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FOOD AND DRUG ADMINISTRATION  
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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
MEDICAL DEVICES ADVISORY COMMITTEE  
+ + +  
OBSTETRICS AND GYNECOLOGY MEDICAL DEVICES PANEL

September 8, 2011  
8:00 a.m.

Holiday Inn  
2 Montgomery Village Avenue  
Gaithersburg, Maryland

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MEETING

(8:00 a.m.)

DR. FALCONE: I'm the Chairperson for this meeting, which the topic is surgical mesh used for repair of pelvic organ prolapse. My name is Tommaso Falcone. I'm the Chairperson of this Panel. I am Professor of Surgery and Chair of Obstetrics and Gynecology at the Cleveland Clinic in Cleveland, Ohio. I'm board-certified in general obstetrics and gynecology as well as subspecialty board-certified in reproductive endocrinology.

And the Designated Federal Officer is Shanika Craig, and who's sitting on my left.

Now I would like to call this meeting to order and I want to also introduce the Panel that is -- that we're going to start from on the left. If you may, please, Dr. Duerhring.

DR. DUERHRING: I'm Dr. Gary Duerhring. I'm a professor in graduate programs and health administration for Central Michigan University, and I'm also the Consumer Rep on this Panel.

DR. GADALETA: Good morning. I'm Sergio Gadaleta. I'm the Vice President of Regulatory Affairs for Becton Dickinson, and I'm the Industry Rep on this Panel.

MS. BERNEY: I'm Barbara Berney. I'm the Patient Representative, and I work with the FDA on a number of other things, including the Ophthalmic Devices Panel.

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DR. FLESH: Thank you. I'm George Flesh. I'm Chief of Urogynecology and Pelvic Surgery at Harvard Vanguard Medical Associates, and I am an assistant professor at Harvard Medical School.

DR. ROGERS: Rebecca Rogers, professor at the University of New Mexico. I'm the Director of the Division of Urogynecology in the fellowship there.

DR. FITZGERALD: I'm Dr. Mary Pat Fitzgerald. I'm a urogynecologist and general gynecologist at Hines VA Medical Center near Chicago.

DR. SEARS: I'm Dr. Christine Sears. I'm an associate professor at the Uniformed Services University of the Health Sciences. I'm a board-certified urologist but have been fellowship-trained in female pelvic medicine and reconstructive surgery, and I'm currently the continence chief at the Walter Reed National Military Medical Center.

DR. BRILL: Good morning. Andrew Brill. I specialize in minimally invasive gynecologic surgery and pelvic surgery at California Pacific Medical Center in San Francisco.

DR. CHAPPELL: Rick Chappell. I'm a statistician. I'm a professor in the Department of Biostatistics and Medical Informatics at the University of Wisconsin Medical School.

MS. CRAIG: Shanika Craig. I'm the DFO for this Panel meeting today.

DR. DAVIS: Ann Davis. I'm Professor of OB-GYN and Professor of Pediatrics and Associate Dean of Students at Dartmouth Medical School.

DR. HILLARD: Paula Hillard, Professor of Obstetrics and Gynecology at Stanford University Medical Center.

DR. DIAMOND: I'm Michael Diamond, professor and Associate Chair of Obstetrics and Gynecology and Assistant Dean for Clinical and Translational Research at Wayne State University.

MS. DOMINIK: I'm Rosalie Dominik. I'm an Associate Professor of Biostatistics at the University of North Carolina, Chapel Hill.

DR. IGLESIA: I'm Cheryl Iglesia. I am a board-certified OB-GYN, and I'm an associate professor in the Departments of OB-GYN and Urology at Georgetown University School of Medicine, as well as section chief of the Division Female Pelvic Medicine and Reconstructive Surgery at Washington Hospital Center.

DR. CODDINGTON: I'm Charles Coddington, Professor of Obstetrics and Gynecology and Chair of Reproductive Medicine at Mayo Clinic.

DR. MATTISON: Don Mattison, Medical Officer in the Intramural Research Program at the National Institute of Child Health and Human Development.

DR. KALOTA: Susan Kalota, private practice urology in Tucson, Arizona.

DR. LERNER: I'm Herb Lerner. I'm the Acting Division Director of the Division of Reproductive, Gastro-Renal and Urological Devices, Center for Devices and Radiological Health at FDA.

DR. FALCONE: Thank you.

So for today's agenda, the Committee will discuss and make recommendations regarding the safety and effectiveness of transvaginal surgical mesh used for repair of pelvic organ prolapse. The FDA is convening this Panel to seek expert opinion on the risks and benefits of these devices in light of the adverse events reported, such as vaginal erosion leading to pelvic pain and dyspareunia, and available information on clinical benefit. The Panel will be asked to provide scientific and clinical input on the Agency's proposed premarket and postmarket regulatory strategies for these devices, including reclassification into Class III, labeling improvements, and postmarket surveillance studies.

The Panel will also consider surgical mesh used to treat stress urinary incontinence, but that will be for tomorrow.

So I'd like to remind everyone, when they do make any comments, to please state your name again, because this is being recorded, so that we can attribute the comments to you personally.

So now we're going to hear some introductory comments from Ms. Craig, the Designated Federal Officer for Obstetrics and Gynecology.

MS. CRAIG: Before I start, I just wanted to remind everyone, if

you haven't signed in at the table outside, please remember to do so before leaving today.

Good morning. Now I will now read the Conflict of Interest and Deputization to Temporary Voting Member Statements.

The FDA Conflict of Interest Disclosure Statement, particular matter of general applicability, date September 8th, 2011.

The Food and Drug Administration is convening today's meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Government employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at U.S. Code 18 Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

The FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under U.S. Code 18-208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that

the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own and those imputed to them, including those of their spouses or minor children and, for purposes of U.S. Code 18 Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the safety and effectiveness of surgical mesh for the use of pelvic organ prolapse.

Based on the agenda for today's meeting and all financial conflicts reported by the Panel and consultants, no conflict of interest waivers have been issued in connection with U.S. Code 18 Sections 208 and 712 of the FD&C Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Dr. Sergio Gadaleta is serving as the Industry Representative,

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acting on behalf of all related industry, and is employed by Becton Dickinson.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

For the duration of the Obstetrics and Gynecology Devices Panel meeting on September 8th and 9th, Dr. Donald Mattison has been appointed as a Temporary Non-Voting Member. For the record Dr. Mattison serves as a consultant to the Center for Drug Evaluation and Research. He's a regular Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on September 7th, 2011.

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

Before I turn the meeting back over to Dr. Falcone, I would like to make a few general comments.

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videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Karen Riley.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area which is beyond the speaker's podium. I request that the reporters please wait to speak to FDA officials until after the meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence any cell phones and other electronic devices at this time. Thank you very much.

Dr. Falcone.

DR. FALCONE: Okay, thank you. So we're going to move on now and get some introductory remarks from Dr. Lerner, who's the acting director.

DR. LERNER: Good morning again, everyone. I'd like to welcome everybody to the 75th meeting of the OB-GYN Devices Advisory Panel.

Over the next two days there will be discussion of surgical mesh repair for pelvic organ prolapse and female stress urinary incontinence. The Panel will hear from industry, the clinical community, the general public, and the FDA. These discussions will assist FDA in assessing its regulatory paradigm for these devices.

Presented on this slide are the names of the members of the review team who prepared the material sent to the Panel for review and which will be presented today, as well as the recently updated Public Health Notification and white paper.

I will now present a high-level review of today's agenda. During the FDA presentation, our scientists, epidemiologists, and clinicians will present in more detail what is outlined on the following slides.

We are here today to discuss surgical mesh and its use in the repair of pelvic organ prolapse and stress urinary incontinence.

This slide demonstrates the characteristics of a mesh. In general, they are interwoven strands of synthetic or biologic material which form the support matrix. The insert is a screen of an electron micrograph of a small portion of a piece of mesh. Different meshes may have different architecture, but they generally look like this. For pelvic organ prolapse and SUI repair, they may be preformed to fit an anatomic space. This will be reviewed by our clinicians.

Since the focus of the discussion today and tomorrow will be

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on the possible need for clinical data for mesh intended to treat pelvic organ prolapse or stress urinary incontinence, I think it's important to outline the role of FDA in the total product life cycle of medical devices.

As outlined in this graphic, the role of FDA may start with a novel device development as industry interacts with FDA to review the preclinical and animal data needed for a device marketing submission and progresses towards the development of a clinical trial which will generate sufficient data to support a marketing application. Once approved, FDA continues to monitor adverse event reports, reviews the published literature for trends of adverse events, and follows the design enhancement as the life cycle of the device progresses.

A similar approach is taken for devices cleared through the 510(k) process. However, FDA has much less authority over labeling of these devices, and some enhancements can be made without notifying the FDA. We attempt to balance the regulatory requirements for device development against the risks associated with any medical device.

Our goal is to put safe and effective devices on the market. If we see trends of adverse events, we work with our Office of Compliance to review these and take regulatory actions as warranted. Taken together, this vision enables FDA to fulfill its mission of protecting the public health.

In this and the next few slides, I will be presenting some of the terms and our conditions that will be discussed in the presentations to follow.

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Surgical mesh is a porous, permanently implanted device made of either synthetic or biologic material used to support weakened or damaged tissue. These materials may be absorbable or nonabsorbable. These were originally used for hernia repair and were presented as sheets of mesh which were cut to size by the surgeons. For the indications under discussion today, surgeons initially did the same thing. Manufacturers have now customized the mesh to fit each anatomic region and package the mesh with accessory tools such as introduction needles.

Adverse events are those which may cause harm to a patient. Listed are some of the main events associated with transvaginal mesh repair. The clinicians will discuss these in greater detail during their presentations.

Once noted, these adverse events should be reported to FDA through our MAUDE database, by the surgeon, manufacturer, or patient.

It is apparent to FDA that the terms exposure and erosion are sometimes used interchangeably to define mesh which is visible within the vagina. However, we also note that, in our literature review as well as our review of the adverse event reports, some have tried to better define these terms.

For example, exposure is sometimes defined as mesh seen through the vaginal wall, and erosion is mesh which has penetrated the bowel, bladder, or other tissue planes. FDA will use erosion in their presentation to mean any mesh seen in the vagina or penetrating into

another tissue plane.

Additionally, extrusion and protrusion have also been used to describe mesh seen through the vagina wall.

These pictures demonstrate what is pelvic organ prolapse: a bulge of organs or structures surrounding the vagina, into the vagina, or extending beyond the vaginal opening, caused by a laxity of supporting tissue of the vagina. Our clinical reviewers will be presenting in more detail these presentations for pelvic organ prolapse.

In general, there are three areas which can prolapse. Noted on this slide are normal pelvic anatomy on the left, anterior wall prolapse, called cystocele, and apical prolapse, which is generally the prolapse of the apex of the vagina seen after hysterectomy. Not pictured is a posterior wall prolapse, called rectocele.

Surgical mesh is considered a pre-amendments device, having been marketed before the Medical Device Amendments were added to the Food, Drug and Cosmetic Act signed in 1976. Until recently, surgical mesh repair for all indications was reviewed in the Plastic Surgery Devices Branch in the Office of Device Evaluation and was mainly used for hernia repair and limited orthopedic indications.

Within the last year, the review of surgical mesh for female indications has been taken over by the Obstetrics and Gynecology Devices Branch. The Urology Devices Branch reviews mesh intended for male

incontinence.

Procodes are a method of tracking specific groups of devices.

We recognize that surgical mesh for repair of pelvic organ prolapse and stress urinary incontinence has evolved over the last few years. Please note, however, that as industry modified surgical mesh for these indications, none of the meshes were evaluated with original clinical data. Rather, the regulatory pathway was through the 510(k) or substantial equivalence pathway.

We also recognize that sling mesh repair for female stress urinary incontinence has long been an accepted standard of care. However, signals from our adverse event reporting system, the MAUDE database, make it important that we bring both of these issues to you for your consideration.

Today, FDA will be asking the Panel to discuss whether the current regulatory pathway for mesh intended for pelvic organ prolapse repair is sufficient for these devices, given the data to be presented. Tomorrow we will discuss stress urinary incontinence.

In the 1990s there appeared new indications for surgical mesh, first, stress urinary incontinence and then pelvic organ prolapse. Please again remember that these were cleared through the 510(k) pathway.

The first signals that there might be adverse events associated with mesh for POP and SUI came from a discussion in AUGS meeting in 2006, as well as from adverse event reports sent to the FDA. This led to a full

review of the MAUDE database in 2007 and the issuance of a Public Health Notification in 2008, regarding the adverse events seen during the review.

FDA, in mid-2010, initiated an updated review of the MAUDE database to see the trends of adverse events reported since the original Public Health Notification. This is the data that will be presented to you today.

In late 2010, several professional societies notified FDA of their concerns with the trends of adverse events in women undergoing mesh repair for pelvic organ prolapse. After review of the adverse event reports and the published reports of similar events, FDA, in July of this year, updated their 2008 Public Health Notification and posted a white paper outlining the thinking behind that update. The white paper and the safety communication are on the FDA website.

Additionally, it was decided to convene this Advisory Panel to help FDA plan its path forward for mesh repair for both POP and SUI.

FDA has concerns regarding the safety and effectiveness of surgical mesh for pelvic organ prolapse repair. Because of these concerns, we are proposing a new regulatory strategy for these devices.

During today's meeting you will hear from industry, the general public, and several professional societies regarding mesh for POP repair. Following that, FDA will make its presentation.

You will hear from FDA a summary of the MAUDE data as well

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as the comprehensive review of the published literature for mesh for POP repair. Following the FDA presentation, the Panel will be asked to discuss the material presented to them and the FDA's proposed new regulatory path for these devices.

Again, thanks to all of you for coming and helping us in this Panel and for participating in the discussion.

DR. FALCONE: Thank you, Dr. Lerner, for the comments and for keeping on schedule.

Before we go on, I'd like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

So we're going to move on now to a presentation by Dr. Ritchey, who's going -- I'm sorry, we're going to do Marjorie Shulman, who's going to talk about the FDA reclassification process.

MS. SHULMAN: Hi. Good morning, my name is Marjorie Shulman. I'm Acting Director of the Premarket Notification Staff. This morning I'm just going to give an overview of device classification and reclassification procedures.

There's two types of devices, pre-amendment versus post-amendment devices, and the Federal Food, Drug and Cosmetic Act divided these devices into two groups: pre-amendment devices or ones that are out

on the market prior to May 28th, 1976, and post-amendment devices are ones that have been found substantially equivalent to pre-amendment devices or reclassified or have undergone the automatic Class III designation, the de novo process.

So the only difference between the two terms, pre-amendment and post-amendment, it just depends upon when the devices were introduced into interstate commerce for commercial distribution.

So classification of pre-amendment devices are classified after the Food and Drug Administration has received a recommendation from a device classification panel, published the recommendation for the comment, along with the proposed regulation classifying the device, and then after reviewing the comments, publishes a final regulation classifying the device.

Reclassification of pre-amendment devices. The Food and Drug Administration may reclassify a pre-amendment device in a proceeding that parallels the initial classification proceeding and based upon new information respecting a device either on FDA's own initiative or upon the petition of a interested person.

For classification of post-amendment devices, they're automatically classified into Class III and remain in Class III and require premarket approval, unless and until the device is reclassified into Class I or Class II, the Food and Drug Administration issues a substantial equivalent determination, or the device is classified into Class I or II by the evaluation of

automatic Class III designation, also known as de novo.

Reclassification of post-amendment devices can be initiated either by FDA or industry, and FDA, for good cause shown, may refer the petition to a panel for a recommendation.

There are three classes of device, Class I, II, and III. Class I is general controls, Class II, general and special controls, and Class III, premarket approval. A device should be placed in the lowest class whose level of control will provide reasonable assurance of safety and effectiveness.

Class I is for devices for which any combination of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device.

General controls include prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facilities, listing of the device types, record keeping, repair, replacement and refund, and banned devices.

Class II is for devices that cannot be classified into Class I because the general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls to provide such assurance.

