.

Regarding randomization, the aspect of perceived morbidity can be challenging in that, from a practical point of view, to run a randomized trial you have to be able to offer the subject something that they are reasonably going to want to get into in a randomized fashion.

Finally, the issue of the device as a tool versus a treatment. All of you are very familiar with myomectomy, and some of the devices that you have seen are really essentially an extension of the surgeon's hands, really, and far more surgical skill is involved.

It is a different matter when we are

talking about either infarcting or ablating the fibroid itself and leaving it there and counting on the symptoms to reside.

We, as you can well imagine, get approached by many of the different companies and developers who are working on these different technologies, and it is important for FDA to really zero in on what are the important questions that need to be asked and answered, and how much of that needs to be done in the pre-market setting versus the post-market setting.

A few other sort of regulatory aspects that I am sure you can appreciate but may not think of all the time is, number one, we are bound under the statute to impose the least burdensome approach that still leads to clinically significant results, and so it really gets down to the "nice to know" information versus the "need to know" information. What do we really need to know?

The aspect of an even playing field, as you can imagine: We are regulating industry. Is it a competitive world, and people need to understand and

appreciate and feel like they are playing with fairness.

Just briefly, what have we used in the past? We touch on this in the background package that we provided to you about a month ago, and looking at endpoints. We have looked at bleeding scores, pictorial blood loss, blood loss assessment charts, and the like.

We have looked at quality of life instrument. For pain, there is the Ruta Menorrhagia QoL, and there is a fibroid-specific QoL. There are contrast enhanced MRI images that are taken right after procedures, as well as downstream several months, and an endpoint that is used in conjunction with bleeding over with our colleagues in Drugs is did that patient ultimately need to return for surgery, and then that would be attached to a particular time spot or multiple time spots downstream from the procedure, or in that case the drug.

There is the question of controls in two UAE trials. In one focused ultrasound trial we allowed firms to use a nonrandomized control group

with hysterectomy, but as you know, when one of those came before the Panel as a PMA, there were some real questions about the value added of a nonrandomized arm, and the issue of follow-up and, obviously, there's post-procedure follow-up issues as efficacy follow-up. We have looked at efficacy at six months, one year and three years.

So why do we have you here today? Obviously, you have had a chance to review the papers in the background package, and I would highlight that those were just some selected papers from a much, much wider body of literature on fibroids.

We are asking you to listen to all of the speakers this morning who are developing products and clearly have a stake in this, describing their products and the clinical trial issues that are before them and before us; and using our prepared discussion questions as a framework to help us answer the sort of overarching question of what type or types of studies are needed to answer the most important questions.

I am going to quickly review the questions themselves.

Question 1 is speaking to the primary symptom being bleeding, but other symptoms are pain, urinary problems, infertility, bulk symptoms. We are looking for you to discuss what do you think is the most appropriate parameter to use in evaluation of device effectiveness, and list a few of the possibilities.

Question 2, to talk about specific inclusion or exclusion criteria which should be made part of the study design, including minimum or appropriate baseline scores, measurements or symptom levels.

For each important outcome measure, discuss what would be an acceptable definition of individual patient success post-treatment, and when that measurement should be assessed.

Question 4 speaks to the issue of a control. As I mentioned, for some products that can be a difficult matter. At our panel meeting two years ago, the notion of a sham control was posed for the focused ultrasound-type device, but many other technologies, a sham control is not possible. So we

are asking you to discuss other control options, myomectomy, UAE, or no control, the patient serving as her own control. What is the role of randomization?

Question 5: We are asking for you to think about and discuss the notion of the study success as opposed to individual patient success. How good is good enough when the study is done? Please comment on what would be the minimally accepted percentage of treated patients who would meet the individual patient success criteria; and if it is a controlled study, comment on whether there is a minimum difference between the percentage of successful patients in each arm that would be needed for the study to be called a success.

Finally, we are asking you for some discussion of the time frame for evaluating these efficacy parameters.

Thank you very much, Dr. Noller and Panel members, and we look forward to an interesting and lively and, hopefully, fruitful discussion.

We are not asking for a vote on the matters. There is no application before you. We are

hoping to see a discussion of the issues. If some of them are converging on a consensus, that's great. If other ones seem to camp out in two or three other locations, even that will be helpful information as well. Thank you very much.

CHAIRMAN NOLLER: Thank you, Mr. Pollard.

Now we are a few minutes ahead, but as soon as I finish a little bit here we are going to take a break. But I want to speak to the eight presenters that have identified themselves.

We are on a strict time schedule today, and each of you have been asked to speak for five minutes, and we will hold you to five minutes. This is not exactly like when you are presenting your product the PMA panel discussion where we want to hear everything you have to say. We only want to hear five minutes of what you have to say.

So I will tell you when it is five minutes, and we expect you to say thank you and sit down.

Also, we have numbered chairs in the front row, one through eight. The order is Dr. Alikacem,

Dr. Burbank, John Greenbaum, Dr. Gee, Dr. Grossman, Dr. Tay, Dr. Cowan, Dr. Venbrux.

We would like you to sit in those chairs. We are going to use the on-deck sort of thing. During the break, we would like Dr. Alikacem to have his computer set up. We would also like to have Dr. Burbank sitting at the table with his computer set up. As each person goes up to speak, the next person hook up their computer.

If we don't do that, you'll only get about three minutes, because we all know changing computers takes time.

During the break, all of the speakers, eight speakers, will need to talk to Karen Oliver. karen, raise your hand again in case some people came in late. There's Karen. You need to submit an electronic copy of the presentation for web posting and to be included in the record of the meeting.

I have right now 16 minutes to 10. We will break until 10:00 a.m. Thank you.

(Whereupon, the foregoing matter went off the record at 9:47 a.m. and went back on the record at

10:04 a.m.)

CHAIRMAN NOLLER: Okay. We are reconvened now. We will proceed with the open public hearing portion of the meeting. Prior to the meeting, eight organizations and manufacturers asked to speak. They will speak in the order of their request, and each organization and manufacturer has five minutes to address the Panel.

I will now read the open public hearing statement. Speakers, please pay attention to this.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of the individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor -- a sponsor, its product and, if known, its

direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Our first speaker is Dr. Nadir Alikacem. Five minutes, please.

DR. ALIKACEM: Good morning, ladies and gentlemen, members of the Panel, members of the FDA. I would like to thank you for this opportunity.

I am Nadir Alikacem. I am the Pole Manager for InSightec North America. Our product is called ExAblate 2000. This is a MR guided focused ultrasound device.

In devising our studies, this is a device that has already been approved by the FDA through a

PMA regulatory path. In devising our studies, we looked at what are the device procedure requirements. We looked at we need to have an outpatient procedure, a procedure that offers an alternative to invasive surgery for certain specific type of patients, based on certain specific inclusion/exclusion criteria, a procedure that offers next day return to normal life, management of symptom relief, as well and most of all, a real time treatment visualization and control.

What is MR guided focused ultrasound? This is a marriage of two technologies. One is the high intensity focused ultrasound that has been around since the Forties, and the MR component is used extensively clinically for imaging perspective.

The marriage of the two technologies produced ExAblate 2000, and the ExAblate 2000 device is illustrated here for your interest. The treatment basically consists of ablating the tissue -- the soft tissue while monitoring the treatment in real time.

What is focused ultrasound? Focused ultrasound basically focuses the heat at very well targeted spots using MR feedback to ablate that

particular spot.

Why do we think MR guidance and control is important? First of all, treating uterine fibroids must have a real capability to provide you with three-dimensional anatomic information of the exact location and surrounding anatomy of the target.

The MR allows you also, which is a very important aspect of the device, is to provide beam visualization during the treatment and during the planning of the treatment.

The other very important component, not only from efficacy perspective but also from safety perspective, is real time MR thermometry that can be achieved during the treatment itself.

Finally, once the treatment is completed, then MR can provide you with a real time outcome of what was performed during the treatment.

3D anatomy can be used. Why is it important? The MR provides you with a full view of the area of interest. That includes the entire anatomy surrounding the fibroid. Most of all, it provides you the feedback from three main directions,

providing you with three-dimensional information for your planning and tailoring the treatment according to the patient's anatomy.

The second element is beam visualization. This is very important, because each patient is different. Patients have surgical clips. Patients have scars. Patients have different various elements of anatomy near and around the fibroid that needs to be identified and dealt with appropriately.

The MR thermometry: This is a very key element, because MR thermometry not only provides a feedback of the target itself, but also it allows you to sample the entire field of view with respect to how well the treatment is performed and what is the safety factor during that treatment.

When looking at the target itself, you can see that focused ultrasound targeted area is very well contained within the target, and the MR thermometry reflects that distribution of heat and temperature across the target that was planned for.

The treatment outcome is also measurable by MR contrast enhanced protocols. This is an

important parameter, because it has the potential to play a very important role in the follow-ups as well as measuring that as a surrogate parameter for symptom relief.

What are the study endpoints for any clinical trials for device? The study endpoint must take into account management of patient symptoms as well as management of patient lifestyle. The patient population that are interested in these minimally invasive -- or noninvasive technologies are those that are highly educated people, want to go back to their quality of life.

The second very important element in any study for the device is that the study must take into account the lifetime of a device, as well as its continuous R&D innovation. This is very important aspect, because every treatment is a unique treatment, and the information are captured and factored in during the R&D continuous innovation process.

CHAIRMAN NOLLER: Time, please.

DR. ALIKACEM: Thank you.

CHAIRMAN NOLLER: Next, Dr. Burbank.

Good morning. My name is Fred Burbank. i am the Chairman of the Board of Vascular Control Systems and one of the primary inventors of the Flostat System. So I definitely have a conflict of interest describing this system.

I am going to try to quickly describe what I believe are the clinical endpoints for global treatment of uterine fibroids using the Flostat System. This system is developed to allow obstetricians and gynecologists to identify and control the uterine arteries without surgery transvaginally.

The system is comprised of three primary elements: A transceiver ultrasound box that does not generate energy or heat; a guiding tenaculum and a vascular clamp that -- All three elements have been cleared in separate 510(k)s.

The tenaculum attaches to the cervix to guide the vascular clamp to the area of the uterine arteries in the three o'clock and nine o'clock position. When advanced along the guiding tenaculum, the clamp can fold the urinary arteries posterially

and superially and, when closed, can occlude the urinary arteries for a brief period of time.

Fibroid symptoms are not like DOVE symptoms. Women who have fibroids do have menorrhagia in the main, measured by an acceptable menorrhagia scale. In addition to that, they have bulk symptoms measured by quality of life instruments or by uterine imaging.

We believe that a woman who seeks our global therapy will seek to have the three following criteria met: Continue to have menstrual cycles, not lose her periods; have reduced menstrual blood flow, measured by some menorrhagia scale; and have improvement in quality of life related to the treatment.

Just as a foot note, menorrhagia uterine volume when treated by UAE are not covariates. Menorrhagia can improve in one patient and have no change in the uterine volume, and vice versa.

Women with fibroids do not have normal periods. This is shown by the only population based study of fibroids published by Donna Day Baird and her

colleagues, who show that women who have fibroids have abnormal periods.

Women who have fibroids probably fall along a menstrual blood loss curve that looks like the red line. The normal distribution of menstrual blood loss, as measured by the alkaline hematin method is in the normal area here. A woman who has fibroids may be asymptomatic for years during her life. At some point, she may move from asymptomatic of menorrhagia to a symptomatic menorrhagia.

Let's say she goes from 150 milliliters of blood loss per menses to 200. If during the therapy she was brought back to 150 and she said to us, my menstrual blood loss can be controlled by my methods of sanitary napkins and tampons, I'm okay with this, then she would be considered a success by us.

Metrics used to measure menorrhagia include a Ruta scale and the PBLAC scale. Quality of life metrics are well known. We have used the two outlined in purple.

The Ruta scale was developed in Scotland and has shown to be valid and reliable. It has high

patient compliance. We have chosen it because of those features.

Our pilot data indicates that women who have been treated with our system, 40 subjects in Canada, have had 100 percent return to continued menstrual cycles. Of those who had menstrual cycle, which is the entire population, 81 percent had a 50 percent or greater reduction in their menorrhagia score on the Ruta scale. Of those that had passed hurdles 1 and 2, 80 percent had experienced improvement in quality of life on the SF-12 questionnaire.

We believe the success for an individual fibroid patient is like a relay race over a hurdle. One must cover hurdle number one, which is continued menstrual blood flow during your periods. Menstrual two is your blood flow decreases an acceptable level for that woman, not to the normal level -- these are not normal when they have fibroids -- and that she have an improvement in her quality of life, and that she must have success in all three in order to be considered a successful outcome with our device:

Retain menstrual cycles; clinically significant decrease in menstrual blood loss on a validated scale, and there are two validated scales to choose from; and clinically significant improvement in quality of life, and there are two quality of life -- there are three quality of life scales that are relative to fibroid patients.

We believe that clinically significant must be balanced against treatment complexity and morbidity. This multi-step criteria, three hurdles for any individual patient, has been reviewed by Doctors Munro, Hutchins, Brill, Gimpleson and Lauffer, and they have written reviews to the FDA indicating that this is an acceptable criteria for outcome.

We have been in the FDA's process for approximately one year. We have worked through many issues with them, and we have not been able to come to agreement on what is patient success for an individual patient for a woman who has fibroids. Thank you very much.

I'll be here all day, if I am asked to come back and answer questions.

CHAIRMAN NOLLER: Thank you so much. Thank you for staying on time.

John Greenbaum will be next.

MR. GREENBAUM: Okay. My name is John Greenbaum, and I am an independent consultant. Right now, I am compensated by Biocompatibles U.K. Ltd., and the product is distributed by Terumo Interventional Systems.

They are makers of embolization agents called GelSpheres, BeadBlock. They make LC Bead and Precision Beads. They are small microspheres, ranging from 100 micron size to 1,000 microns and, in particular for uterine fibroid embolization, the beads are put into the uterine artery. There is thrombus formation, and the fibroid infarcts or shrinks down.

The product is pre-packaged in a pre-filled syringe. It contains a blue dye, and they are color-coded based on the size of the beads that are used.

In the case of uterine fibroid embolization, the company intends the label the product for nothing smaller than 500 micron. Here is

a chart that is hard to see, but it does reflect the different colors for the syringes, their caps, and the labeling for the different sizes of embolization beads, which is very important.

BeadBlock are compressible microspheres. They are 90 percent water, 10 percent PVA. The formability depends on the size of the bead, but as you can see in this particular case, there is the geometry of a sphere inside, I believe, a three-inch catheter lumen.

I want to talk a little bit about the indications for use. Right now, and since 2002, GelSpheres and BeadBlock have been cleared with this indication for use you see up here. They are intended for embolization of hypervascular tumors and arteriovenous malformations .

They were originally cleared as Class III devices before FDA put out the special controls guidance on embolization devices, and it was a substantial equivalence 510(k). They were equivalent to two predicate devices, EmboSpheres, Microspheres and contour emboli PVA microspheres, and that was in

2002. They were cleared for both neurovascular and vascular embolization.

I am a little confused as what's changed. We are here to talk about the design of clinical trials for devices used in uterine fibroid embolization. In December 2004 after about a 10-month review period on a guidance -- a draft guidance, FDA published a special controls guidance reclassifying these devices as Class II special controls, after a thorough evaluation of safety and effectiveness, including uterine fibroid embolization.

In the meantime, physicians have rapidly adopted the use of embolization agents for uterine fibroid embolization. It goes on today every day. In the guidance document that FDA published, they defined the vascular embolization device as intended to control hemorrhaging due to aneurysms, certain types of tumors, and included in that were uterine fibroids and arteriovenous malformations.

These are neurological embolization devices as well, and a neurological embolization device was defined by FDA as intended to permanently

occlude blood flow to cerebral aneurysms and cerebral arteriovenous malformations.

Now I know we are here to talk about uterine fibroids. FDA also stated in the guidance document that FDA believes that the risks to health associated with the intended uses of vascular embolization and the neurovascular embolization devices are the same. That is in the guidance documents.

