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AT

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

OBSTETRICS AND GYNECOLOGY DEVICES PANEL

FIFTY-NINTH MEETING

Tuesday, January 27, 1998

12:30 p.m.

Room 020B

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PARTICIPANTS

Gary Eglinton, M.D., Chairperson
Elisa Harvey, D.V.M., Ph.D., Executive Secretary

VOTING MEMBERS

Donald Chatman, M.D.
Michael Diamond, M.D.
Grace Janik, M.D.
Barbara Levy, M.D.

TEMPORARY VOTING MEMBERS

Thomas Downs, Ph.D.
Michael Neumann, M.D., Ph.D.
Gerald Shirk, M.D.

CONSUMER REPRESENTATIVE

Diony Young

INDUSTRY REPRESENTATIVE

Cindy Domecus, R.A.C.

INVITED GUESTS

Deborah Smith, M.D.
Richard Gimpelson, M.D.

FDA

Lillian Yin, Ph.D.

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**FDA'S CURRENT GUIDANCE DOCUMENT
"THERMAL ENDOMETRIAL ABLATION DEVICES"**

FDA Invited Speakers:

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P R O C E E D I N G S

Introductory Remarks/Conflict of Interest

DR. EGLINTON: We will go ahead and come to order. I would like to remind the audience that there is a sign-in sheet out front. Please do sign in. The government likes to keep track of people who come to these things.

If we do have comments from the audience, please wait and be recognized by the chair. Use the microphones. Be sure to state your name clearly and give full conflict of interest disclosure. We would like to have the transcript clean. If you have any support of any kind, that belongs in your conflict-of-interest disclosure, travel, per diem, expenses, and so forth, involvement with any companies.

We would like to have the panel introduce themselves, please, beginning with Dr. Downs.

DR. DOWNS: I am Tom Downs, Professor of Biometry at the University of Texas, School of Public Health. I am a consultant statistician to the panel.

DR. SHIRK: I am Jerry Shirk. I am a private gynecologist from Cedar Rapids, Iowa. I am a consultant to the panel.

DR. JANIK: Grace Janik from Milwaukee, private practice, Medical College of Wisconsin. I am an advisor to the panel.

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DR. DIAMOND: I am Michael Diamond. I am a professor of obstetrics and gynecology at Wayne State University in Detroit, Michigan.

DR. CHATMAN: Donald Chatman, obstetrics and gynecology, private practice in Chicago, Northwestern. Advisory Panel member.

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

DR. SMITH: I am Deborah Smith. I am an obstetrician/gynecologist and I am the Medical Advisor in the Office of Women's Health here at FDA.

DR. GIMPELSON: I am Rich Gimpelson. I am an Ob-Gyn, assistant clinical professor at St. Louis University in St. Louis, mostly though in private practice of Ob-Gyn in St. Louis, and invited speaker.

DR. YIN: Lillian Yin, Director, Division of Reproductive, Abdominal, Ear, Nose and Throat, and Radiological Devices, FDA.

MS. YOUNG: I am Diony Young. I am Editor of the journal, Birth. I am the consumer panel member.

DR. LEVY: I am Barbara Levy. I am a private-practice gynecologist in the Seattle, Washington

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area and assistant professor, clinical, Ob-Gyn at the University of Washington. I am a panel member.

DR. NEUMANN: I am Michael Neumann. I am from Case Western Reserve University in Cleveland, Ohio where I am on the faculty of the Department of Reproductive Biology and the Department of Biomedical Engineering.

DR. EGLINTON: Gary Eglinton, Chief of Maternal-Fetal Medicine, Georgetown University and a panel member.

DR. HARVEY: Elisa Harvey. I am the Executive Secretary for the Obstetrics and Gynecology Devices Panel.

DR. EGLINTON: The FDA press contact for today is Dr. Yin.

We do have a full agenda. If we have comments, please make them brief and concise, no outbursts from the audience, please. I know there is some emotion surrounding this issue, but we need to maintain a schedule here and some propriety.

Elisa.

DR. HARVEY: I would like to start reading a statement regarding several temporary voting members we have on the panel today.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter dated October 27,

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1990, and amended April 20, 1995, I appoint the following people as voting members of the Obstetrics and Gynecology Devices Panel for the duration of this panel meeting on January 27th and 28th, 1998, and listed are Dr. Thomas Downs, Dr. Michael Neumann, and Dr. Gerald Shirk.

For the record, these people are special government employees and are consultants to this panel. They have undergone the customary conflict of interest review and they have reviewed the material to be considered at this meeting.

This memorandum is signed by Dr. Bruce Burlington, the Director of the Center for Devices and Radiological Health.

Next, I would like to the read the conflict of interest statement for the Obstetrics and Gynecology Devices Panel meeting of January 27th and 28th, 1998.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from

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participating in matters that could affect their or their employer's financial interests, however, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interests involved, is in the best interests of the government.

A waiver is on file for Dr. Donald Chatman for his financial interest in a firm at issue, and a waiver has been granted to Dr. Barbara Levy for her interest in firms at issue which could potentially be affected by the committee's deliberations. The waivers permit these individuals to participate in all matters before this committee.

A waiver has been granted to Dr. Michael Diamond for his financial interest in firms at issue which could potentially be affected the panel's deliberations. The waiver permits him to participate in all general matters for January 27th deliberations.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would also like to note for the record that the agency took into consideration certain matters regarding Drs. Grace Janik and Donald Chatman.

Dr. Janik reported that her partner has a

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relationship with a firm at issue on matters not related to what is being discussed at this meeting. Since this is unrelated to the issues before the panel and it does not involve Dr. Janik or the practice in any way, the agency has determined that she may participate fully in the panel's deliberations.

Dr. Chatman reported a pending study with a firm at issue, however, because the study is not specifically related to the systems under discussion, the agency has determined that he may participate fully in the panel's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants should excuse themselves from such involvement, and their exclusion will be noted for the record.

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

We would like to note for the record that Richard Gimpelson, M.D., who is a guest speaker with us today, has reported several professional relationships with firms at

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issue on matters that are both related and unrelated to the issues being discussed. His professional relationships are in the form of research, consulting, and patent development.

I would also like to point out for the public that transcripts will be available through Miller Reporting Company. Their phone number is (202) 546-6666. Videos are also available through Videovisions. Their telephone number is (301) 438-8726.

I also would like to welcome a new panel member to our panel today. Dr. Grace Janik is a new voting member of our panel. She is an associate clinical professor in the Department of Ob-Gyn at Medical College of Wisconsin and a gynecologist in private practice. She has extensive expertise and experience with endoscopy and laparoscopy, and has spoken both nationally and internationally, and is very well prepared to evaluate a variety of ob-gyn medical devices. So, we are glad to have her on our panel. We welcome her input.

I wanted to point out for the panel the contents of their folder for today. The roster, the agenda, and the discussion questions should be on the top. You also have a copy of the summary of safety and effectiveness data for the Gynecare PMA, which was approved last December for reference purposes.

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In addition to that, you have copies of the overheads for the open public hearing presentations that we are expecting today, and you should have overheads for the guest speaker presentations for Dr. Smith, Dr. Gimpelson, and Dr. Shirk.

In addition, Dr. Gimpelson recommended a couple of references which I have also included in your folder.

If there are any speakers who do make presentations to the panel that we don't already know about, if you could give a copy of your overheads to Colin Pollard, that would be appreciated.

DR. EGLINTON: And now Colin will give us a brief overview of the events for the afternoon.

Introduction and General Updates

MR. POLLARD: Thank you, Dr. Harvey, Dr. Eglinton, and I also would like to join Dr. Harvey in welcoming Dr. Janik to the panel. We are very happy and pleased to have her and we look forward to your participation over the coming years.

I would also like to mention that a couple of panel members are rotating off as of this month. Dr. Blanco unfortunately is not here today because of a health emergency in his family, but he has been a very helpful panel member over the last four years, and Dr. Eglinton,

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this is going to be his last meeting for us as a panel chairperson, and I know he has been counting the months and days down.

I think folks ought to recognize that Dr. Eglinton served first as a full voting member for four years and helped us through a number of trouble areas in the PMA work, especially in the area of home-unit activity monitoring for which we are eternally grateful. After he rotated off, Dr. Yin twisted his arm and he was back as a panel member for four more years and served fantastically well in that capacity, and just to let Dr. Eglinton know that we really appreciate it, Dr. Yin has a certificate from our Center Director of appreciation. We have also put Dr. Eglinton in for an FDA award.

DR. YIN: I would like to read this. Certificate of Appreciation presented to Gary Eglinton, M.D., in grateful recognition of eight years of exemplary service to the Obstetric and Gynecologic Devices Panel. Signed by D. Bruce Burlington, Director, Center for Devices and Radiological Health.

I must add that on behalf of the Center, our Office, Colin and myself, we are grateful forever, and you are FDA's person forever.

Thank you so much.

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[Applause.]

MR. POLLARD: We also happen to know that Dr. Eglinton is reggae fan to such a degree that I would not have the nerve to go out and just pick out any old reggae CD. I had to consult with his reggae mentor, and we got him an album by Lucky Dube.

DR. EGLINTON: Thank you. I know who the consultant was. There aren't a lot of South African reggae stars.

MR. POLLARD: I would like to move on. Very briefly, before we get into today's basic agenda, which is to take a fresh look at our endometrial ablation devices guidance document, I would just like to quickly catch you up to date on--and the audience, as well, the public, as well--with a couple of other FDA activities.

First of all, as I think most of you know, following the panel meeting in October, we went back with Gynecare and finished up the remaining conditions that the panel stipulated for that PMA, and the PMA for the ThermaChoice device was approved December 12th. I believe copies of the summary of safety and effectiveness were available or are available.

DR. HARVEY: I can make them available out front.

DR. EGLINTON: Okay. Also, as I mentioned at the

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last panel meeting, the reclassification proposal for devices used in assisted reproduction, like in-vitro fertilization, and so forth, was published in September. The comment period expired last month and we are in the end phase of getting that published in final, and we are looking forward to that. It has been a long time coming.

Today, we have brought the panel together, invited guest speakers together, to take a new look at a guidance document that the panel participated in developing starting about a little more than two years ago, and I believe you all have copies of it in your folder, and there were also copies out in the front, for thermal endometrial ablation devices.

Following that October '95 panel meeting, we issued that guidance document in March, in final, and it has been in place ever since. What we are asking the panel today is to take a fresh look at that in light of new data, new published work, and just our overall review experience. To that end, we enlisted the help of Debbie Smith with our Office of Women's Health, Jerry Shirk, a consultant to the panel, and Rich Gimpelson, who we divided up a series of discussion questions to take a look at, in particular, the clinical study requirements starting with the basic safety studies and then working our way through the pivotal safety

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and effectiveness study that would support a PMA, and then finally, one last question on the issue of endometrial ablation and uterine cancer.

With that, what we are really asking the panel to do is to take a look at the guidance document, see if and how the guidance document ought to be revised, and hopefully, we will get a full discussion of that amongst the panel members with the help of the guest speakers.

Thank you very much.

DR. EGLINTON: We will have the general public open public comments. We do have an agenda. We have one unpublished change. We will have, first. Dr. Joanne Luoto from the NIH will make some brief comments.

Open Public Hearing

DR. LUOTO: Thank you, Dr. Eglinton.

This will be extremely brief. It is, in fact, ancillary to the committee's charge, but it seemed timely to at least inform the members of the advisory committee, as well as the attendees, and the general public therefore, of an impending NIH conference

I will leave copies out for anyone to pick up, but the committee members should receive one shortly.

Essentially, we wanted to notify you all that NIH, the National Institute of Child Health and Human Development

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will be sponsoring a meeting on non-hysteroscopic endometrial ablation. NIH's mission is research and we would like to determine if and what any necessary research projects in this area might be.

We are looking at a scheduled date at the Lister Hill auditorium of mid-August of this year, so we are under a very short time frame to organize and conduct this conference. The ultimate goal will be to determine what NIH fiscal support for research might be necessary in this area.

The reason I gave you the handout essentially is to provide you with my name and contact points, so that if there is something that you would like to inquire about or volunteer information on, or pass this information on to someone who may have a particular interest in the field, then, I would be pleased to have you do that.

I thank Dr. Harvey for the opportunity to say this. Now, on with your business, so Dr. Eglinton can step down.

DR. EGLINTON: Thank you.

Now we presenters from the public. We would like to have the comments limited, please, to five to seven minutes, and have the comments directed toward the business at hand if possible.

First, from Novacept, Dr. Jay Cooper. Please

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identify yourself, sir, and your source of funding for your visit today.

DR. COOPER: Good afternoon. My name is Jay Cooper. I am a practicing gynecologist in Phoenix, Arizona. Novacept, a medical device company involved in researching electrosurgical endometrial ablation devices, has paid for my travel costs and has provided a consulting fee to allow me to be here today.

My abbreviated oral remarks are intended to highlight issues that are included in a written statement previously provided to the agency.

I have been active in the field of endometrial ablation for the past 15 years. My initial experience was with the YAG:LASER and later with electrosurgical endometrial ablation with resectoscope and rollerball electrodes.

I have been a clinical investigator for new global endometrial ablation technologies and have served as a medical consultant to and on the medical advisory board of a number of medical device companies.

I applaud the FDA's and the panel's efforts to seek input from the clinical community regarding the appropriateness of the current guidance document on thermal endometrial ablation devices.

Effective resectoscopic techniques for ablating the uterus have been available to us for more than 15 years, however, only a small percentage of gynecologic surgeons have embraced the procedure. The complexity and risks of traditional resectoscopic endometrial ablation procedures are undoubtedly two major impediments to widespread adoption of these techniques.

The development of new global, auto-ablation techniques, that are shown to be both safe and effective, will no doubt increase the availability of endometrial ablation. With resectoscopic endometrial ablation, satisfactory results and safe procedures are possible only after the physician operator moves along what can be often a steep and time-consuming learning curve.

The vagaries of traditional resectoscopic ablation are such that even after the clinician achieves the status of expert, his or her ablation technique may vary greatly from another recognized expert. Variations in surgical technique, when applied to individual patient differences, including hormonal status and endometrial characteristics, results in uneven and unpredictable clinical results.

Despite these problems, proper use of existing resectoscopic electrosurgical endometrial ablation devices has proven to be highly effective. Therefore, new global

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ablation devices, which employ the same basic electrosurgical technology and principles as does rollerball ablation, may not raise new safety and efficacy questions. A balance should be struck between the need for testing and the need for these devices to be available. I believe it should be unnecessary in the design of study protocols to retest known characteristics of existing devices. Rather, evaluation of new devices should focus on those issues that are new or different.

[Slide.]

In evaluating a device's safety and efficacy, the following points should be considered. The system should minimize or eliminate operator error and experience or variation in technique. It should allow for a shortened learning curve, employ a known energy source, conform to variations in uterine cavity size and shape, provide controllable, reproducible tissue destruction, allow for shortened treatment times, require minimal analgesia and/or anesthesia, require minimal cervical dilation, produce minimal side effects, result in amenorrhea rates that are equivalent to or better than traditional rollerball techniques, and offer a better quality of life, hence, reduced or eliminated uterine bleeding and cramping.

With respect to performance testing, the current

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guidance document does not distinguish between the critical principles of operation for different types of devices, specifically, the means by which endometrial ablation is achieved.

The sponsor of a global auto-ablation device that achieves its goal through application of either heat or cold, without direct visualization, and which requires closed loop control of the tissue and/or of the device temperature must consider the following design issues.

[Slide.]

1. Tissue thermal conductivity.
2. Software control of temperature and power modulation.
3. A feedback provision to monitor perforation potential.
4. Feedback parameters to monitor the ablation progress.
5. A means to measure and control internal device pressures.

However, there are also devices currently under investigation that do not require closed loop control of tissue or device temperature. These devices, which mimic classic endometrial ablation techniques in their principles of operation, raise fewer technical issues. Therefore,

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testing for these devices can fall under the current standards for electrosurgical devices. For both types of devices, the general parameters I have noted are not inclusive and a more in-depth list is provided in the performance testing table attached to my written statement.

I would like to share some of my thoughts regarding the clinical testing of any endometrial ablation device as mandated by the guidance document.

The initial feasibility safety study as proposed in the guidance document seems appropriate, however, there should be some standardization as to the anatomic location of the endometrial samples to be analyzed. For example, is the depth of destruction the same in the uterine cornua as it is in the main body of the uterine fundus as it is in the lower uterine segment.

For the feasibility effectiveness study, inclusion criteria should address the fact that endometrial ablation is not a contraceptive procedure and women must agree to use contraception during the study.

As well, I would recommend that the study exclude women with cervical stenosis.

For the pivotal study, the control arm should be any single approved endometrial ablation device. As to randomization, if comparison to rollerball or resecting loop

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is chosen, historical data is sufficient. As to endpoints, pre- and postmenstrual diaries are unnecessary if the studied device demonstrates the ability to produce amenorrhea rates that are equal to or greater than those seen with rollerball endometrial ablation technologies. In these cases, abbreviated follow-up could be appropriate. However, if amenorrhea is not used as an endpoint, follow-up should follow the current guidelines.

As a practicing clinician, I appreciate the FDA's willingness to undertake a critical analysis of current guidelines, as well as an evaluation of the appropriate degree of review for new device technologies.

Based on my experience, I believe that the ultimate endometrial ablation system will be one that transfers the expertise from dependence on the clinician operator to a device system that employs a simple technology. In my opinion, the perfect device would be closely modeled after those devices with which we already have experience and fully understand the principles responsible for tissue destruction.