Special controls include performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, tracking requirements, and recommendations and other appropriate actions.

Class III is for devices for which insufficient information exists to determine that the general controls of Class I and the special controls of Class II are sufficient to provide reasonable assurance of safety and effectiveness of such devices, and the devices are life sustaining and/or life supporting, substantial importance in preventing impairment of human health, or present an unreasonable risk of illness or injury.

We also have a part for restricted devices, and under the provision of Section 520(e) of the Federal Food, Drug and Cosmetic Act, the Food and Drug Administration is authorized, by regulation, to restrict the sale, distribution, or use of a device because of its potentiality for harmful effects or the collateral measures necessary to its use; FDA determines there cannot otherwise be reasonable assurance of its safety and effectiveness.

A restricted device can only be sold, distributed, or used either upon the oral or written authorization by a licensed practitioner or under such conditions specified by the regulation. If the device is restricted to persons, for use, with specific training or experience in its use by persons for use in certain facilities, FDA must determine that such a restriction is required for the safe and effective use of the device. Devices such as cardiac pacemakers and heart valves require a practitioner's authorization.

Hearing aids are restricted by a regulation that limits their sale to persons who obtained a medical evaluation of their hearing loss by a physician within six months prior to the sale of the hearing aid. The labeling

of hearing aids must provide information on their use and maintenance.

So any questions?

DR. FALCONE: We'll have opportunity this afternoon to ask questions. So just for the sake of time, we'll move on. Thank you very much.

Okay. So we're going to now hear from Dr. Ritchey about the premarket studies.

DR. RITCHEY: Thank you and good morning. I'm going to spend the next few minutes discussing postmarket surveillance studies, or 522s, as we call them.

Under Section 522 of the Food, Drug and Cosmetic Act, FDA has authority to order postmarket surveillance for Class II or Class III medical devices meeting any of four criteria, which will be described shortly.

Data collected via these studies can reveal unforeseen adverse events, the actual rate of anticipated adverse events, or other information which is necessary to protect the public health.

The first statutory criterion is that failure of the device would be reasonably likely to have a serious adverse health consequence. To date, this is the most common criterion cited for a 522.

The second criterion is that the device is expected to have significant use in pediatric populations. This is a new provision as of the FDA Amendments Act of 2007, or FDAAA.

The third criterion is that the device is intended to be

implanted in the body for more than a year. This is straightforward and is also, to date, one of the most common criteria cited.

The last statutory criterion is that the device is intended to be a life-supporting device used outside of a user facility, as described on this slide. A couple of examples of this type of device include AEDs and home-use dialysis devices.

While 522s apply to Class II and Class III devices for which at least one of the four criteria are met, that does not mean that a 522 will be issued just because one of the criterion is met. A 522 order may be issued at any time after marketing clearance or approval. As per FDAAA, we can also issue a 522 as a condition of clearance or approval for a device that meets the significant pediatric provision.

The Act authorizes FDA to order prospective postmarket surveillance for a duration of up to 36 months, unless the manufacturer and FDA agree to extend that time frame. For pediatric studies, we can extend the study duration to one that is justified based on the particular scenario. The Act also specifies the regulatory actions that we may take if there is noncompliance on the part of the sponsor.

Failure or refusal to comply with the requirement under Section 522 is a prohibited act and renders the device misbranded. Please note that violations may lead to warning letters and enforcement actions, including seizure of product, injunction, prosecution, and/or civil money

penalties.

FDA may identify device issues that are appropriate for studying in a 522 study at any point during the life cycle of a device. Examples of situations that may raise postmarket questions are listed on this slide.

We may order a postmarket surveillance to confirm the nature, severity, or frequency of suspected problems reported in adverse event reports or in the published literature.

We may order postmarket surveillance to obtain more experience with a change from hospital use to use in the home or other environment or with new patient populations.

We may order postmarket surveillance to address long-term or infrequent safety and effectiveness issues of implantable or other devices for which premarket testing provided only limited information.

And we may order postmarket surveillance to better define the association between problems and devices when unexpected or unexplained serious adverse events occur after a device is marketed, if there is a change in the nature of serious adverse events, or if there is an increase in the frequency of serious adverse events.

We convened pre-522 teams at FDA to discuss numerous elements, with the ultimate goal of making a recommendation as to whether or not a 522 order should be issued to address a public health question.

Some of the elements discussed by the pre-522 team include:

- Are the statutory criteria met?
- What is the public health question?
- What is the public health question based on?
- Is the question sponsor-specific, device-specific, or device type-specific?
- For a device for which a condition of clearance is being considered, can and should the public health question be addressed in the premarket rather than in a postmarket 522 study?
- Is there any other source of data or action, or a combination thereof, that can be used to address the public health question?
- Does another ongoing study address the question?
- What types of study designs should be recommended?
- Or what combination of efforts should be considered to address the question?

An order for postmarket surveillance under Section 522 is issued by the director of the Office of Surveillance and Biometrics at CDRH. The 522 order will identify the premarket submissions involved, the public health questions, the rationale for the 522 order, and study design recommendations to assist companies in preparing the postmarket

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surveillance plan. The sponsor then submits a study plan within 30 days of receipt of the order.

The study plan includes all of the elements as listed on this slide: background, purpose, study objectives and hypotheses, study design and population, sample size, the primary and secondary endpoints, length of follow-up, the description of data collection procedures, a full statistical analysis plan, the data collection forms and informed consent forms, reporting as will be happening in interim and final reports, and then the study milestones and timeline.

Upon receipt, FDA evaluates the proposed study plans for administrative completeness and whether the plan will result in collection of useful data that will answer the surveillance questions. Failure to have an approved postmarket surveillance plan or failure to conduct postmarket surveillance in accordance with the approved plan constitutes failure to comply with Section 522 of the Act.

Interim and final reporting is part of the study plan, and a typical schedule for that is an interim report every six months for the first two years and annually thereafter.

After approval of the study plan, the contents of the original submission and any amendments, supplements, and these interim and final reports may be disclosed in accordance with the Freedom of Information Act.

In addition, the status of ongoing and completed studies is

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available on the public 522 webpage at the website listed here.

And this concludes our opening and regulatory process remarks. We look forward to our discussion today. Thank you.

DR. FALCONE: Thank you, Dr. Ritchey.

In fact, we do have a few minutes before we go to the public hearing. We don't? All right, I guess we don't.

(Laughter.)

DR. FALCONE: All right, onward, ho. But the Panel will have lots of opportunity to ask the presenters from the FDA questions during this afternoon's session, so don't worry about that opportunity.

Okay, I'll rescind my rescinded comment. You can go ahead and ask a question, Dr. Gadaleta.

DR. GADALETA: Thank you. Sergio Gadaleta from Becton Dickinson. I had a question for Ms. Shulman.

So in your description of special controls for Class II devices, would clinical studies be an example of a special control that would allow you guys to demonstrate reasonable assurance of safety and effectiveness?

MS. SHULMAN: Yes, clinical studies can be a special control.

DR. GADALETA: Thank you.

DR. FALCONE: Okay. Anything further? No?

(No response.)

DR. FALCONE: Okay. So now we're going to proceed with the

Open Public Hearing portion of the meeting.

And public attendees are given an opportunity to address the panel to present data, information, or views relevant to the meeting agenda. However, Ms. Craig will now read the Open Public Hearing Disclosure Process Statement before we can move on.

MS. CRAIG: You made that sound so powerful.

(Laughter.)

MS. CRAIG: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from

speaking.

I'm going to pass it back over to Dr. Falcone.

DR. FALCONE: Okay. So we're going to go on to the public speakers today. But I do want to go over some logistics.

You will have five minutes for your remarks. When you begin to speak, the green light will appear. Please, again, you know, present yourself and state clearly your names for purposes of the recording. Please do not bring any items with you to the podium, unless it's your presentations. And you will have a yellow light which will appear when you have one minute remaining. At the end of the five minutes, the red light will appear and the microphone will be switched off.

Okay. So the speakers will be grouped into groups of five, and at the end of each group, the Panel will be given five minutes to ask questions of the public presenters in each group. If recognized by the Chair, please approach the podium to answer questions that the Panel will give.

And I will make sure to remind the Panel to state your name again when you're asking a question.

And one more time, I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

So the first speaker will be Brendel France de Bravo. And I will

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apologize up front, by the way, if I ruin your name in any way possible. But when you state your name when you come up, I'll stand corrected.

Well, no one's going to correct me, I guess. Okay. The original person on the list was actually Dr. Zuckerman. Is she here? No Dr. Zuckerman and Ms. de Bravo. Okay. So we'll move on.

How about Kate Ryan? Okay, Ms. Ryan, thank you.

MS. RYAN: Good morning. My name is Kate Ryan. I'm speaking today on behalf of the National Women's Health Network, which is a nonprofit advocacy organization. We work to improve the health of all women. We bring the voices of women consumers to policy and regulatory decision making bodies. We're supported by our members and do not take financial contributions from drug companies, medical device manufacturers, insurance companies, or any other entity with a financial stake in women's health decision making.

First, we're pleased the FDA has convened this Advisory Panel to assess the safety and effectiveness of surgical mesh, in particular, for the repair of pelvic organ prolapse and stress urinary incontinence. The network strongly supports higher scientific standards of approval and more robust postmarket surveillance of implanted devices. This is particularly necessary for urogynecologic surgical mesh products, which have a history of recalls due to severe and permanent side effects.

After reviewing the currently available data on the safety and

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effectiveness of surgical mesh for the repair of POP, the network believes the risks associated with this use of vaginal mesh outweigh the demonstrated clinical benefit. The rate and severity of adverse events reported to the FDA, in conjunction with the FDA's lit review, indicate that vaginal placement of these devices is extremely risky, especially considering there isn't evidence that POP repair using mesh is more effective than traditional repair.

It's important to note, however, that many of the basic questions about the safety and effectiveness of these devices remain unanswered because no premarket clinical data was required.

The network fully supports the FDA's recommendations to reclassify surgical mesh for POP repair from Class II to Class III.

Vaginal mesh is a permanent implant and failure of the device can and has led to serious adverse health consequences. Premarket clinical trials independently assessing safety and effectiveness should absolutely have been required before this device was marketed to and used by hundreds of thousands of women. Women and their healthcare providers deserve to have evidence of safety and effectiveness so a woman can make an informed decision about her treatment options.

We agree that premarket prospective, randomized controlled trials are needed to demonstrate safety and efficacy of vaginal mesh, and we support the FDA's recommendation that premarket studies compare mesh to a non-mesh control arm. Without this comparison, we feel it will be difficult

for doctors to give a woman the information she needs about the risks and benefits of the different options available to her.

To further support both the development of science-based clinical recommendations and a woman's informed decision making, we recommend that studies examine, in particular, whether mesh is safer in certain populations and whether the severity of the condition has an impact on the effectiveness of mesh.

Regarding the duration of the study, we strongly urge the FDA to ask for more than three years of evaluation. Surgical mesh is a permanent implant intended for much longer than three years of use. FDA should require long-term follow-up so that women with POP can factor long-term health outcomes into their treatment decision.

As the FDA noted, the vast majority of the studies reviewed had only 12 months of follow-up and only a handful of studies extended beyond two years. Yet even this limited data showed that the problems are still emerging at this point. Therefore, we recommend that premarket studies evaluate women for two years in the FDA-required postmarket studies that have follow-up necessary to provide women and their healthcare providers with adequate long-term information.

In conclusion, given the lack of rigorous scientific evidence supporting the safety and effectiveness of vaginal mesh, we strongly urge the Panel to recommend that the FDA recall current vaginal mesh used for POP

repair. Products currently on the market should not continue to be marketed until they have been evaluated via the PMA process. Providing evidence of safety and effectiveness should not be limited only to new products, when it is current products that result in dangerous complications, which the FDA has acknowledged can be life-altering and are not rare.

We know that women suffering with POP want options, but they deserve options that are safe and effective, not ones that result in worse health outcomes.

We urge the Panel to recommend that all vaginal mesh, both current and future, be held to a Class III standard. Manufacturers should submit a PMA application to provide safety and effectiveness -- scientific evidence of safety and effectiveness before being able to market their products to women. Thank you.

DR. FALCONE: Thank you. That was very good. On time.

Okay. So since I'm told that the list -- the next speaker is unclear, but I think he's coming up right now. I'll take the next speaker.

DR. MURPHY: Yeah, I'd like to ask that I get Dr. Zuckerman's time.

UNIDENTIFIED SPEAKER: Press the button on the microphone.

DR. FALCONE: Yeah, speak in the mike and please state your name.

DR. MURPHY: Okay. Can you hear me now?

DR. FALCONE: Yes.

DR. MURPHY: My name is Miles Murphy. I'm a urogynecologist and a board-certified OB-GYN. I have served as a consultant and as a researcher for two medical device companies, but in no way was this trip here paid for by anybody in industry. I'm here of my own accord. And I represent a group of pelvic surgeons that have drafted a paper that hopefully you all received, and in no way was that drafting of the manuscript supported by industry.

I'm going to be brief and get right to the point. We know that traditional native tissue repairs have a high rate of failure. Sixty percent of the failures are at the same site as the surgery occurred. The anterior compartment of the cystocele is the most common spot for recurrence, and reoperation for this probably underestimates the problem.

Why is this? Well, we know that, in women with prolapse, the connective tissues are inherently weaker than most women without prolapse and therefore often need augmentation for the repairs.

This is demonstrated by the American College of OB-GYN's publication in 2009, looking at abdominal repair, looking at native tissues versus mesh for prolapse, stating that mesh was more effective at reducing recurrence; also the same with incontinence.

As you all know, there are risks, though, with surgery utilizing mesh, and the FDA has listed these. I would say to you, though, that the only

risk that is unique to the use of using mesh is of mesh erosion. The other risks are there whether you do native tissue repairs or not.

And this has been demonstrated now in multiple randomized trials. And I obviously don't have time to go through these, but almost all of these trials showed decreased recurrence with the use of mesh. The last one down there, the Altman study just published in *The New England Journal of Medicine*, not only shows anatomic decrease of recurrence, but also a decreased subjective report, by the patient, of recurrence.

This paper that we drafted was done after the update was released in July. It describes our interpretation of the literature, and it was cosigned by over 600 pelvic surgeons. I have the list of those names and their e-mails if you'd like it.

This concept that only anatomic cures matter is really new within the last two years, and the studies weren't really designed to take this into account. And I think the FDA should be very careful in not basing policy on potential Type II errors. There was only one study in all of those listed that was actually powered to look at subjective outcomes. And, in fact, it clearly showed a difference in subjective outcomes with the mesh.

Our paper and my presentation is not to imply that native tissue repairs are bad in any way. I do it all the time. I did one yesterday. But it's not always the right choice because pelvic organ prolapse in one patient is not the same as in another, necessarily, and they need to be

treated differently at times.

All procedures for prolapse have complications. They're just not monitored by the FDA.

These are two papers. The first is a landmark study on the uterosacral vault suspension, which, in my opinion, is one of the gold standard native tissue repairs. It's a great procedure. Again, I did one yesterday. But in the initial paper describing it, they had 11 percent ureteral injury rate.

When you look at abdominal procedures for prolapse, this paper on the right shows a 1-in-20 risk of gastrointestinal morbidity following surgery for that.

And I know that there's a lot of talk about the fact that vaginal mesh is so much worse than abdominal mesh, but I would just -- and again, I love the abdominal sacrocolpopexy, but the data on it is not as robust as is implied in the update. The only good recent randomized trial of abdominal mesh versus native tissue repairs showed the same results and no difference in objective or subjective results. And I know there's a lot of talk about how there's long-term data on abdominal mesh, but this is one of the papers. There's a 17 percent follow-up, and half of those were failures.

DR. FALCONE: You're almost done, right?

DR. MURPHY: Okay. Yes, I am. Two more seconds.

There's nothing wrong with macroporous monofilament

polypropylene mesh. The update sends the wrong message to patients and causes a lot of unnecessary fear. We need mesh to help our patients.