Then the guidance goes on to discuss, in accordance with the least burdensome provisions of the Act, FDA will rely upon well designed bench testing and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information.

So here we are, these two firms -- and I do represent other firms and competing businesses, but this is specifically for Biocompatibles -- trying to obtain a 510(k) approval in accordance with a guidance where the company has already obtained a five percent clearance based solely on preclinical and laboratory data with no clinical study for much higher risk

procedures in neurological embolization.

I repeat that is a little bit of a dilemma to us. Higher risk uses such as treatment of neurological AVMs are cleared on the basis of bench and preclinical testing alone. The safety record of embolization devices in these uses has been clearly established in the published literature.

CHAIRMAN NOLLER: Time, please.

MR. GREENBAUM: I thank you very much for your time.

CHAIRMAN NOLLER: Thank you. Next will be Dr. Phyllis Gee.

DR. GEE: Good morning, distinguished Panel and guests. Dr. Phyllis Gee. I am a practicing gynecologist in Plano, Texas, and Medical Director for the North Texas Uterine Fibroid Institute, and I actually do perform MR guided focused ultrasound, and I am accompanying Nadir Alikacem today to speak about MR guided focused ultrasound.

I am also a principal investigator for InSightec.

MR guided focused ultrasound -- think Dr.

Alikacem did a great job of kind of explaining it briefly, but basically it is similar to how a magnifying glass focuses light energy. High frequency sound waves are focused to a point, and at that point the energy density generates high temperatures that are then able to heat tissue and destroy it or ablate it.

During the procedure, the MRI is used to -- both for preplanning of the procedure and as providing imaging during the procedure itself to demonstrate the anatomy as well as temperature feedback of the treatment.

I think that there are a couple of different perspectives that I want to kind of promote today. One is to speak on behalf of the patients that I have been treating, and then on behalf of my colleagues. But from a patient perspective, what patients are looking for are treatments that provide good symptom relief, that concentrate rather on symptom relief than actually eliminating the fibroids or the disease itself, also that tend to be less destructive to the body or less invasive, minimally

invasive, and don't require removal of organs.

They are also looking for low incidence of adverse events that don't require additional medical visits or procedures and follow-up, and they want procedures that are less disruptive to their way of life. So a quick recovery from the procedure and a rapid return to normal function.

From a physician perspective, as a practicing gynecologist what we as providers are interested in, in all of these different modalities, is that the procedure is, number one, safe and is low risk -- offers low risk of patient injury.

We also want robust treatment efficacy -- so something that is going to provide good symptom relief and be sustainable. We want something that is going to treat the patient's symptoms with fairly prompt improvement, that provides real time feedback is, I think, idea, and also offers immediate assessment of the treatment outcome so that you can fairly well predict what you expect the patient's recovery will be, a noninvasive or minimally invasive procedure that renders the organ not necessarily to be

removed, I think I stated, and excellent patient satisfaction.

We also want a procedure that does not preclude patients from having other options in the future.

This is a graph that basically summarizes the trials involving the ExAblate 2000. This highlights the goals of the treatment which follow symptom, quality of life, surveys that the patients would fill out.

Starting with treatment, the initial pivotal trial which is in pink shows the initial 109 patients that were initially enrolled for six months, and those patients were treated. The goal was to treat 30 percent of the tumor -- to have 30 percent of the tumor nonperfused. Most of this limit was placed on the device, because the primary concern was for safety, and we wanted to see what the safety would be.

The purple line, or blue line, depending on your color, is the continued access one where these patients actually had -- After the pivotal trial had been closed, these patients were continually enrolled

with the same treatment protocol. However, line 3 is the continued access 2 which is where there was an enhancement of the treatment that was approved by the FDA so that larger portions of the tumor could be treated.

As you can see here, the initial improvement is significantly improved based on the amount of tumor that you can treat, and actually that is continued even out past the initial dropoff here. So you will see continuous improvement.

So basically, I am here to say that any design for future treatments should include all of these elements and are very important to patients as well as clinicians. Thank you.

CHAIRMAN NOLLER: Thank you. Next, Dr. Jessica Grossman.

DR. GROSSMAN: Hi. I am Dr. Jessica Grossman. First, I would like to say it is an honor to present to such an illustrious panel.

I am President of a company, a new company, called Gynesonics. I founded the company in January of 2005. So we are really quite new. I am a

physician. I was trained in OB/GYN, and we are very early stage. We are developing a minimally invasive device for fibroid tumors.

I am going to talk to you about something a little bit different, because we believe that this is a surgical device for the gynecologists to use in the treatment of fibroid tumors.

Not all devices for fibroid tumors are created equally. Some devices have a known mechanism of action and have been in use for many, many years. For instance, radiofrequency electrosurgery has been around since the 1920s. It has a well known mechanism of action. It has been well characterized in the literature, and the mechanism of action and the performance is easily demonstrated on benchtop models and/or extirpated uteri.

The device that we are developing is a single electrode probe that is inserted either transvaginally, transcervically or laparoscopically. It uses ultrasound for imaging or guidance, and the indications for use would be delivering radiofrequency energy to the target area to ablate or desiccate the

tissue, soft tissue and uterine pathology, including fibroids.

Let's just review the definition of ablation. It is either the removal of or the destruction of tissue.

Some of our key device features, which are illustrated in this picture, are: We are a single needle RF electrode probe. This is an embodiment that is inserted through the cervix into the uterus. Ultrasound is used for imaging or guidance, and in the electrode there is a thermocouple at the actual tip of the electrode to do real time temperature monitoring.

So you can actually monitor the temperature of the tissue as you are treating it. This is all a known technology that is familiar to the gynecologist. It is something GYNs use every day in their practice, ultrasound and radiofrequency electrosurgery.

There are predicate devices for this technology that are out there that have similar indications for use in the desiccation and electrosurgical removal of intrauterine myomas and

other uterine pathology. These devices have been cleared by the FDA under the 510(k) pathway for many, many years.

The VersaPoint device was cleared in 1996 and subsequently cleared as recently as 2004. This is a marketed device that is out there today being used, and no clinical trial data was required to support this 510(k), mostly because it has a known mechanism of action that can clearly be demonstrated on the benchtop and in tissue studies.

So we believe that, because there is such a clear predicate device for our Gynesonics system that we are developing, that we should be able to use the rules of substantial equivalence. We have the same intended use. We have the same technology characteristics. Therefore, substantial equivalence can be determined by performance characteristics and performance testing.

There are no new issues of safety or effectiveness that are demonstrated by this type of electrosurgery device, and any issues can be demonstrated by well designed bench testing.

So in conclusion, I think this is clearly a case where the least burdensome principles apply. Electrosurgery has a known mechanism of action. This is really an ablation tool that is a surgical tool like myomectomy, and substantial equivalence can be proven on the benchtop for uterine fibroids, and clinical trials should not be a requirement for all technologies for fibroid tumors, especially when those tumors are not -- especially when those technologies are not a global device but rather a focused and specific treatment for the gynecologist. Thank you.

CHAIRMAN NOLLER: Thank you. next we will hear from Dr. Sew-Wah Tay.

DR. TAY: Good morning. My name is Sew-Wah Tay, and I am the Vice President for Regulatory --

CHAIRMAN NOLLER: We can't hear you. Please, closer.

DR. TAY: Sorry. My name is Sew-Wah Tay, and I am representing American Medical System. I am the Vice President for Regulatory Affairs and Clinical for AMS.

Unlike the previous speakers, AMS'

interest in fibroid treatment is pretty early. We are still in a very early stage of exploring different technologies and different approaches, but our objective really is to develop a tool to aid the gynecologists in treating fibroid via minimally invasive surgery, and to allow the patients to retain their uterus. Our research has shown that that is a very important criteria for any device to be successful in the market, and the device that we intend to come up with, we are going to present it as the first line of treatment for fibroids and with hysterectomy as a back-up in the event that that did not work out for the patient.

One treatment that we have looked into is cryomolysis, because we do have a technology for intrauterine bleeding treatment with cryomolysis.

In preparing for developing this device, we have done some basic research on what should be a clinical study design that will be feasible for us, and these are some of the information that we have extracted and help us focus on what should be our endpoints in the control groups. Very similar to what

this panel have already considered.

Fibroid, as you know, are benign. The majority of women eventually have it, but really only a small -- 25 percent will be symptomatic. One of the main criteria we found was that women seek treatment for fibroids really to relieve the symptom and improve their quality of life, and again symptoms vary, depending on the type, size and location of fibroids, making the study design pretty complicated.

Again, the desired outcome that patients are seeking is symptom relief, improved quality of life, and obviously, safety.

With that in mind, we have researched -- Our research came up that, really, the primary efficacy endpoint will have to be some kind of symptom relief/quality of life vehicle. The best that we have found out is a Symptom Severity Score, which is a subscore for the UFS Quality of Life developed by Spies.

Success criteria we have decided on is the improvement in the Symptom Severity Score of greater than 10 points at six months post-treatment. Just

like the previous speakers have said, in all the literature data has shown that after six months there is not much change in the patient's symptoms.

The other tricky point that we need to consider in designing the study is what should be the control population. The primary care specialty that treats fibroid patients are primarily OB/GYNs, with abdominal hysterectomy being the most common form of treatment, but as you all know, that is pretty invasive.

Now hysterectomy, on the other hand, really cures the fibroids, because you remove the uterus, and so you don't have anymore fibroids. So it is not a good control for in terms of efficacy.

We did consider using UAEs as a group. However, those are treated by interventional radiologies and do not fit in the patient care that we are targeting, which are primarily gynecologists, and because our treatment is a form of surgical treatment, a surgical tool, sham surgery is really not an option for us.

To come up with a study design that is

practical and feasible, this is what we concluded, is that really the most feasible study design is a single arm study using the patient as their own control, thereby getting matched pair data, and as a vehicle using the Uterine Fibroid Symptom Quality of Life vehicle, and comparing the pre- and post-treatment data with the two different subscores.

Endpoint again is the Symptom Severity Score with the first criteria as defined.

That's all I have.

CHAIRMAN NOLLER: Thank you. Next, Dr. Bryan Cowan.

DR. COWAN: Ladies and gentlemen of the Panel,thank you. I am Bryan Cowen, Chairman of the Department of Obstetrics and Gynecology at the University of Mississippi, and I have a keen interest in cryoblation of uterine fibroids. I have published papers before on the treatment of uterine fibroids in the dual magnet MRI, and I am developing a clinical protocol for pivotal studies on the treatment of cryoblation in uterine fibroids.

My conflict of interest: I am an

investigator for Galile and Wyeth, and I am on the Speaker's Bureau for Wyeth.

Cryoblation is applied worldwide and proven for ablation of benign and malignant conditions. It has been with us for a long time, and it has been in use for over 40 years. The FDA has cleared cryoblation for multiple indications, including gynecology, prostate, renal, liver, breast, thoracic, soft tissue tumors and others.

I am developing a research protocol to assess safety and efficacy of percutaneously laparoscopically assisted cryomyolysis, PLC, for treatment of symptomatic uterine fibroids. We have two endpoints, efficacy and safety.

The efficacy endpoint is Symptom Severity Subscale of the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire, the old SSF-UFS Quality of Life published in 2002.

The safety endpoint is treatment related major operative and post-operative complications. We would compare the two groups.

Of course, there are two control groups:

Efficacy, we would use the patient as their own control; safety, we would compare laparoscopic supercervical hysterectomy as the population. We will talk more about this in another slide.

The inclusion demographics of this study would be premenopausal women who have completed childbearing. We would treat three locations of uterine fibroids, intramural fibroids, sub-serosal fibroids, and Type 2 sub-mucosal fibroids; and of course, the patients must have symptoms. As we know, bleeding is the most common symptom, and bulk symptoms are also associated with uterine fibroids.

The rational for the control group is on this slide, and for efficacy there is no perfect appropriate control group and, by the way, that statement applies to safety as well.

I would validate patient success with the patient as her own control. For safety, I have chosen laparoscopic super-cervical hysterectomy as the best choice, and I thought long and hard about this.

The patient population for laparoscopic super-cervical hysterectomy would be derived from the

same population as the study arm.

Both techniques use laparoscopy, and alternative surgical controls create additional confounding variables.

Safety comparison will be based upon similar incidence of treatment, related operative and post-operative complications. However, as a caveat this would be a nonrandomized control.

Finally, the definition of success: Patients will be included if their quality of life score is greater than 40 points. Patient success is 10-point improvement in the quality of life at six months, and study success will be an improvement of the quality of life at six months when 50 percent of the patients demonstrate a 10-point improvement in the quality of life baseline. Thank you.

CHAIRMAN NOLLER: Thank you. Next, Dr. Anthony Venbrux.

DR. VENBRUX: Distinguished members of the Panel, I come as a physician and as a user, not an inventor. I work at George Washington University. I work very closely with our gynecologists and

obstetricians. I have nothing to disclose and no conflict of interest, although as an academician and as an interventional radiologist that has practice for 19 years, I have received honoraria for guest lectures from every single manufacturer of devices, and I'll just say that.

As you know, fibroids are an extremely common problem, and this is no news to this group, accounting for a large number of surgeries, and for those women who undergo myomectomy for symptomatic fibroids, often they require another procedure.

A technique that has been around since about 20 years now is the use of transcatheter embolotherapy to reduce bleeding. There is a precedent. It has been used in life saving maneuvers in patients who have post-surgical bleeding, postpartum hemorrhage, as outlined on this slide, a pooling of literature.

So using inexpensive material that has been grandfathered in, such as Gelfoam or, more recently, coils -- this case from Sally Mitchell from Johns Hopkins of a woman that had pelvic bleeding,

massive pelvic bleeding, after radiation therapy for extensive cervical malignancy -- this can be lifesaving, as you see this extravasation into the vaginal packing and pelvic packing using coils and Gelfoam can prove lifesaving.

So based on this historic literature then, the concept of taking a tumor, embolizing it, leaving it in the body and having it involuted was born, and Ravina in 1995 in paris developed this technique with this interventionalist to reduce blood loss during myomectomy. When I was at Hopkins in '97, I introduced that and have been doing it continuously.

How do you assess pain related to fibroids if that is one of the symptoms? We use a dirt cheap, inexpensive visual analog scale that is literally 10 centimeters long that the patients mark and, when you do it prior to the procedure, afterwards and later, you can get a relatively unbiased, well validated use of pain level, if that is one symptom. So that is one small endpoint in terms of symptom complexes associated with this.

Imaging: We use MR, but certainly MR

tells us that there are other conditions, such as extensive pelvic varices, in this patient that was causing pain and not her fibroids at all, which was initially thought of, or a large ovarian cyst which you see posterially here in this particular image in this parasagittal MR image.

So what do we do? I spend an hour with each patient. Ninety-eight percent of the referrals come from OB/GYN, and I teach some of the residents and fellows and ask them to come into the interventional suite to see how these are done.

So we talk about risks, infection, bleeding, allergy to medications, contrast allergy with the newer contrast agents -- the risk of a significant life threatening contrast reaction is about one in 40,000 to one in 60,000 -- and certainly, non-target organ embolization which I will briefly allude to on the next slide.

For example, on this image you see that there are vessels coursing inferiorly. A particular one is down into the vaginal area and, if you do inadvertent embolization there, you can get a large

ischemic ulcer. There is the obturator branch there, all of this as part of the things we have to look out for as we learn more and more about our embolotherapeutic techniques.

The most important thing is ovarian failure, and I counsel these women, this procedure is not for every woman with fibroids. Ovarian failure, if you are young at about age 35, the chance of having premature menopause is about four percent; whereas, if you are 45, it goes up to about 14 percent. It depends on who you read in the literature.

We talk to these patients, spend an hour in clinic. When the procedure date is due, we talk to them, give them intravenous access with the following medications, as you see here. We do a femoral arterial access. I will walk you through that in the next few minutes. We do a pelvic arteriogram to look for potential variant anatomy, and finally an abdominal aortagram to look for ectopic blood supply to the uterus that may not be visible.