Ultimately, devices must provide controlled reproducible endometrial ablation with controlled dosing of energy to reflect the precise dimensions and surface area of the uterine cavity.

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In summary, it is both important and appropriate that FDA continue to examine its dual role of protecting public health and safety through appropriate device evaluation, while at the same time, promoting the rapid availability of meaningful new or improved technologies that improve the quality of life.

I thank you for the opportunity to comment on these guideline documents. I will be glad to address any questions or provide clarification to any of these issues.

Thank you.

DR. EGLINTON: Thank you very much, Dr. Cooper.

Next, from CryoGen, Dr. John Dobak.

DR. DOBAK: Good afternoon. Thank you. I am Dr. John Dobak. I am the founder and technology officer of CryoGen. We are a start-up company in San Diego developing a cryosurgical system for endometrial ablation.

I was asked to provide some background information on Cryosurgery and how it relates to endometrial ablation.

[Slide.]

I will start with the first couple of overheads, which are a brief history of cryosurgery, noting first that cryosurgical devices have been cleared for use in neurosurgery, cardiac surgery, urology, gynecology, and numerous other surgical specialties since the 1960's.

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Second, cryoablation of the endometrium has been performed since the 1970's and there are 150 or so cases reported in the medical literature.

[Slide.]

Third, cryosurgical intrauterine probes have been cleared for soft tissue ablation, in fact, CryoGen has a clearance for a cryosurgical intrauterine probe.

Lastly, cryosurgical devices have always been Class II and cleared via 510(k).

It is interesting that given this history, the endometrial ablation by cryosurgery is currently being limited, and an interesting paradox exists in that a physician is cleared to place a cryo probe blindly into the brain and ablate neurological tissue, however, a physician is not currently cleared to place a probe into the uterus to ablate endometrial tissue.

[Slide.]

Moving on to some of the ultrasound characteristics of cryosurgery, this is really a new aspect of cryosurgery in that the procedures can be monitored using ultrasound. This is a picture of a uterus being frozen in a benchtop demonstration, but essentially, the tissue is a frozen mass and most of the acoustic waves reflect off of that frozen mass and create what is called a hyperechoic

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front which represents the ice front, and a postacoustic shadow, which is shown there on this overhead.

It should be noted that this has been used for about 10 years in the treatment of prostate surgery, liver tumors, pancreatic tumors, and even breast tumors more recently. In fact, in the use in prostate surgery, the ice front has actually grown through the capsule of the organ within very close proximity to the rectum, and despite this, there has been very few or no complications of rectal perforation or damage, which shows that ultrasound really has adequate resolution to perform these types of procedures. I think in the case of endometrial ablation, the ice front will only be grown part way through the myometrium, providing a significant margin of error relative to these other areas where cryosurgery and ultrasound are used.

[Slide.]

Looking at some other unique characteristics of the ice ball or the frozen tissue, one, it is important to note that the ice ball grows incrementally. It grows, shown on that graph there, at about a rate of 1 to 2 millimeters per minute, so it is very controlled.

Two, the ice ball grows very symmetrically, shown in those ultrasound pictures on the bottom. The cryo probe

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essentially sees a uniform heat load and the thermal conductivity of the tissue is uniform. Therefore, the cryo probe or the ice ball grows very symmetrical and uniform.

Another important point is that the leading edge of the ice front is non-destructive. The temperature of that ice front is minus 2 degrees and tissue dies at about minus 20 degrees, and that minus 20 degree temperature exists about 3 to 5 millimeters behind that leading ice front, so that if an ice ball were to grow or the ice front were to reach the serosal surface, it is very unlikely that there would be any destruction of the tissue near that serosal surface.

[Slide.]

Looking at some more of the ice ball characteristics, it is important to note that the ice ball really does not distinguish between the endometrium, the myometrium, and the fibroids. Again, this has to do with the thermal conductivity of the tissue. There is really no difference amongst all those tissues, nor is the heat load any different, and if you look at the picture there, that white area is destruction, and in this specimen there is some significant fibroid disease and you can see that the fibroids are destroyed shown by that white area, as well as the endometrium and the myometrium. If you look at the

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ultrasound that was obtained in the freezing of this experiment, you can see that the ice ball grows very symmetrically as in very normal specimens.

[Slide.]

To conclude, I think that the combination of ultrasound guidance, probe placement, cryosurgical understanding, and anatomical knowledge creates a level of control and skill requirement beyond that of the simple global auto-ablative devices.

However, I think that the procedure will simplify endometrial ablation compared to the current techniques.

Thank you.

DR. EGLINTON: Thank you, Dr. Dobak.

Next, from Gynecare, Susan Aloyan.

MS. ALOYAN: Hi. My name is Susan Aloyan. I am the Director of Regulatory Affairs and Quality Assurance at Gynecare/Ethicon which is now a Johnson & Johnson company.

Our ThermaChoice uterine balloon therapy device, a thermal endometrial ablation device, was approved by the FDA last month for the treatment of menorrhagia. I would like to comment on the guidance document from the perspective of a company who just recently went through the PMA approval process for a device to treat excessive uterine bleeding by use of thermal technology. After conducting a clinical

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investigation with our device compared to the rollerball technique, we noted several aspects that would be helpful in future studies.

The guidance document requires use of some quantitative measurement as a primary endpoint to evaluate menorrhagia. We selected monthly blood loss as the primary endpoint and measured this by using patient menstrual diaries. By using a validated and well characterized method of assessing blood loss from these pictorial diaries, we found our data was very consistent and reproducible.

Gynecare felt this was an accurate method of determining if a woman was menorrhagic. In comparison to this, hemoglobin and hematocrit values indicative of anemia were not as closely correlated with menorrhagia. We do not think these measurements are accurate enough to assess the amount of blood loss. This is an indirect measurement of blood loss which can be greatly affected by other physiological factors such as concurrent medications, individual patient variability, diet, et cetera.

Another measurement that we found very useful was the Quality of Life Questionnaires. These questionnaires were completed by patients prior to treatment and at selected time points after treatment. We used the responses from the questionnaires as secondary endpoints to assess the

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impact of the procedure on the patient's lifestyle, as well as to evaluate overall success of our investigational procedures compared to the rollerball treatment. We do suggest using a validated Quality of Life Questionnaire which would ensure consistency among industry for different methods of treating menorrhagia.

Using the patient menstrual diaries and the Quality of Life Questionnaires with an adequate patient population, we were able to demonstrate similar results between uterine balloon therapy and rollerball therapy in treating menorrhagia.

We feel that the patient inclusion and exclusion criteria suggested in the guidance document are appropriate for a study using a thermal endometrial ablation device. We would, however, recommend that post-menopausal patients also be excluded from the clinical investigation. We believe this group of women should be studied separately as the etiology of their bleeding is quite different.

In regard to the procedural requirement for endometrial preparation, we feel it is not necessary to require that the endometrium be pre-treated by hormonal agents or by D&C. Although a particular technology may find this useful, it is unduly restrictive to require that all thermal endometrial ablation studies include uterine

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pre-treatment.

In summary, it would be important to continue to conduct comparative clinical trials on the new thermal ablation devices. In general, the number of patients, the number of investigators and duration of follow-up need to be maintained for scientific integrity and to assure adequate patient and physician experience.

New technologies that are being developed are not similar enough to allow generalization at this time. Safety, efficacy, durability of effect, and issues arising in patient groups at different sites of use are also important issues to consider.

I would like to thank you for the opportunity today to speak.

Thank you.

DR. EGLINTON: Thank you.

Is there any other public comment? Anyone prepared to make a statement that is not on the agenda?

[No response.]

DR. HARVEY: Before we move on, I would just like to make a clarification for the record, that Dr. Shirk is not an invited guest speaker as noted on the agenda for today, but is, in fact, a panel member.

Open Committee Discussion

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DR. EGLINTON: Colin, are you going to introduce the questions?

MR. POLLARD: No. What we asked Dr. Smith, Dr. Shirk, and Dr. Gimpelson to do is each is responsible for one or more of the seven discussion questions, and so starting with Dr. Smith, each will give a brief three- to five-minute discussion preceding that question and then read the question itself. Then, you would open the panel to discussion of that particular one.

DR. EGLINTON: Dr. Smith.

DR. SMITH: Perhaps it would actually make sense for me to read the question first, No. 1, for initial safety studies, because I think then my comments will give more specificity to some of the issues that we are interested to have the panel address and discuss with us this afternoon.

The first set of questions reads: What kind of initial clinical data are needed to establish basic safety before proceeding to treating patients in early effectiveness studies or the pivotal study? These new device systems differ significantly with respect to both the type of energy for ablation as well as the control or monitoring mechanisms for ensuring a safely completed procedure. How should data requirements be tailored for the particular system?

[Slide.]

When we are talking about the initial safety studies, we are talking about primarily two types of studies that we have made reference to in the current guidance document. One type of study is the extirpated uteri study. As we have looked at the kinds of information that has come in to us, as well as information that we have been queried about for devices that might be under development, we have looked at the consideration of the extirpated uteri studies with certain objectives in mind.

If there are design issues that are remaining for the device, and an example would be the length of the probe, these are fairly straightforward feasibility types of issues that sponsors might be addressing, and have tended to be the primary ones looked at in the extirpated uteri studies. However, we have given consideration to, and would like to give further consideration to, issues remaining with operating parameters for devices, such as temperature, fluid volume, pressures and the duration of treatment.

Then, with an emphasis on considering the type of different types of energy modalities and design characteristics that we are being presented with, and likely to be presented with, and also looking at technical aspects that can be looked at, at this stage of development or this

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stage of testing, that reflect issues regarding ablation depth, and here, some of the areas that we are looking at more closely are ablation of the cornual areas in the uterus and issues arising for previously scarred uteri.

We have been presented with protocol outlines and queries that address the use of histopathology in the extirpated uteri studies. Obviously, there are limitations to histopathology under these circumstances given that we have non-perfused organs and that the laboratory environment clearly is quite different from in-vivo studies, and that we are limited to acute--or actually in all of the safety studies--we are limited to acute effects of the device application as compared to later effects, but we would like to have some input on the value of histopathology for these particular studies.

We have certainly not had in the guidance document a specified number of specimens that would be required for this type of study, but have found ourselves exploring two to six as a range, and would invite some comment on that. Clearly, there seem to be numbers that one can at least have some intuition about would be satisfactory.

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Now, the more advanced studies are in the realm of what we call the feasibility safety studies, and this is the

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pre-hysterectomy study for the ablation devices.

Again, we have undertaken reviews, as well as discussions, with the objectives of these studies in mind or the presumed objectives. Here, again, we are aware that there may still be finalization or penultimate determination of operating parameters, and we invite some discussion as to just how penultimate those determinations should be at this stage.

Patient selection is very important. I would link this to No. 2 on the list, as well. Our current thinking is, is that the closer that the inclusion/exclusion criteria are in the pre-hysterectomy study, the better we are able to work with sponsors to plan for the future effectiveness studies.

I think the issue of endometrial preparation also comes up here in that there are potentially some safety issues if, in fact, there are operative or acute surgical approaches to endometrial preparation just prior to treatment versus the hormonal preparation protocols that were just alluded to and that are spoken to in the current guidance document.

I will go to No. 3. I think we have found that it is most profitable all around to attempt to have a more integrated format or what I have been calling a matrix for

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presentation of data in the pre-hysterectomy studies. I also have this point of view about this studies further down the line, where we can actually collate temperature information, pressure sensors, operating time, and anatomic location of the device that can be correlated with where there are clinician functions throughout the process of the ablation, and where we have other diagnostic information such as ultrasound monitoring, an example being what was alluded to a few minutes ago.

It gives us a better handle on, if you will, the kind of mean median and the mode of the data coming in when we are able to have that kind of display rather than a merge of data from all of the different cases.

We feel pretty strongly now that we are interested to see predetermined protocols, prestated protocols for the gross and microscopic pathologic evaluations, and that there would be a predetermined sequence in which a pathologist would approach the specimens coming from these studies.

Similarly, an integrated format for presentation of the pathology data or the pathology information and results that would allow us to fit that with some of the data from the thermocouple readouts and other operating parameters such as previously mentioned.

Again, we have been working in a negotiable way as

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to the number of cases which are satisfactory for this pre-hysterectomy study. When we are looking at some of the new aspects or differing aspects, not only of the energy modalities, but design configurations, we are seeking input as to whether or not we may need a somewhat slightly increased number of cases than perhaps we have spoken to in the current guidance document.

Any questions at this point?

DR. EGLINTON: Is there any discussion from panel members on the points Dr. Smith has raised? Dr. Diamond appears posed pensively.

DR. DIAMOND: A couple thoughts came to mind. With regard to the extirpated uteri, I would think that issues that might want to be included or at least considered is some considerations by the companies of the length of the probe as opposed to the length of the uterus, and if there are going to be variable lengths of probes that are possible, directions as to which ones might be utilized.

Similarly, with regard to the issue--and this probably applies to both of them--with regard to inclusion or exclusion criteria, the role of thinning of the endometrium prior to performance of the procedure.

If a device is being utilized to achieve a certain temperature or for a certain length of time, I would think

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the result is going to be very different depending on how thick the endometrium was, and so I think depending on the ultimate goal that a company might have as to how they intend it to be utilized, that should go into how they would design this portion of their study.

DR. NEUMANN: I would like to ask a question of the FDA, that studies in ablation of myocardial tissue for controlling arrhythmias, there has been work where mathematical models have been used to determine fairly precisely the distribution of the elevated temperature in case of the work I am familiar with, and I am wondering in what circumstances the firms could present mathematical model data instead of actual data on external uteri and whether the presentation of that should be included as an alternative in the document.

DR. SMITH: To my knowledge, we haven't been presented with that kind of data. It is my impression that we would be interested to look at it and to receive it. Whether or not would meet the same kinds of requirements that have satisfied our cardiologists and cardioelectrophysiology colleagues, et cetera, you know, to be determined.

DR. LEVY: They don't have the option to remove the heart and look at it later.

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MR. POLLARD: We have explored that a little bit, the issue of some thermal modeling, and we have mostly explored it in the context of looking at sort of postmarket type changes companies make to their product, and we have had a couple of people in our Office of Science and Technology who have started work on a model. I am not really sure how far along they are. We have mentioned our interest. I think it is a very plausible approach for answering certain kinds of questions. At this point, we haven't seen any data with this respect, you know, in terms of modeling and invalidating the model, and that sort of thing, but I would certainly say that we are open to that kind of question if it looks like it could answer some of the questions we are interested in.

MS. YOUNG: With regard to the extirpated uteri, Item No. 3 is a recommended number of specimens determined by the study objectives, and I wonder if also there should be a recommendation concerning the location of the specimens, from which the specimens are taken.

DR. LEVY: Specimens in No. 3 means how many uteri, how many patients?

DR. SMITH: Right, not the histopathology. The second one raises the issue about the use of histopathology, and I think there are varying opinions as to whether or not

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doing pathologic evaluations of the extirpated uteri have any value. We have a point of view that there are some instances clearly when it does, but it really does all also depend upon what the purpose, what the objectives of the extirpated uteri studies are, and that is something that we are inviting comment on.

Again, to the extent that it would be of value, my approach in review, I think I would tend to have the same inclination as with the pre-hysterectomy studies and with the effectiveness studies is that one lays out ahead of time a design, a protocol for how one would approach that specimen. It would indicate the number of sections, the type of section, where the sections would be from, full thickness, how many cuts, et cetera, et cetera.

DR. EGLINTON: Michael.

DR. DIAMOND: Two other thoughts. There are a number of women who may desire this sort of procedure, who have either have had a cesarian section or a myomectomy or another uterine surgery, and if these new techniques are going to be appropriate for those patients, these may be again early places to try to look at safety. In other words, if you have thinning of the intrauterine segment because of prior cesarean section, how is that going to affect the thermal actions of the devices being utilized and

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it is going to place at risk whatever may be in the anterior cul-de-sac.

Another question probably would be depending upon who the industry is thinking in the long run may end up utilizing these devices, is it going to be obstetrician/gynecologists, is it going to be someone else trained in surgical procedures, or might it be a primary care practitioner or a PA, should there be a component of the safety portion of the protocols which look at placement of these devices by individuals who are less experienced in placing devices into the uterine cavity.

DR. SMITH: Well, I think certainly--and Colin and Lillian, you will comment on this--certainly again that is a corollary to the intended use and indications and if, in fact, there would be an intent to make the device available to other kinds of practitioners other than those who more routinely are involved with uterine surgery, I would think that we would be interested in the type of human factors study work that actually is also ongoing and that we are requiring, for example, with respect to even the use of the controllers and the software, et cetera, that goes along with these devices.

You are adding in an additional aspect of it. Now, whether that would be, exactly where that would fall, I

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certainly appreciate your comment that there would be safety aspects of it that we would like to have considered.

DR. DIAMOND: Depending on the design of the trial, the original design we came up with a couple of years ago, was a randomized clinical trial of these new devices to endometrial ablation. At that point, we thought it was extremely important that the individuals doing endometrial ablations be individuals that were experienced in those techniques. Otherwise, you might see efficacy of one of these newer devices simply because those individuals had no experience doing endometrial ablations.

So, by necessity, then, you selected a group of individuals who had lots of experience placing instruments in the uterine cavity. So, I think you would have to do the safety component if you wanted others, less experienced individuals to do it, not in the efficacy portion of the trial if you are going to do a comparative trial compared to endometrial ablation, because they are two totally different populations of practitioners.