If I took the mesh out of a mesh kit and used a needle driver or a robot to put it in abdominally, I'd be doing the gold standard procedure for prolapse. The deaths in the MAUDE --

DR. FALCONE: You know what that means, right?

(Laughter.)

DR. FALCONE: Thank you very much.

Okay. Well, let's move on to the next speaker. And if you can identify yourself, if possible. Do you know who the next speaker is?

MS. MULLER: I'm Nancy Muller.

DR. FALCONE: Yeah. Come on up. There's no Bruce around, right? Okay.

MS. MULLER: Okay. Well, I'll just get started.

Thank you for your time and attention. In its field, the National Association For Continence is one of the world's oldest, largest, and most prolific in public education and patient advocacy. Our website receives over 35,000 visitors monthly, and we're routinely sought for advice and commentary by the media. No portion of my time or travel for this hearing has been covered by a company. Expenses are paid for by NAFC.

I represent women at risk of stress urinary incontinence, or SUI, and/or prolapse. I disclose that, in 2010, total funding from device

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companies marketing mesh products for incontinence and prolapse represented 27 percent of our total program expense budget, one-third of which was used for outreach to Spanish-speaking farm workers, migrant farm workers.

I'm here to present a position statement of NAFC's board -- those are national thought leaders in the field and patient representatives -- not surgery cases gone wrong, nor speculate on how the body responds to mesh implants that might vary depending on surgeon skill, clinical circumstances, medical history of the patient or her postoperative care.

The numbers of those affected by either diagnosis overlap. Barriers of stigma, lack of health insurance, our fragmented healthcare delivery system, and poor health literacy impede health seeking. Most important is the fact that prevalence is widespread and probably rising; the FDA's July communication announcing this hearing's agenda as one covering both mesh implants for SUI and POP, and therefore my remarks pertain to both.

The inability of SUI surgery to promise lasting results begs for continued research by expert clinicians and continued innovation by industry. There is sufficient research and experience with mid-urethral slings of over 15 years in the U.S. and more in Europe with mesh product, unlike the vaginal mesh kits for prolapse. But there's no justification for withdrawing mesh used for slings in treating SUI, leaving women without long-term success rates

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exceeding 30 percent with only tissue-to-tissue repair options.

Limited research suggests higher durability for mesh for prolapse, but higher complications involving mesh. Still, we're not at a point in our collective knowledge about patient selection or surgical techniques and treatment to arbitrarily remove all mesh from the market with a simple statement that prolapse can be treated successfully without mesh.

Accordingly, NAFC's position statement on this matter is as follows.

First, evidence-based healthcare must be applied in the use of surgical mesh for prolapse and stress urinary incontinence. The complete definition includes data from high-quality research, the judgment of experienced providers, and the needs of patients.

Secondly, medical societies must take responsibility for establishing standardized protocols for surgery and insist on consistent specialized training of all doctors.

Third, we must collectively elevate health literacy concerning these conditions to facilitate shared decision making. Informed consent should be conversational and well in advance of the joint decision reached between a patient and her doctor regarding surgical intervention.

Fourth, innovation to advance knowledge, science, and treatment modalities must be continually encouraged and rewarded in our country. NAFC does not support the arbitrary withdrawal of all mesh

products from the marketplace based on outcomes and research to date.

Fifth, for protection of patient safety, a long-term registry for analyzing all outcomes from intervention is essential in determining a science-based means of patient selection and for generating more generalizable data.

And, lastly, open communication among us all is best in serving patient safety and access to sound innovation, for it's through continuous discovery we can improve the lives of all Americans to offer hope for a better tomorrow.

Thanks very much.

DR. FALCONE: Thank you for keeping to the schedule, too.

Thank you very much.

So we're actually going to go to Brendel France de Bravo, who has arrived. Thank you very much.

MS. de BRAVO: Good morning. I'm Brendel France de Bravo, and I'm pleased to have the opportunity to speak on behalf of the National Research Center for Women and Families. Our center does not accept funding from device companies, and I have no conflict of interest.

Our nonprofit center is focused on reviewing and synthesizing research on a range of health issues, and providing objective, comprehensive, and understandable information to patients and providers. My perspective is as someone trained in public health at Columbia University.

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In addition, I've heard firsthand from women who have suffered painful and debilitating complications from surgical mesh. We share the FDA's concern that serious adverse events are not rare and that there is no conclusive evidence that transvaginally placed mesh in POP repair provides clinical benefit compared to surgical repair of POP without using mesh. And the mesh itself can cause terrible complications that are often impossible to repair.

There's no doubt that the 1,503 adverse reports, including several deaths that were associated with POP repairs, are the tip of the iceberg. These mesh problems were not a secret. They were reported in the medical literature, including 110 studies of more than 11,000 women, which found that 10 percent of women undergoing transvaginal POP repair with mesh experienced mesh erosion within 12 months. One has to assume that the erosion statistics would've been even greater with longer follow-up.

Even if there were some patients whose POP was successfully repaired through surgery with mesh, that is not a good reason to continue to review mesh for POP under the 510(k) process. We agree with the FDA that POP mesh should be reclassified as Class III. The PMA process is needed for each specific device to determine whether the benefits outweigh the risks and, if so, for which women.

In retrospect, surgical mesh would not have been allowed to stay on the market with the very limited regulatory protections of the 510(k)

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process. Patients have been severely harmed as a result, both in terms of their health and their quality of life.

In addition, the financial costs to the patient and to our medical system have been substantial, with many women requiring multiple additional surgeries and yet never fully recovering.

It's unusual for the FDA to change its regulatory requirements for a medical device. So when the FDA admits that the 510(k) process is not adequate for surgical mesh for POP procedures, it is because the research literature and the postmarket surveillance are clearly indicating a very serious problem.

I urge you to support the FDA's plan to reclassify mesh to Class III. We also believe that the best comparison for clinical trials would be with a non-mesh surgical control arm.

Now, the FDA says reclassification will take a long time. So what can you do to protect patients in the meanwhile?

1. Recommend that the FDA make this reclassification retroactive to include all POP meshes currently on the market.
2. Meanwhile, to protect the health of patients and improve public health, POP mesh should be recalled based on current evidence that the risks outweigh the benefits.

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3. Companies whose mesh has been recalled may not want to wait several years to submit a PMA based on prospective data. Therefore, the FDA should encourage companies with POP mesh already on the market to submit well-designed retrospective studies of women who have had POP surgery at least three years ago, comparing the outcome for women whose surgery included mesh with those whose surgery did not include mesh. Now, this design would provide better long-term data in a shorter period of time than a prospective study.
4. During the period when these new regulations are being put in place, the FDA should send a "Dear Doctor" letter to all physicians and draft new labels for all surgical mesh, stating that "the safety and effectiveness of this vaginal mesh for POP repair has not been established and is currently under study."

DR. FALCONE: You have a minute left.

MS. de BRAVO: Thank you.

DR. FALCONE: Thanks.

MS. de BRAVO: In conclusion, I assume that mesh companies will complain that an immediate recall and requirement for clinical trials

places an unfair burden on them in an already difficult economy. We're sympathetic. But the FDA's focus has to be, has to be on public health. Patients are being seriously harmed by these surgical mesh kits because companies have been selling them without their ever having been properly tested.

I thank you, and I hope you'll take these thoughts into consideration.

DR. FALCONE: Thank you. Is Lana Keeton here?

MS. KEETON: Yes, I am. Good morning.

DR. FALCONE: Okay, thank you very much. Good morning. So you have five minutes.

MS. KEETON: Thank you.

DR. FALCONE: Okay.

MS. KEETON: Good morning. My name is Lana Keeton. I am the president and founder of Truth in Medicine, a patient advocacy organization helping patients that have been harmed by synthetic surgical mesh. I am also a medical device expert with over 5,000 hours of research into synthetic surgical mesh used for hernia repair, bladder suspension, and for pelvic organ prolapse.

My experience as a steel broker for over 30 years fueled my research into the physical and chemical properties of polymers used for synthetic mesh, and I have a unique perspective. It is really hard for me to

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stand here today in front of a room where many are hellbent on implanting garbage into humans.

While the rest of the world is going green, doctors and device makers are going dark. Doctors and device makers should follow the example of the well-known company Waste Management and dump synthetic surgical mesh, a petroleum waste byproduct, a recycled garbage, into the city dump.

Medical advisors and consultants, very well compensated, rally around surgical mesh like they're saving mankind. Mesh is not a polio vaccine. Mesh is not a cure for whooping cough. Mesh does not cure anything. It is a petroleum-based waste byproduct from the gasoline refining process.

I ask you, if they won't put it in a car, why are surgeons implanting it into humans? I ask the FDA, the CDRH, and this Panel to make a wise decision.

There is a group of a pelvic organ prolapse surgeons who are outraged; their toolkit has been raided. They submitted a paper to the FDA, calling for the FDA to involve itself in practice of medicine issues. Only they, the surgeons themselves, have the power to change. These surgeons now take the position that their unskilled counterparts do not properly implant synthetic mesh, causing a large number of complications.

I strongly feel these doctors should take a closer look at the bad tool. Have they taken into consideration, perhaps, the design is flawed?

I guess not, since they are defending the tools in their toolkit as opposed to the thousands and thousands of injured patients. And let's not forget the dead ones either.

We probably will not be having -- today of doctors who implant mesh actually research the polymers themselves, instead depending on the company who makes it and the sales rep, or if they actually had mesh implanted in themselves. Doctors look at the inflammatory reaction of the body to synthetic meshes and the ensuing disease process based on their medical training. They do not look at the chemicals that are causing the disease process.

So instead of better patient selection, better physician training, or better informed consent recommended by this group of surgeons, let's stop placing ticking time bombs of petroleum waste byproducts into women for POP and SUI and into men and women for hernias.

Respectfully -- and this is not -- okay -- the FDA's OB-GYN Advisory Panel, which is scheduled to make these recommendations here today on the use of synthetic surgical meshes, is unqualified for its intended purpose, without a chemical textile engineer, a microbiologist, a human tissue engineer, and other experts on synthetic polymers, such as polypropylene and polyethylene terephthalate used in synthetic surgical mesh. And in the manufacture of medical textiles, no valid conclusions will be drawn.

I am calling for all synthetic meshes to become controlled substances requiring a surgeon to write a prescription. Implanting surgeons should manage and/or pay for all of the mesh complications, such as surgical mesh removal, pain management, or other therapies necessary to manage the complications, for at least five years.

All synthetic meshes should be considered a drug under the FDA's premarket approval process. The chemical reaction of these drugs, in concert with the chemical makeup of synthetic mesh implanted in the body, is a biological disaster.

DR. FALCONE: You have a minute left. Thank you.

MS. KEETON: Thank you. Synthetic meshes have to be recalled, reclassified, and tested as a drug for all chemical additives used in the textile manufacturing process, including antimicrobials, surfactants, dyes, and other chemicals hazardous to human health. Thank you so much.

DR. FALCONE: Thank you. Is Bruce Rosenberg here? No? Okay.

So that, I think, are five presenters, and we've decided that we would have the Panel, if they wish, to ask questions of the five presenters. I see three. Where are the other two? Oh, there, okay. All right.

So if the Panel members have some questions for the speakers that have just presented, please identify yourself and then ask the question, and perhaps the speaker can come up to the podium and then identify

themselves again so that we can record the response.

Okay, we recognize Dr. Flesh.

DR. FLESH: I have a question for Dr. Murphy. You said that more than 600 pelvic organ prolapse surgeons signed your document.

DR. MURPHY: Yes.

DR. FALCONE: Can you go up to the -- state your name first.

DR. MURPHY: Hi. Miles Murphy. Yes, that's correct.

DR. FLESH: Why do you think these 600 surgeons, who presumably do these surgeries all the time, could come to such different conclusions than the women who just spoke?

DR. MURPHY: I mean, I think that's an excellent question, and I don't mean to downgrade or denigrate anybody who's had a bad experience with mesh. There's no doubt that any surgical procedure for prolapse can have poor outcomes.

But as people who have dedicated their lives to not simply saying, well, just live with it or, you know, do a procedure that maybe isn't the best chance that they have for a cure, we feel that the data out there, while it's limited, is pretty clear in showing that there is a difference.

And, you know, this fact that you're not going to get subjective -- that we haven't seen a lot of subjective differences is really a flaw of the studies that have been conducted, more so than a fact that those differences don't exist. And I simply feel that that needs to be looked at from both sides

of the coin.

DR. FALCONE: Thank you.

DR. MURPHY: Thank you.

DR. FALCONE: Dr. Mattison.

DR. MATTISON: Also for Miles Murphy.

DR. FALCONE: And state your name again.

DR. MATTISON: You mentioned that one thing that determines outcome is the strength of the connective tissue. Can you comment on pre-surgical characterization of connective tissue strength in patients?

DR. MURPHY: Yeah. Miles Murphy again.

You know, unfortunately, we don't have a lot of great data to say, okay, let's do a biopsy from the patient to determine whether or not their native tissue is good enough to do a native tissue repair. We often look at things like the type of prolapse, what is the leading edge of the prolapse, how severe it is, whether it's well beyond the introitus or within. And one of the main things I use as a criteria is whether or not the rugaetion of the vaginal wall is intact or not.

If you saw that picture I showed, the more mild prolapse, the patient still had good, well-rugaeted vaginal wall that, to me, meant that if I could just get her apex supported with some sutures, she'd have a good repair; whereas, the other one was sort of blown-out, shiny, smooth. In a patient like that, the only way I think I could get a durable repair that would

really work using just native tissues would either -- to do a colpopoiesis, where she would lose coital function, or to drastically trim away a lot of the damaged poor tissue and re-support it best as I could, which would most likely leave her with a foreshortened vagina, which is what we see a lot of.

I had a much more graphic picture that I could've shown, but I didn't want to, of a patient who had total -- her small bowel had completely avulsed through a vagina that had had three anterior and posterior repairs. And that's what happens if you just do native tissue repairs after native tissue repairs, is that the tissue gets weaker and weaker.

So that would be -- I hope I sort of addressed your question there.

DR. FALCONE: We have one more question, and Dr. Rogers put up her hand first.

DR. ROGERS: This is also for Dr. Murphy. Could you please comment how common vaginal evisceration is with native tissue repair? Is that a common occurrence?

DR. MURPHY: Probably not. The problem is things like deaths and pelvic evisceration are so rare that you're not going to find any difference in randomized controlled trials.

DR. FALCONE: Okay, thank you again. Thank you very much, Dr. Murphy.

First of all, the Panel will have opportunity to ask questions this

afternoon as well, to our speakers, the public speakers, but for the purposes of time we're going to move on. And I think, if I'm not -- is Bruce Rosenberg here? Bruce? All right. State your name.

MR. ROSENBERG: It's Bruce Rosenberg. Thank you.

I'm from the National Meshoma Foundation. That's a nonprofit. The National Meshoma Foundation receives calls from both men and women suffering from mesh-related postop complications.

Meshoma is essentially defined as a tumor of mesh. CDRH recognizes meshoma as a complication of mesh, as seen on this MedSense survey. I don't know if you can see it because the print is very small, but I'll define it as I go along.

The CDRH study, the recent study, the Medicare data study, it states that the predicate for mesh for gynecological devices is suture and evolve from hernia mesh.

Let's look at the issue of 510(k) predicate creep using Gynecare Prolift as an example. Notice it shows ULTRAPRO hernia mesh, in 2008, as its predicate. And you may not be able to see it up there, but I'll define it as I go along.

Now, notice that the ULTRAPRO 510(k) lists VYPRO under the hernia mesh as a predicate in 2004 and of a hernia device. Now, notice that VYPRO lists PROLENE mesh as its predicate in 2000. Okay.

We have a statement here on the summary of safety and

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effectiveness under device description. It states this material is non-reactive; this material, when used as suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. And that's a fairly bold claim, and that's why they allow it in the human body.