Here is a normal. This was done for other reasons, the normal uterine artery in a young woman.

Here is a patient with large -- with enlarged, excuse me, ovarian -- excuse me, correction -- uterine arteries in this patient who had two large fibroids midline, as you see here. This is the early image. This is the late image, and then as we come up and over and go down into the uterine artery, we are going to be embolizing these vessels here and here.

So how do we do that? We select out using roadmapping technique. We guide our catheter in, and then we use a number of different agents. The most commonly used clinically are the embolic spheres, not PVA anymore, and finally the ability to embolize, whether it is BeadBlock, whether it is Embospheres, and to reach an occlusion which then gives you this kind of a picture.

CHAIRMAN NOLLER: Time, please.

DR. VENBRUX: Thank you very much.

CHAIRMAN NOLLER: We have now finished hearing from the eight speakers that had indicated that they wanted to speak ahead of time. We have a few minutes left in this session, and we would like to hear from anyone else in the audience that has not

spoken. Is there anyone who would like to speak at this time? If so, please rise. Yes, sir? You will be limited to five minutes, as the previous speakers. We also ask you to please disclose any conflicts. State your name, too, please.

DR. STABINSKY: Thank you. My name is Dr. Seth Stabinsky. I have no conflicts. I am a shareholder in Albion, Incorporated, and Scineras Medical. Scineras Medical has a license to cryotherapy in women's health, but to my knowledge they are not currently working on anything in the fibroid area.

I just would like to, first of all, thank you for the opportunity to speak, and I would just like to point out, I think, that there are -- that it will be very important for the Panel members to consider the various types of energy sources. I don't think one size fits all.

My background is both as a trained OB/GYN, practiced for five years, did an endoscopic surgery fellowship, and then went into industry. In my early days at Stanford, I had the opportunity to do some of

the original bench work on the VersaPoint ablation system, and I think that it is very important to note that, when RF is used under direct visualization in a hysteroscopic manner. It is quite safe. It is directly visualized. Gynecologists are comfortable with that.

I don't think that, for example, RF has the same kind of visualization that something like cryo would have under ultrasound guidance. So I would just ask the Panel to be considering that as they move forward thinking about protocols, that one protocol may not necessarily fit all devices.

The other thing is that I think, while there is a six-month -- While it makes sense to look initially at six months, and I know that FDA has been considerate of being least burdensome to industry, six months of observation after a fibroid ablation treatment may or may not portend what is going to come in the future, and that while post-market studies are fine, it is going to be very important to look at regrowth in fibroids and the effect there.

That's pretty much what I wanted to say.

thank you.

CHAIRMAN NOLLER: Thank you. Are there other speakers? Seeing no other speakers, we will close the open public session.

Nancy, is there anything FDA would like to discuss as a result of these presentations?

MS. BROGDON: Yes, thank you. The staff would like to respond to a question raised by one of the speakers.

CHAIRMAN NOLLER: Thank you. Mr. Pollard?

MR. POLLARD: Thank you, Dr. Noller. First of all, I would like to thank all of the speakers. I thought that was a highly informative session we just heard from and, when taken together, really illustrate a lot of the complexities and difficulties that we have here at FDA in terms of giving guidance to developers who want to bring their product to market for treating symptomatic fibroids.

One question was raised regarding embolic products and a guidance document that FDA issued recently, and I just wanted to clarify that that guidance document was issued accompanying a

reclassification of the general category of certain kinds of embolic products from Class 3 to Class 2, and it did include uterine artery embolization as one of the indications covered there.

There's kind of two caveats there. Number one, that was done to simply recognize that at that point FDA had already cleared two 510(k)s for embolic particles, but these were, in fact, based on clinical trials specifically for treating fibroids, and our policy regarding that hasn't changed, and that reclassification process did not change that, and elsewhere in the guidance document it speaks to the possibility that later FDA may develop a guidance document specifically for UAE.

I also wanted to highlight -- to comment further there, no clinical data was needed for neurologic and other peripheral vascular applications, and I just wanted to mention that.

The risk profile for those patients is a whole lot different than women who are being treated for fibroids, and I think that is part of what has gone into how FDA has approached these kind of

products in the past when they are specifically being indicated for treating fibroids.

One last comment I wanted to make: I think there were some very good comments about the aspect of some of these products are viewed as being simply an extension of the surgeon versus an overall treatment, and I think we are hoping to get some nice discussion from the Panel on that.

I would say that, as I mentioned in my opening remarks, that we are not trying to sort out 510(k) versus PMA issues here, but really from a clinical trial design point of view when a product is indicated for fibroids, you know, what are the right kinds of questions to ask in a clinical trial, recognizing, as I think some very valid points were made here in the last half-hour, that not one trial design may work for all these different kinds of products.

CHAIRMAN NOLLER: Thank you, Mr. Pollard.

We will now go to the general Panel discussion, and that is what we will do for the rest of our time today.

By the way, can we put up the questions that you had summarized. Put up the first one, please, and we will go through them in order.

I think the Panel recognizes how difficult an area this is, and we are asked to -- have been asked by the FDA to help them -- help guide them in designing trials for all these different devices and methods of treatment that are likely to come forward in the near future.

It is complicated. First of all, as we know, most women with fibroids don't have any symptoms. A lot of them don't even know they have them.

On the other hand, there are women that have severe symptoms, but not every woman with symptomatic fibroids has the same symptoms. For some, it is bleeding alone. For some, it is pain. For some, it is mass effect; some, it is multiple.

How to design a trial that addresses these various problems that women may have that are undergoing treatment? A pain scale would be useless for the woman who has no pain. Mass scale is useless

for the woman who has no mass symptoms. Are multiple endpoints necessary, multiple evaluations necessary?

There are different numbers of fibroids, different sizes of fibroids and, as we've just heard, many different methods of treatment.

So this is a tough task, and I think the reason we are being asked to do this is because FDA has appropriately realized how hard it is to decide how to design appropriate trials to determine whether or not these various treatments are safe and effective.

Our first question is up on the board. Actually, I might argue a little bit with the first statement, that the primary symptom of problematic fibroids is bleeding; because for some women it is pain or bulk, but those are mentioned as other symptoms. But bleeding certainly is one that can even become life threatening.

We have been asked to discuss what we believe to be the most appropriate parameter to use in the evaluation of device effectiveness, and we have heard bleeding scores are available. We have heard

quality of life scores are available. You can measure size by various things.

What do we think is the best way to evaluate success, if you will, of treatments? The floor is yours. Yes, sir? I guess you are going to have to identify yourselves individually.

DR. SHIRK: Dr. Gerry Shirk. I guess I just want to make some comments, because I've obviously got the most longevity with this Panel. Dr. Mike Diamond, Dr. Barbara Levy and myself helped establish the criteria for endometrial ablation, which is obviously the other treatment for abnormal uterine bleeding in women and, basically, was probably one of the major reviewers for most of the endometrial ablation devices.

The question there was really simple. Basically, we had essentially no pathology. The idea was to rule out pathology. These patients were not going to reproduce, and we didn't have that question. And obviously, one of the questions here is reproduction or future reproduction.

Also, these patients, you know, all had

bleeding problems that they wanted terminated. So the only issue was basically bleeding. We also had a standardized procedure that we were doing already, although I wouldn't call Rollerball ablation totally standardized. There's obviously lots of ways to do it.

So that, you know, the issues were fairly simple. So that a simple method of grading of bleeding with a PBLAC score -- basically, there's some other sophisticated things now, but the PBLAC score, you could argue one way or the other, but if the patient was going to make an error, it was going to be in the area of basically fastidiousness and using too many tampons which would preclude more failure than --

CHAIRMAN NOLLER: Can you explain that scoring system a little bit?

DR. SHIRK: Basically, it is a scoring system that uses standardized tampons and pads and how much of the pad and tampon are used, and equates fairly well with the amount of blood loss, you know, if it is done correctly, and I think this is pretty well documented that it works extremely well and

coming fairly close.

We set up -- Obviously, the criteria in ablations were that the patient had to have at least 150 milliliters of blood loss to qualify for any of these, and that the endpoint was 75 milliliters of blood loss, had to be a success. So it was easy to set up parameters, and also double-blind studies.

So that we basically had a fairly straightforward job. The problem I see with uterine fibroids is that there are a lot of different issues with this. obviously the largest being abnormal uterine bleeding.

These patients, even if you treat their fibroids, are not always going to come down to a certain level. You can't set 75 milliliters as an endpoint, because some of these patients have, obviously, myosis along with their fibroids. So they have other uterine pathology.

We don't know what their normal menstrual bleed would be, what effects hormonal bleeds are having. Obviously, a lot of these patients are perimenopausal or in their forties, and so they do

have hormonally associated luteal phase kind of things that affect their bleeding. So that bleeding becomes a very difficult issue with this as far as quality of life.

Also, most of these patients are using this as basically an avoidance of hysterectomy, which is a treatment. So there is a treatment for fibroids, and that is hysterectomy.

So I think our challenge today is basically more a quality of life challenge and a patient choice challenge than basically with all these devices, rather than trying to achieve a goal that gives us a hard answer like we did with endometrial ablation.

CHAIRMAN NOLLER: You mentioned bleeding and QoL scores. If you had to design a study, what would you use?

DR. SHIRK: As quality of life?

CHAIRMAN NOLLER: Well, quality of life, bleeding. What do you think is an appropriate --

DR. SHIRK: It is difficult, because I would probably use some kind of quality of life score,

because this is totally based around quality of life. I mean, if you were going to have to go to a hard score so that you could quantify objectively, then obviously you have to go to some type of PBLAC score or some other scoring for bleeding, and set a minimal fact and also size reduction in fibroids. Also you have to include into this safety.

CHAIRMAN NOLLER: Dr. Sanfilippo?

DR. SANFILIPPO: I think we also should look at what's been published in the literature, and at least one study comes to mind recently in *Fertility and Sterility*, which was comparing uterine artery embolization versus a laparoscopic myomectomy.

While the authors admit it was not the best randomization, it was the first attempt at a prospective study. But the bottom line of this and the point I am bringing up is the quality of life was really their endpoint.

So what I'm trying to say is, if we look in the literature, I think as we design these studies we can keep that in mind, because that is kind of an established endpoint or at least there is some

reference to it. So for what that is worth.

CHAIRMAN NOLLER: Dr. Snyder?

DR. SNYDER: Well, Dr. Shirk alluded to this, too. One of -- I'm not sure that a lot of the term alternative to hysterectomy -- because these are all different available choices, but hysterectomy being the definitive surgery for this, I think one of the endpoints that measures quality of life issues and one of the final endpoints is just, you know, the number of patients that ultimately need retreatment, a second procedure or a hysterectomy, you know, encompasses all of the things that we are talking about.

CHAIRMAN NOLLER: Dr. Sharp?

DR. SHARP: I think that, in terms of outcomes, I think we need to realize that some are quite subjective, and some are more objective. I think quality of life is clearly a key issue for most people who have symptoms.

The challenge with that is that it is subjective, and there are studies to suggest that patients who participate in studies in many cases want

to please the investigator, be a good subject. So the question is should there be some more objective data?

I think the endometrial ablation studies were a great example of that, where you saw that basically the five devices that have all been approved and have been studied with randomized clinical trials have all shown success rates in the 85-90 percent, that the more objective endpoints, the amenorrhea endpoints, are all over the map, ranting from about 13 percent up into the higher 40 percent.

So I think -- If these are going to be studied, I think it would be worthwhile having some more objective data as well, and I think, for example, it may not make as much difference to the patient whether the fibroid has shrunk by MRI, but I still think that is useful to understand how much these devices are affecting the actual tumor biology.

So I would put a plug in for having some measurement of objective data as well.

CHAIRMAN NOLLER: Dr. Cedars.

DR. CEDARS: I think, as was mentioned by one of the speakers, because the primary indication in

most cases for any kind of intervention is patient symptoms, that that really has to be your endpoint, because there is nothing medical -- and I tell my patients this all the time when they come in and complain. You know, medically I have no reason to take the fibroid out; you need to tell me when the symptoms are such that it necessitates some intervention.

So I think the endpoint really needs to be what brought the patient into the office, and that might be bleeding. It might be symptoms, bulk symptoms. But I mean that really is the endpoint, because that is the driver to intervene.

Then in terms of comparators of one versus another, then you look at more hard criteria such as economic impact, risk of the intervention. So you can look at more hard endpoints when you are doing comparators, but if you want to look at success rates, I think it's got to be based on quality of life issues, because that is what is driving any kind of intervention. Otherwise, we wouldn't do an intervention.

CHAIRMAN NOLLER: One problem with quality of life scores -- and we have heard everybody speak to those. The one problem that I always have with them is the placebo effect that Howard has mentioned. If you put the patient to sleep and woke her up and didn't do anything, 30 percent of them perhaps would be better. And what does that translate to in a score? You know, six points, four points, nine points, 13 points?

Many of the quality of life systems really haven't addressed that at all. Yes, Marcelle?

DR. CEDARS: Well, I think that that is true in a finite period of time, but as was mentioned, you shouldn't look at "cure, recovery, success over one month or three months," but over a longer period of time. And if what you are getting is a placebo effect, six months later that is not going to be there. So that also goes into study design in terms of where do you measure your endpoint for "success," whatever that is.

I think it needs to be a longer time frame, both because you get away from the placebo, but

also because some interventions may have a very rapid recurrence of symptoms.

CHAIRMAN NOLLER: Dr. Emerson?

DR. EMERSON: A couple of points, and many of these may just show that I know nothing about the clinical situation that you are actually treating these patients in.

First, one aspect is, if you are treating symptoms, that's great, but ultimately we are really treating fibroids. So we can -- I, too, do tend to agree that there should always be some objective measure of the fibroids, but whether or not that is the cause of the symptoms is always questionable. So we've got to decide, you know -- Ultimately, you have to make a guess. Somebody comes in with symptoms, and you are going to go with several things.

It is not immediately clear to me that repeat treatment is bad. Certainly, if I get headaches every day, I take an aspirin every day, and it's not the end of the world, and that is a minimally invasive procedure. So some of these things that, if you had one procedure that was having more tendency

for adverse effects and then another one, that said it's a very simple thing. You walk into the office, you are treated, and you do that every year or so -- you know, which would you choose? I don't know, but it seems that something has to be considered, which does bring us to the quality of life.

We have to watch on the quality of life measurements, that almost always when we choose some tool, we can talk about a tool that is directed toward the immediate effects and what might be adverse experiences of the treatment, or we could talk about something that is the long term effects after a treatment had worn off.

Again, if you are going to consider the repeat treatment idea, you would want to capture the very acute phase adverse experience -- this is part of that quality of life -- and weigh that against the idea of what the long term aspect would be.

Then the last point I want to make is that, if we bring up a placebo effect, realize there's three things that can be going on here that we often refer to as a placebo effect.

One is a real placebo effect, and this is the idea that, if we took somebody and didn't treat them versus we took somebody and we gave them the magic pill, that those two people would have different outcomes. So that's the real placebo effect, and you can never tell about a placebo effect unless you have an arm with no treatment.

The other thing that can come in there is just the natural course of the disease. Somebody has an exacerbation, and that the disease would have gone away on its own, and the belief, I think, is that fibroids don't really go away on their own, but the question is whether they would always progress. I mean, if have some women who don't have that.

Then the third is a statistical term that we call regression to the mean. That is to say that the day that some woman decides to come in to be treated, it is probably her symptoms are worse right then than they were six months before, and maybe than they would be six months later.

So if we take a woman who is having symptoms that just go up and down and up and down,

staying really on average the same, the day that she is going to the doctor is probably one of those tough times, and that anytime you select any -- any population based on a threshold -- I don't care what it is -- any threshold that you do -- Look at Tiger Woods, you know.

No, we didn't look at Tiger Woods. We looked at that person who was having a really good time their first year in golf. Well, the next year they are going to do worse, just because the fact that we selected them based on this threshold means that not only are they probably a little bit unusual for the population, but also their measurements at the time we selected them were a little bit unusual for them.