MS. DOMECUS: I think it is an interesting point, Dr. Diamond, but I would be concerned about somewhat forcing industry to use the lesser skilled investigator when they are doing clinical studies trying to assess their device. I think that you want to primarily eliminate as many variables

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as possible, so that you could find out what your device can do in a best case scenario, and I think the purpose of the postmarket surveillance--and there is pretty extensive postmarket surveillance requirements on these devices--it is intended to get at your issue, which is when it is brought to the more general practitioners, what happens.

DR. DIAMOND: But I think that is the whole point. I agree with you, you don't want to, as part of the efficacy trial, to be utilizing individuals that are less experienced, you want to be able to assess the best possible efficacy on both sides of the comparison.

I think this panel would like--I will speak for myself rather than the panel as a whole--I would like to see that sort of safety data if I am being asked to make a decision on potential labeling and the potential use, so as I say, depending on what the company is thinking the long-term practitioners for this device would be, that may be something that they would want to consider, FDA may want to consider placed on the specific document.

DR. SHIRK: Don't you think, though, the argument is not the person who is using the device, because obviously, if the device is placed where it is supposed to be, and assuming that if it is placed where it is not supposed to be placed, that the failsafe systems in these

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devices will terminate use of these devices, that the real question is basically the adequacy or inadequacy of the workup, the preoperative workup of the patient in most of these devices, and so really, the technical skills of the individual using the device, assuming that the device is a failsafe system, basically, would negate operator error as far as at least the thermal effect and effectiveness, and also safety.

Certainly, those are issues that we have talked about a lot, but obviously, one of the questions that would be important in this thing would basically be if intrauterine pathology does exist, what effect does this device have on that, and certainly that is where your operator inability--my basic question about this is if you reduce the technical ability to do the procedure below the technical ability to work the patient up preoperatively is the major issue and the final effectiveness, so I would think that the thermal devices or the devices themselves are protecting against inappropriate positioning of the device.

MS. DOMECUS: Just to clarify, I would agree with you, Dr. Diamond, if the company was seeking a labeling claim to prescribe it to, you know, PAs and nurse practitioners, et cetera, but if they are not, I don't think that they should be forced to include the lesser skilled and

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knowledgeable as investigators.

DR. EGLINTON: Are we satisfied with the discussion of this first--Dr. Shirk?

DR. SHIRK: The only other question I would ask Deb is obviously, you didn't talk anything about comparison with the animal tissue studies, which are the only live tissue studies that we really have as far as depth of penetration, and stuff like that, in comparison to what these--over time--what these devices are capable of doing in a live situation.

Certainly, it is difficult to figure out tissue damage, like in the pre-hysterectomy patients, obviously, the tissue damage that is there is not always reflected in the histopathology that you see, and how will you address basically the comparison of animal studies especially 48-hour tissue studies versus, you know, the pre-hysterectomy studies.

DR. SMITH: Well, I think that again some of these things are spoken to briefly in the current document. This is where we would certainly be looking for further discussion and input from the panel or recommendations to seek input from other sources.

I think that I would like to see that question answered in terms of not just the issue of the correlation

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with some kind of in-vivo data albeit animal to human, but whether or not there are some issues that arise out of differing energy modalities more specifically, that would compel us to be seeking or would, if not compel us, would certainly give us the inclination to want to see more of that animal data and to try to make some interpretations of that animal data.

I don't know whether other panel members would want to comment on that.

Again, that particular point that you are raising, I think speaks to the last or perhaps the second of the two questions that is embedded in the first area, about data requirements, if there should be data requirements that are tailored for particular systems.

I am not sure that we can--I mean the global debate of the type of studies that you are talking about and their application to humans is one issue, but then beyond that, whether or not we have any issues that are specific to specific treatment, tied to particular systems or energy modalities, I think would be the way that I would want to look at that subset of safety studies or any other set of studies.

That is what we are really confront with now, I think, in terms of a reformulation of the guidance document,

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is how global we are or where we need to develop more specificity that arises out of the different design configurations and the different energy modalities.

DR. LEVY: Maybe to simplify and to put some caps around these things, I guess, as a panel member, I would want to see some long-term animal data of some kind prior to looking at extirpated uteri information and pre-hysterectomy information.

I am not an expert in the energy systems, but I can certainly see that different types of energy will lead to short-term versus long-term tissue damage. For example, the presentation we had showing us that the death of the ice ball isn't necessarily the death of long-term tissue destruction, and when you are looking at very short term, you do the hysterectomy and you look at it under the microscope, we are not really going to know long-term tissue destruction in that information, so I guess we ought to look at a tiered approach that says we do want some animal data from live animals who are followed for X period of time, whatever period of time we think that is appropriate, 48 hours or two hours, or whatever we think is correct, and then look at that histopathology followed by extirpated uteri studies and pre-hysterectomy studies.

DR. SHIRK: The other thing I would add is that

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all these studies should have some kind of a statistical model built into them. A lot of the studies that we review don't have numbers that are large enough to be statistically significant or even evaluated on a small group basis, on a statistical analysis, and so essentially, I don't know how you feel about it, but other than just giving you a ballpark figure, it really doesn't give you a real answer as to what your tissue studies are really saying.

I think that developing a statistical model that these studies have to be done in would be important, too.

DR. DIAMOND: I guess in some ways, I would disagree--well, while I agree that to take a probe that you are intending for human use for any of the different types of ablation, to apply that to a uterus of an animal, which unless you go to monkeys, you are talking about uterine horns as opposed to uteri, you are probably going to have to go to a different size, a different configuration, and then the applicability of the data from one to the other, I am not sure about.

Effects on endometrium, I think might be very appropriate, but to look at--for example, we showed before an ice ball around a uterine horn, where it is very thin, there is no comparison, I don't think, to a uterus, which is going to be great depth to it.

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So, I think it is nice to say that would be a good thing to have, with regard to endometrium it might be appropriate, but I think it is going to have to be device-specific as to whether you are going to be able to use that in a small animal, unless we want to require that you use primates, and even for primates, you start talking about most forms of monkeys, unless you go up to apes, you are probably still going to have very different uterine sizes and very difficult jumps from the device having to be used in animals to the applicability of humans.

With regard to the histopathology, often histopathological conservation, I think you can see what you want to see. How do you grade the amount of fibrosis or the amount of regeneration is going to be in some ways an arbitrary process.

For that sort of delineation, again, it can jump out at you, you can do statistical analysis, I would be all for it, but I think that that is a big burden to say that we need more than the sort of numbers that you have indicated here for the extirpated uteri and for the initial safety trials.

DR. NEUMANN: I think another issue on the statistical analysis is that in terms of safety, we are really looking for the outliers, and I think if we just

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determine an analysis to get an appropriate confidence interval, that perhaps we will miss some important information.

DR. SMITH: Dr. Diamond, just for clarification, when you making your point about the histopathology, were you speaking to the extirpated uteri studies or back on the issue of the animal studies?

DR. DIAMOND: I was referring to the extirpated uteri, as well as the second stage, if you will, of clinical trials, of the safety component where people are going to have hysterectomies shortly afterwards. I guess you could apply it to the animals also, but that wasn't the intent that I had in mind at that point.

DR. SMITH: Well, certainly what different sense of I see and the microscope may be different things, and we are aware of that, but more specifically, as I said, one of certainly my concerns in the review would be that whatever is your definition, for example, of fibrosis, or your definition of something else, that we would have an identification of the protocol and criteria at the onset of that aspect of the study as opposed to once the specimens come.

DR. NEUMANN: I think related to that, too, just for clarification of this question, in those studies where

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temperature mapping is done, that the people submitting the studies should validate their techniques, because there are ways that one can do temperature mapping studies that disturb the system, hence, the result is not characteristic.

DR. SMITH: Again, are you making reference to both the extirpated uteri and pre-hysterectomy studies or to per-hysterectomy studies in particular?

DR. NEUMANN: I think all three. I would include the animals in there, too.

DR. EGLINTON: Any other comment on this first question?

Okay. Dr. Shirk.

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DR. SHIRK: I am going to discuss the next three questions. The first of these questions is how should new inclusion/exclusion criteria be handled, and this represents the present submission guidance documents, inclusion criteria and exclusion criteria.

Obviously, the inclusion criteria includes that the procedure be done for benign reasons, that the patient has previously failed medical therapy, that the uterine size be below 12 cm of depth. Those are the major criteria.

The exclusion criteria obviously include any other significant intrauterine pathology that we could think up.

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This is the only present study that is of public record that we have. It is the Gynecare study, and these were the inclusion/exclusion criteria included in that study. As you can see, these followed the inclusion/exclusion criteria very exactly and, in fact, sometimes were more strict than they inclusion/exclusion criteria that the panel itself had set up. So, this was obviously a study that was well defined and inside of the submission guidance document.

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If you look at the exclusion criteria, however, there are two or three areas in the exclusion criteria during which these procedures are being done on a hysteroscopic basis, and the question is basically how or should these be included in future studies, either as separate units or as far as inclusion criteria in studies that are ongoing.

The first of these is should post-menopausal women who have bleeding problems on HRT be considered for treatment. Right now this is certainly one of the major indications, they are probably one of the more common indications for hysteroscopic endometrial ablation.

There are a large population of patients out there

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who have significant problems with bleeding on HRT or who do not tolerate the combination therapy and do not wish to go on a cyclic therapy, but wish to maintain their HRT and who do not want to bleed.

Some of these issues need to be looked at as far as the use of HRT. Certainly, one of the most important issues would be the issue of efficacy. Here at the endpoint of total amenorrhea is what the patient is looking for. Obviously, this has not been the endpoint that we were looking for in the pre-menopausal patient, so that the criteria certainly would have to be more exacting as far as the efficacy is concerned and what percentage of these patients would really achieve a goal for this.

The other issue obviously would be careful preoperative patient evaluation. Certainly, these patients would need to have their uterine cavities evaluated much more critically than the patient in the pre-menopausal state basically because of the risk of pre-malignant or malignant disease process going on and also because these patients again are looking for total efficacy of 100 percent amenorrhea in this situation.

The next question is what are the technical risks in post-menopausal patients. These patients certainly have much higher incidences of cervical stenosis and a much

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higher incidence of a very small uteri, so that the thermal effect may be more risky in a small uteri, so the issue of basically stenosis and small uteri, again are risk that I have alluded to already, the risk of endometrial carcinoma. This certainly in this population is much higher than in the menstruating population, and this would be a risk, not only at the time of the procedure, but in the follow-up time of the long-term follow-up time of the procedure as to what risks these patients do have of developing endometrial carcinoma over time.

I think the main thing is to look at this thing in a total risk-benefit ratio. Basically, a lot of these patients are patients that are having bleeding problems that would cease and desist if you simply cease and desist their hormone therapy, which obviously has essentially only the risk of the aging process that would occur and does occur in 75 percent of the women in this country who don't take hormone replacement therapy, is the risk of the procedure itself, the risk of anesthetic, the risk of the procedure outweigh, do the benefits and the returned replacement therapy essentially outweigh the risk of simply terminating the estrogen, so that this obviously would be a very complicated risk-benefit ratio to look at and makes this issue fairly significant as far as how we want to look at

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this population.

But certainly I think it is a population that we have to address or will need to be addressed, and will ultimately be addressed because of two reasons; because it obviously is a large group of patients that the companies themselves would want to look at and also, whether we like it or not, those people doing the procedure are going to use it in this fashion, whether it is indicated or contraindicated, unfortunately, I think that we have to be realistic.

The other significant exclusion criteria that we should look at is basically should it be done with patients with uterine fibroids. Again, the issues are efficacy, and we are really dealing with two issues here.

Basically, the issue of whether this is done on a patient that just has fibroids and what is the outcome, or is it being done on a patient who is having a concomitant myomectomy. Certainly, there are a lot resectoscopic myomectomies being done at this time, and I would guess that in a significant number of those patients who have finished their child-bearing, that a concomitant endometrial ablation is also being done on these patients simply because most of these patients are just tired of bleeding. They want it stopped, they want a simple procedure to stop it, and so

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that both the resectoscopic myomectomy is being done followed by a rollerball or combination resection, rollerball endometrial ablation.

Certainly, this is two different populations where you are saying the patient just has a large uterus with fibroids, and you are not doing any of the fibroids and/or you are trying to resect it, resect the submucosal fibroid, and do a concomitant myomectomy, but certainly, these are two different patient populations that need to be looked at and the data evaluated over time.

Certainly, with the latter procedure, the question of whether to--where you are using one technique to get rid of a fibroid, and then switching to another technique, doesn't make any sense at all.

I guess I will open it up to discussion for the panel.

DR. EGLINTON: Dr. Chatman.

DR. CHATMAN: With respect to the post-menopausal woman that you were talking about, as you know, one of the major reasons for discontinuation of HRT is abnormal vaginal bleeding. Obviously, you would like those patients, if you are a proponent of HRT, on the medication. There is supposed to be some very, very important health benefits from that.

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I would think that this would be a separate group of people who could be evaluated. Obviously, you need a different probe size probably, as Dr. Diamond has already alluded to, you need to be more aware of the fact that the endometrium is thinner, that the myometrium is thinner, but I think that population needs to be studied very, very carefully for this purpose, for endometrial ablation.

Whether you like it or not or whether I like it or not, people are going to do this for patients. Patients want this. They don't want to bleed while they are taking hormone replacement therapy. So, I think it is an important group to study. It may not be possible to integrate them into the general group of pre-menopausal patients, and it may not be reasonable to do that, because they are a different population, but I think it is something that needs to be done. I think that the population is going to become larger, they are already demanding, so they will become even more demanding, and I think, again, if you are a proponent of hormone replacement therapy, then, you want to keep the patients on the medication, and I think this is certainly one of the main reasons I see in my office why people stop hormone replacement therapy is abnormal vaginal bleeding. I think it is worth working up a corollary protocol to investigate these patients because they do present slightly

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different problems from the pre-menopausal patient who has amenorrhagia for other reasons.

With respect to the patients with uterine fibroids, my own opinion is that you probably shouldn't be doing an endometrial ablation for patients with uterine fibroids. If a patient has fibroids that is causing them to have bleeding, then, you resect the fibroids, and the patient should stop bleeding. If she has another problem, then, you treat the other problem. This, as you alluded to, you treat the other problem separately.

So, we don't need to be--I don't think we need to look at that group of people, but we do, I think, need to look at the post-menopausal woman bleeding on hormone replacement therapy.

DR. LEVY: I think it is my suggestion that we deal with post-menopausal women as either an addendum to the guidance document or a separate guidance document for several reasons. Number one, as you nicely pointed out, the safety issues are different. We are not dealing with people who are anemic, who have a significant medical problem that requires attention in some fashion.

We are dealing with people who are uncomfortable with a symptom that is not medically harmful to them. So, the definition of safety for post-menopausal women needs to

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be different.

Similarly, as you pointed out, the definition of effectiveness is going to be different for post-menopausal women, and for that reason I think we really need to address post-menopausal women as a totally separate population that we deal with either as an addendum to this guidance document or as a separate guidance document, because all of our definitions are going to be different, and just including post-menopausal women as a different arm of the same study, I don't think will work because our definitions need to change.

MS. YOUNG: I think also I agree with Barbara about that, that they should be treated differently. I think that also the definition of what a bleeding problem is, is a different--that requires a different type of definition.

One has to be very clear the extent to which we are talking about, the extent of the bleeding, and what constitutes a bleeding problem in HRT women, if that is the same as what the definition of bleeding problems are for pre-menopausal women.

DR. SHIRK: I think the answer to that is yes and no. Okay? It doesn't make any sense, but basically, there are obviously a group of women who are on post-menopausal

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therapy that have breakthrough bleeding problems, and that is caused by the hormone itself. Okay? They just do not tolerate the progestins.

There are obviously another group of women who have developed intrauterine pathology or who had previous intrauterine pathology that was present prior to them going into menopause, that is being obviously aggravated by the hormone replacement therapy.

That group is fairly significant if you work these patients up. I mean you look at the studies. I did a study I presented at the NAGL meeting a couple of years ago that basically we looked at 650 endometrial biopsies versus 200 hysteroscopies, and the amount of pathology found in the biopsies versus the amount of pathology found if you really looked for pathology with hysteroscopy, and certainly Dr. Gimpelson has had similar results or anybody who has done it, that looks at it, and certainly, there are new studies with saline infusion sonography.

There is a significant number of these patients that have polyps, who have submucosal fibroids, that fall into this group, so again, the question, you know, is that you have got two groups here.

So, one group you treat appropriately. You diagnose the intrauterine pathology and treat it, and that

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group obviously doesn't need an endometrial ablation. They just need the pathology treated. But the group of women who is having breakthrough bleeding or intolerance to progestins on hormone replacement therapy certainly, you know, present a major problem.

Again, with new designer hormones, the question is where do we stand with this thing where you have got one new hormone that is on the market right now that basically causes no endometrial stimulation, so that obviously doesn't cover your secondary symptoms either, but how important are they.

DR. LEVY: I think, too, Jerry, we need to distinguish between intolerance to progestins with respect to bleeding and intolerance to progestins with respect to all the other side effects of progestins, because I don't think anyone here is going to say that it is going to be safe to do an endometrial ablation procedure and then not use progestins in women.

So, I think we need to be very clear when we talk about intolerance to progestins, it is only with respect to bleeding.

DR. DIAMOND: Three separate comments. First of all, on first blush, I also think that I would prefer to see post-menopausal women, number one, included, and, number

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two, probably put it as a separate group as compared to the pre-menopausal women, although I am not sure that with appropriate considerations and perhaps slightly different entry criteria, you could not mold them into one protocol.

The second point is there may be a little bit of linguistics here. The second line of the question is for abnormal uterine bleeding, and in the post-menopausal woman, there are two different ways I could come up--and I will give you a third--and that is regular withdrawal bleeding for women who are cyclical hormone replacement therapy.