This is now a package insert from the manufacturer, related to PROLENE, the predicate device, and there's supposed to be something related to, you know, comparison to these materials. It says it elicits a minimum to slight inflammatory reaction which is transient. The mesh remains soft and pliable, and normal wound healing is not noticeably impaired. The material is neither absorbed nor is it subject to degradation or weakening by the action of tissue enzymes.

This is another insert. It says it's inert, virtually inert. And then at the bottom it states -- and I know you can't see it up there, but the mesh is not absorbed nor subject to degradation by tissue -- the action of tissue enzymes. It retains both integrity and strength. This is what the patients and surgeons see.

This is a photograph of mesh placed in the human body. This is what it's supposed to look like. This is a healthy piece of PROLENE, polypropylene. And this next picture is a picture taken by a manufacturer, of what the mesh looked like, according to them, one year later. Now, we don't know how often this happens. It may be a rare event. But we can see that it does happen, and it's significant in some percent of patients. So it needs to

be noted and needs to be more studied.

This is a close-up of that. This is polypropylene implanted in the human body. Is this truly safe? I don't know the answer to that. I'm not a scientist. But I'm here to ask for further study. I think the Medicare data is indicative that more study is needed of Medicare data and insurance carrier data to see what the true outcomes are and the true safety and effectiveness of these devices.

There's some history with this. Remember now, the claim was that it's non-reactive and that it retains its strength indefinitely in clinical use. Now, we've seen that doesn't always happen. I don't know what rate that is. These claims right here -- and this here, I'm having trouble seeing it. One moment. There's some history in 1975. Now, the predicate to PROLENE was Marlex.

In 1975, the Texas Medical Board, before the device amendment, stated that they were having some problems with Marlex, which is polypropylene, as stated in this document, due to rejection phenomenon and that one lady spit Marlex fragments for nine years before clearing up. It's very difficult to get out.

We have some more history. In 1975, the analysis shows that degradation begins to occur after only a few days.

This study is from, I think, 2008, University of Missouri. The CDRH is familiar with the researcher in the study. In conclusion, the hernia

mesh material will be degraded and damaged while in vivo. They're talking about polypropylene and PTFE. And I'm saying a hernia.

DR. FALCONE: You have a minute left, okay?

MR. ROSENBERG: Okay. And I'm saying hernia, but as we see in the 510(k), the manufacturers are asking us to accept that, as predicate devices, hernia devices, polypropylene, that there's similarity enough. The material should be safe for implantation.

This is a study by Klinge and Klosterhalfen and Schumpelick. These are major researchers for industry. 1999. Chronic inflammatory tissue reaction, even after years. In conclusion, inflammation around anaplastic materials used to repair defects in the abdominal wall persists for many years. So we cannot control the reaction, and there's something to be said about that. We can't tell what the outcome is going to be for all patients. There needs to be better patient identification and matching of these devices.

1998. The same researchers. Fifty percent reported, over a decade ago, with missed feelings and --

DR. FALCONE: Thank you very much. So we're going to move on now to Dr. Myers. Dr. Myers. Again, you have five minutes, and state your name for us, please, and who you represent.

DR. MYERS: Good morning. I am Dr. Deborah Myers. I am president of the American Urogynecologic Society. I have no financial conflicts with industry. My travel to this meeting has been supported by my

society. I'm going to be presenting our comments on the use of transvaginal mesh in prolapse, which have been taken from our detailed written submission.

The American Urogynecologic Society was formed in 1979. We are a nonprofit organization comprised of 1400 members of physicians and allied health professionals. We are the largest professional society representing female pelvic medicine and reconstructive surgery. The society is dedicated to treating pelvic floor disorders in women, which includes prolapse, and our society promotes the highest quality patient care through excellence in education, research, and advocacy.

AUGS does not support the blanket withdrawal of currently available transvaginal mesh products from the market. It is important that the FDA and the Advisory Panel here clearly distinguish synthetic mesh used for stress urinary incontinence from that used for transvaginal repair of prolapse.

At this time AUGS does not support the routine use of transvaginal mesh for the repair of prolapse. We do recognize, however, that there may be circumstances when the placement of transvaginal mesh is beneficial and appropriate. This is a decision making process that occurs between the patient and surgeon. Many reconstructive surgeons view transvaginal mesh as an important option in their toolbox.

Given the potential risks, AUGS suggests future placement of

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transvaginal mesh for prolapse repair should be judicious and be performed only by surgeons who have extensive training, education, who practice in high volumes of these procedures, and are able to track short and long-term outcomes, both objective and subjective.

AUGS recommends a comprehensive informed consent process as already outlined by the FDA.

AUGS firmly believes that appropriate training and education of surgeons who place transvaginal mesh for prolapse repair is essential. Our society plans to develop and make publicly available education and training recommendations to help guide hospitals in their privilege and processes for the use of transvaginal mesh in prolapse surgery.

AUGS recommends that the FDA invoke its power under Section 522 of the Act to require postmarket surveillance for existing and future transvaginal mesh devices for prolapse repair. Mandatory compliance with a postmarket registry is necessary to provide an accurate estimate of both benefits and harms, getting the numerator and the denominator.

AUGS would support a postmarket registry to better define the long-term risks of these devices. Until such a registry is created, the society encourages all surgeons to track their outcomes so that information is available to credentialing committees and the insurers.

AUGS supports the requirement of premarket notifications or premarket approval applications for transvaginal mesh for new prolapse

mesh devices or for significant modifications of existing devices. Should the FDA determine that Class II with special controls is the best mechanism to require such testing, our society is available to help the FDA develop these special controls.

Premarket clinical trials need to be well-designed, prospective cohort studies that assess clinically relevant functional, quality of life, anatomic outcomes as well as an assessment of adverse events; a minimum of one year follow-up prior to market clearance of approval; need to have an additional two to four years of patient follow-up. Mandatory FDA reporting of results following the device clearance are needed. Randomized controlled trials may be appropriate in certain cases, but may not be the primary study design for approval.

Our society also supports the --

DR. FALCONE: You have one minute left, okay?

DR. MYERS: -- upcoming comments of the Society of Urodynamics and Female Urology, and supporting the comments also of the Society of Gynecologic Surgeons.

I think our ultimate goals here are to promote safe and effective care for women who have prolapse, to encourage innovation while maintaining patient safety, and to maintain a broad range of treatment options to meet the varying needs of our patients with these problems.

Thank you.

DR. FALCONE: Thank you very much.

So I think, Richard Reid. Mr. Reid. Please state your name.

DR. REID: Sorry.

DR. FALCONE: Okay.

DR. REID: I can't see without the glasses.

Richard Reid. Sydney. Minimal conflict. Paid my own way. I want to look at, briefly, some universally applicable biomechanical principles. What is prolapse? What might biomaterials offer? And where I think that the trocar-driven meshes go wrong. And I'm going to look at this in overview. Anatomic, in real time, images can be seen on my website to support what I'm saying, and also I believe there's data in the syllabus.

Firstly, anatomically, the pelvic floor sits at the bottom of the abdominal cavity, and every cavity needs a floor. Unfortunately, there's a hole in the bucket here, creating the largest hernia portal in the body, namely, the levator hiatus, which things can slip through.

Nature, of course, knew this and has provided an interactive closure mechanism consisting of endopelvic fascia and pelvic floor muscles. The pelvic organs are suspended to the axial skeleton, as everything is, by fibroelastic tissue. This connective tissue is organized somewhat like a flag at half-mast on a flagpole. At front, the anterior DeLancey Level II represents the blood hammock. At back, DeLancey Level I and posterior DeLancey Level II form a strong suspensory area called the vaginal suspensory axis, that is,

the suspension of the vagina.

Now, this is fibroelastic tissue, not a ligament. It can absorb short-term forces, but it will fail under load. And, in fact, the main purpose of the endopelvic fascia, as DeLancey has told us, is to keep the organs in the proper place above the levator plate.

The pelvic floor muscles themselves are adaptive for chronic load-bearing, and they work in two ways. Firstly, the anterior part, which is a sling muscle, basically narrows the hiatus, which reduces the portal. And secondly, the posterior part has a trampoline-like action and it deflects the abdominal forces, thus taking the load off the somewhat friable endopelvic fascia.

These things are damaged in childbirth. Muscle damage can widen the levator hiatus, and fascial damage allows the organs to slip forward, where they sit above the hernia portal. And all in all, abdominal forces now, instead of being reflected, tend to organize into an extruding herniating type vector.

The mechanical lesions basically can be categorized as fracture of the flagpole, that is to say, tearing of DeLancey Level I off the paracervical ring or tearing of the rectovaginal septum in the mid-vagina off the paracervical ring. And tearing the flag is the same thing anteriorly. And depending upon whether these tears occur, different kinds of prolapse patterns will evolve; cystocele anteriorly, rectocele in the mid-vagina

posteriorly, and if the tear is high, we can get descensus.

In terms of the posterior compartment, this occurs through an evulsion mechanism, it occurs in the mid-pelvis, and the torn rectovaginal septum is reflected inferiorly, and you can see here, before dissection and after dissection, that classical line that is pretty much present in all recto-enteroceles. And cystocele also. The defect occurs in the mid-pelvis and creates a hernia defect through which something can be pushed.

The second component is collagen fatigue, as has already been discussed. Basically, collagen homeostasis continues in all connective tissues, and the stimulus is Valsalva pressure waves. But when the hammock is de-tensioned, there are no pressure waves and so there is gradual collagen decline. So quite apart from genetic problems, people with chronic prolapse acquire the kind of collagen deficit that Miles showed you with that lack of rugae.

Is there a role, then, for biomaterials? Well, an optimal repair strategy should certainly address the mechanical defects in an anatomically correct way. Anteriorly, we should rebuild the trampoline. Posteriorly, we should rebuild the vaginal suspensory action.

DR. FALCONE: You have one minute left.

DR. REID: But these results can be disappointing, as seen here. Despite my best efforts, I have 30 percent failure rate over 10 years from native tissue repairs.

So it is probably helpful to look at addressing the collagen weakness. And when we look at biomaterials, a surgeon has to work out, is he putting in a suspensory strut or is he replacing the bridging graft?

Neoligaments are important from the viewpoint of tensile strength, but a bridging graft doesn't need to be all that strong. It needs to be non-morbid. And here are my results, as shown in purple, which shows what was achievable with a remodeling biological graft that disappears after three months.

Native tissue repair resolved in 38 months; the biological graft in 20 months. That's a typo. The absolute flattening of the Kaplan-Meier curves at 20 and 38 months mean that both native tissue and xenograft are anatomically curative. Polypropylene mesh --

DR. FALCONE: That means that you're over.

DR. REID: Okay.

DR. FALCONE: Thank you very much.

So we're going to hear from Tom Margolis, if Tom Margolis is here. He's here. Please state your name as well.

DR. MARGOLIS: Tom Margolis, a pelvic surgeon in the Bay Area around California somewhere. I represent only myself, and I came out here on my own dime.

I would like to thank the FDA for inviting me to speak on this serious issue of transvaginal surgical mesh complications. My comments

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pertain only to the transvaginal implantation of synthetic mesh for pelvic organ prolapse and stress incontinence. These comments are based on my knowledge, experience, education and training as a pelvic surgeon, and on observations made during scores of salvage operations I've performed on women who have experienced mesh complications over the last decade.

Transvaginal implantation of synthetic mesh, for any reason, is a surgical theory and technique that defies core surgical doctrines.

In 1982, the CDC adopted the American College of Surgeons' wound classification system that classifies wounds according to the likelihood and degree of wound contamination during surgery. In this system, vaginal surgery is classified as clean-contaminated, carrying a risk of wound infection of 3 to 11 percent, as compared to clean wounds, which carry a risk of infection of 1 to 5 percent.

The vagina is classified as clean-contaminated because normal vaginal flora cannot be surgically cleansed from the operative field. These normal flora include a diverse array of bacteria, including, but not limited to, staph, strep, *Klebsiella*, *Peptococcus*, *Peptostreptococcus*, bacteroides, all of which are found in wound infections.

The implantation of contaminated synthetic mesh through the vagina defies basic surgical tenets because, by definition, it is not performed in a sterile manner. In fact, so-called mesh erosion, the most common mesh complication, is in reality mesh infection with chronic wound breakdown.

Time does not permit me to expound upon the plethora of other complications associated with transvaginal mesh, such as damage to bowel, bladder, and blood vessels, vaginal scarring, dyspareunia, need for multiple repairs, and destroyed personal lives, but the MAUDE database has already started to look at that.

What it's like to remove mesh, from the surgeon's perspective, can perhaps be appreciated by this analogy. Extirpation of vaginal mesh is akin to taking a hammer and chisel and trying to remove the rebar from a sidewalk, while leaving the cement otherwise intact and not damaging the water mains and power lines below. It is difficult, if not impossible, to remove all the mesh and do it safely.

Nearly 20 years ago, FDA Commissioner Kessler wrote, It is not the culture of U.S. medicine to report adverse events to the FDA. He speculated that only one percent of serious adverse events are reported to the FDA, an estimate consistent with a 1986 survey of hospitals by the Government Accountability Office, which found that 99 percent of problems associated with select medical devices had not been reported to the FDA's postmarketing surveillance system. Thus, the recent adverse mesh findings already published by the FDA represent only a small percentage of the total number of women affected.

The counterintuitive surgical technique of vaginal mesh implantation was seemingly invented to accommodate new devices which

made it easier for doctors with less surgical training to operate. These doctors were apparently seen as a target-rich environment for the marketing campaign, which convinced many of them that this inherently risky approach was safe. It's quite possible that some device manufacturers financially incorporated so-called key opinion leader surgeons into their promotional endeavors, which may have further facilitated the publishing and dissemination of misleading and sometimes fabricated clinical data.

On a positive note, there are numerous superior options to the use of synthetic mesh for stress incontinence and prolapse. The MMK or Burch procedure is still the gold standard surgery for stress incontinence, as are the sacrospinous fixation and sacrocolpopexy for vaginal prolapse, vault prolapse.

It is firmly established in the world's literature that when these procedures are combined with traditional repairs, as indicated, their success rates are second to none. Furthermore, with fewer complications than mesh, they are simply the best procedure in the repertoire.

In summary, synthetic mesh for prolapse and stress incontinence produces an unacceptably high and clearly avoidable plethora of life-ruining complications in women, and there are numerous safer surgical alternatives with superior success rates.

I hope the FDA will, through firm action, help save others from the painful experience that thousands of unfortunate women have had to

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suffer through so far. And, again, I'd like to thank the FDA for inviting me to speak on this important issue.

DR. FALCONE: Thank you very much.

Michael Carome. And if I ruined your name, just state it correctly, please.

DR. CAROME: Good morning. My name is Dr. Michael Carome, Deputy Director of Public Citizen's Health Research Group. I'm testifying today on behalf of myself, Dr. Sydney Wolfe, the director of our group, Dr. Daniel Elliott, a urologic surgeon specializing in female urology and pelvic organ prolapse, or POP, at the Mayo Clinic, and Dr. Lewis Wall, Professor of Obstetrics and Gynecology and a Professor of Anthropology at Washington University.

We have no financial conflicts of interest related to the specific products being discussed today. Dr. Elliott is a paid consultant for Coloplast, serving as a resource for physicians trying to learn about the company's male incontinence sling, with an approximate income of \$2,000 per year.

On August 25th, we petitioned the FDA: (1) to immediately ban the marketing of all currently available nonabsorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP because these devices offer no clinically significant benefits in comparison to surgical repairs without mesh and have high rates of serious complications; (2) order all manufacturers of these mesh products to recall them; and (3) require that

any such mesh product that is proposed for marketing in the future be classified as a Class III device and approved for marketing only under a PMA.

In terms of benefits, most women who have POP on pelvic exam are asymptomatic and do not require any treatment. For symptomatic women with POP, the gold treatment is relief of symptoms. Therefore, the assessment of the benefits of surgical procedures for POP repair necessarily must focus on symptom relief rather than anatomic outcomes.

A review of the scientific literature reveals that while transvaginal POP repairs with mesh appear to result in less prolapse being detected on pelvic exam following surgery, in comparison to non-mesh repair procedures, the use of mesh does not provide any better outcomes in terms of relief of symptoms and quality of life measures, which ultimately are the clinically significant indicators for measuring clinical treatment success in this condition.