That regression to the mean idea is what we have to worry very much about these trials. In fact, I disapprove of the use of the term "using a patient as their own control." Instead, what we are doing is we are measuring the change on that patient, and there is no control. It's just that our measurement is the change rather than that.

CHAIRMAN NOLLER: Yes, Dr. Chegini?

DR. CHEGINI: I always as a biologist looking for something that ends to some meaningful results. In my opinion, particularly working in a reproductive endocrinology and fertility division, I'm looking at the true population of patients that you have.

One, they have bleeding symptoms. Another one that you treat for infertility. Of course, you design the experiment for measuring the blood loss for one group, but there have to be some other assessments and measurements for the one that you do infertility. What was the problem?

First of all, you treat a patient for fibroids to improve their infertility. If they desire reproduction, you are not going to have those patients subject to hysterectomy. So, therefore, you have to manage those patient populations very differently.

My other comment is: As we know, coming up the last few years, we know there are African American population, they are having much more symptomatic fibroids versus the Caucasians. Are we

going to include patients in a clinical trial situation that include equal numbers here?

The other question I also have is the quality of life during that six-month period. None of these devices absolutely look at when you are blasting a tissue and you are providing a dead material in that area, it is very well established to every single area of research that some of these apoptotic or necrotic cells -- they actually can cause inflammation and leads to other and further problems locally.

If those patients that they are undergoing these kind of treatments and they are desiring fertility later on, are they impacted by these local blasting the material, particularly if we define energy devices that we are talking about and that are coming into the market?

DR. BAILEY: Is there any additional discussion on this topic? Dr. Shirk.

DR. SHIRK: I think the infertility thing brings up the whole safety issue with this thing, as basically, obviously, with uterine embolization we know that submucosal fibroids and pedunculated

intrauterine fibroids have a tendency to slough out or, basically, to get infected. Obviously, you can see the same thing with pedunculated fibroids that are subserosal with, obviously, necrosis and the effect on the abdominal contents, namely, the bowel and bowel perforation.

So that, again, we've got to address with all these issues, especially the necrosing type of technologies, you know, what areas of treatment are effective or appropriate and what aren't.

The other issues would be basically, obviously, reproduction. I don't think there is any data on any of these technologies as far as reproduction, basically incidence of uterine rupture, what pregnancies, obviously, affect on fertility in itself.

Obviously, there is a subset of women who are going to want to use these technologies to maintain their reproductive status. We, obviously, have significant data regarding surgical treatment of these patients, but we certainly don't have a lot of data regarding any of these other necrosing

technologies.

CHAIRMAN NOLLER: Dr. Sanfilippo.

DR. SANFILIPPO: To complement what both Dr. Shirk and Dr. Chegini said, I think maybe -- and I don't know if it belongs in the inclusion/exclusion criteria more specifically, but I think we are talking about two different populations, and we are going to have to define that very clearly: (a) you are interested in a future fertility; or (b) you are not.

Then the other question in between is, well, what happens if you are not interested in future fertility, but you conceive. Is it going to be the same problem like the endometrial ablation concerns that have been expressed?

So I think, as we do our study design and assessment, my opinion is different populations have to be addressed separately, and then we also have to monitor those who conceive subsequently but didn't plan to.

CHAIRMAN NOLLER: Yes, Dr. Hillard.

DR. HILLARD: One of the other issues, building on the idea of different populations, is

patient age. So not only are there differences in desire for future childbearing, but one has to look at the background reproductive function or menstrual function of women, which is different for women in the 20-40 age group compared to women in their forties.

So I think that that is important to consider as one looks at studies, is some stratification and sorting by age and menstrual function and proximity to menopause and the background hormonal status as well.

CHAIRMAN NOLLER: Dr. Sharts-Hopko.

DR. SHARTS-HOPKO: I wanted to build ion the earlier discussion about quality of life. I think that is what drives consumers, and I think the definitive answer after a more conservative procedure is always going to be did they keep trying conservative procedures, and ultimately did they have a hysterectomy.

CHAIRMAN NOLLER: Yes?

DR. SANFILIPPO: And one other concern that we really haven't talked about, and the good news is it is a very small population, but what about

establishing criteria if there is a rapid growth of this mass and the presumption is it is benign, but in reality it is not?

So I think there has to be some -- whether it is again exclusion criteria to state that defined rapid growth wouldn't qualify for any of these procedures, because the necessity for a tissue diagnosis is clear under that case.

So as we design this, I think we have to keep that population in mind.

CHAIRMAN NOLLER: Yes?

MS. GEORGE: One additional comment, I guess, I would like to bring up is I agree with all of the ideas that everybody has been talking about, but from the manufacturer's side, all of this stratification of data and analysis will require significant numbers of patients and a significant length of time, and will delay the ability of getting the products out there.

So one of the things maybe would be reduction of indication of use, so that you can get things out there sooner with smaller focused areas,

and then maybe having multiple releases and things like that might be something to consider as well.

CHAIRMAN NOLLER: Dr. Chegini?

DR. CHEGINI: I agree with that question, but one other thing I would like to mention. We have been performing a series of detailed -- I want to call it biology of all these tissues, and we realize that there are substantial not only differences between the normal and the tumors, but also between African American versus Caucasian, and so on and so forth. But there have to be certain numbers. Otherwise, a statistical analysis, in my opinion -- it makes absolutely no sense if you don't have power.

You can come with a P value of 0.05 or 0.- whatever, but what does it really mean, because there is substantial differences among all these patients. Every individual patients are different. So, therefore, by accumulating all of the 30 or 40 or 20 patients and you come out with a P value -- I don't believe that is really a factor to include in that.

CHAIRMAN NOLLER: Ms. George?

MS. GEORGE: And I think I guess what I

was trying to say is reduce -- you know, focus on a particular population. Have the indications of use being maybe a little bit more narrowly focused to get the product out there sooner, to be able to get it in use for a population that you do have good data for, and then continue separate studies either as post-market approval studies or as totally separate submissions.

DR. CHEGINI: One other thing I would like to mention, particularly with the industrial representative, is: What is the cutoff size for this fibroid to be established under this rule, because some of the smaller ones could be also problematic, and because the technology cannot properly detect and eliminate some of those, are they going to look at 5 centimeter or larger or 10 centimeter and lower, or what are those criteria? I think that is also very important as well.

CHAIRMAN NOLLER: Dr. Shirk.

DR. SHIRK: I would agree that we need to look at all this carefully statistically, and I agree with you that it becomes, obviously, almost cumbersome

and onerous to the companies to look at all these and do all these studies.

The other issue is basically that, you know, the FDA can recommend, but they can't really put contraindications and, obviously, for a lot of these things, especially in reproduction, doctors can use any device they want to, if they feel that it has a use in treatment.

So even though you basically design something to do something and say "and this isn't included in it," you can't stop the physician public from using it for things that it wasn't designed for, if they feel it is of benefit.

CHAIRMAN NOLLER: Let me refocus this a little bit, because we sort of morphed into question 2 a little bit.

Question 1 was: What would we consider to be the most appropriate tool for deciding device effectiveness.

Now let me introduce something here. If we could agree that the major symptoms are bleeding, pain and mass symptoms -- there will be others, but

those are the main ones -- let me suggest that for bleeding, perhaps you could use a bleeding tool and have to reduce bleeding by X amount, and a quality of life tool. So two measurements, and you would have to reduce bleeding and improve quality of life by X points.

For mass, you could have quality of life, plus you could have some objective measurement such as reduction by 20 percent, 40 percent, 80 percent, some percentage.

The problem one is bleeding, because there it is really all sort of quality of life, though there are separate pain and quality of life scores. But perhaps a combination of a couple of scores and trying to make one objective and one less objective. What do the Panel think of that sort of idea? Yes, Hugh?

DR. MILLER: I would support that approach. I don't think that there has to be one unifying tool in a disease process that manifests itself in many different ways. So I think it is more appropriate to have multiple tools.

The tricky part will then be the hierarchy

of how those tools are used in assessing success or lack of success following the treatment. But I think that part of it can be worked out, particularly if it is done in the development of the design.

CHAIRMAN NOLLER: Russ, Nancy, then Dr. Romero.

DR. SNYDER: And I agree with what you said about objective measures, and I think Dr. Sharp brought it up earlier, too. I think it is important if symptoms include either abnormal bleeding or just pressure symptoms or size issues, we need to have objective measurement of decrease in size. But there's now good studies that show that a change in size doesn't correlate with change in symptoms, you know, for sure, and reperfusion is important in that, although I am sure that we are going to find that reperfusion or tumor growth doesn't necessarily correlate with symptoms either.

So I really like what you said about approach, that we are going to have to have, you know, blood is the symptom that is being treated, and then some objective and subjective way of measuring the

change in that.

CHAIRMAN NOLLER: Yes?

DR. SHARTS-HOPKO: I think, with having women self-assess their bleeding, women of today are not going to fool around with a lot of process procedure. It has to be easy. There are visual scales. I think you could probably get away with, you know, rate of utilization of standardized feminine hygiene products, but it is going to have to be easy, if you want a large sample.

CHAIRMAN NOLLER: Dr. Romero.

DR. ROMERO: Yes. I would echo the comments made by Dr. Miller with regard to the not only feasibility but probably the wisdom behind using multiple measures. I think there are many studies, particularly in the public health literature, where a combination of measures is used.

I think that in this case, particularly in light of what Dr. Cedars said earlier regarding considering a study design that actually matches endpoints to presentation by the patient, it seems that in combination with multiple measures, would be a

very strong design.

So for instance, you have eligibility criteria that enroll patients on the basis of, let's say, what they identify as their primary complaint or the primary reason for them presenting, and the entire sample is provided with these multiple measures, but you can do then subgroup analyses that focus on endpoints on the basis of their presentation.

So it seems that there is a logical connection, and it would add strength. Now I know statistically, you know, as was pointed out by Dr. Chegini and Dr. Emerson, that then, of course, you have to increase your sample size because of the power requirements when you do subgroup analyses, but it seems that we deal with that all the time. So that is one point.

Then just the other one with regard to the comment around racial/ethnic differences that may already be in the literature regarding the severity of symptoms by racial/ethnic subgroups. I mean, there is a large literature around health disparities, but I think we have to be careful about whether there is

biological plausibility with regard to differences in presentation and severity of symptoms or pain, for instance, and other psychosocial measures that may have maybe equal amounts or even more to do with it -- for instance, delay in seeking treatment among certain groups because of socio-structural factors.

So whether their insurance status or their social circumstances or whatever preclude seeking care, for instance, earlier may have much more to do with it than any biological basis. So I would just say, you know, we need to keep that in mind.

Certainly, then it would argue against a study design that necessarily goes in the direction of pursuing those kinds of questions.

CHAIRMAN NOLLER: Paula, then Russ and Gerry.

DR. HILLARD: Really just echoing comments by previous panelists related to multiple measures, I would agree that multiple measures based on the patient's presenting complaint would be appropriate, but I would also just echo that I think quality of life has to be always included.

CHAIRMAN NOLLER: Russ?

DR. SNYDER: One, I agree with what you were saying, Diane. I mean, ultimately we are going to have to have a symptom focused approach, and then be able to analyze these subgroups.

The problem is I am afraid that we are going to just require larger and larger numbers, because within each subgroup, I'm afraid there's going to be some subgroups -- I mean, if you just look at menorrhagia, you are going to have to have a subgroup with the intercavitary pathology. You would have another subgroup that's got a single myoma, another subgroup that's got multiple small myomas, and another subgroup that's got coexisting adenomyosis.

I don't have a solution for that, but --

CHAIRMAN NOLLER: Gerry, then Hugh.

DR. SHIRK: I just wanted to address using some type of a bleeding score. The question is: Obviously, when we do the ablation, we basically had a floor or a ceiling, I guess, for the endpoint, and obviously those were designed on some of the studies that show that women who go over those limits,

basically, were in an iron deficiency state, that they were losing iron, that they could in time maintain their iron stores.

I guess my question would be: If we set a bleeding endpoint, do you basically set a ceiling or do you basically set a certain percentage of reduction to a life quality kind of situation, so that you would have to say on any given patient, are we going to say 50 percent reduction of amount of bleeding where that means going from 1,000 cc's of blood loss, so 500 is adequate or 300-350, or whether we are talking about really putting a certain ceiling on the bleeding?

CHAIRMAN NOLLER: Hugh?

DR. MILLER: Maybe this is clear, but when we've been talking about quality of life, it seems to me that our focus has been the reduction of symptomatology from before and after. But it seems to me that an equally important quality of life issue is something that has been alluded to, but we haven't really called it quality of life, which is what is the invasiveness of the procedure that the patient is being subject to?

Since we are talking about multiple approaches to this problem, one of the scales or one of the quality of life scores that has to be included is what the patient has to go through to achieve that improved quality of life. If we are talking about one procedure that is minimally invasive, can be done as an outpatient, doesn't require surgery, that has to be viewed in a different light than something that does require surgery, that is more invasive, that has some inherent poor quality of life to get to the better quality of life.

CHAIRMAN NOLLER: The morbidity of the technique. Scott?

DR. EMERSON: So I guess, *a priori*, I would think that major safety concerns I would have is one that Dr. Chegini brought up, is just this idea of leaving the necrotic tissue in the body, and then what sort of things will that lead to with the systemic or local area.

The other one that one the presenters brought up was the concept of embolizing the wrong vessels and what effects it would have. And there's

other, I guess, safety issues that are there, as with any procedure, but those are sort of the main two that I look at, this concept of treating fibroids focally rather than doing the hysterectomy.

Then we come to the efficacy versus effectiveness question, too. The efficacy is, well, did we successfully remove the fibroids? The effectiveness is: Does removing fibroids treat symptoms?

Some of it, I sort of look at as -- I have a question in my mind of what is the purview of the FDA in devices here, is saying, you know, there is this question that has to go with -- you know, is it possible that a patient has pain, since that is an easy thing to deal with, and that the gynecologist removes the uterus, and the patient still has pain, in which case that was just medical judgment of saying it could be that the fibroids in the uterus were causing the pain, but it turned out not to be.

So is that -- You know, when we aren't going to remove the uterus, we also have the questions that the bleeding can persist, infertility can

persist, and we have those issues.

One of the -- Where I am coming at here is ultimately, we are looking at different procedures that have been recommended for removing fibroids, and then there is the medical judgment as to whether removing fibroids will treat the symptoms.

Now with bleeding, it seems clear to me. We can go through and say we can measure whether removing the fibroids is often enough the cause of the bleeding, that we can detect an improvement in the bleeding by removing the fibroids, but that is mixing the two things.

Infertility, I doubt that -- It's just an old logistic thing. I doubt that somebody is going to be looking at the true idea that removing the fibroids has improved fertility, but it is certainly possible to do that, to be able to look at that.

Again, on pain we've got these quality of life measurements, but I would be very, very interested to find out how much we should be absolutely looking at, whether the effectiveness question is there or how much of that is just the

physician judgment after we have demonstrated that it is safe to remove the fibroids and it is efficacious. We really did. We did de-bulk them or whatever, and then it's up to the physicians to establish whether -- the effectiveness of removing the symptoms.

CHAIRMAN NOLLER: Let me interject here, just looking at time, and we have six questions -- 2 and 1 get twisted in. But, Nancy, have we helped at all on 1 -- Colin? -- before we go on to 2?

MR. POLLARD: I would say, in general, yes, you have. I don't see like an overwhelming consensus on the specific question here, but I think you have certainly given us a lot of great input on this. Really, that is all we are genuinely looking for.

So unless you saw everything converging to one spot on this -- and maybe that is just the nature of this kind of question -- I would say I don't have any further suggestion regarding that.

CHAIRMAN NOLLER: Okay. Unlike yesterday, we don't reach consensus and vote. We are just sort of sense of the panel, trying to help FDA.