I think that group, who is not having breakthrough bleeding, that is not having bleeding because of pathology, is a group that is at lower risk for problems of endometrial hyperplasia, endometrial cancer, but I think it is going to be very important to distinguish between which of those three situations the bleeding occurs in.

The last comment is that if you are going to include a protocol with post-menopausal women, for the reasons that have been elaborated upon by many people, I think it would be very reasonable to include into the protocol considerations of other means of monitoring after the endometrial ablation process, and that might be, number one, repeat endometrial biopsy at times, although that might meet some patient resistance.

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Another alternative which might be more acceptable would be thickness assessment by transvaginal ultrasound to get an idea of thickness, but to incorporate something like that into the protocol, particularly in the beginning when we don't know exactly what is going to be the outcome in this group of women.

DR. GIMPELSON: I want to address three issues. One, one of the exclusion criteria which I think for most of the balloon type devices is probably valid, but I think for other devices that we see on the horizon, excluding the septate uterus, in the those devices that are really not anatomically dependent, I think it probably not a valid exclusion criteria, and I think that has to be looked at in some of the devices that are not anatomically dependent.

I think as far as the fibroids in the commentary, we know that about 25 percent of women who have surgery for fibroids will wind up with a second operation. Nonetheless, often women will have one large fibroid that is easily removed hysteroscopically, laparoscopically, whatever, and then have multiple small fibroids which may well respond to an ablation type procedure before they have the chance to grow to a larger size.

So, I think the fibroid issue is probably an issue that is valid, that has to be looked at.

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The third area, the post-menopausal, I am going to take a little different stand and that my feeling is that probably very few of the women that we do endometrial ablation on are really at medical risk of loss of life or limb, and can easily be treated with an alternative procedure, hysterectomy, although choose to have endometrial ablation, which is essentially safer and easier on them, as opposed to the post-menopausal woman on hormonal therapy, if there is a reason she stops her hormonal therapy, she does now become at risk of possibly loss of life or limb, and therefore, the indication for the endometrial ablation to allow that woman to continue on medication that is valid to her life and the bleeding she is experiencing is obviously as quality of life intruding as the bleeding that the 29- or 30-year-old woman is having, who is maybe soaking her clothing.

So, I think the post-menopausal woman definitely should be included in these criteria, and I think, as Mike said, the cyclical bleeder is probably at very low risk, should probably I think be right in with the criteria we have now, and I think we may have to look at the others with non-cyclical or with pathology, but I think those post-menopausal women should definitely be included in these types because they will truly benefit from ablation more

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than the women who aren't at menopause.

DR. LEVY: I agree and disagree. I agree they should have an opportunity to be studied. On the other hand, to put them in the same group means that I mean for quality of life index for those people, complete amenorrhea is the only acceptable outcome for them. I mean these are women who say flat-out I will not bleed, I do not want to bleed, and so I think for us to design studies that include them right in with premenopausal women is a can of worms, because our outcomes are going to be different for these groups.

DR. GIMPELSON: So, most will probably achieve amenorrhea.

DR. SHIRK: We don't know that.

DR. EGLINTON: Diony.

MS. YOUNG: Yes. I would like some clarification. Under the exclusion criteria for Item No. J, I can't recall in the Gynecare study whether, in fact, women who had had previous surgery, such as cesarean section, were included or excluded, I can't remember that, and I just want to ask about this question of previous uterine surgeries, because it seems to have been some difficulties in making up one's mind as to whether that will be an inclusion or an exclusion criterion, and I would like clarification of the statement,

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"unless these patients have previously been included in the safety study." What exactly does that mean?

DR. LEVY: I guess I can clarify that from the previous document. If the sponsor had considered including women with previous uterine surgery and studied the effects of the ablation device, whatever it is, on those women, and demonstrated safety, then, they were included in the study. If those uteri that had had surgery were not tested in the safety phase, then, they were excluded from the efficacy phase.

So, it was the decision at the beginning of the study to include or exclude those women. If they were included, then, they had to be included in the safety phase to document that the scar could tolerate the device, whatever it is, without damage to the patient.

DR. SMITH: I think in the previous discussion, in my points, we were calling for confirmation in a sense, or any new feedback on the issue of the previously scarred uterus when those safety studies were being done.

We have been approaching it that way and are seeking clarification and confirmation particularly in the face of what would be anticipation of additional energy modalities and different design configurations, that that is the way that we would still approach that.

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MR. POLLARD: I would just add in response to your question that was an exclusion criteria for the Gynecare study, and if you recall from October, we did talk a little about this with respect to the labeling. I don't know if we made it a contraindication or a precaution, but at any rate, there is something in the labeling addressing that aspect, as well.

DR. LEVY: I have another comment with respect to the fibroid issue. Some of these technologies coming down the road may very well manage submucosal or intramural myomas without resection, and I think the panel needs to discuss the issue of not having any pathology.

I know all of us who have done hysteroscopic myomectomies have at least seen reports of leiomyosarcomas that have been identified at the time of hysteroscopic resection, and I just bring that up as an issue, that these global devices, if they are being used in women with submucosal or intramural fibroids will not be getting any pathology.

DR. SHIRK: I think again that depends on what group you are talking about. If you are just ablating somebody with fibroids without resection, obviously, you are not going to have any pathology. Obviously, if you resect a fibroid, then, obviously, you have got your pathology or

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hopefully the whole fibroid removed, I guess there would be two things that I would also add with the resection process, obviously, there are certain times when you resect fibroids where you are not capable of resecting the entire fibroid or you leave a fragment of part of the fibroid there.

The question is, is the ablation, balloon ablation, going to help with the increased kill in these areas. The other question would be how many patients with fibroids also have concomitant adenomyosis. I mean if I look at most of my path reports from hysterectomies from fibroids, a lot of these patients also have adenomyosis and probably most of the patients we are treating with endometrial ablation are patients at least with superficial adenomyosis.

Mike.

DR. DIAMOND: With the commonness of uterine pathology, particularly fibroids, I would like if, in the long run, there could be a way that these devices could be applied to that group of patients. The question is coming up with appropriate study protocols and staying within some safety boundaries to do that.

For example, if there was a protocol where a patient came into my office today and tomorrow I did an ablation on them, I am not going to know very much about

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that patient. If, on the other hand, I have been trying medical therapy with this patient, I have been trying other conservative methods with the patient, and so I have been following the patient for a period of time, I may know more about them.

For example, with regard to leiomyosarcomas, we did a study, 95 percent of the time someone with a fibroid uterus, leiomyosarcoma is going to be the largest fibroid that is present. Similarly, over time, leiomyosarcomas usually have a very fast rate of growth, so if you are following someone for a period of time, if that is part of the protocol, if that is part of clinical practice, I think you can greatly minimize that risk, although obviously, you are not going to be able to totally eliminate it.

DR. SHIRK: You are going to be able to see a leiomyosarcoma on color flow doppler ultrasonography. It will light up like a light bulb.

DR. LEVY: So do bizarre leiomyomas, though.

DR. SHIRK: But at least you still have a suspicion. I mean the answer is you would be able to find those patients that have high suspicion rates for leiomyosarcoma.

DR. DIAMOND: If you have those suspicions, that is not the person for ablation no matter how you are going

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to do it.

DR. SHIRK: Of course. So, it is going to be an exclusion in that subgroup.

DR. DIAMOND: But I would like to see if, in the long run, we could make fibroids either a relative contraindication as opposed to an absolute contraindication even find protocols where they could be included.

DR. SHIRK: My feelings about this last question are two. Basically, the safety issue, if you resect a fibroid, how much myometrium do you still have left, is there enough safety margin there to carry you through the procedure with causing, you know, serosal damage, and the other question would be basically changing horses in the middle of the stream.

You can argue whether you should or shouldn't do an ablation on these patients, but basically going from hysteroscopic procedure where you can continue with an ablation and do it in probably as rapid a time as you could do it in changing horses to a more expensive way of going with an ablative system, does it really make sense.

DR. LEVY: I guess I understood the question differently, which was to say in women with fibroids, would we be using these global ablation devices without resection of the fibroids. That was my understanding of the question.

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Colin, did I misunderstand it?

MR. POLLARD: No. I would say that we were just really looking at that in terms of a very general question. I would actually like to hear the discussion on both angles just in terms of trying to give guidance--this is essentially trying to give guidance to sponsors who are preparing protocols for us to look at and whatever--I mean there could a number of answers on this question, it seems like.

DR. EGLINTON: Any other discussion on that question?

DR. LEVY: I guess I have one more comment on Question 2, as you have divided it here, but just more issue, and that is with regard to the age of the patients. As we have been looking at the data, there clearly seems to be some division in success rates and efficacy rates in women who are under 40 years old versus women who are over 40 years old, and we probably should talk a bit about whether we want to stratify data that way, so that it can help sponsors in the future and help clinicians decide when these procedures are appropriate or not appropriate.

DR. SHIRK: That is certainly a question. Obviously, it depends on the patient's estrogen supply. There is a common denominator in that. Again, it brings up

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the question with the post-menopausal patients, can they be included in the--if you stratified patients--could they be included into a standard protocol, and you are obviously looking at those patients below 40, those patients from 40 to 50, and those patients then from menopause on. I mean there is three different patient groups, and being able to stratify them out, so that you could look at the data from all three groups.

DR. CHATMAN: That doesn't make for a lot of work. I mean if you want to do it the way Barbara was suggesting, I mean it doesn't make for a lot of work at all for anybody who is doing research in this area. It naturally falls out of the data that you gathered to begin with. You are not operating on anybody whose age you don't know.

DR. DIAMOND: But it makes a big difference in how you are going to power the study, whether you are going to try to have sufficient power to identify differences in each of those three cohorts or whether you are going to look at the entire group as a whole, so it makes a big difference.

DR. SHIRK: Certainly, I mean if you were doing a study, a pre-menopausal patient group, and most of your patients fell between 45 and 50 years of age range, your efficacy is going to look a lot better than if you have got a lot of patients below the 40-year age range, simply

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because a significant amount of those ladies are going to go, have amenorrhea just because nature deemed it so, and certainly their estrogen load is falling off significantly, so, yes, I think it is important to look at the different stratification in these patients.

The question would be basically whether you could include this post-menopausal group into a standard study if you did stratification or not.

DR. CHATMAN: If a company came in here, let's say, with an ablative device, and all the patients are between 45 and 50, and they claimed X results, X kind of efficacy, I think they would get quickly discredited, I will put it that way.

DR. SHIRK: I agree.

DR. CHATMAN: This is kind of a natural result. I think that Barbara suggested is kind of a natural result of any research project, and maybe what Mike says is true. You have to have enough numbers of patients below 40 in order to make a statement about it as compared with those above 40. It in the data.

DR. SHIRK: Well, certainly, the Gynecare study was stratified.

DR. DIAMOND: But the Gynecare study actually for the control group, which is the endometrial ablation,

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actually was the inverse. They had greater success rate in the under-40 women as opposed to the over-40 women.

So, I am not sure we can really sit here today and say with a lot of certainty that we really know that 40 is a good cutoff and that we have enough scientific foundation to suggest that companies ought to be required to do two separate cohorts, have power to each of those cohorts to be able to make a distinction, because we just don't have the data, I don't think, just to say that that is truly a cutoff.

DR. SMITH: Dr. Chatman, to avoid the scenario that you have described, we have, in fact, been recommending, notwithstanding, as Dr. Diamond says, the fact that we don't have as confirmatory information as we might all collectively like to have, we have, in fact, been recommending that sponsors look at designing their studies to use 40 as a demarcation plane and to have sufficient numbers of women in the 40 to 50 age group, and then under 40, so that we can look at this efficacy issue a little bit further.

DR. EGLINTON: Colin.

MR. POLLARD: Yes. I just want to add in that context of the recommendation we make, we haven't required that those studies be sufficiently powered to show a

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statistically significant difference or the ability to reject a null hypothesis.

If you recall from our October discussion, when we were looking at that very finding you just mentioned, one of the aspects of that study was in the stratification cells, you didn't have--well, I think the power was somewhere in the ballpark of around 60 percent or something like that.

DR. DIAMOND: Sixty to 65.

MR. POLLARD: Right. So, it is not like we require sponsors to do larger studies, it is simply in the context of the number that they do enroll to stratify based on 40 years of age. That was the number that was chosen just based on trying to get a decent fit, but if the panel wanted to recommend a different cutoff point, that is certainly something that would be worth considering.

DR. SMITH: I think the other part of it is that at the same time, we have been discussing with sponsors what their hypothesis is with respect to what they believe the efficacy of their device is going to be, either with respect to producing amenorrhea or some change in menstrual bleeding status. If one does that, if one undertakes that exercise, it then clearly feeds into other aspects of study design and factoring in that issue of age, and then yields, hopefully, a sample size and sub-sample sizes that will be appropriate

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to the hypothesis.

DR. EGLINTON: Rich.

DR. GIMPELSON: Besides your sample size, you could divide them every single year if you wanted to, but I am not sure if you have the post-marketing time period or even pre-marketing time period constraints that you would want to put. These studies may take 10 or 15 years to see if there is really an difference in the 21-year-old having this procedure versus even a 40-year-old having the procedure. It may require a 10-year follow-up before you could even draw any kind of valid conclusion besides the large sample size.

Not being a statistician myself, I don't know, but I just know you would need a long follow-up, more than the three years required now to draw conclusions on which age is better.

DR. EGLINTON: Any other discussion on this?

Okay. We will move on to 3, please.

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DR. SHIRK: The next question was should alternative primary study endpoints be allowed, and by the criteria, basically, our endpoint is basically, at this point, determined by the study sponsor themselves. The ACOG guidelines are obviously recommended. The Higham's scoring

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system obviously is one of the most accurate that we have. The studies proposed needed to be within 10 percent of the standard hysteroscopic endometrial ablation resection procedures.

In general, most of the studies have been using the rollerball ablative procedure. Basically, it is technically easy to do, and I am not sure that it is not the least efficacious of all of the procedures, but certainly it has become the standard.

The question is basically what other kind of procedures or procedural endpoints could we use as far as figuring out where the studies should be marked against rather than just basically efficacy in comparison to a normal endometrial ablation procedure.

Basically, we looked at certainly amenorrhea as an endpoint. Certainly, this was the gold standard on our initial ablation studies. If the procedure is to be an elective alternative to hysterectomy, then, the endpoint should be amenorrhea would be the argument there.

Certainly, in the post-menopausal group, as we have talked about, this certainly would be the endpoint that we would be looking for and how close are we coming to that. Obviously, from our experience with hysteroscopic endometrial ablation, and the different numbers of

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procedures that have been available to us, I think it is pretty obvious that getting 100 percent amenorrhea as a goal is not a possible goal.

There is certainly a number of manuscripts, though, for reviewing, using amenorrhea as an ideal endpoint. Again, like I said, this is an impossible endpoint to achieve, but certainly could be used as one endpoint, so this is obviously an arbitrary endpoint.

At the other end of the spectrum as to amenorrhea as a strict endpoint, just looking at surgical satisfaction or the patient's satisfaction score as an endpoint, and again this is probably the most subjective endpoint you can get to, because some patients, if we look at some of the data presented basically in the literature and also in the Gynecare study on individual patients, show that some patients who had poor outcomes still had significant patient satisfaction, so that I am not sure that this data is going to show you.

It is obviously dependent on the patient themselves, and there is really no close relationship between efficacy of these patients and the way the patients looked at it. There is certainly several studies in the literature that are available, that look at patient satisfaction and could be used to help construct an endpoint

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that could this as a specific endpoint, but again an extremely subjective situation, and I am not sure how appropriate it is in an objective situation.

Another one would be hematocrit, although obviously seems to be a very objective endpoint, it may not represent the magnitude of failure or success in this patient at all.

As we all realize, we all have a lot of patients who are having extremely heavy periods that are socially incapacitating from different pathologies that basically have normal hematocrits, and other patients who have what you would call normal periods, who have very low hematocrits, not based essentially on the amount of bleeding they are doing, but basically on the nutritional status, so that again you would have to reflect the patient's total iron stores at the time of the procedure, which may be fairly difficult to ascertain, look at the patient's oral intake and also iron absorption abilities, and obviously, in this endpoint, there is no measurement of physical disability to the patient as far as the amount of bleeding that she is still having and how well she survived the problem, so certainly hematocrit, even though it would be a rather objective endpoint, seems to me an extremely subjective kind of endpoint for this type of study.

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Another endpoint that we could use would be the long-term hysterectomy rate, how many of these patients that have the ablative procedure for abnormal bleeding ultimately end up coming back for hysterectomy between the two groups.

The biggest problem with this endpoint, number one, it would require far too long a follow-up period. I mean you are talking years and years.

It also would require a series of those patients treated for failure of the procedure versus those patients treated for other pelvic pathology, such as ovarian masses and other pathologies, and cancers like a cervical cancer or something like that, that came up, that was totally unrelated to the procedure.

Also, the statistical significance could be biased by the consumer themselves and this no hysterectomy attitude that some of the patient population has, and certainly those patients seeking endometrial ablation have a significant attitude towards no hysterectomy, so I think that again this would be a very difficult endpoint to reach.

Obviously, there is articles in the literature that compare endometrial ablation to hysterectomy as two different endpoints, so that again you could come up with a design for the use of hysterectomy rate, but I think it would be long term and difficult to do and impossible.

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Another endpoint would be costs. Obviously, the cost analysis of the procedures over time, hysteroscopic procedures versus hysterectomy are a common variable in the literature. One could look at the cost data in these patients and look at not only the acute cost data, but the cost data over time as to what other treatment modalities would be necessary to treat patients that had less than adequate outcomes from the procedures, but again, I think this would be very time-consuming and far more complex than anybody would want to get involved in, and it obviously involves a lot of different social issues, so that I don't see cost as a major issue.