In terms of safety, on the other hand, a review of the literature demonstrates that use of mesh leads to a high rate of serious complications, many of which require additional surgical intervention and some of which are not amenable to surgical correction and result in permanent and life-altering harm to women. These complications include those listed on this slide.

The FDA, based upon a review of reports submitted to the Agency, concluded that serious complications associated with surgical mesh for repair of POP are not rare.

Overall, in terms of risk/benefit assessment, given the absence of evidence for clinically significant benefits and the overwhelming evidence of very serious harms, use of synthetic surgical mesh products for transvaginal repair of POP is not ethically justified.

The experience with surgical mesh products for transvaginal repair of POP provides a poster child example of the fundamental failure of the 510(k) premarket notification process to protect the public's health and welfare. Multiple mesh products specifically designed for transvaginal POP repair were allowed by the FDA to come onto the U.S. market based on only in vitro animal testing data and a determination of substantial equivalence to an already marketed device.

Despite a complete lack of clinical data demonstrating that invasive mesh devices were reasonably safe and effective for transverse repair of POP, these devices have been heavily promoted by industry and their highly paid physician consultants. As a result, tens of thousands of women have been seriously harmed, many permanently.

One of our co-petitioners, Dr. Elliott, stated the following: As a urologic surgeon specializing in female urology and POP at the Mayo Clinic, I have refused to use any transvaginal mesh kits for POP. But I am in direct daily contact with referral patients who have been previously treated with them. As a result, I'm fully aware of the complications, their management, and their potential lifelong ramifications. The end result is oftentimes

physically and psychologically devastating for the unsuspecting patient.

Our other co-petitioner, Dr. Wall, stated: Once a device has been approved for release into the marketplace by the FDA, device manufacturers will do everything they can to sell as many devices as possible, irrespective of whether or not the use of such devices is truly in the best interest of patients. Under these circumstances, the interests of patients are subordinated to the profit motive and the interests of company shareholders. The IOM, indeed, has recently declared that the current 510(k) premarket notification process for medical devices is fatally flawed.

In conclusion, we endorse the FDA's belated proposal to reclassify nonabsorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP to Class III and require PMA evaluations. But this action alone is insufficient. To properly protect the public health, the FDA also must immediately ban all such mesh products currently available and require manufacturers to recall these dangerous and ineffective devices. A grace period allowing continued marketing of these devices would recklessly endanger women. Further clinical trials with the current devices that have been tested, as requested by the FDA, would be highly unethical.

Thank you for your attention.

DR. FALCONE: Thank you very much.

Before we go, I think we've had five presenters, and therefore,

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if the Panel would like to ask questions of the last five presenters only and the -- but we will have opportunity, if they're around, to ask everyone this afternoon. But for the last five, I recognize Dr. Hillard.

DR. HILLARD: So I have a question of Dr. Myers.

DR. FALCONE: Please state your name again, just so that they can record you.

DR. HILLARD: So one of the things that you called for is asking individual physicians to track their outcomes, and I would like to ask you how realistic, feasible, or likely you believe this to be.

DR. MYERS: I'm Deborah Myers.

In response to the question about physicians voluntarily tracking their particular outcomes, I agree that it would be only a well highly motivated physician who would be able to do such a thing. I think, given the current state, though -- and we're hearing a lot of information pro and against mesh -- that it would be very wise and would behoove somebody to do that.

In light of the fact that not all may, in fact, voluntarily track their outcomes, that is why we have supported the thought of a postmarket registry being mandatory to get this kind of information, to get these outcomes.

DR. FALCONE: Yes, Dr. Coddington.

DR. CODDINGTON: Dr. Myers. Sorry about that. You talked

about designated surgeons performing an increased volume, about practice surgeons.

How would you go about delineating these individuals, since the individuals with board certification in obstetrics and gynecology have for years been able to do pelvic surgery?

DR. MYERS: Deb Myers again.

Responding to the question about high-volume practices, that would be a recommendation for surgeons placing these devices at this time. I look to the other literature that have looked at high-volume practices, in the bariatric literature, and that we have some studies already within our literature that have looked at outcomes for what high volume is, that that would improve results and decrease morbidity and mortality.

What that actual number is, I think, is what you might be asking me. I don't have that number, but that would be something that, I think, our society would be willing to look into. And I think that actually research would be a way to go to find that answer.

DR. FALCONE: Okay, thank you. The next question is --

DR. MYERS: Excuse me. It might also be able to obtain through a registry as well, that, you know, in a registry you would be finding what your numbers are and your result and outcomes.

DR. FALCONE: Okay, thanks. Dr. Chappell has a question for both Tom Margolis and Michael Carome.

DR. CHAPPELL: Thank you. If I may solicit quick answers from both of -- do I need to identify myself?

DR. FALCONE: Yes.

DR. CHAPPELL: Rick Chappell.

In research, I know that when a treatment is considered both high risk and potentially highly effective, then it is initially used as salvage therapy, in this case, mesh devices, TVM, or abdominal surgery implantation, after perhaps failure of native tissue surgery. And I imagine, although I'm not a practitioner, that's also a common strategy in a clinic, that is, you proceed to the riskier intervention that may be a good fix after the less risky one has failed.

What are your opinions on this for both research and for clinical practice, please?

DR. MARGOLIS: Thank you.

DR. FALCONE: State your name.

DR. MARGOLIS: Thank you. Tom Margolis.

I think it's wonderful to consider research, but one must first understand the core biologic principles of the procedure that you're considering. Again, and I don't want to sound redundant, but, you know, basically putting a synthetic -- implanting a synthetic device into the body through a contaminated field is a breach of core surgical rules to begin with. So you would never perform that procedure because of its basic biologic

incompatibility with Mother Nature.

DR. CAROME: Mike Carome, Public Citizen.

I mean, you're proposing that maybe these should be reserved for rescue treatment. But we know, from what we know in the literature, these devices are dangerous and have not been shown to be effective even in rescue therapy. And so there's no evidence that the benefits outweigh the risks. In fact, the evidence shows that the risks outweigh the benefits, and we would oppose reserving their use for even rescue therapy without some new device coming on the market that's been appropriately tested under a PMA. And until that occurs, they shouldn't be used at all.

DR. FALCONE: Thank you very much.

Dr. Fitzgerald has a question.

DR. FITZGERALD: A question for Dr. Myers, please. Dr. Myers, how can we help advise the FDA as they try to weigh putatively decreased reoperation rates, as they try to weigh that against the risks that are unique to the use of mesh? We're comparing two different aspects, perhaps, of operation, trying to compare mesh complications to reoperation rates. How can we help them understand those different risks?

DR. MYERS: This is Deb Myers again.

Are you asking me in terms of a research trial?

DR. FITZGERALD: Just as we try and understand the clinical practice where a patient might be, perhaps, facing an increased reoperation

rate if mesh is not used compared to the risk of mesh being used in a clinical practice.

DR. MYERS: I understand.

DR. FITZGERALD: What do you think?

DR. MYERS: In response, I think one of the outcomes that does need to be looked at and would be done probably through a research trial would be to look at recurrence rate and reoperation rate as opposed to adverse events as well. So it would be through that type of a trial, with that particular outcome, you would be able to get your answer.

At this point in time, many surgeons will use mesh for a recurrence, kind of, as I think someone has already said, as a salvage operation. And our society does not support the routine use of mesh, you know, in all prolapse repair. But without further research and knowledge of what that really is, we are in effect -- you know, it is an opinion.

DR. FALCONE: Dr. Myers, I have one question for you. And you're suggesting randomized clinical trials. What would be your control group?

DR. MYERS: Deb Myers again.

We are actually recommending well-designed prospective cohort studies as one of the primary ways for approval. A randomized controlled trial for approval, we feel, would be difficult for that very reason, is that we don't really have a good, established gold standard control or any

real randomized controlled trials for our current non-mesh traditional repairs. So to determine what that control group would be for a randomized controlled trial of non-mesh versus mesh would be very difficult.

DR. FALCONE: Dr. Brill.

DR. BRILL: Andrew Brill.

A question for you, Deb Myers. Michael Carome just said, from the Public Citizen's group, that their group believes that the FDA should withdraw all present devices from the market until further told. Now, part of AUGS' position is that PMAs should be instituted for any forthcoming devices and/or/if there's a change in design of a present device.

What was the rationale within your organization to not apply these principles to devices presently on the market?

DR. MYERS: For currently existing devices, we have recommended in our statement that we wanted postmarket surveillance. Primarily, we were initially thinking through a registry. After hearing further comments this morning about other types of postmarket surveillance, which can include clinical trials, we do feel that there are some devices out there, products that already have evidence and that could be utilized. There are those who do not, and we would suggest that those devices that do not would need postmarket clinical trials.

DR. FALCONE: Okay, thank you. We're going to move on, but everyone has the potential to this afternoon. Hopefully Dr. Myers will still be

here.

DR. MYERS: I will be.

DR. FALCONE: Okay, great. So we'll ask her then. So we'll just move on so we can finish the public forum.

Okay. So the next person.

DR. ELSER: Hi. Dr. Denise Elser. I'm here representing the American College of Obstetricians and Gynecologists this morning. I'm a urogynecologist practicing in private practice in the Chicago area, and I also have a faculty position at the University of Illinois. I'm a fellow of the American College of OB-GYN. It's the national medical organization representing 56,000 members who provide healthcare for women in this country. I have no conflicts of interest to disclose.

Today I'm here to represent the college's concerns and suggestions regarding safety and effectiveness of transvaginal placement of surgical mesh for pelvic organ prolapse, or POP. There's a few comments on the synthetic slings used for stress incontinence. We've provided you with detailed written testimony, and we'd like to thank you, the FDA, for holding this Advisory Committee meeting and for the opportunity to speak.

The college applauds the FDA's efforts to protect women's health and educate providers and shares its concerns regarding the safety and effectiveness of transvaginal mesh. The college supports the FDA's willingness to reconsider how it clears products.

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The overall message I wish to deliver is that we don't yet know enough about the effects of transvaginally placed mesh for prolapse repair. Large-scale registries are urgently needed so we can understand the number of mesh-augmented repairs that are performed and then know how many are associated with complications. We need to be able to balance the risks and benefits to our patients who undergo surgeries.

The college is very willing to work with the FDA to develop a registry and make this a reality. Then, using the registry data, we can conduct the rigorous trials and long-term follow-up of synthetic mesh and native tissue repair as we move ahead. It seems that additional premarket data on safety and efficacy, as well as the postmarket surveillance, are warranted.

As noted in the FDA's safety communication, the transvaginal placement of surgical mesh has the potential for serious and sometimes permanent complications that alter the quality of life of women undergoing the procedures. Reports to the MAUDE database do give us some estimates of the frequency of complications, but it's still unclear how many women have had the mesh placed. Without that denominator, we can't adequately counsel our patients to understand the outcomes of mesh surgery and to know which factors are associated with these complications.

Low success rates were frequently cited as a reason why -- low success rates of native tissue repair were often cited as why innovations such as vaginal mesh were needed. But success rates based solely on anatomic

outcomes are inadequate. Our patients don't care so much about what their POP-Q measurements are, but whether or not they feel a bulge and are bothered. So newer definitions of success need to include patient satisfaction and quality of life; outcome reporting defined as a return of the bulge or recline to reoperation. Future studies need to include complications, and the total operation rate for a recurrence or for the complication.

While it appears that most patients who had mesh implanted heal well without complications, and native tissue repairs can result in complications and chronic pain, eventually the best method to compare the two is a randomized controlled trial with adequate length of follow-up and blinded assessment of outcome by independent observers. Outcome measures should include quality of life and cost-benefit analysis. And this is not necessarily recommended for premarket.

We urge the FDA to require a rigorous level of evidence in its guidance to understand on the premarket and postmarket surveillance.

Considering that native tissue repair is an option for many women, it makes sense to use vaginal mesh judiciously for vaginal prolapse repairs. Mesh may be best for those considered high risk, in whom the benefit of mesh justifies the risk of complications. For example, women with recurrent prolapse, particularly in the anterior compartment, and those of medical comorbidities that may preclude more invasive and open or laparoscopic procedures may be good candidates for vaginal mesh.

Surgeons placing vaginal mesh must have experience with reconstructive surgical procedures and a thorough understanding of pelvic anatomy. They should undergo training specific to each device, but we recommend against the FDA mandating that this training come from the manufacturer.

Finally, a few words on incontinence. The introduction of synthetic mid-urethral slings has revolutionized the treatment of stress incontinence for women, allowing for minimally invasive surgical treatment in an outpatient setting. We believe these procedures are relatively safe. Attempts to accurately assess success rates and extent in rates of complications is difficult. Without the data we can't assume that new products are equal to or better than existing products in terms of safety and efficacy. We recommend using standardized terminology, as published by the International Urogynecologic Association and International Continence Society, in future reporting.

To summarize, industry and the FDA should work together to develop a registry for surveillance for all current and future mesh implants. The college is very willing to support this effort. Outcome reporting must clearly define success, objectively and subjectively, and must include complication and the total reoperation rate. Rigorous effective trials of native tissue repair and comparing this to vaginal mesh will be required in the future.

Thank you very much. And we support the FDA's efforts to ensure safety for our women with prolapse. Thank you.

DR. FALCONE: Thank you very much.

The next presenter. I think it's Beverly Pennington. Please state your name, and you have five minutes.

MS. PENNINGTON: I'm Beverly Pennington.

DR. FALCONE: Push the button there.

MS. PENNINGTON: I'm sorry. My name is Beverly Pennington, and I have not taken any financial support for my travel expenses. I'm a professional wedding consultant, and I'm a member of Truth in Medicine and a victim of medical mesh. I'm pleased to be here today to request an immediate recall of all synthetic mesh products.

I believe the public is in harm's way from dangerous risk and side effects of all synthetic mesh, especially in light of the absence of any premarket testing. In the beginning I thought, what harm could a tiny piece of mesh do? After all, mesh couldn't talk, it couldn't fly, it wasn't alive, and so what possible harm was there?

But the truth was that mesh can harden, tear on implantation, move around within the body, cause infection, cut like shards of glass, and cause the immune system to go into full battle fighting foreign objects with giant body reactive cells, while sometimes encapsulating the mesh.

If vaginal mesh had been classified appropriately, it would have

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required premarket testing, and I wouldn't be standing before you today.

Shortly after having mesh implanted for third-degree cystocele and rectocele, I had emergency surgery to remove some of the posterior arms of the mesh, what had abscessed bilaterally, and the tape was removed in an emergency setting. Little did I know that I would leave the hospital with open, draining wens for nine-plus weeks trying to heal. I was in a significant amount of pain and along with the embarrassment, I thought with healing -- I thought that healing would never take place.

Then, within a few short months after the surgery, I discovered that I had tissue-tracking granulomas that seemed to travel along the rest of the arms to the vaginal area. There were more doctors, more tests, and a decision was made. It was too dangerous to have the -- to remove the rest of the arms, so just leave it alone and go to a pain doctor.

After extensive research to make sure having a synthetic mesh implanted, instead of just sutures, was safe, I thought I had done my homework and was in the clear. So when I didn't find any warnings from FDA, I felt that it was safe enough for me.

I was provided with a brochure that talked to the answers to all my problems and quality of life. The pictures alone were worth a thousand words, and I too wanted that all-important again quality of life, riding bikes, tennis, swimming, and much more. I felt that if the FDA had approved it, whom I trusted, and the pharmaceutical companies had tested it, then it was

okay.

Synthetic mesh never went through full clinical trials. Instead, it seems they were snuck on the market for use on the unsuspecting public by the Section 510(k). If only I had known that, in 2008, FDA had issued a letter warning medical facilities and professionals of over 1,000 adverse events and complaints from women, ranging from erosion through variant epithelium, bowel, bladder, and blood vessel perforation, which occurs during insertion of transvaginal surgical mesh, discomfort and pain, infection, urinary problems, abscess, and recurrence of prolapse and/or incontinence.