Let's change the slide and put Number 2 up, just because it is a little different: Based on a response to the previous question, which is sort of out there somewhere, comment on any specific inclusion or exclusion criteria which should be made part of the eligibility criteria for subject enrollment, including minimum or appropriate baseline scores, measurements or symptom level.

let me just throw in something important that Ms. George mentioned. As I heard these things, fertility, not fertility, age strata, symptoms, bleeding, mass, pain, race differences, etcetera, etcetera, I am starting to see a 20 x 20 table with numbers 1 and 2 in all the cells.

If we could help FDA focus on, gee, the appropriate women would be -- and I'm just going to make this up -- women that have excessive bleeding who are overage 18 and under age 40, or something, or maybe we want them 40 to 50, who knows. But is there some group of women that are not eligible that we should exclude, and is there some large group of women that could be studied that would serve as a basis for

whether or not a technique works, and then it could be expanded after it is on the market? Dr. Cedars, and then Dr. Emerson?

DR. CEDARS: Well, I have a couple of things. One has to do with the categories of patients that Ms. George was talking about, and how do we sort of focus this and make it realistic.

I can see both sides of the coin. I really think, clearly, people who want future fertility and people who don't want future fertility are separate groups. The caveat is that what I fear will happen is what has happened, is that they develop a technology to be applied to women who say they do not want to seek future fertility, and then we never get the answer to the question for the other group.

So I don't quite know how to get around that, because you can't study them at the same time, but because the group that has fibroids that doesn't want to preserve fertility is such a much larger group from an industry point of view, that's where the money is. So that is where they invest their time and money, and then we don't get an answer for this other

population, which is frustrating.

The other issue that I want to make -- and I saw this happen a lot when uterine artery embolization arose, and this gets back to the point that a lot of these women are in the forties, and they are having abnormal bleeding for other reasons -- is a lot of this was being driven -- the radiologists were trying to get us to partner with them, but what they really didn't want us to do was to evaluate these women and control their bleeding hormonally, because then they didn't do the procedure.

So I think there needs to be some inclusion criteria where hormonal treatment or evaluation and treatment -- they fail that before they undergo a procedure, because a lot of these perimenopausal women -- it's true, true unrelated. Yes, they have fibroids. Yes, they have abnormal bleeding. But it's not the fibroids causing the abnormal bleeding. It's their perimenopausal status.

So I think somehow in the inclusion criteria or the prerequisites for study, that needs to be controlled.

CHAIRMAN NOLLER: It was Scott, Paula and then Russ.

DR. EMERSON: I would think that it would be easy to do clinical trials that are directed toward symptoms specifically. So in other words, that you could do a clinical trial in those who presented with bleeding symptoms, and again I would think that there might be some differentiation that needs to be as you are then measuring success as to whether the bleeding symptoms were blood loss or whether they were length of periods or something that is more of a quality of life issue as to what the patient was actually complaining about.

Similarly, pain is a group that you could test separately, and then the fertility issue is another one, although again I don't have a feel for those. But all of these are things where we are simultaneously combining the issues that you just brought up as saying we are combining the question of whether we can treat the fibroids and whether the fibroids are leading to those symptoms. It's just this question of which the indication will come out

for.

CHAIRMAN NOLLER: Paula, Russ and then Jonathan.

DR. HILLARD: Building on Marcelle's statement about failure of hormonal therapy, I would potentially broaden that to failure of other medical therapies that could be hormonal or hormonal delivered by an IUD; for example, particularly with relationship to bleeding, but also potentially related to pain, failure of other medical therapies might be a criterion.

DR. EMERSON: A qualification question on that. On these things where we are doing this hormonal therapy, are you viewing this as a safety issue or are you viewing this as a statistical power issue? So are we trying to eliminate those people who the therapy is not likely to work for, or are we trying to eliminate people because we don't feel it's safe?

CHAIRMAN NOLLER: There's good hormonal therapy for a lot of women for this. So one of the things to consider would be -- in the eligibility

criteria would be anyone who has not already failed hormonal therapy. That would be a potential.

DR. HILLARD: It's not so much safety. It's just that it's a less --

CHAIRMAN NOLLER: Good care. Russ? Russ has the floor.

DR. SNYDER: I wanted to answer Dr. Emerson's question with yes, because you know, I think there clearly is a safety issue. You heard from the reproductive endocrinologist that she wants to make sure that patients have been offered an alternative of failing medical therapy, failing an IUD.

The gynecologic pathologist wants to make sure the patient doesn't have another etiology for their bleeding like endometrial cancer and cervical cancer, and that's really important, too.

One of my fears is that patients, you know, with their own self-perceived symptoms will search out a therapy and bypass another important step, which is to make sure that what they think is causing their problem is indeed what is causing their problem.

Then I think I can kind of summarize. So I think there is, one, a safety issue there. The second is what we are talking about, is what has the patient been adequately given a description of the alternatives with their risks and benefits of established ways of treating the disease? In other words, have they been given -- you know, told that hormonal therapy will work, and IUD or a hysterectomy?

CHAIRMAN NOLLER: Jonathan?

DR. WEEKS: I am going to start by raising a question, and that is: If we make the inclusion criteria "The inclusion criteria is that the patient isn't going to be seeking future childbearing," then does that not open up a better opportunity for a randomized trial where the control group is hysterectomy, kind of tying into some of the comments that Dr. Cowan made. That is one thought.

The second thought is, as a maternal fetal medicine person, I agree with Dr. Cedars' comments about a failure to follow up on women who would want future childbearing, but it is not as common, certainly. But there are a number of women who have

large fibroids that have had second trimester pregnancy losses or difficulty getting pregnant. conservative measures have been attempted, and they are going to undergo myomectomy.

That is a group of women who could potentially benefit from a number of these therapies. I would push for a study of that subgroup of women. It is a small number, but if those women can be successfully treated, then it sort of opens the door for a lot of women in the middle who maybe do want future childbearing, have symptoms but not severe enough to seek a hysterectomy or a myomectomy.

DR. HILLARD: I was going to comment on the failure of hormonal therapy. There are a lot of women who are dissatisfied with hormonal therapy, even if it is effective. They are concerned about continuing to ingest a metabolically active product over a long period of time when they could just go out and get a definitive answer. So I wouldn't want to exclude them.

CHAIRMAN NOLLER: Absolutely. Yes, Dr. Romero?

DR. ROMERO: I'm just a little confused, because I think the comments made by Dr. Snyder and Dr. Cedars were fundamentally different. My sense was that one had to do with coming to a point at which there is the strength of credibility or belief in diagnosis, and the other one had to do with excluding the possibility in a study design when testing a particular device -- excluding the possibility that what we might conclude as failure, if you will, may not have necessarily been failure, because what was precipitating the symptom or what was assumed to be precipitating the symptom may not have been.

I think those are two very different things. From a clinical study design perspective, it seems that there would be a desire to have eligibility criteria such that whatever the intervention is that is being tested, that there is statistically some strength behind whether it has actually had an effect or not.

So it seems to me that, if the fibroids are not necessarily -- and I'm not a clinician, obviously, but if the fibroids are not necessarily

causing the problem and that can be excluded prior to enrollment in the study, that that would be a given. So I don't -- It seems that your comment had more to do with sort of clinical certainty around the diagnosis.

CHAIRMAN NOLLER: Dr. Shirk and then Dr. Emerson.

DR. SHIRK: I guess that my concern about we are obviously talking about contraindications for doing the procedure. Obviously, other than ruling out other pathology -- other associated pathology, one of the questions again is location. Obviously, it becomes an eligibility criteria.

Basically, we know from uterine artery embolization that, obviously, pedunculated fibroids have particular issues. Do you include or exclude those? I tell my patients a lot of times, fibroids are like realists; they dissolve location.

So the submucosal fibroids are much more likely to cause bleeding than a fibroid that's out in the subserosal area. Is there any specific problems with treating those? Obviously, in some of the

embolization studies, there has been a group of those women, a fairly high percentage of them, that will slough, you know, submucosal fibroids. So in treating their bleeding, you are basically, obviously, creating -- with an embolization or something that is going to cause death of the fibroid, basically another clinical issue.

So I would think one of the criteria that we would have to exclude or decide to include or exclude is basically location.

CHAIRMAN NOLLER: Dr. Emerson.

DR. EMERSON: I just wanted to clarify. When I spoke of statistical power, that was exactly this point you were making, that we can home in on a group that has a very highly likely chance to benefit from the treatment, and going with that is also the thing to make certain that then the benefit of the treatment would generalize to the patient population that it was less likely to do. But being a statistician, we can always deal with throwing in patients that it does nothing to, and just as larger sample size. But we want to make certain that it is

safe in that population, and then any population that we have excluded that we haven't excluded something that we would have gotten a very different answer.

CHAIRMAN NOLLER: FDA comment? Is that what you are working on?

MS. BROGDON: Yes. I think when you are ready to leave this question would be a better time.

CHAIRMAN NOLLER: Well, we are pretty close, because it's just about time for the noon break. Colin?

MR. POLLARD: Thank you. This has been a great discussion we are hearing, and in particular, we are very sensitive to the issue of infertility and not having the answer regarding pregnancies.

One thing, and it is really just a different twist on the same question, and FDA is in part responsible for some of the studies you have seen with focused ultrasound and UAE that we don't see women who desire to become pregnant. That was partly our concern relating to safety and so forth.

So we contributed to that. So maybe the question we would like to hear a little discussion of

is: Even if the primary complaint is bleeding, if she is of childbearing age, should we -- maybe this is not exactly the way to answer the question. Should we be excluding those patients who desire future pregnancy or should we not make that an exclusion criteria and simply put in some kind of requirement to follow those who do for pregnancy? I think that's the concern.

It was connected to the safety side of the question, but that's kind of where that was.

CHAIRMAN NOLLER: That's a good question, and actually, this is a wonderful thing for us to talk about at lunch, unlike yesterday. We can talk about these ideas.

MS. BROGDON: No. I think not, because the whole point of this is to have the discussion in public.

CHAIRMAN NOLLER: Okay. All right. So please talk about basketball. Let's break. We will met at ten to 1:00, so we can have another couple of hours.

(Whereupon, the foregoing matter went off the record at 11:57 a.m.)

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

Time: 12:54 p.m.

CHAIRMAN NOLLER: Let's come back to order. We have sort of worked our way through one and a half of the six questions, but in looking down the list, they are so interrelated, we are sort of answering some of the others.

We are talking about eligibility criteria, and I am not sure we can get a whole lot farther on that. Dr. Snyder wanted to make a comment, and then Dr. Cedars.

DR. SNYDER: I am going to start off by saying, you know, I always come clean, and I am going to be a hypocrite here, and I have no political aspirations. So I figure that's okay.

The reason I preface that is because, if I was on an IRB today, I would be singing a completely different song. But with what Mr. Pollard brought up, I would be real reticent as a panel to want to preclude women altogether who are still desiring or have any plans for future pregnancy, because otherwise we would be in the exact same dilemma we are today

with uterine artery embolization.

You know, we had the first one of those in 1995. We were reminded of that today. We are now 11 years into this, and it is still regarded as a contraindication to the procedure, and all we've got as obstetrician/gynecologists to counsel patients who do conceive post-uterine artery embolization is a few case series.

I would much prefer as a clinician to be able to counsel patients as to what do I need to advise you as far as risk associated with as pregnancy goes, route of delivery and everything else. The only way we are going to get that is if we have some well designed clinical trials looking at the issue.

CHAIRMAN NOLLER: Marcelle.

DR. CEDARS:I agree, except that I think that they really are two different populations, and the endpoint of what they want to achieve, success, is different in those two patient populations.

So for me, it is almost two different studies, because one is much more of a symptom driven, whether it's bleeding, whether it's pain, I don't want

to have a hysterectomy but I want to get rid of these symptoms, which is very different than saying there is infertility and there is a fibroid in place.

So I think that the fertility patients or infertility patients need to be studied, because I agree with you completely; because otherwise what happens is we are left with absolutely no data. However, I think that is a different study.

What you could do -- and you could design that very easily, because we don't even have data, for that matter, about myomectomy and impact on fertility, other than submucosal fibroids -- would be to randomize people between myomectomy and X, whatever that procedure is, who want to maintain fertility; because the issue would be the same in terms of functionality of the uterus, both for conception, implantation, labor, with myomectomy and whatever that procedure is.

So to me, it is a different study. I don't think you can put them all into one. I think, in the study that is looking at symptoms, you really would exclude people. What I would just put a plea in

for is that there is an arm that looks specifically at women who want to preserve fertility. But I think they are two different patient populations.

CHAIRMAN NOLLER: Hugh?

DR. MILLER: As a maternal fetal medicine person, we are constantly faced with this, and to me this is no different than the panoply of drugs that women bring into pregnancy with them for which we have virtually no data. It's gotten a little bit better, but still, it's difficult to counsel people.

I guess I would hate to hold women in general hostage to this one group, as important as I think it is and as much as I would like to encourage companies to study pregnancy because of what you said earlier, which is it's a small population.

There is not a lot of financial incentive. In fact, there is a tremendous amount of financial disincentive. The medical liability, potential risk of rupture, the very things that we have discussed today are all disincentives to studying this population.

So I think the natural state of affairs is

that women who are not likely to be reproductively active are going to be enrolled in these studies. There will be some that will become reproductively active, will be subject to case series, because there is not going to be an incentive to do it any other way. I mean, I really don't think so.

I think what we can ask companies to do is to follow women, particularly women who have the potential for being reproductively active, but I think more than that is not realistic. It's just not going to happen.

CHAIRMAN NOLLER: Dr. Weeks?

DR. WEEKS: I agree with you. I think it is difficult. But I'm not certain that I agree that it is not doable, again especially if you lump in the patients that have large fibroids that have lost pregnancies in the second trimester; and yes, some of these ablation procedures, there's a future risk for abruptio, etcetera, but those same patients, if they are undergoing a myomectomy, take on a significant risk that they just have an outright hysterectomy, to begin with.

So I think the counseling is difficult. It is a difficult study. I feel that -- I agree with Dr. Cedars that the younger women and the perimenopausal women are physiologically different. The measure of success will be different, the long term outlook is -- The time interval is different.

So that the best way, I think, to study the patients who are looking to future fertility is to specifically go after infertility patients or patients who have had pregnancy losses that we think are due to fibroids.

CHAIRMAN NOLLER: Dr. Shirk.

DR. SHIRK: I think, obviously, what happens when a patient gets pregnant is an important issue, but I think probably the primary issue in a group that wants to maintain fertility is basically their impact on fertility itself or fecundability.

Basically, like uterine artery embolization, do you develop a uterine artery problem with follicular phase defects? Basically, what is the effect on the ovary and ovarian function? These are questions we have no idea about.

Obviously, from the limited data we have, probably if somebody gets pregnant, they probably progress through a fairly normal pregnancy. Rupture would obviously be the main issue, but I think one of the bigger issues with reproduction is basically the question of what impact does this have on a patient's ability to achieve a pregnancy.

CHAIRMAN NOLLER: Let me do something here. I am going to carve out about 10 minutes for some audience interaction here, and then I am going to jump to questions 4 and 6, because they have issues that we really haven't talked about. You might want to sort of look at those. But let's see if there -- Based on the panel discussion, have there been any -- or are there any thoughts from some of the members of the audience? We would entertain one minute questions or comments, if anybody would like to do so.

Please rise, and come to the podium, and state your name.

DR. ISAACSON: Keith Isaacson, just here as an interested observer today. Just some comments from the earlier this morning's discussion.

I think, number one, I just want to talk about objective measurements. I don't think that we can use -- and you guys have brought it up several times -- that we can use the fibroid size as an objective measurement of success. I think the uterine artery embolization data has already shown that fibroids that reduce in volume between 15 and 40 percent in size will have the similar effect on symptomatology.

Number two, I think Dr. Shirk brought this up. But certainly the size of a fibroid -- A 2 centimeter submucosal fibroid, can cause a lot more bleeding sometimes than a 4 centimeter one. So again, the size may be irrelevant.