In exploring at least from my standpoint other endpoints as far as the one that we have looked at as just simply efficacy, all of them have several downfalls that obviously preclude using them as endpoints.

Any comments that the rest of the panel has or any other ideas that someone else has as an endpoint?

: You probably knew that I would have a go at the surgical satisfaction item, patient satisfaction. It is notoriously difficult to measure, but by the same token, that doesn't mean that it shouldn't be measured, and the I think the fact that it is a subjective endpoint isn't, in

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and of itself, a good reason for eliminating it as an endpoint to be considered in conjunction with perhaps the first endpoint.

The Gynecare study showed that the use of patient diaries was very useful in terms of determining quality of life issues, and I would like to speak very much in favor of using some sort of measurement for patient satisfaction for devices, such as this.

MR. POLLARD: I don't think Dr. Shirk was saying this either, that there would not be a quality of life questionnaire. When the panel met in October of '95, when we originally developed the guidance document and recommended having a quality of life questionnaire, there was a very strong read from the panel that, in fact, a quality questionnaire be a critical component of the study protocol.

What our question really is targeted at is the primary study endpoint that, in fact, defines what the study hypothesis is, you know, how you power it, what your samples size is, so we are not backing off of that aspect anyway.

DR. LEVY: I think we need to stick with what we determined in 1995, and not make a change.

MS. DOMECUS: I had a comment which partly goes to Question No. 4, but you raised in your looking at amenorrhea

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as an endpoint and you said that if the procedure is to be an elective alternative to hysterectomy, then the endpoint should be amenorrhea, and I guess I don't agree with that.

I think that hysterectomy should be considered as an option for the control group, but if it is, I don't think the success has to be defined as amenorrhea. I think that the thermal endometrial ablation procedure can have a reduced effectiveness as compared to hysterectomy if there is a compensating reduction in risk.

So, I think that hysterectomy can be in the control group, and the amenorrhea doesn't have to be the definition of success if that is the case.

DR. SHIRK: The only thing about hysterectomy as an endpoint is you are using 100 percent. I mean basically, just say it is 100 percent, there is no control group, you just say you have to shoot at 100 percent and how close can you get to 100 percent, and I think that it is a way of doing it, and I am not sure that it is a realistic way of looking at the data.

MS. DOMECUS: I am not saying it should be imposed, but I think that if sponsors want to pursue as an option, they can certainly look at the surgical risks that may be reduced by not having a hysterectomy.

DR. SHIRK: Anybody else have any ideas as to

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other endpoints that we might come up with?

MR. POLLARD: Could I just ask the panel to follow up on that? If, in fact, a sponsor was going to pursue comparing the amenorrhea rate of their new device to hysterectomy, then, how would that--maybe we are getting ahead of ourselves to one of the questions down the road--first of all, how close would it need to come and then, secondly, how long would you have to follow that patient.

DR. LEVY: I guess that data would be so confusing to me that I would have a hard time looking at it, because I would want to see the quality of life indexes, and I would want to see when there wasn't complete amenorrhea, what kind of reduction, so I would see myself requiring the same sorts of diaries that we were requiring anyway in our outcomes.

I mean it is not only amenorrhea or not amenorrhea, but it is reduction in bleeding since bleeding is the real issue that we are trying to treat. So, that is why I suggested that we just continue with the same criteria we have got since they seem to be working pretty well.

DR. CHATMAN: It is like comparing apples and oranges.

DR. DIAMOND: Practically, I would agree. I think it is going to be very difficult to compare them, but if

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someone had a device or a method of creating amenorrhea, I don't think I would have a problem with comparing that with hysterectomy, but I think amenorrhea would have to be the endpoint you are comparing to, not other grades of bleeding, and would those other grades of bleeding then be a failure.

MR. POLLARD: Just to follow that up, so then how would you do that?

DR. DIAMOND: The answer that we came up with a couple years ago was 20 percent, that since these newer forms of ablation were less invasive than rollerball ablation that we would accept not quite as successful, so we said within 20 percent, so I would probably throw out that same figure.

You might be able to make an argument, maybe you can say 25 or 30 percent because now you are comparing a major surgical procedure with all its inherent risks to a device that might be able to be done in the office or maybe you could even accept a greater number of failures, maybe up to 25 or 30 percent.

DR. LEVY: What I am saying there, though, Mike, is that if it is failure, and it is in that 20 to 30 percent range, I not only want to know failure, but I want to know how much of a failure. In other words, it still is going to require diaries and quantification in some fashion, so that

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we can determine--

DR. DIAMOND: Well, yes and no. I mean if a device existed where you could have only a 20 percent failure rate, only 20 percent of people have any bleeding whatsoever with this new form of endometrial ablation, I would be willing to accept that as compared to a hysterectomy where there is no bleeding whatsoever.

Eighty percent of people are going to have success with this new device, and I would assume, therefore, that the 20 percent that are not successful, but they have some amount of bleeding, that many of them will have a great deal less bleeding than they had originally, if they are less successful than the other 80 percent. I would be willing to look at that.

DR. SHIRK: I think coming up with a device like that would be very difficult.

DR. DIAMOND: Exactly.

DR. SHIRK: Even with our ablation techniques, I don't think you are going to see much more than--I mean the best you are seeing 60 percent amenorrhea rates, I mean you are not even getting close to your 30 percent.

DR. DIAMOND: I agree with you. I think practically, at this point, I don't think that exists, but if it did.

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The one other point I was going to make--and I don't have the paper with me, so it's hard to specifically recall the point--but originally, we had said we wanted to see the bleeding scores, the Higham's scores, if you will, go down from 150 to 75, and that sounds like it is going half to what it was originally, but if you actually go back to that original paper and look at it, it is really not half, it's about a third, and I don't remember exactly how that comes out, but there is not that much difference there, and I would wonder whether those extremes ought to be expanded a little bit, either pushing 150 up to 200 or the 75 down a little bit, because it is not half of the original bleeding as you would assume from those two scores, 150 to 75.

DR. SHIRK: Again, I think the presents studies basically are double-arm studies, so that comes within the double arm rather than setting the limits on the scores themselves, so I mean I don't think the Higham's scores have anything to do with, you know, with essentially the--I mean the outcome is basically outcome based on rollerball ablation or hysteroscopic resection/ablations versus the device itself, so that is just a means of basically quantifying both of them.

DR. DIAMOND: I don't think you are right from the

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point of view that you treat both arms equally, so from that point of view you are not biasing one way or the other, but if we are saying that for these new ablation devices we are willing to accept 20 percent less, which is what the original guidance document said, then, you begin to perhaps get into some gray area.

Ideally, I would like to have seen greater separation.

DR. SHIRK: So, you are saying it shouldn't be equality?

DR. DIAMOND: No, just greater gradations in the scores, greater increment.

DR. SHIRK: For both procedures?

DR. DIAMOND: For both arms.

MS. DOMECUS: There is somewhat of an issue with that in that we are raising the bar for every company that came after the first one.

DR. DIAMOND: If you alter that, you probably would be.

DR. EGLINTON: Are we finished that question? Okay. Jerry, I think you have one more.

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DR. SHIRK: This is certainly a critical issue especially to the companies, and that is what alternative

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controls could be used to shorten the review process.

The standard control for the PMA studies, for the studies that we have set up so far, have been double-blinded studies or at least randomized studies with the use of hysteroscopic resection/ablation as the control procedure. The two groups required equivalence and needed to be large enough for statistical analysis.

This review process certainly extended the process as far as the fact that it became a numbers game, how long does it take us to get the numbers to get two groups large enough for this process to happen.

It also has the process of denying the patient procedural choice, so that these patients, a lot of them are coming to these physicians because they have got this new procedure in, and then they are denied the choice of this procedure because they are suddenly in a randomized study, so what are some of the alternatives both for the manufacturers themselves and for the patients.

Obviously, the first part of that would be no active control group, and the question is how would you set that up. Obviously, there has got to be some standard that you are shooting at, and what standards could we use.

Certainly a standard could be constructed in several ways. You could construct it from the data

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available from the body of literature, so from a retrospective study, certainly the body is large enough, and this takes out some of the operator bias out of the thing that, you know, people do different things different ways, and that if you use a large enough, broad enough study, that you could get an overall idea of what you could with hysteroscopic ablation from multiple techniques, so it would maybe give a more accurate idea of where these devices really should have to shoot at.

Another way would be basically to go to some of the larger foreign data banks, Great Britain, Sweden, Finland, some of the countries that have socialized systems with large data banks where everybody that has a procedure is banked and they are long-term follow-up evaluated, and certainly you could create a large enough group out of this to create a comparison group.

The other way would be to set up our own control from the existing studies that we have and use out control standards as a therapy target. Basically, the problem with standard control is that it doesn't allow for a bias patient situation, so that one of the problems with the standards is basically that the company can get a biased situation.

Another way to look at this is basically to say, well, let's have a down-sized control group. This

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alternative provides the assurance that there is no selection bias in the study by the fact that you do have a control group that is large enough to pick up any control bias, so it is randomized.

It limits the number of patients who are denied the investigational procedure that they may desire, so it meets the patient's situation, so that we could look at this, so it meets both the company's desire to limit the number of patients they have to recruit and also gives us some idea as to--or keeping any kind of bias out of the game.

The problem would be, obviously, if the control groups are too small, they would probably have to be referenced to some standard that we set, so that you would still have to set a standard target for these patients as to where they wanted to get to, so they would have to be referenced to a standard.

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The other alternative would be to set up some kind of an alternative control group, and again, we would, instead of using hysteroscopic resection/ablation procedure that was set up as our previous guidelines, the question would be could we use other procedures and the endpoints for other procedures as an endpoint, as a reference point for

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the device procedures.

One of those certainly would be D&C. My answer to that is obviously, there is a question as to whether it even can ever be considered a therapeutic procedure, probably not. It is even a poor diagnostic procedure, is rapidly being replaced by both transvaginal ultrasound with saline infusion and endometrial biopsy or diagnostic hysteroscopy and endometrial biopsy, so that, you know, D&C probably doesn't represent a very good procedure in that it is pretty much a dead procedure as far as most of us are concerned anyhow.

Hysterectomy. Certainly, the definitive long term therapy for abnormal uterine bleeding is hysterectomy. The objective endpoint is amenorrhea, but other comparisons could be used rather than the amenorrhea associated with hysterectomy, such as disability time, sexual dysfunction, psychological perception, and safety, so that one could theorize using different things about hysterectomy, but again we talked about that when we talked about amenorrhea and that hysterectomy obviously may not be a very rational endpoint or control point in these studies.

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What about medical therapies? Certainly, there would be no short-term medical therapy that would provide a

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treatment, and if there was a short-term medical therapy that could provide the patient with treatment for problems, it should be used rather than she is no longer a candidate for endometrial ablation, so certainly medical therapy has to be looked at a long-term situation.

Obviously, probably the gold standard for medical therapy is high-dose progesterone therapy. These certainly are the mainstay. The idea is obviously to create somewhat of a pseudo-pregnancy state, but the big problem is basically the significant side effects that most of these patients have and don't want to tolerate, things like depression, breakthrough bleeding, and multiple other things that ladies get on long-term progestin therapy, weight gain.

But you certainly can use birth control pills as a long-term medical therapy, and you can use them either on a cyclic basis, like they are designed, or you can use them on a continuous basis, so that the patient takes them continuously and never bleeds, would be pretty much the same as using medroxyprogesterone, which is on a continuous basis, and you again can use it oral or if you are going to use it on a long-term basis, more appropriately probably use the depo forms, so that the patient doesn't have to take pills every day and come in for her shot fix every two to three months as one does for long-term contraception.

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Other progestins are obviously synthetic or naturals that are available, so there is a lot of different progestins on the market that we can use for long-term progestin therapy, but again, the down side is just basically the fact that a lot of patients do not accept the significant subjective side effects that they get, and obviously, some patients get a significant amount of breakthrough bleeding, so that the treatment is as bad as the problem they began with, so you never know whether they are bleeding because of their initial problem or bleeding because of what you have given them.

Another drug that could be used is danazol. This obviously can be used on the short term. It is an androgenic type of drug that has both an androgenic impact on the endometrium and also an impact on the anterior pituitary. The big problem there is there is significant metabolic problems.

It has some significant hazards both in creating liver and renal damage, and so that these patients have to be monitored carefully on a two- to three-month basis with chem panels, and also there are significant habitus changes, body habitus changes that occur in these patients.

When I was talking about resection of endometriosis laparoscopically, I used to talk about

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Danocrine as a therapy, but said that after a year of Danocrine therapy, you get a patient who is fat, hairy, and essentially poor because she has broken the bank paying for the medication, and so it really does have a significant cost effect to it also, so you have got a limited time frame that you can use it, and it has got a fairly significant amount of cost.

[Slide.]

The last of the medical therapies that would be available would be the new GnRh analogs. This a group of genetically developed hormones that are similar to the GnRh releasing factors, and they work simply by blocking the anterior pituitary from releasing follicle-stimulating hormone.

The result is hypothalamic-hypopituitism to the endocrinologist or basically simply complete ovarian suppression and shutdown, so there are no estrogen or progestin produced by the ovaries.

Right now it has two problems. Basically, it has a limit of six months before you start getting irreversible bone loss and other problems related to the severe menopausal changes that these patients have, so that there are some long-term health issues there.

Also, the cost of the therapy is extremely high.

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You could theoretically use this with add back estrogen therapy, however, this may also defeat your answer, so that it may be an option for a long-term therapy, but at this point, not a very good option.

Certainly, any other options that might result in menopause from a medically-induced standpoint are unacceptable, and that would be basically chemotherapeutic agents or radiation, and those obviously are totally out.

So, again, I don't see any medical therapy that basically has a practical application as far as an arm to a control study.

So, any ideas about other things that we could look at or comments on what I have said about the control arms?

DR. CHATMAN: I would like to ask a question about the premise, that is, that we need to decrease or shorten the PDP process. Since we don't have any experience with it, we don't really know how long it is going to be, to begin with, but I mean certainly, as you have pointed out, none of the alternative control groups really are useful. I mean a group of patients who had D&C is certainly not comparable to the ablation group, and a hysterectomy is a different operation altogether. The medical therapies that you talked about are all awful except for certain

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situations.

Now, if you need a control group, in order to shorten the PDP process, an alternative control group to shorten the PDP process--

DR. HARVEY: I am sorry. I guess I am a little confused. We are not really discussing the PDP process per se right here. We are just talking about alternative control things right now.

DR. CHATMAN: Did I misunderstand here? Alternative control could be used to shorten the PDP process, isn't that what it says here?

DR. DIAMOND: That is what your question wrote.

DR. HARVEY: That would apply also to the PMA process.

DR. SHIRK: The initial question I had on here, but it involves the whole review process, but I guess, you know, one of my questions would be what about using the limited size control groups rather than using the full double-arm system. I mean that obviously reduces your situation. Obviously, any of the other types of things, you know, if you try to go to a double-arm system, and you use another control group, there is not a very good control.

The other only other control you might use would be go back to ThermaChoice and use it now as your control

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group, and mark all of the other ablative devices off of the ThermaChoice, you know, would that be a fairer comparison? I don't know. Then, you could make two equal arms, but there is two questions here.

Basically, are there any other things that we could use as controls other than hysteroscopic resection/ablative techniques as far as a control, and the second is how should that double-arm system be set up, should we basically have a complete double-arm system, should we have no arm, just a single-arm system, or should we have a compromise where basically, the control arm is a much smaller than the research arm.

DR. EGLINTON: Tom Downs might be able to comment on double or triple randomization 2 to 1, 3 to 1, something like that?

DR. DOWNS: Yes. For a given total number of women in the study, you get the best power when the arms are of equal size, so if you have unequal arms, then, you don't have as good a chance of detecting an inferior device or a superior one, for that matter, to the control.

So, I would think that equal arms would be best.

DR. SHIRK: What about using it in different way, using it with a situation where we set up the standards, like you would in a single-arm situation, where you don't

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have another arm, but the idea is using the smaller arm as basically just to keep the company from putting in a bias.

I mean is a double-arm there basically--my question would be is a double-arm there to create the data, so that you have got a double-arm study, so you have got two things in compare to? We have certainly got enough data about hysteroscopic ablation that we could create a number, a standard number that everybody has got to shoot at.

That might be fairer than in reinventing the wheel every time with another control arm, but the question there is basically, then, if you have no second control arm, then, you obviously can introduce as much bias, so that one--one function of the control arm would also be obviously to get rid of the bias in the study, and couldn't you do that with a smaller arm.

I guess the question is what are we trying to create, what are we trying to accomplish with a double-arm system, are you trying to avoid bias or are you really trying to create a standard to shoot at, and is that really realistic to every study, to create a new standard to shoot at.

DR. EGLINTON: In the sense that the patient population may vary from one study to another, the randomized control trial is the only way to guarantee the

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absence of bias.

DR. DOWNS: That is right. There could be age differences, any number of things that could chance it.

DR. EGLINTON: Rich.

DR. GIMPELSON: This covers a little of my presentation, too, so I am kind of glad it is all being discussed now.

I am a little puzzled on at this point, even the need--I understand the statistical importance in studies, but the need for a control arm even now, because it seems like the choice obviously would be for a company to choose a control, do they wind up choosing the same control with ThermaChoice and have roller, or does a company say, well, I am going to take ThermaChoice because that is more of a work comparing two, and I won't have to have as much amenorrhea or some of the other factors, or look for the product that is out there and say, well, this fits in, there still can be a bias even in choosing the control that fits their product when it seems like the ThermaChoice study laid some nice groundwork down as far as what constitutes success.