Treatment of various complications of mesh can put patients at an increased risk for blood clots, hemorrhage, blood transfusions, reconstruction, pneumonias, disfigurement, paralysis, chronic pain, drainage of abscesses, hematomas, and in some cases even death.

Here again the importance of clinical trials cannot be stressed enough. How many women and men have to be injured and maimed by synthetic mesh before the FDA pulls it from the market?

As a wedding consultant, I must have every detail perfect for the bride in order for the event to go perfectly. Just one small overlooked detail can mean disaster for a consultant and a bride. One minor mistake can cost me my reputation and put me out of business. So it only makes sense that I would have serious doubts about the 510(k) process and the approval of synthetic mesh, for not taking appropriate measures to keep dangerous

products off the market.

Playing with the lives of the American public is serious, and it is not taken lightly that so many lives have been affected by defective mesh. As a victim of mesh, it is really too late for me to get completely well or rid of it 100 percent. Even the smallest piece of mesh in me becomes like a giant festering splinter trying to inch its way out, causing a body-wide inflammatory process as it tries to rid itself of the mesh. I am seven weeks postop from my fifth surgery, where an enormous amount of mesh was found.

The healing process has slowed down, and it's taking me longer to bounce back. I have suffered greatly from painful bilateral perirectal abscesses again and removal of arms anteriorly and posteriorly, along with obturator nerve damage.

So what can be done to correct defective synthetic mesh? All synthetic mesh should be recalled and banned for sale and use on the American public.

I am thankful for the recent second warning put out by the FDA, and I can honestly tell you that I now have almost everything you have warned us about. As a United States citizen, I can assure you I am overwhelmed by the lack of concern and safety shown to American women. Unless you have walked a day in my shoes, you cannot fully understand my pain and suffering. Thank you.

DR. FALCONE: Thank you very much.

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Can I have the next speaker, please? I think it's Janet Holt.

Please state your name, and you have five minutes, okay?

MS. HOLT: Hi, my name is Janet Holt. I'm an injured patient, and I paid for my own travel today.

On the 17th of August I spent a really great day with my grandson. We were on our way to watch *Mr. Popper's Penguins*. From the back seat he quietly asked me, When you go blind, are you going to be able to get a seeing-eye dog? Out of the mouth of babes. This beautiful seven-year-old boy only has memories of his grandmother being sick. We are ranchers. When animals get sick, they die, and he is afraid.

He doesn't remember, at age two, I had tried to teach him how to play baseball. I love baseball. When he was three I had mesh permanently placed inside my body. He played baseball his first year at age five. By then I was really sick and I only made it to two of his games.

I'm only 54 years old. How could a minimally invasive surgery leave anyone permanently damaged? The mesh shrank 30 percent, it folded in half, it eroded into my vaginal walls twice, and it abscessed at the creases of my leg/groin areas.

In an interview with CBS, Dr. Danby stated, Mesh erosion is mesh peeking through the tissue. As a patient who has had mesh erode twice into her vaginal wall, this remark is insensitive, and shows the disconnect between patients and doctors who use synthetic mesh for the treatment of

POPs and SUIs. It is more like a cigarette burn that leaves the entire vaginal wall red and inflamed, and each step you take rubs the open wound against the other side. It is complete torture.

I have traveled to speak before the IOM, and I have participated in a rally on the dangers of mesh here in D.C. I've traveled to submit a paper at hearing held by the Honorable Senator Herbert H. Kohl, Chairman of Senate Special Committee on Aging. And I spoke at town hall meeting in Dallas held by the CDHR [sic], and I participated in a Capitol Hill briefing sponsored by Truth in Medicine, and I've traveled here to speak to you today.

At this point I have to admit I'm overwhelmed with travel. For God's sakes, I'm the injured patient. At times I have traveled to these hearings and meetings with ice packs between my legs to control unbearable swelling, and I have stood for hours when my body was so inflamed I could not sit. And I've been a wheelchair when I could not walk. All of this from a piece of mesh placed inside my body during a minimally invasive surgery that has left me permanently damaged.

Why is it my job to tell you about a piece of mesh cleared through the 510(k) process? Where were the clinical trials? Doctors should be standing here telling you about the harm it has caused their patients, not the injured patient standing here telling you how they have been injured. Has the practice of medicine reached a point where patient safety and quality

of life are no longer an issue?

Product safety and fostering innovation, as stated in the mission statement of the FDA, is an oxymoron. Dr. Shuren, at a Medical Device Manufacturers Association annual meeting, said, If anyone is looking for a piñata for your child's birthday, I'm available. This will continue to be the position that the FDA is put in if clinical trials are not required for all permanently placed medical devices.

The American people do not understand, as patients, that they are the clinical trials, and their insurance carrier will pay for those clinical trials. If it fails or harms the patient, it hasn't cost the pharmaceutical company a dime. In fact, if it permanently harms a patient like me, the pharmaceutical company gets to stand up and yell bingo. They have now taken a healthy woman who had to have eight surgeries because of their product, and now she spends most of her time at a pain management doctor, who fills up her cabinet with pain medication that may be manufactured by the same company who harmed her.

The use of synthetic mesh in a woman's pelvic floor is the gift that just keeps on giving.

The IOM's July 2011 report stated, The committee does not believe that there is a public healthcare crisis related to unsafe or ineffective medical devices. I disagree. There is indeed a public healthcare crisis related to unsafe medical devices. Standing before you as an injured patient

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discussing the safety of a medical device that no clinical trials were done to evaluate the safety of that device is a public healthcare crisis.

We do not need further studies to evaluate the safety of mesh already on the market. We have already done the clinical trials on unknowing women, and I was one of them.

You have had or will have five women from across the country who are members of Truth in Medicine speaking before this Panel. Together, we have needed 43 surgeries due to the complications of synthetic mesh placed in our pelvic floors for POPs and SUIs.

We are at a crossroads today. Do we protect the public and do no harm, or do we foster more innovation of an unsafe medical device? As an injured patient, I believe the use of mesh that is marketed for minimally invasive surgery for POPs and SUIs should be recalled as an ineffective medical device. Thank you.

DR. FALCONE: Thank you very much.

The next presenter should be Sherrie Palm.

MS. PALM: I am Sherrie Palm, the founder and president of the Association for Pelvic Organ Prolapse Support. I have no financial relationship with anyone involved in any mesh protocol, and neither does APOPS. I'm here of my volition.

I'm simply a woman who's had transvaginal mesh surgery to repair her pelvic organ prolapse. I had three of the five types of POP. I am a

success story, and I'd like to share some insights with you.

My urogynecologist utilized a transvaginal mesh procedure for my surgical repair. I had concerns about repeat surgery. I wanted to be fixed and be done with it. POP surgery is not a cakewalk. It's a rough surgery to go through.

Repeat surgery is an all too common occurrence. I've been extremely pleased with the outcome of my surgery, and I got out of this deal how to investigate the benefits of looking for a specialist in POP procedures. As a woman's pelvic floor health advocate, I really felt the need to weigh in on this topic.

It's really vital that the Committee members recognize that the common denominator for every single woman is to decide to return the body to normal. This is what drives women to seek treatment and surgery for POP. And all women with POP have symptoms. All women with POP have symptoms. They just don't talk about it. They're too embarrassed by the symptoms. They don't tell their doctors. They don't tell their husbands. They don't even tell their friends. They tell me every single day. Believe me, they have symptoms.

Now, I admit, I'm a bit more proactive than the average woman. I networked to find the best urogynecologist. I checked her credentials. I went to my appointment with my questions in hand, I expected answers to my questions, and I got them. My physician is an expert. She

took her time with me. And my successful transvaginal mesh procedure substantiates that this treatment option does have great merit.

I recognize that few women do their homework when approaching POP treatment. Because of this, some women have transvaginal mesh procedures performed by physicians without the proper training and expertise for this procedure. With so many organs, muscles, and connective tissues coming together in a tightly compacted area, it truly takes an expert to get it right. A urogynecologist or urologist should be the physician of choice.

When the efficacy of a medical procedure is questioned, the catalyst comes from complaints filed by individuals who suffer complications after having procedures by physicians with inadequate training or experience.

Now, my heart goes out to these women; it really does. They had pain and dysfunction prior to surgery, and now it's compounded. They're living in hell every day. I think we need to hear their voices, absolutely. I've spent some time listening to their stories.

However, eliminating this beneficial procedure from POP treatment options is not the answer. Monitoring who can perform the procedures is a much more practical direction.

Advancement of any medical pathway will always be littered with the X factor of those who add procedures to their itinerary as though they're picking up a tool at Home Depot. It's always been this way. It

probably always will. Thankfully, we have the FDA to monitor and create some ballast for us.

I feel strongly that transvaginal mesh procedures should be recognized as a valuable option and choice for pelvic organ prolapse treatment. I also feel strongly that these procedures should only be utilized by physicians who are specialists and have gone through the intensive training necessary to perform them.

I'm hopeful that the FDA will consider monitoring the training protocol rather than preventing urogynecologists and urologists from performing transvaginal mesh procedures. It's likely that the majority of complications that occur are the result of inadequate training and experience. POP surgery is best left to the experts.

As a women's pelvic floor health advocate, every aspect of the impact of POP has for women is a top priority to me. Every layer. Transvaginal mesh is just one of them.

Pelvic organ prolapse is an American woman's health issue -- it's not an American woman's health issue. It's a global women's health pandemic. There are three million women in this country alone with POP. This needs to be recognized and acknowledged.

It's imperative that the FDA is intricately involved in the global path to cover diagnostics and treatment for POP, along with coordination from NIH, WHO, and GHI, for I think it will address the perception of POP as

well as the reality of a status quo in all matters POP related, including transvaginal mesh.

DR. FALCONE: Thank you. And the fifth speaker will be Marian Goldberg. Please state your name, and you have five minutes. Thank you very much.

MS. GOLDBERG: My name is Marian Goldberg. I am affiliated with Truth in Medicine. I have received no remuneration for participation in this meeting.

We are the meshies, women whose lives have been irreparably damaged by synthetic transvaginal mesh, by implantation of TVM kits implanted to remediate stress urinary incontinence and pelvic organ prolapse. Our surgeons were experienced. Yes, experienced surgeons who assured that surgery would be minimally invasive and a piece of cake. Instead, we were left permanently injured, robbed of our pre-mesh lives, as we knew them, due to mesh complications.

Because the FDA's 510(k) clearance process does not require premarket testing, we went into our mesh implantation surgeries uninformed. We, the injured, became your guinea pigs in your postmarket trials.

Doctors, whether we were the 1 in 10 or the 5.3 in 10 who suffer from mesh complications, I guarantee that no meshie would have agreed to TVM kit implantation if we knew the results would leave us

devastated and debilitated with chronic pain and suffering, haunted by unresolved grief secondary to mesh-related losses.

Doctors, I guarantee that no meshie would have chosen TVM surgery knowing that we would need to travel thousands of miles at high cost for repeated mesh removal and for repeated pelvic floor repair and reconstruction surgeries.

Doctors, who in this audience will risk surgery that could leave you plagued with chronic pain from a rolled-up or hardened or fragmented mesh product or from nerve damage, pain that never stops when you sit or stand or walk?

Doctors, who here will consent to a device that can make it impossible for you to work or to have sexual intercourse at all? Are you ready to have no sex in your life? Are you ready to have your marriage end? Or to lose your livelihood?

Doctors, who among you will volunteer for a permanently implanted device that cuts, slices, and burns through your genitalia, your urethra, your bladder, or your rectum, that could leave you incontinent or unable to urinate independently forever?

Doctors, I doubt that you knowingly would take the risk. I don't see anyone rushing to sign up on the dotted line. Therefore, knowing what you know now, the destructive, debilitating, life-altering nature and extent of TVM complications, doctors, why haven't you taken these products off the

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market? Why hasn't there been a recall of synthetic TVM kits yet? Why haven't these devices been classified as Class III devices so safety and effectiveness testing will be mandatory?

Doctors, I want to congratulate the FDA on the issuance of the 7/13/11 warning regarding TVM for POP. However, knowing what you know now about TVM, why hasn't there been a warning issued about TVM kits used for SUI? Aren't the properties of synthetic mesh the same whether the mesh is used for SUI or POP? Aren't the mesh complications for both the same or similar?

Doctors, knowing what you know now, why are you still playing the odds and gambling with women's futures by continuing to implant synthetic TVM devices? Women are human beings. We deserve the same quality of life as you do.

Doctors, you are now informed practitioners. Your knowledge gives you the power to change things. Your knowledge makes you liable for your actions. Your knowledge necessitates responsibility. Thank you.

DR. FALCONE: Thank you very much.

So the Panel will now have the opportunity if they have any questions for the last five presenters. Okay, Dr. Mattison.

DR. MATTISON: Dr. Elser. You commented that ACOG would support studies that had adequate length of follow-up, but you didn't define what you meant by that adequate length of follow-up.

DR. ELSER: Dr. Denise Elser from ACOG.

The length of follow-up has not yet been determined. But because most studies have been reported at one year or less follow-up and we see that that erosion rate or other complications can increase with time, or contraction can increase over time, that most likely two to three-year follow-up will be considered a minimum.

DR. FALCONE: Dr. Fitzgerald first. Dr. Sears after that.

MS. FITZGERALD: Dr. Elser also, please. Dr. Elser, ACOG recommended that they would like to see establishment of registries, perhaps, as one mechanism. Do you think that there should also be registries for non-mesh prolapse repairs?

DR. ELSER: I would love to see tracking of every case done for long-term follow-ups, so we can say what's the true success rates in everyone's hands, not just the research centers or the NIH-funded networks. I think being able to mandate a registry or get enough volunteers on native tissue repairs would be much more difficult. I don't know how it would get implemented. But I can say that if a hospital is buying a device, or a surgery center, at least the initial data would have to be entered on which patients or characteristics had which device placed.

DR. FALCONE: Dr. Sears. No? Okay. Dr. Rogers.

DR. ROGERS: I have a question for Ms. Palm. So in your testimony you discussed that these surgeries should be only performed in the

hands of expert clinicians. Do you have any suggestions on how that would be determined?

DR. FALCONE: State your name as well, please.

MS. PALM: Sherrie Palm.

I do feel that there should be -- currently there is a lot of training that's going on where mesh is manufactured, and I feel that they need to change their criteria a bit. I think a position should be board-certified as urogynecologist or urologist, fellowship trained, something before they're allowed to actually do transvaginal mesh surgeries.

I don't know. I'm not a doctor. I don't know how that stuff works. But I've spoken with a lot of women who've had complications or had to have repeat surgeries when they've been operated on by -- and I'm not dissing the gynecologists, but by gynecologists that are not certified in the specialty field. And the problem with having procedures done by physicians that, to me, should be very much involved in the pathway but on a diagnostic level, and then the patient should be referred to a gynecologist or urologist for the actual procedures.

Women that have procedures done by gynecologists that they've known for years and years, the comfort zone is there for them, and I understand why they would go ahead with that but -- because women don't recognize that they need to do their homework. They need to research the doctor, check their credentials, find out what their records are and how good

they are and how many procedures they've done as far as transvaginal mesh surgeries or any other kind of POP surgery, for that matter. And if some of the criteria was set wrapped around that, it may have an impact on the end result -- not may; it would impact on the end result, I have no doubt.

DR. FALCONE: Dr. Coddington.

DR. CODDINGTON: For Dr. Elser, please. Having just heard Ms. Palm recommending subspecialty training, how would ACOG support this sort of aspect?

DR. ELSER: ACOG knows and understands that there are many gynecologists who are very experienced pelvic surgeons and treat prolapse and incontinence on a regular basis. We would be willing to work with AUGS to help define criteria, who would be considered well trained, so what minimum training requirements are and experience.

We know that our colleagues in other fields, such as cardiovascular surgery at a hospital credentialing level, look at how many procedures someone's done in a year to maintain their privileges for a certain procedure, and it may be that a certain volume and a certain success rate is needed to continue to perform procedures.