Dr. Cedars brought up hormonal therapy, and to my knowledge there is not a hormonal therapy that is FDA approved for fibroid treatment. So I am not sure that you can really say or that we should say that patients should fail hormonal therapy before they are entered into a study, since we don't have a hormonal therapy that is FDA approved.

My last comment is regarding Tiger Woods.

He is still -- He's been number one in the world for the last four years. I would say that's pretty good. Thank you.

CHAIRMAN NOLLER: Any other comments from the floor? One more, I see.

DR. GREENBAUM: I thank you again. I know I've had my five minutes.

CHAIRMAN NOLLER: Affiliation, too?

DR. GREENBAUM: I'm sorry?

CHAIRMAN NOLLER: Name and affiliation.

DR. GREENBAUM: I'm sorry. My name is John Greenbaum, and I represent Biocompatibles.

CHAIRMAN NOLLER: One minute.

DR. GREENBAUM: I asked for the input of Dr. Robert Worthington Kirsch in the course of this presentation, and Dr. Kirsch is well published in the area of uterine fibroid embolization and does quite a few of these procedures a year.

In the event that this Panel does suggest and recommend the use of clinical trials to support UFE indications, Dr. Kirsch's input was, first of all, these therapies are for control of symptoms. Patients

don't come in and say they have a fibroid and want the fibroid treated. They have symptoms to be treated.

Dr. Kirsch recommends, and I recommend, that the Panel require trials only of those devices which are physically, chemically unique and measure endpoints that are related to the symptoms for which the patient sought treatment.

Second is to require comprehensive bench and laboratory preclinical testing in support of the kinds of issues and questions that are being asked of here.

Third is, when it comes to the measurement of blood loss, the UFS QoL is a validated fibroid-specific tool. Measuring blood loss against the PBLAC method requires the use of a 15-year-old sanitary product, which women really don't care to use.

Last, if I don't get the input later, Dr. Kirsch gave me a lot of input that he felt that this Panel's time and effort and FDA's resources should be well spent on the issue of fertility.

My clients are developing drug eluting products that are related to uterine fibroid

embolization. The issue of fertility is not well studied.

CHAIRMAN NOLLER: Thank you. That's two minutes. thank you.

DR. GREENBAUM: Thank you very much.

CHAIRMAN NOLLER: Anyone else? Name and affiliation, please.

DR. STABINSKY: Hi. Seth Stabinsky, and I am also here as an interested observer.

I think that the issue of including women who want to keep their fertility in these trials is -- I agree with the Panel member who talked about the IRB, you know, if you were sitting on an IRB that you just wouldn't be able to tolerate that. However, the need to know that for our patients is incredibly important to know whether these methodologies are going to allow them to have safe pregnancies in the future.

It is not just a matter of whether they can get pregnant. It is if the pregnancy doesn't -- if they do get pregnant, we have all the problems that could be associated with the pregnancy, IRGR,

etcetera. That is not really fair to the fetus.

I thought that Dr. Cedars' comment was really great, the notion that this is a separate study, and also the understanding that the medical device industry can't support that study. You know, I think it would be very powerful to have a committee -- to have a panel like this, you know, have a conclusion that says the NIH should fund a study like that, because I think that there is a definite need to know that answer. It affects a large number of women, and we can't risk the safety of babies in a small study, and the device companies can't put money into that small market.

CHAIRMAN NOLLER: Thank you. Other comments? First and second. You are first. Name and affiliation, please.

DR. TAY: My name is Sew-Wah Tay from AMS.

I just wanted to point out the uterine fibroid symptom of quality of life questionnaire actually is a composite fibroid symptom kind of question that covers almost everything that was discussed here, including pain, bleeding and also bulk

symptoms, and it is validated.

So that actually is a pretty good quality of life questionnaire to use for endpoints here.

CHAIRMAN NOLLER: Thank you.

DR. ALIKACEM: Nadir Alikacem with Insightec.

I just would like to make sure that we are -- from my personal perspective, that we are not making two things into one. Fertility -- that's a claim to make somebody fertile, for whatever reason. Making pregnancy safe, I believe, is different from fertility. Thank you.

CHAIRMAN NOLLER: Thank you. Other comments from the floor? All right. Thank you for those. Some very thoughtful comments.

Let's look at question 4 for a minute, because we really haven't talked about this. We have sort of avoided it. We've talked about most everything else, but selection of an appropriate control arm for surgical procedures can be challenging. The panel has criticized nonrandomized control groups of hysterectomy patients in the past.

For some procedures, small control is not possible.

Discuss other possible control options, myomectomy, no control. Dr. Emerson favors a patient as her own control. It was suggested a laparoscopic super-cervical hysterectomy from the floor today.

A procedure, whatever it is, what is "control" or should there be no control? Dr. Sharp?

DR. SHARP: I think, since we are talking about minimally invasive techniques, I think the question of using uterine artery embolization as a control is a reasonable one. I know there was mention of using the laparoscopic sub-total hysterectomy to compare that to a device.

I think that is probably not the same. That is a hysterectomy comparing something that is being performed to treat a fibroid, but leaving it in place. I think uterine artery embolization actually has been studied enough now that it is considered a standard of care, and I believe has been recognized by several organizations.

So I think that would be a reasonable randomization arm.

CHAIRMAN NOLLER: Before we go on to the next, would you see it as randomized or a series of each?

DR. SHARP: Obviously, randomization would be nice, to decrease the bias going into the study. Obviously, you wouldn't be able to blind that, but randomized, nonetheless.

CHAIRMAN NOLLER: Dr. Emerson and Dr. Cedars.

DR. EMERSON: Well, I am going to see somewhat on what Dr. Cedars said, so she gets the chance to say that I misunderstood it completely, when she was speaking earlier and saying that, to women coming in, you are frequently telling them that this is a symptom sort of issue and that, when you actually have the procedure is when your symptoms are bad enough. So that then what we have to do is be able to identify women who -- and I'm making these numbers up -- are at some level of equipoise. Do they have it now or do they have it in six months, and randomize them.

So that you do have to worry that is that

the patient population that you are trying to find out about? Is that more mild disease, and it won't carry forward to the more severe disease? But that still allows that comparison to say you are perchance just randomizing them to having the procedure or having it delayed, but if it can be delayed enough, you still have the chance of looking at, say, six month quality of life.

CHAIRMAN NOLLER: Dr. Cedars.

DR. CEDARS: I guess I have trouble with using uterine artery embolization as the control, as the standard, because here you have a procedure that never itself has been compared to what we consider a gold standard and has not been used in people who want to preserve fertility, and it is now going to become the standard against which other things are going to be tested. That makes no sense to me.

I think, if you -- The procedures that are standard are either myomectomy or hysterectomy. And since most of these women are choosing less aggressive procedures because they want to preserve the uterus, then I think you are looking at comparing myomectomy

to -- a surgical myomectomy to X; and certainly, for the women who want to maintain fertility and thereby, obviously, want to maintain their uterus, that is what their alternative would be, to have a surgical myomectomy or to do XYZ. But I have a real sense of dis-ease at using uterine artery embolization as the standard by which we grade other things.

CHAIRMAN NOLLER: Dr. Sharp.

DR. SHARP: Just a thought on that, and I respect that. I think, in terms of using myomectomy, although it has been around for a long time, I don't know that it has been studied that well in terms of really looking at numbers.

I think comparing like procedures to like procedures is always helpful, and I don't think comparing a uterine sparing procedure which is minimally invasive to a hysterectomy, which is not minimally invasive, is like.

I just would argue that, even though uterine artery embolization has not been around that long, there's actually now a fair amount of data from that, and although we don't have a lot of pregnancy

outcomes, I don't know, again, that we have that data with other methods either.

CHAIRMAN NOLLER: Dr. Shirk?

DR. SHIRK: Well, I guess, basically -- First of all, most women that are looking for the procedures that are necrosing are, obviously, looking at ways to avoid surgery. Okay? So I see a surgical arm as being not an acceptable thing for most patients going into a study.

Also, when we did the endometrial ablation studies, you were using a procedure that would be similar, I guess, to uterine artery embolization that had been somewhat standardized, and then comparing the other techniques of doing the same procedure to it. So I mean, I guess basically I would have no problem in saying that using uterine artery embolization, which we do have a lot of data on and is basically judged on life quality, as basically being a control arm to which you could compare other technologies that are going to cause necrosing kind of injuries to the fibroids, talking about the same kind of injury, however you get it.

CHAIRMAN NOLLER: Let's discuss a little different thing. What about no control, essentially case series, that the decision is that if you achieve X results in these 200 women that you are going to use your new procedure on is good enough?

Everybody hates it, I know. Dr. Emerson, Dr. Miller.

DR. EMERSON: And here I thought that I was in something about OB/GYN, but I get to make my standard cancer statement.

You know, cancer has been doing this for years and years and years, and cancer has now the number one killer of people.

CHAIRMAN NOLLER: Dr. Miller.

DR. MILLER: I think ixnay on the no control group. I think we ought to be able to come up with some suitable control group, and I like what has already been suggested, which is a comparable control group.

I don't know. I guess I would favor the uterine artery embolization as a comparable control group.

CHAIRMAN NOLLER: Russ?

DR. SNYDER: I agree with the no control issue. I think, though, what we have been talking about, we are going to have to accept that there is not the perfect study to study this, and it is going to depend on what symptomatology we are looking at. Like Dr. Cedars was saying, if we are really going to look at an issue of fertility, then it is going to be myomectomy versus another procedure. If we are looking at other symptoms, then another control group may be appropriate for one study, and I just think we are going to have to accept variation.

I also want to say, though, that ultimately the only thing that is going to control for a disease that has as much anatomic variation as fibroids do as far as location, size, and if there is no correlation between size, location and symptomatology, it is going to require a randomized controlled trial.

I don't think that it is unrealistic for us to expect that that is going to get done, and it was done for uterine endometrial ablation with a

multi-center randomized trial between hysterectomy and endometrial ablation.

I do think that there are some patients that are so stratified on one end of the spectrum that they wouldn't enter into such a trial, but there are others that really understand the dilemma that we as clinicians are in, is that I don't know what the ultimate hysterectomy rate is going to be for patients undergoing endometrial ablation.

If they are at a point and they are trying to make an informed decision between a major invasive, definitive surgery versus a temporizing maybe permanent procedure, and they understand that we as clinicians can't counsel them as to the facts, that they are willing to enter a randomized trial, that has major implications for them.

CHAIRMAN NOLLER: Nancy?

DR. SHARTS-HOPKO: I support the randomization. I think that this would be a case where they would have to do a second level of consent after the randomization.

DR. SHIRK: Well, with endometrial

ablation, we never did do a randomized hysterectomy versus ablation trial. I mean, that wasn't part of the gig. When we first started ablations a long time ago with a laser, basically, you know, that was a different era for the FDA. But basically, all we did was show that it decreased menstrual flow, and basically then we moved to the Rollerball. So they changed the procedure to the Rollerball.

That really was almost a 510(k) type of thing, and basically only when we got to the global endometrial ablation devices did the FDA require PMAs and basically then had a "standardized" procedure in the Rollerball ablation, which wasn't really standardized, because the power settings were different. The size of the ball was different. All kinds of things were different, but -- I won't go into that, but basically, I can see that we are in similar parallels with the myometry.

Basically, most of them are basically necrosing kind of procedures that we are talking about, and so that with using the data that we have and the procedure that we have already with uterine

artery embolization, we've got a parallel situation.

CHAIRMAN NOLLER: Howard?

DR. SHARP: Just again to talk about randomization and why I think it would be important, I think we are dealing with great heterogeneity when we are talking about fibroids. We've talked about that.

If you introduce -- or if you can mitigate the bias, that is going to be extremely helpful. So I think that is the one thing that randomization does. So I would argue for that.

CHAIRMAN NOLLER: Hugh?

DR. MILLER: I was just going to say the obvious, which is that by having a comparative trial, it doesn't preclude the comparison within each of those groups in a case series type fashion, as you originally suggested.

CHAIRMAN NOLLER: One of the things, too, that I meant to bring up this morning, just as we were going along -- One of the things that leads to the type of trial it is, is what the manufacturer -- what they want their indications to be.

You know, we can say we want infertile,

fertile, all ages. For the instrument, they only want an indication for women over age 40 with their tubes tied, for instance. You know, that is what the trial is probably going to be about. So that will -- The trial will depend a little bit on what they are asking for, too. Marcelle?

DR. CEDARS: One of the things that is required, and I think we as physicians and sometimes as investigators forget, is that when you present something to a patient, you really have to be in equipoise. I mean, you really have to feel like you don't know what the answer is; and if you are convinced you know what the answer is, absolutely none of your patients are going to want to be randomized.

So I think, you know, certainly, for the fertility patient, the standard of care is a myomectomy. So to say myomectomy versus this, whatever "this" is, is not illogical. Yes, one is invasive, one is maybe not or less so, but we really don't know in terms of the outcome which is going to be better.

I would argue, we don't know that for

uterine artery embolization, because it has never been compared head to head. So to say that that, all of a sudden, which is something that has been done based on case series, is going to become our standard against which we gauge other things doesn't make sense to me.

I think that you can absolutely randomize these people, but it is incumbent upon the investigator to be honest with the fact and not have their own biases and really admit that we honestly don't know for both short term and long term what's the best option for these patients.

CHAIRMAN NOLLER: Jonathan.

DR. WEEKS: I agree 100 percent, especially if we are talking about a separate study for patients who are looking to have future children. I don't follow these women long term anymore. So this is more of a question. But if in the other study, the patients who are not expecting to have children in the future, who have completed their childbearing -- if the gold standard is a hysterectomy -- So if those patients are going to be cared for in a normal clinical fashion, most of those patients today,

even with things like uterine artery embolization, are undergoing hysterectomy.

If those types of patients are going to randomize, and I guess you can argue whether it should be uterine artery ablation or not -- I still favor hysterectomy. But if those patients are then randomized to noninvasive techniques, ultimately the hysterectomy long term might be another measure of success, because you have uterine artery ablation, you have your other newer technology, and at one year or two years out, how many of those patients have then undergone a hysterectomy becomes another component of the success definition, if you will.

CHAIRMAN NOLLER: That, actually, is a nice lead-in to question 6: Typically, FDA has asked manufacturers to provide pre-market evidence of treatment success at the six-month point after surgery, with the understanding that the women will be followed for a minimum of three years. What is the appropriateness of this?

Nancy, before we go on, did you want to say something?

MS. BROGDON: Mr. Pollard has a question about randomization. I don't know if you want to continue where you were going?

CHAIRMAN NOLLER: No, I'll read it all again.

MR. POLLARD: This kind of brings us back to question 4 again. Sorry. It's a tough question.

I think I understand the points being made if somebody was going to pursue the infertility indication, the points about randomization that Dr. Cedars makes. I think that was pretty straightforward, but I think we also heard that it is probably unlikely that a sponsor is going to pursue that indication, for a variety of reasons.

So that backs us up to what is the more probable symptom, which would be the most common complaint from fibroids, which is bleeding. So if bleeding is the indication that is going to be pursued, then is there a role, or what would be the role of randomization? What would be the control group chosen?

I guess I would like to just press the

point a little bit harder without trying to direct it in any regard. I heard the point half in jest about cancer and, you know, when you -- just a single series, and look at patient improvement. Obviously, an important component of that is what is the outcome measure for that symptom, and what is the size of the effect?

Is the panel as a consensus or as a group, are there camps of groups who don't believe that we can define an outcome measure and a size of effect in a single arm setting, if bleeding were the indication?

CHAIRMAN NOLLER: A 100 women who are anemic from bleeding probably from their fibroids -- if 98 of them are made a whole lot better by the technique, it is probably a good technique. That sort of single arm study series is what you are suggesting would be appropriate in some cases. Is that right?

DR. EMERSON: I just wanted to raise the question: Are all instances in which you are treating women for bleeding -- is it really medically indicated or is some of it the quality of life of menorrhagia?

CHAIRMAN NOLLER: Practically, it's both. We have women who use 12 tampons an hour and say they have normal periods, and others use two a day and complain about the heavy periods.