I think efficacy is probably easier to look at than safety. I think efficacy numbers and quality of life can be interpreted reasonably well. I guess is a control arm needed just for safety to see that indeed--because it is

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hard to say, well, we have three perforations in this, is this really as safe when they only had two in the other without a comparable arm, but you also have a different technique.

DR. DOWNS: I think the control arm is needed for the validity of the safety and the efficacy decisions that we make.

DR. SHIRK: But, Tom, what are we really trying to do? I mean basically, when you are giving them a 20 percent leeway, that is a big leeway in this game. I mean you are really only shooting at a certain target, and if you randomize to a smaller control group--I understand what you are saying--couldn't you get away from the two--the two basic issues are basically the numbers game, trying to reduce the numbers name to speed this process up and also provide the--I mean we are not looking at the patient's choice.

I mean like I said, the patients in some of these studies are coming because they want this "new" procedure, and then you turning it around and saying basically, now you have got to be randomized.

DR. DOWNS: You can use the Gynecare for a control group, I don't really care, but I think you do need a control group to maintain the validity of the safety and the

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efficacy.

DR. LEVY: Tom, can we use historical controls? I mean I think that is the real question we are getting at.

DR. DOWNS: If we knew all the important variables that determine the outcome, then, we could adjust the historical controls to account for that, but I don't think we do. Some people say, well, like in the Gynecare study, the older age group did better, but people say that they shouldn't. I guess I have that turned around. The older age group is not necessary, and yet the older age group didn't do so well.

DR. LEVY: I think that was my point. When we originally designed it, we really agitated over this a long time the last time we went through all this, the two-arm versus the one-arm study, was that this group of patients is so diverse, that to get a clean study, it really required a two-arm randomized study to give us clean enough data that we could analyze it, and the statisticians are telling us that the kinds of data that we have even from the older studies that have come through don't have enough historical data in them for us to be able to use them adequately to assure that there isn't bias in the patient selection.

It is just that is just a huge population and too difficult to do.

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DR. EGLINTON: To use historical controls, it is necessary to have a very precisely characterized population, so that the statisticians can then make adjustments for variations in the study in the control population, and those adjustments are what we always argue about later.

The only way around that is upfront don't do it, just do a randomized control trial and ensure that random allocation results, and then you will be clean.

DR. DOWNS: I think that we are opening the door to a lot of problems if we drop control groups.

DR. LEVY: The second part of that question is could the control group now be altered to say standard hysteroscopic ablation techniques or approved balloon devices. Now that we have one that is approved, I don't think there is a problem with expanding our control arm to be a control arm that includes the Gynecare device since it is the one that is approved, and allow that to be the control arm.

MR. POLLARD: I would just say, getting back to a comment Dr. Shirk was making a moment ago about the 20 percent, I think part of the clinical decision that went into accepting the 20 percent was essentially a clinical acceptance of a lower performance on the part of the new devices because you are comparing them to a hysteroscopic

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method that had some known risk factors, that people looked at the two technologies and said, well, maybe I can live with a lower effectiveness because I know I have done away with that issue of fluid intravasation and what happens with that.

The study hypothesis--and maybe I would like a little panel discussion--of if one were to choose the ThermaChoice device as the control, what the panel thinks about that with respect to how good the new device has to be.

DR. LEVY: My own personal viewpoint, those would have to be equivalent. I mean the null hypothesis would have to be that there was statistically significant difference between those two devices, so to me that would be very different than using hysteroscopic ablation resection as the control arm.

DR. DIAMOND: I would agree with that.

DR. EGLINTON: Is that satisfactory, Colin? Any other discussion on this point? Rich.

DR. GIMPELSON: If you are comparing it with the ThermaChoice, also remember there may be an element--we still have criteria for what is success and what is not success, and there could be a difference in the results of levels, yet, something could be extremely cheaper and

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easier, and I am not sure why that would be--if it still falls under the criteria of what FDA considers a success.

DR. LEVY: FDA can't consider cost.

DR. GIMPELSON: No, I am not saying the FDA needs to consider cost, I just saying you are saying these two have to be equivalent, but if they fall into the criteria of what was initially set up, they may be different, yet, still satisfactory irregardless of cost. There should still be allowance for variance.

DR. DIAMOND: There would still be allowance for variance.

DR. GIMPELSON: Or safer, there would probably be a safer method.

DR. DIAMOND: Not significantly different as opposed to within 20 percent. Those are two different things. Basically, what would you be looking for? I think if you use the Gynecare project as the control group, a test of equivalence as opposed to is there a difference between them.

DR. EGLINTON: Any other comment on this question? How about a 15-minute break from now.

[Recess.]

DR. EGLINTON: Let's get started again.

We will have Rich go ahead and assume the podium

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here and move on with Questions 5, 6, and 7, and try to summarize as we get to the end.

DR. GIMPELSON: I want to thank the panel for inviting me and giving me an opportunity to speak here. Hopefully, it will be enlightening. Following Dr. Smith and Dr. Shirk, though, I kind of feel like I am following Noah and I am going to give a talk on floods, but I will try to enlighten you as best I can and give you my opinion.

Fortunately, like I said, Dr. Shirk has really covered most of this No. 5. Do you want me to read this whole question?

Definition of Success and Justification of Sample Size. Related to both Questions 3 and 4 is the issue of study hypothesis and justification of sample size. The study hypothesis employed for the only approved device was that the treatment success rate with the new device was equivalent to the success rate of the control, within a 20 percent margin (because of the expected relative improved safety profile of the new device). Limitations in sample size meant that the observed clinical success rate actually was required to be within 12 percent of the control. Given the study options discussed above, does the panel have any further recommendations regard FDA review of these proposals?

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As I mentioned earlier, we are looking at devices and we are looking at, first, just success, you know, what does success mean. We have talked of amenorrhea, hypomenorrhea, which is left open to interpretation, could be staining, light flow, normal flow. A patient has clots, now doesn't have clots. There is a significant, I think, quality of life factor with this procedure and what it does for patients, and as I had mentioned earlier, that we have a patient who says she soaks her clothing and bedding with blood. Obviously, success of the procedure may be quite a bit different for her than someone who is right on the border.

I think some of the success as far as patients are concerned is also open to interpretation because we all know, those of us who have done the procedure, that you can tell there are some patients where amenorrhea is really the only success they want.

So, you may have a procedure that is successful statistically and mathematically, but yet to that individual patient, it is a failure, and we have to deal with that as far as the patient goes. I think as far as the FDA panel, I think that is something to think about, but I think that is just something we have to live with.

The diaries, I would have to say even though there

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is a margin for patient interpretation subjectivity in the diaries, the Janssen score, I think probably is an excellent idea as far as being able to quantify whether the procedure was successful or not, and I think with the criteria that were established for the ThermaChoice with over 150 to get into the study, and under 75--and the results are actually quite a bit under 75 in most of the patients--but under 75 is success even taking into account what Dr. Diamond brought up earlier, but I think this is a criteria that has been set and is probably a reasonable criteria to follow, and in reality, probably most patients will be well above 150 coming in and probably well below 150 going out if the procedure is successful and used on the right patients.

I think the quality of life issues are important. I think this has to be taken into account, and I think the patients have to be--you know, we could have great numbers and if all the patients are not satisfied, then, obviously, the procedure is probably not a successful procedure.

So, I think we have to look at the patient's satisfaction, dysmenorrhea their ability to go to work, and the other questions that may come up in quality of life. I think as a clinician, that is probably more important to me than the numbers. The numbers, I think are easier to look at and easier to compare, but I think how the patient feels

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after the procedure, I think is probably more important.

So, as far as success, I think probably the score, this numerical score, and the patient quality of life are probably the two most important factors that the panel should be looking at.

Sample size is a tough one for me. As I said earlier, I am not a statistician. I am accepting the numbers that the FDA has come up with already. Other than my own bias, as you heard earlier, that I would almost like to see the study with a much larger sample size and even smaller or no control because the efficacy is fairly easy to see, but the larger--at least my patients having the procedure--the more likely I am going to see if there are complications that may come out that need to be known about.

The only problem is if you don't have a control, you have no way to know what is the chance of this complication coming out in the other arm, however, if there is unique complications that occur, probably the larger your sample size, the more likely those unique complications can come up and some of those could be devastating to the point that it might warrant either re-evaluating a method.

So, I don't feel comfortable necessarily recommending that the FDA panel change their sample size, nor do I feel they should raise the total sample to 300 in

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each arm or whatever. I think that might be unfair to the new companies who are coming down the pike.

But I think I would go towards more of a larger sample--like Dr. Shirk--a larger sample arm and a smaller control since I think most of the complications I think are out there now and we could compare. So, I think a historical comparison, as far as I am concerned, is comfortable to me. I can live with that in the treatment of my patients. That is it I think on Question 5.

DR. EGLINTON: Michael.

DR. DIAMOND: One comment and then one question for the FDA. I think to maintain a control group, a concurrent control group is essential.

I don't understand the question, though. I don't understand the sentence about three-quarters of the way through, "Limitations in sample size meant that the observed clinical success rate actually was required to be within 12 percent of the control." Can somebody explain that?

MR. POLLARD: As a non-statistician--and I may have to get a little buttressing of my explanation here from one of our biostatisticians--the 20 percent margin is the actual hypothesis. I have been yanked.

DR. VISHNUVAJJALE: Lakshmi Vishnuvajjale. I am a statistician with the FDA.

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The 20 percent difference you are looking for is the true difference in the whole population in the whole universe, and what you need to get in the sample proportions to be reasonably sure, which we usually interpret as being 95 percent confident that you will not be better than 20 percent for the true rate is you can only be 12 percent different in the sample proportions because it is a small sample size, how good you have to be. The sample difference only estimates the population difference, and if you have a very large sample size, you are going to have a smaller margin of error. If you look at it like a confidence interval, you are going to have tighter bounds, and if you have a small sample size, your bounds are going to be very wide.

The sample size that you have there requires that you cannot be more than 12 percent in the sample in order to be 95 percent sure that you won't be more than 20 percent in the true rate. I don't know if it helps or confuses more.

DR. DIAMOND: I think it is probably different than what we originally intended when we made that recommendation to the FDA. There aren't that many of us that were actually there at that time, as well, but if we are thinking that the endometrial ablation the conventional way was going to give you a 90 percent success rate, however

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success is defined, and we were saying we would allow a 20 percent variance, at least what I had in my mind when I said yes, I would vote for that, would be that 20 percent of 90 is 18, and so anyplace from 72 percent up to 90 percent success I would have found acceptable.

What I hear you say is really you had to have 78 to 90 percent success.

DR. VISHNUVAJJALE: The given sample size, yes. You cannot go with the sample proportion without taking into consideration the size of the sample.

DR. DIAMOND: That is more constraining than I realized it would be when we were giving guidance as to what we thought was reasonable.

MR. POLLARD: I would just add--I mean some of that was a function of the sponsor's proposal to use. The sponsor could have chosen to do a study with a larger sample size that would encompass that entire 20 percent.

DR. DIAMOND: I guess my point, Colin, is--your point is a very good one--but my point was that if we are talking about the future and what our original guidelines were, I think our original guidelines were broader. At least that was my intent. Barbara I know was here, I don't know if Michael was part of that panel or not.

DR. EGLINTON: What you would be looking at,

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though, would be if you had a sample size of five patients, and you had a 20 percent lower efficacy, the confidence interval around that includes zero, so your estimate, the point estimate is 20 percent less effective, but the confidence interval is zero to 100 percent. That is what she is talking about.

If you had 10,000 patients in the sample, you know, you could have a larger decrement, but with the number of patients they had, their 95 percent confidence interval included 20 percent, so they really were stuck with 12 percent. It had to be that close with that small sample size.

DR. LEVY: And actually, I think to a large extent, we are talking around an issue that is not really an issue, because the numbers came in very good, and the expectation probably is that with all of these devices, that they will also be good enough that it is kind of a moot point.

DR. DIAMOND: The next device may not come in as good. It may have greater variance from the conventional endometrial ablation, in which case that difference becomes very significant as to whether it is a failure or success.

DR. VISHNUVAJJALE: If you have greater variance, you need larger sample size.

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DR. LEVY: But then you just need a larger sample for us to really look at it, Mike, and say whether it is or isn't.

DR. DIAMOND: Sure, that would get you there, but this was a different interpretation than I had appreciated.

DR. EGLINTON: The problem is that a larger variance means that your point estimate is less secure, so you really should do more studies, more patients to see if you can tighten that variance.

DR. DIAMOND: The question is how far off from the gold standard were we as a panel recommending it be is the question I am posing.

DR. EGLINTON: If you ignore the confidence interval, then, you have to be willing to accept 60 percent.

DR. DIAMOND: That's right.

DR. EGLINTON: Or with a sample size of five patients, you have to be willing to accept zero percent.

DR. DIAMOND: Five patients, we weren't thinking about basically. With 100 or 200, I don't know.

DR. EGLINTON: The variance is what handles that problem for you.

DR. VISHNUVAJJALE: The more variable your population is, the larger number of patients you need to make the confidence interval tighter, as tight as you want.

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DR. DIAMOND: The question is whether 20 percent is the endpoint of that interval or whether it is the midpoint.

DR. VISHNUVAJJALE: The 20 percent for the true value would be the upper limit. You can't be any more than 20 percent. In order to do that with that sample type, you couldn't be any more than 12 percent.

DR. DIAMOND: And that is why I guess I am saying at least in my mind was different. I thought the 20 percent was the midpoint as opposed to the upper limit.

DR. VISHNUVAJJALE: If you say the midpoint, you are not even specifying how wide the confidence interval could be, and the guide said it could be 60 points wide, in which case you hope it will be the middle, but you don't know for sure that it will be.

DR. GIMPELSON: It would depend on how many sample and how many control --

DR. VISHNUVAJJALE: Yes, it depends on the sample size and if you have more patients, more subjects, you don't have to be within 12. You can be 19, 19.5, but I think these manufacturers usually find the middle ground where it is not worth it to get that many patients, but they can live with it. In this case, maybe it is even more, if you are going to be as good or better. You can probably deal with

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that sample size and still be successful in showing that it is less than 20 percent.

DR. GIMPELSON: As Dr. Levy brought up earlier, if someone wants to compare it with ThermaChoice, then, these numbers are not the same numbers.

DR. EGLINTON: I suspect what will happen at that time four or five years from now, and maybe none of us will be here, but, you know, just based on having been here before, what likely will happen then is people in the panel then will look at the equivalence.

I mean the null hypothesis will not be challenged. There will be no difference between device X and the ThermaChoice, and the panel members will want to know what was your power, and if you determine that to be the case, you couldn't reject the null with an 80 percent power, that might be okay. There is Michael's 80. But that is what is going to determine your sample size.

DR. GIMPELSON: But with each new device that comes out, that then compares with roller, the next device could choose to look at what has been approved and choose sort of the one that they are most likely to--

DR. EGLINTON: Right. What people talked about really is if you are going to compare it to a previous standard, they wanted it to be 80 percent as effective, but

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if they are going to compare it to a new device that was generated during this regime, they are probably going to want it to be equivalent, I am guessing, for the future.

DR. VISHNUVAJJALE: Actually, when you said you want them to be equal, that is what I was thinking. You have to specify. You cannot just say equal because when you agreed to the 20 percent, you were saying they are equivalent for different reasons. Maybe you have better safety. And now you say to use this as a control, you want them to be more equal, you still have to say within 3 percent, 5 percent. If you intend it to be zero percent, you have to say that, too, and if you want it to be zero percent in the sample, they have to do better than zero in order for the upper limit to be less than zero.

DR. YIN: Could you explain to the panel also that we don't really need a comparison if someone come in and they said that we want to demonstrate my product is good without comparison, can you explain that to them because I think someone in the audience did ask that question?

DR. VISHNUVAJJALE: But that is not really a statistical issue.

DR. YIN: I know. That is what I wanted you to say. That is more legal.

DR. VISHNUVAJJALE: Well, if I understand the PMA

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regulations, you can come in and you don't have to compare to anything, and the device can stand on its own if you can show its merit and basically convince the panel members, I guess you will win approval. You don't have to compare. In this case, they are comparing to another device.

DR. YIN: Thank you.

DR. GIMPELSON: So, somebody at the FDA agrees with me, is that right, that you can just have a large sample?

DR. VISHNUVAJJALE: I didn't say I agreed.

[Laughter.]

DR. GIMPELSON: You will allow it.

DR. VISHNUVAJJALE: Yes, that is a possibility.

DR. LEVY: Allowing a company to come to us with such a study is one thing. Whether the panel will consider that science is a separate issue. So, what is allowed by statute versus what the panel will look at as science are two different things.

DR. VISHNUVAJJALE: Actually, since you interpreted that as my agreeing with it, I should say considering the kind of population you seem to have, I agree with all the people who were saying that you need to have to have a randomized study.

Maybe in time when you have several more of these,

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you will be ready for a one-arm trial, but I don't think you are now.

DR. GIMPELSON: I will put my tools away now.

DR. EGLINTON: Is there any further discussion on this point? Michael.

DR. DIAMOND: In light of the suggestion, though, it sounds like if we are going to say that they want to compare to the Gynecare product, it can be equivalent, we need to define whether we will make a suggestion of whether it's 5 percent or 3 percent or 10 percent.

I guess what would help me in making that recommendation is to know if I said 5 percent, what are the limits I am applying with the sample size, if I said 10 percent, what are the limits that I am applying.