DR. CODDINGTON: Just one other thing also. You mentioned about training and not from industry. Industry wouldn't be a part of it or would collaborate or be further in training, such as she mentioned --

DR. ELSER: Yeah.

DR. CODDINGTON: -- the urogynecologists?

DR. ELSER: Dr. Elser again.

Right now there is a dilemma in our country. When someone leaves residency or fellowship, how do they get trained on new procedures? And at the present time, that falls really to the physician to either learn from a colleague or to get trained by the industry, who's having a cadaver course or a proctorship. And we would not like to make it mandated that industry must provide this training -- we'd certainly welcome collaboration if they have some great resources to provide for us -- but to get our societies and our hospitals and training programs more involved in teaching physicians new procedures.

DR. FALCONE: Dr. Davis.

DR. DAVIS: Do you see any significant differences between ACOG and AUGS' recommendations, either orally or in our documented material?

DR. ELSER: I've not read AUGS' full written statements, too, but orally, I think we have a very similar message.

DR. FALCONE: Dr. Rogers.

DR. ROGERS: I have a related question. So in your presentation you called for high-quality randomized controlled trials, and in Dr. Myers' presentation, representing AUGS, the call was for cohort studies. I would appreciate a comment on the different conclusion of the two societies.

DR. ELSER: Our committee at ACOG felt that a randomized controlled trial, to let us take surgeons with similar skills, volume, taking care of prolapse patients of similar severity, to help us define who is better, you know, which outcome is going to be the best. I think there's a lot of value in cohort studies and the retrospective collection of data.

I get frustrated when sometimes retrospective data is considered not valid, but certainly there's a lot to be learned from patients who have been through experiences and surgeons. But a randomized controlled trial may help us define some of the answers.

DR. FALCONE: Dr. Brill.

DR. BRILL: Andrew Brill.

Dr. Elser, it wasn't clear to me whether ACOG is taking a stand on whether these devices should be reclassified.

DR. ELSER: Our stance is we don't have a stance to ask that these be reclassified into Class III. We would like to know that products coming on the market, and available for our patients and for surgeons to use, have had some implantation, that we know they're safe and they've been used in women in a clinical trial.

DR. FALCONE: Anybody else?

(No response.)

DR. FALCONE: Okay. So we're going to, in fact, take a 10-minute break at this moment, and then we have other public speakers.

It's 10:35, so 10:45.

And for the Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members of the audience. Thank you.

(Off the record.)

(On the record.)

DR. FALCONE: Ms. Eileen Crowley, come up, please.

Where are the Panel members?

(Laughter.)

DR. FALCONE: Is Ms. Crowley here? We are going to wait for the Panel members, though, even if I have to personally go up there and drag them back.

Where's Dr. Coddington?

MS. CRAIG: He's not in the ladies' room.

DR. FALCONE: He's not in the ladies' room, no.

Dr. Coddington. There we go.

Ms. Crowley?

Okay, let's move on then to Dr. Christian Winters, please. So Dr. Winters, as you know, you have five minutes, and then there's a little yellow light that goes on saying you have a minute left.

DR. WINTERS: Good morning. My name is Christian Winters. I'm a urologist. I have no conflict of interest. And I'm representing the AUA,

who is hopefully paying for my trip today.

However, the AUA, which is a premier urology association for the advancement of urology and urologic care in the United States and across the world, represent approximately 13,000 urologists in the United States, and urologic health professionals, as well as 5,000 international members.

The AUA applauds the FDA for revisiting this issue because we agree that complications, such as pain, sexual dysfunction, urinary tract injury, and vaginal mesh exposures, can occur after the use of mesh techniques for the treatment of pelvic organ prolapse. However, the AUA feels it's important to recognize that many of these complications can also occur with non-mesh procedures. And also many women undergo mesh procedures without complications and with favorable anatomic outcomes.

So the AUA believes that certain benefits may benefit from mesh techniques, and mesh products should be continued to be available. We believe it's a choice. The use of mesh techniques should be a choice that is made after a careful discussion between the surgeon and patient. We believe that complete withdrawal or restriction of mesh techniques may prevent some women from having access to effective therapy for the treatment of pelvic organ prolapse.

We believe an informed consent process is essential, and the AUA strongly agrees with the FDA that the informed process should be rigorous. It should be complete and comprehensive, which includes

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discussion of the risk and benefits of all available treatment options. The consent process should inform patients of all treatment available, including native repairs as well as abdominal procedures. If transvaginal mesh is considered, the surgeon should review possible adverse outcomes specifically associated with the use of mesh and how they would be managed and the fact that they could be lifelong experiences. And, in fact, this consent process, the AUA thinks, should be standard

Training is essential. The AUA agrees that surgeons who utilize mesh techniques should be already accomplished pelvic surgeons who are familiar with the techniques of anatomy and pelvic surgery. Then these surgeons should be trained in specific mesh implantation techniques, and in addition, they should be able to recognize and manage complications associated with the use of vaginal mesh.

In addition, there is much more data that's clearly needed, and the AUA agrees with this. The data needs to determine safety and efficacy of mesh use in pelvic organ prolapse repair. The AUA suggests mandatory registration, by industry, of all implanted mesh products to be used for pelvic prolapse so these patients can be followed, and for surgeons, where they may see after subsequent surgery so we can identify what materials were implanted into our patients.

The AUA is also supportive of efforts to increase postmarket study of mesh products for pelvic organ prolapse, through the use of clinical

trials and mandatory registries.

We do want to make a distinction, however, between mesh for prolapse and mesh for incontinence because the AUA feels this is a critically important distinction. There's extensive data that exists that supports the use of the synthetic mesh slings with minimal morbidity, compared to the alternative surgical techniques.

In fact, the AUA has recently concluded a guideline for the management of surgical stress incontinence, and we concluded that synthetic mid-urethral slings are an appropriate treatment for women with stress incontinence. In fact, our guidelines demonstrated that the risk/benefit ratio of the mid-urethral sling demonstrated clear benefit when compared to conventional procedures in use. In addition, we feel that any restriction of the mid-urethral sling would be actually detrimental to women who desire surgical treatment of stress urinary incontinence.

Lastly, urologists are intricately involved in the treatment of incontinence and pelvic organ prolapse. And, in fact, we are performing a joint specialty without gynecology colleagues, called *Female Public Medicine & Reconstructive Surgery*, which has been recently recognized by the American Board of Medical Specialties. So in future discussions regarding the use of prolapse and incontinence, the FDA believes that there should be interaction with the urology advisors on the gastroenterology panel as well.

Thank you very much for your time.

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DR. FALCONE: Thank you. So we're going to move on to the next speaker, which I think should be Ms. Oberman. Please state your name, and you have five minutes to make your presentation.

MS. SCHUYLER OBERMAN: My name is Alicia Oberman, and I'm speaking on behalf of the Women's Health Foundation, and I have no conflicts. And I again hope that the Women's Health Foundation is paying for my flight.

We at the Women's Health Foundation have a very simple mission. It is to improve the pelvic health and wellness of women and girls. We appreciate the FDA convening this meeting to discuss this common condition, pelvic organ prolapse, and one surgical treatment thereof, which is surgical repair using mesh.

I am particularly grateful to participate because two years ago this October, at 32 years old, I underwent a nearly seven-hour surgery to, among other things, correct fairly severe pelvic organ prolapse, including uterine prolapse, rectocele, cystocele, and stress urinary incontinence.

I was extraordinarily fortunate because I had an excellent surgeon and was consequently able to make informed decisions about a procedure and a condition that will affect me for the rest of my life, despite the surgery. I asked questions, knew about the risks, spoke to a woman who had six procedures and nearly died, but made the decision to go ahead anyway because of the impact that pelvic organ prolapse had had on my life.

Nine months after surgery, I did a triathlon, something which I could not and never would've been able to have done had I not had the surgery. As a board member of Women's Health Foundation, I believe it is critical that other women are afforded the same opportunity.

In addition, I have three daughters who all have my pelvic floors and who all have my genes and, consequently, possibly bad connective tissue. So I truly appreciate any and all opportunities to bring this issue of pelvic organ prolapse to the forefront of conversation.

At WHF we believe that women deserve to be educated and empowered in their healthcare choices. In our area of pelvic health, women are often not given the information and choices they need to make good decisions when dealing with pelvic issues. Diagnosis of pelvic organ prolapse -- and I speak from experience -- can be intimidating and devastating to understand, let alone to try to find out what your options are for treatment.

So the first thing we would like to say is that women at all stages in life need to better understand exactly what is going on with their bodies. This discussion with the FDA's oversight is hopefully going to bring much needed attention to women's pelvic issues, both surgical and nonsurgical.

Once a woman is told that she has a condition like POP, we would advocate for a thorough educational process that includes information

on pelvic anatomy and physiology, uterine prolapse, rectocele, cystocele, what things she can do to minimize the condition symptoms, what she needs to do to prepare for surgery, and a knowledge base to help ensure long-term positive surgical outcome. That would include potentially being referred to pelvic floor physical therapists or information on appropriate exercise programs, as well as a list of do's and don'ts and an explanation of why you have that list of do's and don'ts.

And this might be something that the industry makes available in their mesh kits, for example. Right now it's available on many websites like ours, but it is often missing at a doctor-patient relationship.

Secondly, we would like to urge the FDA to consider editing the review of complications from mesh procedures with a perspective on the training and expertise of the practicing physicians. Do the results of surgical treatment with mesh vary when analyzed through a lens, or is it the type of surgeon performing the operation and his or her training, both medical training and training with this type of a particular product?

Like any other implantable device that has risks, we urge women to seek the best medical care they can find and afford. And a necessary part of this is questioning their doctor about their expertise with the procedure and the products being used, if any.

In our world of pelvic health, specialty physicians, urogyns, urologists, gynecological surgeons exist, yet many women do not know it.

Well, as for the discussion for the various medical societies and their PR and marketing strategies, we believe that national forums like this have the potential to help women better understand the role of specialty treatment paths for conditions like pelvic organ prolapse.

Finally, as an organization that advocates their patients, it also seeks collaboration with physicians and industry. We urge the FDA to find a balance between cautious guidance and innovation. Mesh has been used for many, many years in many surgeries, like hernias, quite successfully. We believe it has a place in the pelvis as well, but within the confines of an appropriate diagnosis, a well-trained surgeon, and a properly informed, educated, and supported patient.

We would urge the FDA to focus its efforts on creating better risk disclosure mandates, better patient education materials, and to work with the medical specialties that utilize mesh in their daily practices to ensure that placement only occurs after rigorous and applicable training. Thank you.

DR. FALCONE: Thank you very much.

Just one last call for Eileen Crowley. Is she here? No?

(No response.)

DR. FALCONE: Okay, Dr. Stanford.

DR. STANFORD: Good morning. Ed Stanford. I'm a private practice urogynecologist and minimally invasive surgeon. I'm here representing the AAGL. I don't have any disclosures. I have been funded for

postmarket studies. And AAGL is paying for my travel.

AAGL has been in existence for over 40 years. It's a leader in promoting minimally invasive surgical science and technology. We have over 5300 members worldwide. And we have developed several diagnostic and treatment guidelines in gynecologic disorders and treatments.

I'll just remind the Panel that we are in an evolutionary phase. Remember, in 1992, *The Green Journal* published a paper saying laparoscopy was considered a technical gimmick. Negative bias was towards laparoscopy. Our former president nearly lost his privileges by doing laparoscopy. And the question was, how do we credential for these procedures? This was retracted, finally, in March of 2010, and now laparoscopy, as we know, is a gold standard in treating many disorders in GYN surgery.

We applaud the FDA. We think this is going to help women in the long run, and many of the suggestions, we think, are really very good. However, if you review the Executive Summary and the update, we feel that there are several statements and references that are somewhat misleading to the public.

The real issues at hand that cannot be addressed, I think, by the FDA but need to be addressed on a national and global level is credentialing, training, as has been set forward by AUGS and ACOG and others, we need to monitor outcomes, and I think a registry is a good idea, but that's a personal opinion and not from the AAGL particularly. We also

need to learn how to rescind or grant privileges in a judicious manner, particularly when there's inadequate success or volume is too low.

The other real issue is this update is going to lead to millions of dollars of indirect healthcare costs, and it'll target all surgeons, even those who are experienced.

Complications. We believe that erosion is overstated in the FDA guideline. Most erosions are treated in an office setting, and we know that with proper surgical technique and proper dissection, the mesh really doesn't care how it got there; it really can be an inert and well-accepted product.

Serious complications. The comment by the FDA is serious complications associated with surgical mesh for transvaginal repair of pelvic organ prolapse are not rare. We disagree in general. Complications are not rare for any pelvic organ prolapse procedure. There are many biased statements in the FDA Executive Summary and update. We don't know what the denominator is, but if you look at the math that's in the update, it's less than a one percent complication rate. We know that it is higher. But if you exclude extrusion, which is an office-based treatment, the number of complications is actually relatively low. So it is probably more rare than the update insinuates.

We don't think there's an actual increase over the last three years. There's an increase in reporting. And there is no MAUDE for

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non-mesh or ASC.

Now, ASC complications, they can be done very successfully and have been by many surgeons, as you can see here; mesh erosions of less than one percent and no bowel obstruction. But the literature also shows bowel issues in up to 1 in 20 patients, and other complications: postoperative stress incontinence, anal incontinence, transrectal and transvesical mesh erosion, and mesh infection.

We also see complications with native tissue repairs: bowel dysfunction, 33 percent; urethral occlusion, 11 percent; sciatic neuralgia and neuropathy and recurrent prolapse.

If you take a look at the literature, we agree that non-mesh repairs can be and often are successful as mesh repairs. The vast majority of POP literature concerning surgical treatment of POP consists of studies which do not meet the FDA's criteria. Using systematic reviews and randomized controlled trials, RCTs, will limit the ability to provide comprehensive conclusions, and when attempting to answer questions related to surgical practice, single-arm and retrospective studies may provide meaningful answers to clinical questions.

As far as RCTs, outcome bias is inherent in this. The statement in the Executive Summary is that mesh should be superior. But which patients? How are you going to control this? And, again, there is no control group identified. So will this be for primary repair, recurrent prolapse,

Stage III or Stage IV versus Stage III or Stage IV, menopause status, other demographic issues. And who controls the surgeon's expertise?

We do have some studies already out there that show that some of these questions are already answered. And observational and retrospective studies may be adequate and are less costly.

Lastly, other issues such as mesh shrinkage we don't think is well supported in the literature. If you take a look at the RCTs and sexual dysfunction --

DR. FALCONE: Thank you. So the next presenter is Ted Benderev. Maybe not. Is he coming? Oh, okay.

DR. BENDEREV: Good morning.

DR. FALCONE: Please state your name, and you have five minutes.

DR. BENDEREV: My name is Ted Benderev. I am a practicing urologist specializing in the surgical repair of prolapse, and I'm also president of TranSense Medical. I greatly appreciate the opportunity this morning to present a technology that I conceived in an effort to improve the outcomes in prolapse mesh surgery.

My goal today is to describe the complications of mesh surgery as associated with tension and the challenges facing surgeons in an effort -- their efforts to improve the technique and reduce complications; and lastly, to present the opportunity for new sensor technology to increase patient

safety.

Each surgeon who goes into the operating room goes through a balancing act. A prolapse surgeon's goal is to restore the normal pelvic anatomy and function. Surgeons have incorporated mesh into their surgeries in an effort to reduce recurrence. But the tensioning of mesh placed requires a balancing act to support the tissue sufficiently without over-tightening. Over-tightening of the mesh may result in the complications of pain from traction or pressure on adjacent tissues and may contribute to erosion into adjacent tissues. Tension currently is an art in the surgeon's hands but poised to become a science.

What is the role of tension? Many mesh systems require anchoring or suturing to the sacrospinous ligament or surrounding tissues to provide support. The pain complications appear to be associated with tension settings. A causative relationship of tension to pain is supported by the development at times by pain on the side where mesh is placed more tightly and by the relief of that pain many times when that mesh tension is surgically released.