DR. EMERSON: There's the distinction there that you could randomize the women where it is more quality of life, because those are the women who might be wanting to delay this and might be having more variability from period to period as to how much bleeding there is; whereas, if it is really medically indicated, that's where it is more important that you have the best standard of care as your control group, and delaying may not be that best standard.

CHAIRMAN NOLLER: Marcelle?

DR. CEDARS: I have a couple of comments. One goes back to the comment about hormone treatment, and I wasn't talking about hormone treatment with fibroids as the indication, but the reality is that most of the people who bleed from fibroids are also in the perimenopause.

So the question is they have had their fibroids for 10 years; now at 45 they are bleeding.

Is it their fibroid that makes them bleed or is it their perimenopause, which is why I was talking about hormonal treatment initially, not as a treatment for their fibroids but as a treatment for their bleeding, which is in fact, as we have said, what they came in for. They didn't come in and say I have fibroids; they came in and said I have bleeding.

So I think treating them with hormonal medications first is appropriate.

Then secondly, I still think that you have to randomize the people, even the people that you are evaluating just for bleeding. The question is what is your comparator. If you are going to use something like uterine artery embolization, then the duration of the study becomes -- or the duration of the follow-up becomes relevant, because it is likely that most things would give you a short term benefit.

The question is what is the duration of that benefit, and how many people ultimately come back to either another procedure, another minor procedure, or ultimately a hysterectomy?

So I still think you have to randomize

these patients, but I think the two questions that are brought up by that are, one, what is the comparator; and two, what is the duration and endpoints for following?

CHAIRMAN NOLLER: Let's hold the endpoints -- or the length of time for just a minute and see if there are any other comments about the single arm sort of approach.

DR. CHEGINI: I don't have a comment as regards to your question. But if the industry come along and promote these devices for fibroid treatment, if you exclude the infertility patient, you actually have to assign only the treatments for uterine bleeding problems.

There are studies already indicating that majority of women that they have high incidence of fibroids, they actually occur between age 45 to 50, and those are also the bleeding problems. So if they design their studies that you do not include patients that they desire reproductive success in that way, so you are ignoring one group all the way.

CHAIRMAN NOLLER: Yes, Gerry? Gerry,

then Russ.

DR. SHIRK: My only argument for a double arm maybe with uterine artery embolization is that you get data on what is good, better, best, and that you are also collecting data on the procedures that -- one procedure that is already proved. Basically, you get an idea of what complications are coming out of your control arm, as well as what complications are coming out of the new necrosing technology that you are looking at.

So that, basically, it is not only are you using it as a control arm for a similar type of procedure, but you are also getting some data on the overall success and, basically, complications of the procedures in general.

CHAIRMAN NOLLER: Russ.

DR. SNYDER: I was just going to comment specifically on the question that was asked. You know, if we are going to just pick abnormal bleeding or menorrhagia as is what is being studied, I don't again think it is impossible to have a randomized control trial that is going to answer and take care of

the heterogeneity in this whole issue.

If it is not a randomized controlled trial, however, we are going to have to require a lot of stringent criteria. It is going to have to be some way to, one, evaluate the endometrial cavity, either hysteroscopically, hysterographically, to know that we are also not dealing with a submucous myoma. You know, we are going to have to have some way to verify that we are not treating dysfunctional uterine bleeding in a patient that also has a 4 centimeter intramural myoma.

It is just going to require a lot more selection criteria to be able to get valid scientific evidence, if we are not going to rely on the randomized controlled trial.

CHAIRMAN NOLLER: Other comments? Hugh?

DR. MILLER: Well, I guess I would just add that, even in the setting of a randomized controlled trial, because of the variability that has already been mentioned, it is still going to be important to monitor those different variables to make sure that the sample is proportionate in those areas;

because I don't envision these as being a thousand patient trials. They are going to still be small, and it would be easy to throw the analysis off by having a misproportion of patients.

CHAIRMAN NOLLER: Let's talk about follow-up then. Typically, six-month follow-up -- how are they doing at six months? And some decision is made then at the panel or by FDA, but the patients in the trial are followed for three years.

Now I have heard a couple of people say, you know, we need to see how many had hysterectomies at three years or something, which I think would be wonderful. But in fact, just based on delay and delay, I would guess that no sponsor wants to wait three years after their last patient has been entered before they bring it to the FDA for a PMA.

So that is a long time, even though it is information that we would like to have, and really more post-market. Dr. Emerson?

DR. EMERSON: Well, I was going to let pass the trial of 1000 patients, but since I can address both of these at once: Where is it written

that there can't be a trial of 1,000 patients, and where is it written that there can't be a trial that lasts three years? This is what happens in a lot of other diseases, that the studies last that long.

So I don't understand why that is automatically a criterion, that we would just say, oh, it's okay to do science that we don't really care about, just because we are trying to do this. The criterion should be what we care about and, if it takes that long to do it, we should do it.

CHAIRMAN NOLLER: Russ?

DR. SNYDER: You know, I'm sitting here thinking, what's the problem with this? Well, the problem is, one, we are asked to comment on the safety and the efficacy. We can do safety with a very short time frame, and we can do one measure of efficacy in a short time frame. But the real measure of efficacy that my patients want to know about is what is the chances that they are going to need to undergo a second procedure, a hysterectomy, on top of this other procedure in the next five, 10 or 15 years until they are menopausal.

So part of the problem is how are we going to define efficacy, because there is a short term efficacy and a long term efficacy.

CHAIRMAN NOLLER: Good point. Ms. George. Who else?

MS. GEORGE: I've been listening to all the comments about doing the clinical trials and all of that, and one of the things I just want to remind us of is that the United States is supposed to be the best place to have medical care, and what's happening is that more and more of the products are getting approved and used safely and effectively everywhere else in the world much faster -- China, Japan, throughout Europe, and we do have monitoring and regulatory work we have to do in those countries as well, clinical trials we have to do. But we are having products that are taking three, four, five, six, 10 years longer to get approved here in the United States.

DR. SANFILIPPO: Could you share with us another country -- I mean, to me it's one year or three years -- okay? -- for follow-up. What would be

the standards in some other countries? Would it be like a design for one year and then a PMA at that point, or help us understand that.

MS. GEORGE: It does vary by product, and it is usually risk based. It is a risk based profile that we have to put together, that you define it with clinical people that you partner with, similar to this kind of an environment. So depending on the country and depending on the protocol, there is a lot of variation that happens with the practice of medicine, because we do have to address that through the risk profile.

The FDA does accept risk profiles. So that, you know, the question was where is it defined. It isn't defined just for that reason, because the FDA does partner with us to sit down and say, okay, what are the risks associated with this. What are the oversight that goes on, the control mechanisms and things like that.

So that's why it does take a while to define them, but there isn't a black and white, you know, it's six months or it's a year. It's based on

risk and what it is you are trying to focus, and what the risks of not having the care available are, not just the risks of having it.

CHAIRMAN NOLLER: I don't quite understand risks. Many of these procedures, the risk is over in 48 hours or something, if you are talking about procedure risks. But the risk of another procedure in this case, this specific case, fibroids isn't over for six months, one year, five years, 10 years; because if many of them fail at one year, where 80 percent of the women need a hysterectomy after a year, what was the need of the procedure in the first place? That is sort of what we are talking about. Yes, Marcelle, and then Gerry.

DR. CEDARS: Wouldn't some of that come under what they list as the indication for the procedure? I mean, if they list, you know, long term treatment of abnormal bleeding or if they list -- you know, I mean, could you -- because I do believe, to some extent, to have them have three-year data before even coming to market is a tad bit onerous for the company.

On the other hand, six months worth of data is almost inconsequential. So somewhere between there is what is reasonable. I would say a minimum of a year, you know, with some requirement for post-market follow-up, but that would also dictate what they are able to say in their indications and expectations for use of the device, I would think.

CHAIRMAN NOLLER: Gerry?

DR. SHIRK: Well, first of all, the long term follow-up and failure hasn't even been established for myomectomy. I mean, basically, the genetic predisposition -- you know, these people, if you do a myomectomy and you took out every fibroid you could see, these patients may be back in three years -- you know, if they've got a predisposition for fibroids, back in the same position they were.

So I think it is a long term, three-year thing. To sort of hold these procedures to a standard that we don't even hold our own surgical procedures to may be too much.

The other thing, obviously, as Elisabeth said, there is basically two things, basically. A lot

of these companies that are developing these technologies are small companies. They don't have a lot of money to do long term studies. If you are developing cancer drugs, that's one thing. You are generally big companies and stuff, but this whole industry here is driven by smaller companies. I mean, it is basically -- You know, we do have to take into account some of that.

Obviously, we need to take in consumer protection. Also, a lot of our technologies, at least surgical technologies, aren't being put into effect, not because of the FDA but because we get a lot of lawyers out there trying to sue us and sue companies.

CHAIRMAN NOLLER: Hugh, then Dr. Romero, then Dr. Emerson.

DR. MILLER: I was just going to say that, since I was the one who brought up the 1,000 person study, I don't think anybody sitting around this table would advocate for mediocre clinical trials.

On the other hand, there is a pragmatic component which, if we can't trials off the ground because we can't fund them either in the private

sector or in the public sector, then those -- you know, whether they are being done around the world still means that our patients aren't going to have access to those procedures and those technologies.

So it seems to me that we are constantly balancing risks and benefits in any individual procedure, as we are in study design. So nothing is perfect, but we are trying to derive the most benefit with the least risk.

In terms of the issue of follow-up, I think -- to the gynecologists on the panel -- if a year seems reasonable, then a year is reasonable. it is not everything that we would want, but it is most of what we would want.

CHAIRMAN NOLLER: Dr. Romero.

DR. ROMERO: I guess, in the way that some of these time periods are being stated, I am coming away with the impression that there's a certain arbitrariness about it; and I wonder if, given the methods that are currently used in clinical practice with regard to treatment of fibroids prior to hysterectomy, for instance, if there are data that are

already out there that can be consulted with regard to what is the rate -- for instance, like Dr. Noller was using, I think, just as example -- if there is a certain percent of the patient population that is treated less than basically, that within a year's time or whatever the case is, that then subsequently undergo hysterectomy, seems that the data that are out there for the standard of care that is currently used should inform this discussion in terms of that being a goal or the point beyond which newer technologies would be assessed.

So that if, just to use your -- you know, what you threw out, I think, just as an example of 80 percent of patients who undergo a less invasive procedure have undergone subsequent hysterectomy in a year's time, it seems that that should be some gauge. So that may be not the three-year burden that seems onerous, but either a smaller -- a lower rate in the same time period or, if it is an appropriate different time period based on the data that we have.

CHAIRMAN NOLLER: Dr. Emerson.

DR. EMERSON: Just as there are different

time frames of efficacy and whether you are looking for the very short term effects or the long term effects, the same is true of safety, and the same is true of such issues as -- you know, it may well be somebody who wants to preserve their reproductive potential that two years is enough, and then after that having the hysterectomy is not the end of the world.

So it is very hard to judge all of these things, and again I would agree entirely with the statement that of, if a year seems reasonable, then it probably is, because that is what we are usually going on, is our understanding of the disease process and our understanding of when the bad events would happen and how well we can be able to assess that, how important those events are and how likely they are to happen. The medical judgment comes in there.

Then just as one comment, I will note that in the cancer world the small start-up biotech firms are very small, and are faced with this exact same problem.

CHAIRMAN NOLLER: I am sensing that maybe

FDA would -- Colin, you just looked a little agitated. Is this going the way you wanted or have we exhausted what we can do usefully for you on this question?

MR. POLLARD: I'm sorry if I looked agitated. I just wanted to point out, just in case there was any clarification needed, that model that you see up there is a six-month pre-market model. The three-year part is in a post-market setting.

CHAIRMAN NOLLER: I think what people were starting to suggest is perhaps a 12-month pre-market.

MR. POLLARD: I'm not agitated. I'm just-

CHAIRMAN NOLLER: No, I thought maybe you thought we had carried this as far as we could go.

DR. WEEKS: This is a question for folks that do these types of surgeries. But the shorter we make it -- Since these procedures won't be blinded, the shorter the follow-up, then perhaps the more important fact is, you know, that this isn't blinded.

The second statement I will make is I think a 12-month pre-market follow-up seems about right. It is arbitrary. I would be concerned if that is all there was, though, particularly again since it

is not blinded.

CHAIRMAN NOLLER: Dr. Chegini and then Russ.

DR. CHEGINI: I think the reason one year is probably adequate, because first of all, these tumors are hormonally dependent, absolutely. Number two, they are very slow growing tumors. They don't grow or double in size between a matter of a month or two.

If you recognize that, so at least following whatever device anybody is making and claiming that it dissolved the tumor or some liquid of material there is going to be dissolved and so, therefore, the following tumor that they are coming up, it may take longer for them to grow than six months. So I think a longer period is definitely necessary, regardless of whether the outcome of that treatment is fertility or bleeding.

CHAIRMAN NOLLER: Russ?

DR. SNYDER: You know, again, I will always believe that there is short term efficacy and long term efficacy, and there's going to be different

definitions of success from one patient to another; because some of my patients -- if I told them that there was going to be a 25 percent chance you need a hysterectomy in the next 10 years, they are going to go, well, why wouldn't I just have my hys now; and others are going to go, gosh, you know, that would be great, you know. I can delay. You have a 75 percent chance I'm not going to.

So there's going to be individual patient definitions of what would constitute success. But in looking and having reviewed the articles that were included in our packet, you know, there were a couple that had follow-up at 24 months and one in there that had follow-up at five. But the incremental increase in failure after one year was very small.

You know, referencing the one by Dr. Spies that did actually make the statement that there was likely -- long term failure was more likely in those not improved at one year. So I am very reticent to want to do six-month looks as opposed at a minimum look at a year.

DR. EMERSON: I will just note that,

depending upon how you define what follow-up you want over a year, you don't really have to follow everybody for that year. So if it's a time-to-event sort of analysis and so on, then you are happy averaging over that year. It doesn't absolutely have to be that it's a year from the accrual of the last patient.

CHAIRMAN NOLLER: Ms. George.

MS. GEORGE: A couple of the presenters asked us while they were presenting, were we going to consider the devices that all devices were equal in this process. It sounds like we are coming to sort of a consensus to say that they are all equal. Does everybody feel that way still, because I think that we heard some people saying that they thought that their solutions were, granted, not talking 510(k) or PMA but clinical trial focus. Are we coming to that consensus?

CHAIRMAN NOLLER: I was quite impressed at how different many of them were. What's everybody think? Marcelle?

DR. CEDARS: Well, I mean, equal in terms

of what? I think that, getting back to what Russ said in terms of safety and efficacy, they are all going at the same endpoint, but the path to get there is different and, therefore, their safety might be different, and the risks might be different.

So I'm not quite sure what it means to say they are all equal. Does it mean that, if one passes, the other does or would it somehow eliminate each of them from doing their independent trials? I don't know what your comment is asking, I guess.

MS. GEORGE: I guess what I was asking was -- We are talking about, you know, like a one year on the pre-market, and if we are saying that is for all of the device submissions, that I heard we heard about a couple of very different, some that already have -- the technology is already approved, but it's just the specific use, or if it is the specific focus of bleeding or if it is the specific focus of fibroid ablation or whatever. I guess that is what I was asking.

CHAIRMAN NOLLER: It will depend a bit, too, on what indication is being asked for, and that

may vary, I suspect, a fair bit among the various devices. Marcelle?

DR. CEDARS: Yes. I mean, if that is what you are asking, then I would say yes, that if there is an indication for abnormal bleeding with fibroids, then the duration of the study ought to be the same for all of them.

CHAIRMAN NOLLER: And Colin suggested that they wanted as level a playing field as possible and don't want different rules for every device, but that will depend a little bit on how safe it is and what the indication is being asked for. Russ?

DR. SNYDER: My comment now is totally a question. So, you know, things that we require as far as a device, are those same issues going to be applied equally to the truly pharmaceutical treatment, the same symptoms and the same tumors?