DR. EGLINTON: I think--Tom, correct me if I am wrong--but I think what you are saying if you say you want it to be equivalent, you are accepting 20 percent error in essence if you way you want a power of 80 percent. It might only be 80 percent as effective.

DR. DOWNS: Here, it is not really a question of the absolute difference in percent success between the two. What really counts is the power, the statistical power to detect this. If you don't find any difference, but your statistical power detecting a difference is only 5 percent,

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well, that is worthless. It just means a small sample size, you have no chance of detecting a difference.

DR. DIAMOND: I am sorry. I didn't catch the FDA representative's name -- Lakshmi. I thought you were saying that we can't just say equivalence, we have to say within what range we would like the two observations to come up to be, and she gave the example of 3 percent or 5 percent.

DR. DOWNS: Well, for that, I think they picked the sample sizes in advance and then determined--I don't know, I wasn't in on that.

DR. VISHNUVAJJALE: What was the question? I didn't hear all of what you said.

DR. DOWNS: How did you determine the 20 percent?

DR. VISHNUVAJJALE: Twenty percent was agreed to. That was not determined by the statistician.

DR. DOWNS: But that was given the sample size.

DR. VISHNUVAJJALE: No, 20 percent was agreed on and the sample size was calculated from there.

DR. GIMPELSON: Twenty percent was the panel recommendation.

DR. VISHNUVAJJALE: Twenty percent was the panel recommendation because it had a better safety profile.

DR. DIAMOND: Did I misunderstand you? If we now want to say, if a new company wants to compare this to the

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Gynecare product, can we just say that or do we need to say within what percent--

DR. VISHNUVAJJALE: You have to say within what percent. You have to specify something or the other. You have to say have 200 patients in each arm, and whatever comes up there, we will accept, but you still have to either say what true proportion you are willing to accept, and if you want to go by the sample proportion, you have to be very specific, which is usually hard.

DR. DIAMOND: I am confused. That seems to be different from what Dr. Downs is saying.

DR. VISHNUVAJJALE: Well, he was talking I think about a different issue.

DR. EGLINTON: It depends on what your null hypothesis is.

DR. VISHNUVAJJALE: It depends on what your null hypothesis is. Also, what you are assuming and what you are--he was under the impression, if I am correct, that you have a certain sample size and decided you can detect 20 percent, but that was not the case.

DR. EGLINTON: You could say you are willing to accept a new product that is 80 percent as effective as the [ThermaCare] with a 90 percent confidence interval, but then you might be accepting a device that is only 60 percent as

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effective as your previous standard.

DR. DIAMOND: My preference would be to say the Gynecare device is going to be the control group, the new product needs to be equally efficacious.

DR. EGLINTON: So then you are specifying zero percent with a confidence interval and an 80 percent power.

DR. VISHNUVAJJALE: There used to be a statistical association T-shirt which said, "Being a statistician means never having to be certain." You cannot say you want it to be equal. If you are requiring the true proportion to be equal, then, in the sample, you are requiring the sample proportion to be actually better.

Actually, I don't have it now. I have a slide for tomorrow's presentation I can show you.

DR. HARVEY: Please don't talk about that. Please don't talk about tomorrow.

DR. VISHNUVAJJALE: No, I am not going to talk about it, I am going to say the two things that enter into that, and one of them has to do with the sample size, and one of them has to do with the difference you are willing to accept. So, you cannot say equal. You have to come up with 3 or 5 or 1.5, whatever it may be, you have to come up with the difference.

DR. DIAMOND: Maybe I am beating a dead horse, but

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if we want to say it could be equivalent, is that good enough or do you want more?

DR. LEVY: I think FDA wants to say equivalent plus or minus--what confidence interval we are willing to accept, so 95 percent confidence interval.

DR. VISHNUVAJJALE: Yes, how tight you want the 95 percent confidence interval to be, you can say that. You want to be within 3 percent, but 95 percent confidence, but you are never within zero percent with 95 percent confidence, and you are never 100 percent confidence with anything.

DR. EGLINTON: At this point, we are approximately 80 percent certain that Monica Lewinsky did work at the White House.

[Laughter.]

DR. EGLINTON: I said work.

Is that okay, Colin, are we square, are we moving toward Rich's taxi?

Okay. On to Question 6.

DR. GIMPELSON: Length of Follow-up after Treatment. Current FDA guidance is that study subjects in the pivotal trial be followed for one year premarket with the diary scoring system and an additional two years postmarket with follow-up visits and questionnaires for a

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total three-year follow-up on each patient.

Some evidence suggests that there is little difference in patient outcome at six months and one year post-ablation. Other recent evidence suggests that, depending on age and other factors, failures continue to be reported well past three year post-treatment.

What does the panel think about a shorter premarket follow-up, for example, six months, coupled with a longer postmarket follow-up, or example, five years?

I agree. In my practice experience, I am not seeing much change either between six months and a year. I rarely use a medical preparation on my patients, so most of my standard method now is a resection followed by roller, so I don't think there is going to be much change, and I am not waiting for any hormonal therapy or hormonal levels to return in a patient who has been suppressed.

I think the six-month following treatment would be fine, but I think you have to take into account those patients who have been medically suppressed and add additional time in, because some places we are still using Depo Provera post-op and then claiming, you know, significant levels of amenorrhea when, in reality, they probably didn't even need the ablation because they could have just given the Depo Provera.

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So, I think whatever drug is--and it would vary from whether you are using Lupron versus Provera versus a birth control pill versus Depo Provera. So, I think the medical preparation would take into account, but I think six months in those patients who did not receive any medical preparation, either a suction curettage or a resection at the ablation, would probably be sufficient follow-up as far as the premarket, and I don't think you are going to see much change in that first year.

I think as far as once you--I am sorry, as far as from the time of the end of the procedure--once the procedure is finished and you have approved it, though, I think you probably need a minimum of three years follow-up after the procedure, again taking into account medical preparation. Now it is kind of like the one-year premarket and then the two-year postmarket, you are really only doing at three-year follow-up total.

My suggestion would be probably a minimum of at least three and a half years of follow-up with three of those years are more post--I would love to see, I am sure the company is behind me I am working with--I would love to see a 10-year follow-up, so that we could really know what really happens to these patients, and eliminate the bias of all of us who are doing these procedures, and I think it

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behooves physicians doing it to keep their own personal records since I don't think you are going to go to a 10-year follow-up, but I think we have to be honest with ourselves for our patients.

So, I think a three-year minimum. I don't know, the five pushes us too much. We do see some patients having problems at three years, not really failure, but just may start spotting, maybe some pain, other factors that may be related to the ablation technique, and with these newer techniques, which are slightly different and maybe affect the uterine cavity differently, I think this little longer follow-up is probably valid.

So, I think a shorter premarket and a longer postmarket follow-up.

DR. LEVY: I think the problem with that is that this is a guidance document and a large number of the studies do involve medical therapy, medical preparation, and I think it was the sense of the panel when we came up with these guidelines, that was exactly the thing we were trying to obviate was the effect of the medicines on the menstrual pattern for these women.

As you say, depending upon the medical therapy that is chosen by a company, that amount of follow-up may or may not be enough.

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I guess I would be willing to say that we could alter the guidance document a bit to say that six months to a year, depending upon the protocol, might be reasonable, so that it is not etched in concrete, not that a guidance document is etched in concrete anyway, but the real issue we had was medical therapy.

DR. GIMPELSON: I agree because that really skews the success, but I think the longer follow-up is probably valid with these newer procedures, too, to indeed see if they will stand the test of time, but I am not sure, again, from two to three years is a magic number.

MS. DOMECUS: I think we have to be realistic, though, about a five-year postmarket follow-up. I just think the patient retention rate is likely to fall off and how valid is the data going to be if you don't have a significant portion of your population left.

I think five years is really difficult practically.

DR. GIMPELSON: That is an important point, yes.

DR. EGLINTON: Michael.

DR. DIAMOND: I think the year follow-up, at least at this point, remains very important. I think we don't have that many trials with six-month follow-up versus a year to be able to make good comparisons between them.

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Certainly, within the realm of what has come to this panel, it is one study, and I think it would be premature. The other component of that is another device that is being evaluated that is being evaluated may be effective as far as our failure/success criteria, but it may not be as effective over a longer period of time, and we don't have a way of assessing that, plus what we had actually put together in the original guidance document was the idea that every patient had to have six months follow-up, and we would allow the fact that some patients that could be presented to the panel at such a time, that not every patient would have gotten the one-year follow-up, in other words, taking into account that there is going to be a variation of time over which those patients are enrolled.

So, we have already, in my mind, already addressed the issue saying for the last patient enrolled, all you need is six months follow-up. By that time, for the first people involved, you will have over a year most likely.

DR. EGLINTON: Jerry, do you have any other thoughts on that?

DR. SHIRK: No, I think that, I mean, you know, you could argue for the six-month follow-up, but certainly I think trying to extend the follow-up out past a three-year

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standpoint is, you know, it is going to be hard to keep patients in a study that long. I think it is not realistic for us to expect the companies to keep people in studies that long.

Certainly, there is some failure over time, but that involves a lot of different factors unrelated sometimes to the therapy itself, and I think the criteria are pretty reasonable right now.

DR. GIMPELSON: So you would still favor just the two-year postmarketing?

DR. SHIRK: Yes, because anything beyond that is cumbersome and then somewhat onerous to the manufacturers themselves, and I don't know that we gain that much information.

DR. EGLINTON: Colin.

MR. POLLARD: I just want to comment on two things. First, your point, Dr. Shirk, just to clarify, so everybody is aware, in the postmarket follow-up period, we are not requiring the study subjects to maintain the menstrual diary scoring system, it is simply a question of questionnaires and visits related to their bleeding status, need for a repeat ablation or need for a hysterectomy, that kind of data.

Then, just trying to get an understanding of Dr.

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Diamond's point about six months versus one year, in the study, you were saying that it was your understanding that--could you repeat that, you were talking about six months from the last patient treated?

DR. DIAMOND: The thermal endometrial ablation device, page 13, I guess it is No. 1(d), follow-up. Twelve months of follow-up data will be required prior to PMA approval, however, the PMA will be submitted once six months of data has been obtained for all subjects, so for the last patient enrolled, all you would need was six months follow-up.

MR. POLLARD: Right. The difference between submitting the PMA versus approving the PMA, not whether or not you would actually collect one year data. Okay.

DR. EGLINTON: So, is there any feeling, is there any strong feeling to try to change what is on page 13? It is okay the way it is? Okay. Rich, on to No. 7.

DR. GIMPELSON: Endometrial Ablation and Uterine Cancer. Does the current clinical experience justify concerns related to the diminished ability to recognize the symptoms of endometrial cancer post-ablation? Is there a role for postmarket studies to help answer these uterine cancer-related questions?

Then, another question was proposed to me after

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this had been printed, about is there a possibility that endometrial ablation and the damage it causes the uterus possibly predispose someone to endometrial cancer. I don't have the answer, so I probably shouldn't have brought up the question, but we are not seeing a lot of cancers appearing. You know, part of it is the screening of these patients to begin with. Probably some of it is the total destruction of the endometrium in some patients.

So, we are not seeing large numbers of endometrial cancer, even small, you know, the numbers are very small as I will relate when we get to it. However, the only other qualifying factor I guess is that the first endometrial ablation was done in 1978 with some myomas being done in the mid-seventies, but as far as actual total ablation of the endometrium was 1978, so we are only now coming on the 20th anniversary of the very first patient done.

So, there may be an element of the unknown that is going to pop up in the future, but at least at the present time, we are not seeing patients coming in--I will sample my patients with abnormal bleeding, what I consider abnormal following an ablation, and have not picked up even any hyperplasia in any of my patients, part, but some of that can also be some difficulty in sampling, but just from communication with other physicians around the country, and

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then in the literature, there is not at this time endometrial cancer appearing in large numbers in our patients, but I think this is time we still have to watch these patients.

As far as just the worry of cancer in the ablation patient, I have my own philosophy on this, and I am very conservative in this area, I am guess very liberal in trying to get the procedure out, but as far as the protection of my patients, I want, first and foremost, I am doing a procedure that once I have treated this organ that I am leaving in, it may be difficult to evaluate, and so I think it is so important that this organ is properly evaluated prior to treatment.

I think the literature is very clear that hysteroscopic evaluation at the present time is probably the single best way to evaluate abnormal bleeding. We have other literature talking about saline-infusion sonograms and biopsies and D&Cs and suction D&Cs, but I think we know from our studies that all these have some lesions missed that are picked up on hysteroscopic exam.

I think if we are going to be treating this organ, I really think that the uterus should be evaluated as thoroughly as possible, which would be by hysteroscopic exam prior to any method of endometrial ablation including those,

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you know, even laser that has been out for 20 years.

I don't see any other option. I think that is the safest way. There were six cancers that I reviewed when I did my paper--and I think you all have a copy of that--and these patients were all, for the most part, probably you could say a high risk. Most of them were obese, they were hypertensive. Most of them were diabetics, maybe anovulatory, but we all have lots of patients in our series with these same categories.

Every one of these patients actually had hyperplasia prior, somewhere prior to the endometrial ablation. There is even a question that one of them maybe even had--well, two of them probably had cancer. One was documented because the cancer was picked up at the time of the ablation, and one had metastatic cancer 15 months following the ablation, so there was a question whether that woman may have had cancer at the time also.

Only one of the six was actually the prior to the ablation, and the findings in most of them were what is called simple hyperplasia, so the other factor that comes in is even if we are not going to require hysteroscopic evaluation of our patients prior to this procedure, the fact that someone has "the diagnosis of simple hyperplasia," which most people consider not even precancerous, these

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patients all developed cancer, and there is a literature, Gambrell had 6 of 11 patients in his series that developed endometrial cancer, that had a diagnosis of simple hyperplasia.

So, one, not pertaining to this panel, maybe we have to relook at what is the etiology of endometrial cancer and is simple hyperplasia not so simple, but I think these patients should be evaluated properly beforehand, and I believe in the guidelines it is allowed, you know, treated hyperplasia, the patients with treated hyperplasia are allowed to be ablated, but I think that may be something that at least the panel needs to relook at.

I am not so sure if my six cases is a large enough sample to draw on, but it is biased the way I take care of my patients, so if I have a diagnosis of simple hyperplasia, the first thing, we go to the pathologist to find out is this really the diagnosis because some labs are more liberal calling it than others.

But I think the panel has to look at this potential risk of cancer because we are only coming upon that now, as I said, the 20-year anniversary on the very first patient is just coming up, so we really don't have a long-term follow-up on anybody who has had endometrial ablation, but I think we should at least go into the

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procedure with a patient at as low risk as possible.

DR. LEVY: I think there a couple of issues. In the literature, as far as I have read it, Rich, it doesn't look like to me that there were women who had endometrial cancer subsequent to ablation who had the cancer masked by the ablation, and I think that is one of the things that was really concerning to the panel.

In other words, those women still had symptoms, as I understand it, they bled, is that correct?

DR. GIMPELSON: Well, they bled and were diagnosed with cancer, but they maybe didn't bleed when they had hyperplasia from some element following the ablation. In other words, they bled and the cancers were picked up, but it is not necessarily good to pick up--you

can do an umbilical biopsy and find the metastatic cancer on someone who maybe should have been treated a different way to begin with.

DR. LEVY: I guess I want to separate out the one patient that probably had cancer at the time versus what our real issue is, is will this procedure mask a cancer that wasn't pre-existing, someone who is appropriately evaluated and followed up, I mean everything has been done right, and 10 years down the road, she develops endometrial cancer.

As I understand the literature that I have read,

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it appears that those women demonstrate the symptoms of endometrial cancer relatively early, they bleed. Is that correct or not correct, or does anybody have any other data to support something different?

DR. SHIRK: I think that is correct because basically, you know, I think the confusion comes from the initial description of the procedure itself by Milt Goldrath, and he termed it an "iatrogenic Asherman's syndrome." All of us obviously assume when we hear the term "Asherman's syndrome," that you have got all these crazy intrauterine synechiae in there and that you have got things blocked off here and there, and most patients after an ablation do not have intrauterine synechiae. I mean I have been back on lots of patients that have had previous ablations, and looked back in, and they do not have a lot of intrauterine synechiae, so how do you want to define Asherman's.

Basically, what we are doing, what you do basically is end up with a smooth cavity inside that is basically constricted, but also just a low cuboidal epithelium in it, and so I don't see that that is really a major problem. I don't know if there is any data from any of the new devices as to anybody going back and re-hysteroscoping those patients as to what the inside of

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the uterine cavity looks like, but my guess would be that they have got a very normal--they have got an open cavity, so that if there is any endometrium in there, it is going to communicate with the outside, and that anybody who develops a cancer is going to have the same symptoms as anybody else.

I mean one would have to subjectively hypothesize that probably an endometrial ablation reduces the risk of endometrial cancer simply because there is less endometrium there to catch cancer, but obviously, that is not something that has ever been shown either as a population, but certainly I think that clinically, those patients who have had endometrial ablation are probably going to have the same symptoms that anybody else had.

DR. EGLINTON: What causes you to go back in and rescope those women, I mean what kind of symptoms caused them to require hysteroscopy again after they had had endometrial ablation?

DR. SHIRK: Obviously, there is a failure rate on an endometrial ablation, so if you are doing a significant number of endometrial ablations, and you reevaluate those patients, you are going to re-hysteroscope them.

DR. EGLINTON: And when you did that, what is the frequency with which you find any hyperplasia, or have you found any cancer?