CHAIRMAN NOLLER: Actually, I think Nancy would be the appropriate person to answer that question.

MS. BROGDON: Maybe I could defer to Dr. Emerson.

CHAIRMAN NOLLER: Nobody here knows anything about drugs.

DR. EMERSON: Only to the extent that I'm sitting on the committee at the same time.

CHAIRMAN NOLLER: Yes, Gerry?

DR. SHIRK: On endpoints, I guess one of the things we haven't addressed, I guess, or doesn't seem to me like we have addressed -- we've talked about outcomes as far as clinical outcomes and success or failure, but we haven't spent very much time on safety.

CHAIRMAN NOLLER: No, we haven't. Let's spend some time on safety.

DR. SHIRK: And if we are going to talk about outcomes, we also have to talk about -- Maybe that's device specific, but --

CHAIRMAN NOLLER: Colin?

MR. HILLARD: Yes. I am going to -- At first, I wasn't going to say anything. I think I will give you a partial response on the drug question. Obviously, this is a device panel, and we set our own mark.

I will say that we had -- We collaborated -- Actually, NIH spearheaded a symposium last year, a second symposium on fibroids, looked at the whole realm of fibroids, everything from the biology to the drug side of it. We did have a session where we looked at clinical trial design for treating fibroids, and a couple of the presenters spoke to the drug side of things, and our colleagues -- and it's still a fully developed program, but where it was headed was, in fact, looking at abnormal uterine bleeding, using PBLAC and actually, regarding the issue of using old tampons and pads, basically the way you do it is you revalidate a newer, more modern tampon or pad, and then you do a nested validation within the trial itself to just recalibrate it.

They looked at two endpoints, namely reduction in bleeding by the PBLAC score and looking at need for surgery at some point down the mark. But the one big difference there is using a placebo control and having a management regimen for the women on the -- Well, you would have a standard management regimen for managing all the patients and then,

obviously, there would be some points where things would kick out.

Anyway, that's sort of a quick overview of it, and I don't presume to speak for our colleagues in CDER. But that is a quick snapshot of it.

CHAIRMAN NOLLER: Thank you. Safety. Gerry, since you brought it up, what do you say about it?

DR. SHIRK: Well, I think each of them has safety issues. Obviously, having been involved a little bit with early myolysis, both from a laser standpoint and then a thermal standpoint, there is obviously the big question of when you interrupt the surface of the uterus, whether it is through laparoscopic means, with cryoblation, some other hot thermoblation device as to adhesion formation and problems like that even, I don't think there is any doubt about what happens as far as internal adhesions with the patients who have had uterine embolization.

I mean, does this create a significant problem with adhesions and subsequent pelvic pain problems? There is the issue of, obviously, necrosing

tumor and, obviously, creating bowel problems or creating infection problems.

So I think that each of these necrosing technologies is going to have its own safety issues that are involved with it. The idea of using the compression device for the uterine arteries -- I mean, you are right at the ureters. I mean, are there going to be a significant number of ureteral injuries in these patients where you are crushing the ureter for a significant length of time, too?

So I think these are all safety issues.

CHAIRMAN NOLLER: And it is more than just the 48 or 72 hours after the procedure. It could be years later, much like it is in some drugs, for rare complications that are not found out about for years and years. Yes?

DR. SANFILIPPO: And maybe in a sense this is directed to Gerry. I mean, were there some criteria to look at safety with the ablation techniques, and was there some thought of the time frame to identify that, or how did you determine safety?

CHAIRMAN NOLLER: Gerry?

DR. SHIRK: I think it was -- That's pretty easy, because that was just abnormal outcomes. I mean, most of the safety problems are going to be immediate with some kind of interperitoneal problem or infection because of the thickness of the uterus and the fact that you were just treating one thing, the endometrium.

So you are basically trying to thermally destroy the endometrium. Here we are doing something that is destroying the myometrium. That is a deliberate through and through injury.

CHAIRMAN NOLLER: Even there, you could argue that you need a 30-year study to find out if endometrial cancer doesn't bleed in those few. So any of these things could be potential long term complications.

DR. EMERSON: I was going to mention the cancer and also the question of can any of them have long term effects on fertility, that would be not immediate but a few years down the road in fertility development?

CHAIRMAN NOLLER: Marcelle?

DR. CEDARS: Well, I mean, I think if we are going to have one year as the sort of time for follow-up, I would be -- I think it would be unanticipated that an adverse event, even some of these more delayed adverse events, would occur. I mean, they are either going to be acute procedural events or, if there are going to be infections or something else, certainly within, I would say, probably three months you are going to have an answer to that.

So if our sort of endpoint is one year, I think you are really going to get all the potential adverse outcomes except maybe the person who gets pregnant and ruptures a uterus, but since they are not going to be indicated for people -- likely, for people who want to preserve fertility, that is going to be caught in the post-market three-year follow-up. But I think any other injury or safety related issue would be really sort of pretty short term or, certainly, captured in the first year.

CHAIRMAN NOLLER: Other comments?

DR. EMERSON: And I will note that on something like the cancer surveillance that is the 30 years, which is impractical, would also be something that could be picked up far later in such things as case control studies and things like that. That is sort of the only thing you would have for those really long term, and probably even some of the fertility sorts of things could be that mechanism.

CHAIRMAN NOLLER: We've gone over virtually all the major items here. The one that we sort of finished and, I think, gave some direction to, probably the most important one, is Number 1. We talked about that at some length.

We still have some time, but I have the sense that we are starting to run down on ideas. We have sort of talked this out about as much as we can.

Who has some thought provoking discussion stimulating thing to say? Oh, Russ will.

DR. SNYDER: Yes. This is not thought provoking. I just have some concern. I am worried about trying to throw out this pictorial based assessment of bleeding as some sort of standard.

CHAIRMAN NOLLER: Throwing out as in excepting it?

DR. SNYDER: Yes, because I have some real concerns about the reproducibility. I mean, we were given three studies. Two validated each other. Of course, there is always a question of the measure of validation, and one that decided they didn't validate it altogether.

Then when I heard that others are talking about this, because not only do I worry somewhat that every investigator would have to validate that it is reproducible in their own hands with whatever items that they are using, but we are also going to be left with a huge subjective assessment of whether bleeding is -- In other words, I don't think we can have just a quantifiable measure to satisfy whether it was successful as far as decreasing bleeding is concerned.

That is also going to be subjectively determined by the patient. Hence, again, you know, I have more comfort in the survey, I think, in assessing effectiveness than I do in this attempt at quantifying blood loss.

CHAIRMAN NOLLER: Yes, Nancy?

DR. SHARTS-HOPKO: You know, years back -- Decades back, you could get women to weigh their pads or save their pads. You're not going to get that now. I mean, you are going to have to deal with women saying their bleeding has improved and, if you can get a pad count and an estimate of saturation, I think that's the best you are going to be able to do.

CHAIRMAN NOLLER: Oh, we're going good here. Gerry?

DR. SHIRK: Well, the only reason for using like a PBLAC score would be basically if you really wanted to put a ceiling of treatment. I mean, that's what we did with the ablation things. We needed a ceiling that you couldn't go above.

CHAIRMAN NOLLER: In case you made it worse?

DR. SHIRK: Well, or in case you did. I mean, you had to have something that said this was a treatment success. So to get below that ceiling, you had to go below it, but basically -- So we needed a quantifiable kind of a thing, and it was simple and

wasn't totally onerous, and that worked well. But I think in this thing where it is a life quality issue, again if it is built into the Fibroid Life Quality kind of questionnaire and you have some way of quantifying it -- My question was, if we go with -- If you go with a percentage drop, or do you put a success ceiling on it?

CHAIRMAN NOLLER: Marcelle?

DR. CEDARS: Well, I don't think -- I think you are going to have a lot of difficulty validating -- you know, to do another validation study and say the pads, the napkins, whatever are different now than they were when that standard was established. I think you would have a very hard time doing that. However, I don't think you would have a hard time -- I mean, we have done studies even recently where you show them the pictures, the diagrams, and they mark it down.

I mean, I don't think they are going to save it and bring it in and do all that stuff. And granted, the tampons and the pads are very different now than they were, but the likelihood is that all the

patients have a similarly different protocol; and since they are going to be compared against either themselves or, if it is a randomized study, the other group, both of whom are using the same standard, if you will, the current market standard, I still think something somewhat more objective than "I just think I'm bleeding less," you are going to have to have something.

That, short of weighing and measuring, is all you are going to have. So I think you have to still use something like that.

CHAIRMAN NOLLER: Dr. Romero, then Dr. Sharp and then Colin.

DR. ROMERO: I think I would just like to make a more general comment with regard to this question around objective and subjective measures.

In research design, I think there is a probably misplaced that -- and measures are truly objective and, therefore, better and they are quantitative, just the dichotomy between the hard science of quantitative data versus qualitative.

I think maybe we should just be a little

careful to recognize that this concept of objectivity is on a continuum. The high likelihood that there wouldn't be a randomized study introduces bias on the side of the objective -- the measures that we are calling objective.

So I think, if we are going to be concerned about we are calling the symptom -- measurement of change in symptom by patient as quality of life measures, they are symptom measures. I think using the term quality of life, to a certain extent, sort of demeans those measures, and I don't know that that is appropriate.

The fact that it is unlikely that there would be randomization does introduce a bias in the area of these objective measures that we are giving a lot of weight to. So I just think that it is probably important that we remain cognizant of that, because -- Well, I'll just leave it at that, and just the whole literature around -- I think, in response to a specific comment that was made around bleeding, for instance, regardless of, I guess, the correlation with objective measures of increase or decrease in

bleeding, to a certain extent, if the patient believes that less bleeding is taking place, and that was their primary complaint, then less bleeding -- or maybe less bleeding isn't taking place, but the complaint has been addressed.

So I would just -- Just a general comment around how we are valuing these measures and the terms we are using.

CHAIRMAN NOLLER: Dr. Sharp.

DR. SHARP: Occasionally, at our institution we have a journal club, and you are all familiar with that where you really look at articles in depth. It might be wise or helpful for a group of smart people, including epidemiologists and people who know all this stuff, to actually look at some of these different studies, because we've got -- There were three on the PBLAC.

Some of them were done in women that were not even necessarily complaining of menorrhagia, and then other studies were done in women coming to a menorrhagia clinic, so clearly different populations.

Then there is this Ruta score, and then

there is also the quality of life UFS score. It might be nice to actually have a group look at those and see which ones may be validated or may be more appropriate.

CHAIRMAN NOLLER: Mr. Pollard.

MR. POLLARD: Just two points. One is it was just to highlight that FDA has used the PBLAC scores for numerous studies in the past, and has a pretty good track record with them. The package that we sent out to you, we did not try to make it a truly expansive package, you know, completing addressing those. So that comment from Dr. Sharp is an interesting idea, to really delve into that.

The second point is -- and maybe this was intentional or maybe oversight, but we kind of past question Number 5, and it's a tough one.

CHAIRMAN NOLLER: That's why we skipped.

MR. POLLARD: We are probably going to get kicked out of this room in about 12 minutes, but I think it also speaks to a question I brought up earlier, which had to do with the size of the effect. That is, obviously, indication and outcome measure

specific, and I am not sure whether you want to comment on this or not. But if the panel thought they had some input here, we would appreciate it.

DR. SHARTS-HOPKO: Well, I think the crux of the matter with Number 5 is something we have talked about a number of times today, and that is that success is as the patient defines it.

So if the person has the procedure and six months or a year later they are happy, and they believe they have improved, then they are not going to running back for another procedure. If they believe otherwise, then they are going to go running back for another procedure.

So I don't see that -- I mean, I think we have laid out various things that we want to monitor, but the bottom line is that the patient decides whether or not she is finished with treatment.

DR. SHIRK: How can you answer Question 5 if you don't have a defined study and a statistical way you are going to look at things. Then you can put a quantity on the bottom line. Obviously, with our ablation devices we had defined endpoints.

If you are going to use quality of life, then I don't think any of us know what endpoints we want. How much reduction in scores do we want or where do we want to go? So I think that would be an issue that would have to be discussed when the PMAs are designed.

DR. EMERSON: I guess I always answer Question 5 by I still bend over to pick up a dollar, but I won't cut your grass for it anymore. So it's the question of, you know, the amount of effect I want to see depends upon what is the cost of the therapy otherwise, and so if I am worried about lots of late occurring effects and I am worried about that the endpoint is merely a surrogate for the thing I really care about, I want to see a big difference. But if it is something that has no side effects and is a clinical endpoint that matters a whole lot to me, a .1 percent improvement is something that I would like to have.

So it's very hard to answer it in a vacuum.

CHAIRMAN NOLLER: Marcelle.

DR. CEDARS: Yes. I mean, I was thinking sort of similarly when I was just scribbling down stuff when I was reading this. To me, it is what is the risk, and what is the benefit? The more invasive, the more risky the procedure, the more benefit I want to see before I would think it was reasonable.

So it depends what your measure is going to be. So 25 percent improvement might be adequate, if it is a fairly inconsequential intervention. I would want to see 50 percent improvement, whatever that is, if it were more invasive.

So I mean it would have to be something -- I think it is going to have to be more than like a 10 percent for the patient to recognize it as an improvement. So I think you are in the 25 to 50 percent and up for the patient to -- for it to be clinically relevant, more than statistically relevant.

DR. CHEGINI: I have a general comment to all of you that take care of these patients.

As you all know, more and more specialists outside OB/GYN taking care of these patients and using these devices. Are these physicians familiar with the

hormonal status of these patients, that they are maybe influencing the abnormal bleeding or their pain and so on and so forth?

So following surgical procedure that they do, who is going to look after those problems and symptoms? I think you are. So, therefore, is it going to be a bridge between the two disciplines or how we are taking care of the patient and the consumer's points of view, patient interest rather than industry's?

CHAIRMAN NOLLER: You raise a good issue, and certainly, there has been some problems in that area among the various specialties. I am not sure that is -- That could wind up being a gripe session here among the gynecologists. I think we had better avoid it, but it is a good point, that ultimately we often wind up taking care of them, regardless of who has performed the procedure that may or may not work.

I don't think we helped you out a lot, Colin, there, but who knows? Julia? You have one minute.

DR. CAREY-CORRADO: Okay. Thank you all

so much. This has just been an awesome two days, and we appreciate all the tremendous effort and quality of thinking that has gone into your discussions. And than you in particular, Dr. Noller. We are going to miss you very, very much as our Panel Chair.

I did want to add one comment to the discussion of today, and that is that one of the things that we have to keep in mind is device labeling. You all talked a lot about labeling yesterday, and these -- The design of studies to evaluate devices to treat fibroids need to yield a body of data that we can put in the label.

We have to feel like those data are good enough to share with people across the country so that they can make an intelligent and informed decision. So one thing that at least I am going to be taking away is that you have identified benefits of different types of outcome measures, and I think, frankly, the truth is somewhere involving a mixture of them, depending on the study design.

There is certainly a place for what we are calling quality of life. The more objective, what we

are calling more objective, also has value. We have seen repeatability with respect to endometrial ablation studies, and so that PBLAC score does seem to be somewhat, not uniform, but at least have wide applicability.

So I think we are going to be using a combination, but again we want to share the closest we can get to the truth based on what are essentially small studies. That's all I wanted to say.

CHAIRMAN NOLLER: Thank you. Ms. Brogdon, anything additional?

MS. BROGDON: Nothing specific. I just wanted to thank the Panel for your expertise and your energy that you brought to this discussion.

CHAIRMAN NOLLER: I am supposed to remind you to turn in your little thingees. The questionnaire is about the place, if it didn't get shredded. If it did, Dr. Bailey can send you another one in the mail.

DR. BAILEY: Let me know.

CHAIRMAN NOLLER: I thoroughly enjoyed my time with this Panel and working with FDA. It has

been a pleasure. It's actually been a lot of fun, particularly the phone conferences that were terrific.

This meeting of the OB/GYN Devices Panel is adjourned.

(Whereupon, the foregoing matter went off the record at 2:18 p.m.)

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