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DR. SHIRK: I have never found any cancer or hyperplasia, but then I have always--you know, I have never avoided anybody with hyperplasia, and I know that we had, at the last meeting, when we were talking about labeling, I mean we got into a big-time discussion about this issue, and obviously, everybody on the panel knows where I stand with this thing, but since then, I feel even stronger about it because I had a patient that I saw about a year and a half ago, that I did an endometrial biopsy on, had adenomatous hyperplasia treated with progestins, took her off, and six months later she came back--had her on progestins, re-biopsied her, she went negative, so she had a normal endometrium on biopsy. Six months later she was back with bleeding. I biopsied her again. She has atypical endometrial hyperplasia. I did a vag hist on this lady, and she has got Stage I endometrial carcinoma.

So, I mean basically, I mean you are playing with fire when you are playing with adenomatous hyperplasia. I mean it a premalignant situation.

DR. EGLINTON: Because your biopsy sample is such a small area, she could have had cancer from the very first visit.

DR. SHIRK: Yes.

DR. EGLINTON: Then, you had best not be resecting

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that.

DR. SHIRK: But again, I mean the question of this also comes back to our exclusion criteria that was initially set up, and that basically reads malignant pathology as documented by endometrial biopsy, adenomatous hyperplasia, or even atypical adenomatous hyperplasia is not an exclusion criteria of these studies.

DR. GIMPELSON: So, I think there is plenty of patients who would be candidates for ablation even if you exclude those with hyperplasia. In my opinion, I think even simple hyperplasia from just my review, I think that should be an exclusion criteria unless a protocol is set up to look at that, you know, if there is a group of oncologists, someone who wants to follow the treatment of endometrial hyperplasia with ablation, I think that is a worthwhile protocol to pursue. Then, we could find out maybe it's a good treatment for it, but I think until we have that protocol, I think those patients, even with simple hyperplasia, even treated simple hyperplasia, the tendency of those patients is to stop their medication when they don't bleed, should be excluded.

On the other hand, do the way pre-ablation to evaluate them, which is with a hysteroscopic exam to make sure we are not missing hyperplasia in somebody

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preoperatively, so it has got two different things, one, just excluding those who are already documented, two, how do we really evaluate the patients coming. Right now an endometrial biopsy is probably sufficient. I don't think it is, but that is pretty much what is allowed.

MS. YOUNG: Three of your six cases were women who were diabetic and obese.

DR. GIMPELSON: Right.

MS. YOUNG: When you have the combination of those factors, do you think--I mean six, of course, isn't very many--but should the combination of those factors be considered to be a risk factor for women who are going to have ablation?

DR. GIMPELSON: Yes, and include also hypertension, and even another patient who had polycystic ovaries. So, these patients all had other risk factors, but in most of our experience, we have done patients who are obese, hypertensive, diabetics. Now, we may find out that that was a mistake.

At this point, I do the same as Jerry, I have a very low threshold. We advocate doing hysteroscopic surgery very easily and very quickly, so if I have a patient who has a change in her bleeding pattern, if she is a year amenorrhea, and she starts bleeding, I evaluate her, or if

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she has a change in her pattern, we will evaluate her, and we have not picked up, you know, just from my own size, you can guess that a lot of my patients are probably going to be obese, because they are comfortable in my office, and so I have a large number of patients that big like me, because they know I won't talk to them about their weight.

So, I worry. I worry a little about that, too. I keep a close watch on these patients, and we may find out that this in the future might be an exclusion criteria. There are some people who won't do the obese hypertensive diabetic because of the same fact. They say, well, you are not going to do hyperplasia, but this woman is sort of sitting there as a hyperplasia nidus, so I think absolutely that is a good question, and I think they are real, but we are not seeing it. We have all done those patients, and we are not seeing hyperplasia in the follow-up of those patients yet or cancer.

DR. LEVY: I would like to suggest that this is an absolutely fabulous subject for NIH funding and support for the kind of conference that we are going to discuss in August.

MR. POLLARD: We brought this to Joanne Luoto's attention, and, in fact, I would like to at this moment introduce Mary Beth Jacobs. Would you stand up, Mary Beth.

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Mary Beth, Dr. Jacobs is the Director of our Division of Life Sciences within our Office of Science and Technology, and Dr. Richter, our Deputy Office Director asked Mary Beth to look into this particular question.

Actually, it started out on the flip side, and I just wanted to maybe follow-up real briefly with a remark Dr. Shirk made about the fact that, well, because you are ablating so much of the--and this is kind of looking at the other side of the question--that you are ablating so much of the endometrium that you could have hypothesize that, in fact, you are reducing your risk of uterine cancer, endometrial cancer.

That was actually originally the question that was posed to Dr. Jacobs, and I was wondering if the panel might comment briefly on that aspect or even if it is just to the effect that we don't really have any data.

DR. SHIRK: I don't think there is any data. The answer is everybody has been looking at the other hypothesis. I mean one of the initial questions about endometrial ablation when we started doing it, and started doing investigative studies on it at all was basically there was a hue and cry from the ivory towers that basically, that we were going to hide all this with our Asherman's, we were going to have all these people down the line that we are

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going to have endometrial cancer, and we couldn't find it.

I think time has obviously answered that that is not true, but I don't anybody has enough data to look at the reverse. I mean you would have to have huge patient populations to be able to look, to have a significant answer as to whether it really reduces the incidence of endometrial cancer.

DR. LEVY: I think from the standpoint of this question, the issues really are that the panel at least doesn't have a current concern that the ablation itself masks cancer, and that, secondly, I personally would like to see a reporting requirement, not so much that there would postmarket studies, because that is a big burden on the companies, but that we have some mechanism for physicians to know that we want to see reports of cancer developing after ablation, and that is a different thing than asking the companies to do postmarket studies. There is better science there, and we will actually learn a lot more about the real prevalence of this situation.

DR. GIMPELSON: A national registry.

DR. LEVY: Yes. I personally would rather see it done that way than ask the companies to do it.

DR. JACOBS: Let me just briefly tell you what we found when we looked into the question that Dr. Richter

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asked us to address, which was the case of uterine cancer and what we might know from the point of view of animal models or human exposure or in-vitro models.

We spoke with scientists here who are experts in cancer at a tox center that FDA has in Arkansas and also with people at NCI, and here are the things that we found.

First of all, estrogen, as you all know, is a well-known risk for endometrial cancer, and therefore, if there is tissue remaining, this could be a concern, but was thought to be a low-level concern because there is probably little tissue remaining.

In general, if there is damage to tissue, there is a proliferative response, and that depends on the type of the tissue, and for endometrium, one would expect proliferation because it is a tissue that can proliferate.

However, studies looking at damage to tissues and whether or not it is related to cancer have found that it is chronic irritation to tissues which is associated in some cases with development of cancer rather than an acute exposure. So, in this case, there was not a high level of cancer because people said this is an acute exposure, it is not the kind of chronic exposure which we can in some cases associate with cancer.

In addition, when we spoke to the epidemiologists

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at NCI, they said let's look at the most comparable condition and that is IUDs, and IUDs could be seen as a kind of chronic irritation. In fact, the studies looking at cancer risk in IUD patients have found a lower risk of cancer, so that was an additional factor for looking at this as a potentially lower concern for cancer.

Of course, we then checked on the abstract, we found yours, as well. I think you are in the best position to address the clinical factors which you are.

We are going to have the person who is head of that group at NCI come over and talk with us as we are further along in numbers of patients in the U.S. who have this. Right now the prevalence is very low, so even including this on any of their studies would not produce too many patients, but it is possible that they have other studies or becomes a factor that it might be something for them to study.

MR. POLLARD: The other thing I wanted to add was that we will be getting together with Dr. Luoto as they gear up for that conference, and one of the things that we can talk about is some kind of reporting mechanism. We have postmarket surveillance folks here in our center, and we may be able to work some kind of arrangement out. We will definitely look into that.

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DR. EGLINTON: Back to this Question No. 7, with maybe a slightly different twist, it sounds to me like we have heard at least two practitioners say that they consider hyperplasia to be an exclusion criterion before endometrial ablation, but unless I am missing something, I don't see it listed as an exclusion criterion here in our document.

It sounds to me like we have got a pretty strong case for an exclusion.

DR. SHIRK: That was my point.

DR. DIAMOND: How do you feel about it? You have been sort of silent about hyperplasia.

DR. CHATMAN: I think that what has been said I certainly agree with. I wouldn't do a patient who has hyperplasia, simple adenomatous.

DR. LEVY: I am sorry, Don. You would or would not?

DR. CHATMAN: Would not.

DR. EGLINTON: Dr. Janik.

DR. JANIK: I also agree it should be an exclusion criteria and even more so than maybe small fibroids which may be so prevalent and are irrelevant, if that is an exclusion criteria, that this is especially should be.

DR. EGLINTON: I had the same thought about fibroids. I mean how many women are there in the world with

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fibroids.

DR. JANIK: It may be 50 percent depending on the population, intramural, subserosal, it really shouldn't matter.

DR. EGLINTON: At this point, it looks like in the document, the only women with fibroids who are not excluded are those who have pedunculated or sessile fibroids, or something like that, but everything deeper than that is an exclusion, and are the resectoscopic people really happy with that as an exclusion?

DR. GIMPELSON: I think Jerry's point is that if you are going to resect the fibroid, then, you are probably going to just use that same method to do the ablation.

DR. EGLINTON: How about intramural fibroids that really don't impact the endometrial cavity? They are excluded on our list.

DR. LEVY: I think we excluded them to keep the study as simple and reasonable scientific study, just for the very reason that there are so many women with fibroids that it makes for a very difficult analysis when you include them in the initial safety and efficacy studies for a new device, and, in fact, it would make it very difficult on the companies to know, since most of us, at least I don't understand the science behind how an intramural myoma causes

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bleeding abnormalities, but we know that some of them do.

So, the reason for keeping fibroids on the exclusion criteria was to simplify the science of the study.

With respect to hyperplasia, I will play the devil's advocate for just a minute here, because I, as well, do not do ablations on women with hyperplasia, but there is a group of patients who have had in their past a history of hyperplasia perhaps related to some episode of chronic anovulation for a period of time, which has resolved, and they have been normal for a fair period of time, and I won't define "fair" for the moment.

But it was that group of patients I believe that we did not want to see excluded from an ablation protocol.

DR. GIMPELSON: I exclude those, too, but I do back on some of those patients and go over that path report with a gynecologic pathologist, because sometimes those aren't really hyperplasia, and then we can treat, but I want to have the opinion of someone who really has a lot of expertise looking at that kind of tissue.

That is my bias and maybe I shouldn't have looked up all that literature and I probably wouldn't feel that way, but if a patient has hyperplasia, I try to get all her old records, in fact, I won't do it without getting her old records, and if she has hyperplasia anywhere along the line,

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then, I just tell her, you know, her option is medication or hysterectomy, in my hands. I just don't want to do an ablation on her.

There is not that many fortunately, and I just think those few can go without ablation at this point in time, but I know there is others who may feel that if it is resolved--the problem is those are the ones also who may not take progesterone, and we don't know if it comes back, you know, as Jerry's, where he had the one that came back following treatment.

DR. JANIK: And plus how do you know it is really resolved, how good of a follow-up, how frequent were the biopsies, lack of bleeding, one biopsy, there is not good criteria what would be considered resolved and for what time period, so I agree with you, I would exclude those.

DR. GIMPELSON: But I am a little nervous and I have a few who are polycystic ovary, where we know also already have this real risk, but also obese hypertensive diabetics, I have done these patients, and I watch. I just think they need to be watched closely, too. They may turn out to be an exclusion one day. I think at this point they are not because we are not seeing those patients turning up with any more problems than the others, not masked cancer, nor even masked hyperplasia.

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I have not picked up a hyperplasia in any of my patients who had maybe procedure failure or even sort of procedure reduction, you know, where we re-evaluate them, but they chose to live with the slight bleeding they are having, and still have not picked up hyperplasia in any of those patients. Have you, Jerry?

DR. SHIRK: No.

DR. DIAMOND: I would agree that it would be reasonable at this point in time to exclude patients with hyperplasia of any type, but the other issue is with regard to intramural fibroids. I think the one other point there is that even if the fibroids are not impinging on the cavity, they still may cause distortion of the cavity or enlargement of the uterine cavity, such that a device may not work as well, whatever means an endometrial ablation should be done, may not work as well in that group as in others, and that would be a reason to still continue to exclude them at this point.

DR. JANIK: One other small comment about that. Are you going to screen everyone with ultrasound then to make sure they don't have intramural fibroids, or will it only be those that are clinically apparent on exam?

DR. DIAMOND: No question, we require the companies to do ultrasonic exams, so I think by process of

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elimination, we were saying those that were clinically identified, and those are the ones that are going to causing distortions of the cavity, such that the devices may not fit as well or be as appropriate.

DR. JANIK: So then if fibroids were found on ultrasound, but not clinically apparent, those people could be included because it wasn't clinically determined. Do you know what I am saying? If you don't have it consistent, you can have one group that may have these fibroids and another group that won't. The 2 cm myomas, you won't know.

DR. EGLINTON: And that is what lobbies most strongly for a randomized control trial. They should show up in both arms. I think that we have agreed that we want any degree of hyperplasia as an exclusion criterion, and we will leave the fibroids alone as they stand in the document.

Did we come to the end of Question 7 then?

DR. GIMPELSON: Yes.

DR. EGLINTON: I think we came to the end.

DR. GIMPELSON: Thank you.

DR. EGLINTON: Any other comments by members of the panel or by Colin?

MR. POLLARD: We plan to use the transcript and our notes to go back over the guidance document and really study all of the comments, and so forth, very carefully. We

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probably will enlist the help of the usual cast of characters, but I was wondering whether you--

DR. EGLINTON: You didn't mean tonight.

MR. POLLARD: Not tonight.

[Laughter.]

MR. POLLARD: I was wondering whether you thought any purpose would be served in just briefly going through all seven for a quick take.

DR. EGLINTON: That is why I was very careful to summarize 4 through 7 as we came back, so that we wouldn't have to do that.

MR. POLLARD: I think we are in pretty good shape. We got a really good discussion of all seven of those questions, and like I say, we will probably enlist the help of a couple of the panel members to help us sift through some of those thoughts and we will work towards getting a new guidance document out later this year.

DR. EGLINTON: Can we invite any comment from members of industry, any brief comments? Did we stir any embers? Yes, sir.

DR. LOFFER: Franklin Loffer, Associate Clinical Professor, University of Arizona, private practice, Phoenix, Medical Advisory Committee of Gynecare, T and E being paid by them, and an ablationist since 1984.

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I would speak to two areas. One, Gynecare asked that their follow-up be limited to six months. I understand why they did, and I understand why the FDA refused that, and I also understand that it is the mood of this committee to continue to require a year's follow-up to assess the results.

But I think an equally important area are some of the problems that show up on later follow-up. Specifically, you don't see post-tubal ligation syndrome in the first six months. That is something that shows up later, so there are some potential problems that might show up.

The second area that I would like to make a comment about is in patients with post-menopausal bleeding, I am not sure that amenorrhea is an appropriate endpoint. It is really those patients staying on hormonal replacement therapy.

Thank you.

DR. EGLINTON: Thank you. Any other audience participation? Yes, sir.

DR. DOWNES: Good afternoon. My name is Ellis Downes, gynecologist from England. I apologize. I was late due to the British Airways is not as sufficient as American Airlines.

DR. EGLINTON: Did they pay for your travel and

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expenses here, sir?

DR. DOWNES: If only. If only. I am a lecturer in gynecology at Leeds University, hysteroscopist. I am a paid advisor to U.S. Surgical.

I just came in on the end of your discussion, and I just wanted to make a very interesting point about the comments relating to the problems of obesity and hypertension, a mixed group of patients who potentially may be at risk of endometrial hyperplasia, as to whether the panel should consider whether these patients should be excluded from trials by virtue of a possibly increased risk of hyperplasia.

I just wonder really whether we need to take our minds back to where we started with office hysteroscopy for diagnostic purposes in terms of actually being able to reduce the anesthetic morbidity for these patients, you dread doing. You bring them in, and you say I am doing this woman, she is a smoker, she is overweight, she is hypertensive, and you want me to give them a general anesthetic.

I do believe it may be a goal, as we try to develop this technology, but for some patients who are not medically terribly fit, they may be suitable patients to have an office procedure to deal with their symptoms than to

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resort to hysterectomy, which may potentially greater morbidity and mortality.

I would agree that these patients need to be followed up very closely long term, but I am not sure there is enough data in the literature to support them being an exclusion criteria for endometrial ablation.

Thank you.

DR. EGLINTON: Thank you. If I can get your card, I can give your name to the 430-pound diabetic I delivered last night before coming here, 430 pounds, not one pound less.

Any other comments? Dr. Yin, do you need us to stay longer?

DR. YIN: No, but I do want to take this opportunity to thank Dr. Gary Eglinton one more time, though, that he has served FDA for eight years, and it is not just come in and do whatever. We asked him to do homework, we asked him to come in when he really did not want to, and Colin sent homework, Colin went over and haunt him.

DR. EGLINTON: Worse than that, Colin knows where I live. He has appeared at my doorstep.

DR. YIN: Yes, and at the ungodly hours and regardless. I do want to take this opportunity and have all

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of you give him big cheers.

[Applause.]

DR. EGLINTON: Thank you very much.

DR. YIN: I represent the whole Center and FDA.

Thank you.

DR. EGLINTON: Is there a motion for adjournment?

MS. HARVEY: So moved.

DR. EGLINTON: Is there a second? Any objection?

We are adjourned.

[Whereupon, at 4:50 p.m., the proceedings were recessed, to be resumed at 8:30 a.m., Wednesday, January 28, 1998.]