Currently, vaginal prolapse procedures are done by feel or sight without quantifiable measurements of mesh tensions. Therefore, consistency of tension settings and clinical results between surgeons is variable. Without tension indices, experienced surgeons cannot document and share the mesh tension settings of their techniques with new surgeons or other experienced

surgeons. And community surgeons cannot learn from their own difficulties to improve the placement of mesh in future patients.

We have a tension monitoring technology that measures tension during mesh and graft placement. It allows the study and development of optimal tension settings by experienced surgeons with the goal to reduce the complication of over-tension, and we expect that tension-setting indices will enable more reproducible mesh placement and allow standardized training.

In summary, this may be the right time to consider opportunities for the quantification of a technique with mesh and tissue grafts for pelvic organ prolapse surgery. The TranSense sensor may be the optimal device for this purpose. We invite the opportunity to work with the FDA, researchers, and manufacturers to incorporate tension measurements using the TranSense sensor into future studies. Thank you.

DR. FALCONE: Thank you. The next presenter should be the Law Offices of Sybil Shainwald. And maybe not.

How about Maria Costa. Ms. Costa.

MS. COSTA: Good morning. And for those you in the back, I am standing.

(Laughter.)

MS. COSTA: My name is Maria Costa. And by the way, I'm not getting any money out of this. It's cost me a day of my work.

I have benefited from the use of transvaginal mesh for the treatment of both prolapse and incontinence and would like to share my story with you.

Up until my surgery, I was going to the bathroom at least on an hourly basis. This becomes very difficult, especially at night. Also along with that, I was wearing multiple pads a day; very uncomfortable.

After talking to a urologist, he wanted to put me on pills for the rest of my life. I don't even take vitamins well, so that was not an option. I received a second opinion from a Dr. Guerette at the Female Pelvic Medicine Institute of Virginia. After extensive testing, Dr. Guerette made a recommendation for surgery. Again, I've been through several surgeries over my lifetime, and I had lots of questions. Those surgeries always are apprehensive.

I looked into his experience. I looked at how many people he had done surgery with. I even asked for a couple of names of people that he done surgery on. And they called me; I didn't call them.

I received surgery for both the prolapse and incontinence, and since I did not have to go to the bathroom, that alone -- on an hourly basis, that alone has made it very worthwhile. This is extremely important because I have a long commute. I live in Fredericksburg, Virginia, and I commute to D.C. on an hourly [sic] basis using good, old 95. And those of you familiar with 95 know the experiences there.

I no longer have to worry about a cough, a hard laugh, or losing control. My life has been positively changed by this mesh. My age is 59, I'm not 90, and I don't want to live through the rest of my life using the pads or using a pill. So I thank you.

DR. FALCONE: Thank you. Let's see. So I think that's one, two, three, four, five.

Okay. So do the members of the Panel have any questions for the last five presenters? So, yeah, Dr. Brill.

DR. BRILL: Andrew Brill. A question for Dr. Stanford. Yeah, state your name.

DR. STANFORD: Oh.

DR. FALCONE: Yeah, please.

DR. STANFORD: You have to ask a question.

DR. FALCONE: First your name and then we'll consider your question.

(Laughter.)

DR. STANFORD: Edward Stanford.

DR. BRILL: Good.

DR. STANFORD: I can sit down now?

DR. BRILL: Yeah.

(Laughter.)

DR. BRILL: So among the concerns you had from the evaluation

of the FDA's statement that was published, you stated that you thought erosions were over-exaggerated, and I wondered if you have a figure so at least we know what your perspective is on that, especially in the context of how many are being done in the office and what that percentage really is versus true -- what would be called serious adverse events.

DR. STANFORD: Probably the easiest way for me to quote my personal experience is my published studies: 153 patients followed for two years, one extrusion. It was preventable.

Most recent studies looking at a transvaginal mesh procedure, the one-year and now up to 18-month data looks to be less than about five percent extrusion, and none of those required any surgical excision, only office-based trimming, basically.

If I were to use my personal experience, I have not had to take one out in the office except for one sling mesh that became infected. I think most experienced surgeons would treat it in the office, and I would throw a number out of somewhere between 70 and 90 percent. It doesn't mean that you wouldn't take them in the operating room for convenience or pain control, but I would have to say that this is a minor surgical complication. And I think if you look at something like the Dindo classification, it upgrades it inappropriately.

DR. BRILL: That's it.

DR. FALCONE: Okay, Dr. Mattison, go ahead.

DR. MATTISON: Also for Dr. Stanford. The presentations from the AUA and ACOG, as well as AUGS, recommended registries for patients that have used -- that have been treated with mesh surgery.

Does AAGL have any recommendations?

DR. STANFORD: To be fair, I haven't asked the rest of the board or our directorship about that, so I don't have a societal comment on that. Personally, I think it's a great idea. The problem is, who will fund it? If the FDA wants to fund it wholly, fantastic. But the problem is going to be funding. And then what do you do with the registry numbers? What do you do with the information? Who controls the data?

We have a number of networks and stuff out there that are controlling data, that, I think, it shows that there has to be less bias in how the numbers come out. So I'd be concerned about what to do with the registry.

DR. FALCONE: Dr. Iglesia.

DR. IGLESIA: Yes, I have a question for Dr. Winters.

DR. WINTERS: Hi, I'm Chris Winters.

DR. IGLESIA: Yes, Dr. Winters, my question relates to training, surgical training, and what the AUA's ideas are regarding training in order to mitigate risks and help with the learning curve for these technically advanced procedures.

DR. WINTERS: That's a very good question, and I think the

biggest problem is it's very, very complex because many localities where the surgery is done are quite different in their needs and in the make of physicians that actually do the surgeries. So it becomes a very multifaceted solution.

I guess a global idea, first, is to identify surgeons who do this surgery already, pelvic surgeons, meaning those that are accomplished at gynecologic surgery. The best way to consider doing that would be in a sense that if you're locally credentialed in your hospital, and in the new era potentially of JCA standards, looking at this on a yearly basis and tracking the numbers of the procedures that the individual is doing.

So that individual is credentialed or pre-credentialed, if you will, for gynecologic surgery, to do these procedures using native repairs, alternative approaches. Then that should potentially be, at that point, the introduction of the mesh technology to these procedures.

How that's implemented, I don't know. Ultimately, I would see some partnership, potentially with the societies making some recommendations, perhaps, that could be applied on a local basis with some variability based on the local construct. But I think the genesis is making sure the technology is in the hands of an established, requisite pelvic surgeon already.

DR. FALCONE: Dr. Brill.

DR. BRILL: Andrew Brill.

I have a question for Dr. Benderev, please.

DR. BENDEREV: Hello, I'm Ted Benderev.

DR. BRILL: Just as a segue to the previous question, I was intrigued by your interest in standardizing or objectifying prolapse repair, and you brought to issue the difference between art and science.

So I ask you, as someone who's interested in this area of pelvic organ prolapse, do you think that this can be standardized in the context of the training that we're hearing about, that in fact there is a best practice technique with each device?

DR. FALCONE: Push the button and state your name.

DR. BENDEREV: My name is Ted Benderev.

I do believe that we can do a better job of standardizing the way we do surgery. There is an opportunity to do this. Each of the training programs that I've gone to are given by manufacturers. The question that always comes up, how much do you tighten these materials? And their IFUs, you know, talk about not over-tightening. I do think this is something that we can measure and then look at the results of that later to see if we can actually standardize that. I think it would help.

DR. FALCONE: Any other questions?

(No response.)

DR. FALCONE: Okay, thank you. Okay, let's move on. The next presenter will be Victor Nitti. Please state your name, and you have five

minutes for your presentation.

DR. NITTI: Good morning. I'm Vic Nitti. I'm the president of the Society for Urodynamics and Female Urology, and I'm also Professor and Vice Chairman of the Department of Urology at New York University Langone Medical Center.

Our society is a society of over 500 members, including physicians, mostly urologists and gynecologists, researchers, nurses, and other healthcare professionals, and our mission is dedicated to the treatment of -- or part of our mission is dedicated to the treatment of female patients with problems such as prolapse and incontinence.

In the spirit of full disclosure, I wanted to inform the Panel that I have worked with several companies who manufacture mesh for transvaginal pelvic organ prolapse repair. However, I've not worked in a capacity that has been involved in the development of training of physicians in the use of or promotion of transvaginal mesh for pelvic organ prolapse. They were for other things.

The following statements were formulated and unanimously approved by the SUFU executive committee at its meeting on the 19th of August 2011, and they were made first and foremost with a patient's interest and welfare in mind.

We reiterate what has been said by some of the other societies, as we believe that the use of mesh for stress incontinence is

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distinctly different than that of pelvic organ prolapse repair.

Complications seem to be the main focus of why we have come to this point, and we do recognize that mesh procedures are associated with some unique complications that have been discussed. But we also want to state that it's important to recognize that many complications are not unique to mesh and are known to be caused by non-mesh repairs.

SUFU believes that there does exist a population of patients for whom mesh has potential benefits. In these individuals it may be appropriate to consider the implantation of transvaginal mesh if all the potential risks are understood by both the surgeon and the patient, and it is our position that the consideration for use of mesh should be done on an individual case-by-case basis and only after an informed discussion between the surgeon and the patient.

We do not support the blanket withdrawal of currently available products from the market. However, we do realize that measures can be taken to optimize potential benefits and minimize potential complications. The informed consent is a critical part of this process, as mentioned by some of the other societies, and we believe this is very important.

Training is critical, and not only should surgeons be trained in the use -- in pelvic surgery, but also in the use of specific products that they may choose to use. And also rigorous training in the principles of pelvic

anatomy and pelvic surgery is important. This should all be done prior to attempting any implantation of transvaginal mesh.

We do have some concerns for patients previously implanted with transvaginal mesh. We believe it's important to inform patients who have had successful, uncomplicated mesh procedures for pelvic organ prolapse that there's no need to have mesh explanted if there's no problems. We recognize that long-term ramifications of vaginal mesh are not yet clearly understood, and therefore we recommend that patients undergo routine checkups and follow-up care as needed and inform their healthcare providers of any problems or bothersome symptoms.

Patients undergoing mesh explantation should be thoroughly informed of the risks and benefits of mesh removal. And, furthermore, we believe that patients with symptoms that are not clearly caused by a mesh complication must be informed that the removal of mesh may not necessarily improve and could worsen their condition.

SUFU recommends an improved postmarketing surveillance process for existing and future devices for pelvic organ prolapse repair. Mandatory compliance is necessary to provide an accurate estimate of benefits and harm. And until such a registry is created, we would encourage, as did AUGS, that all surgeons track their outcomes so that they have the best information available to hospital credentialing committees and insurers.

We also recommend considering implementing mandatory

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registration of all implanted products by the manufacturer, so that the availability of this information to the patient and surgeons performing future surgeries will optimize the results of those future surgeries.

We support a premarket approval process for transvaginal mesh that requires clinical trials using patient-centered outcomes, and we're supportive of the FDA's call for better data upon which to determine whether or not to use devices for pelvic prolapse, determining their safety and efficacy. And an establishment of a mesh registry post-surveillance database can be an important further step.

Further studies should be designed not only to assess safety and efficacy but also to better define patient populations for which mesh has potential and optimal benefits.

And we, as the AUA, also recommend that the FDA consider future panels, including members from the urology and gastroenterology advisory boards, since urologists are actively involved in the treatment of women with pelvic organ prolapse.

DR. FALCONE: Thank you. Just to go one last time, is Eileen Crowley or the Law Offices of Sybil Shainwald in the room?

(No response.)

DR. FALCONE: They're not. We're moving on to what I think will be the last of the public speakers, Ed Varner. Ed.

DR. VARNER: Thank you. I'm Ed Varner, and I represent the

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Society of Gynecologic Surgeons. We are surgeons who are active in surgical education and promote research in areas related to gynecologic surgery. We are very pro-women's health and really want what's best for women.

I represent some members who are totally opposed to transvaginal mesh, many others who perform many of the procedures, and some, including myself, who use mesh only in select patients.

Many gynecologic surgeons see a role for transvaginal mesh due to its potential for improvement of outcomes over that seen with native tissue repairs that utilize what may be defective tissue to begin with. However, the information that is available from clinical trials, including several RCTs performed correctly, does not yet allow us to understand benefit versus risk.

What else do we need? I think, first, we would like to see some standardization of definitions of success and failure for use in upcoming clinical trials and in premarket clinical evaluations, if deemed necessary by the FDA. The most common definition to date has defined failure as Stage II prolapse. This is not consistent with what patients perceive as failure, and not at all -- and really not all early Stage II prolapse is symptomatic and many do not progress further with time.

I think the best definition would be the one which includes the symptoms of the bulge and the sign of protrusion felt or seen by the patient and documented to be out by exam with Valsalva in the upright position.

All adverse events should be documented with complete descriptions of the entire course of the event. We still don't know that much about adverse events. Not all contractures are the same. The true incidence of life-altering complications is really unknown. We've got very uncommon reports of these in the randomized trials and the cohort studies. But we, as referral physicians, see a lot of it, and a lot of them are severely disabled, as you've heard today. I think thorough descriptions of these adverse events is extremely important to determine possibly why they occur.

We strongly believe that longer outcomes are very important. Both failures and adverse events frequently occur after two years postop. We've all seen that.

The extension of, you know, existing clinical trials and possibly a postmarket surveillance plan could accomplish some of this longer-term follow-up without as much effort as it would take to perform a new clinical trial.

Lastly, it would be extremely helpful to see translational studies to better understand tissue reaction to mesh in patients that have good outcomes as compared to those that have vaginal contractures and agglutinations.

And, in addition, it would be good to see whether patient factors, like connective tissue makeup or composition, mucosal atrophy, pelvic floor muscle and nerve function, play a part in failures or success of

these procedures.

So what else do we need? Better training. You've heard that. Why is this taking so long? What's the new science?

So, in summary, the SGS is in agreement with the FDA group that the present data on mesh is incomplete regarding benefit versus risk. This is true for other procedures for pelvic organ prolapse as well. These mesh procedures have yielded mixed results that may be surgeon or patient dependent at times. We are not convinced that the low-density monofilament large-pore polypropylene mesh itself is the reason for most of the adverse events but feel that further translational studies designed to look at tissue reaction to this mesh are important.

At this time, the use of transvaginal mesh for pelvic organ prolapse should not be widespread until we have well-designed, longer-term studies. For now, thoughtful, discriminate placement of the vaginal mesh to pelvic organ prolapse should be performed by trained surgeons with experience in complex reconstructive surgery, and only on patients who are perceived to have an unacceptable risk of clinical failure when other procedures are performed.

DR. FALCONE: Thank you very much. So I think that is the public speakers. Are there any more? If not, we're going to -- does the Panel have any questions for the last two speakers, then? Dr. Sears first. Then we'll go around the room. Go ahead.

DR. SEARS: Thank you. Chris Sears from the Walter Reed National Military Medical Center.

I have a question for Dr. Varner from the SGS. One of the things that you said right at the end really struck me, as we were talking about privileging of physicians, and what I had heard from prior -- what I think I heard from prior societies was at least training in the native tissue-based repairs. And I think what I heard you say -- and correct me if I'm wrong -- is more training than that. So training in more sophisticated procedures.

Could you elaborate more on that? Is that you should be able to do the alternatives, whether it be sacrocolpopexy, et cetera, not just other transvaginal-based tissue-based repairs? Could you clarify that a little bit, sir?

DR. VARNER: I think credentialing is going to be a huge political issue. And right now we don't have enough real, real well-trained pelvic surgeons to take care of the problem. I think we will. You know, with the new fellowship programs and that sort of thing, we should have them within a reasonable amount of time. But I think we need to approach this very carefully. That was the last sentence I was going to say in my talk. But I think that we, as a society, are going to look into this very carefully, and I know that AUGS is as well, and I'm sure other societies will as well.

But, you know, I think numbers of procedures are important,

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personally, but I also think judgment is probably the most important thing.

DR. FALCONE: Dr. Brill.

DR. BRILL: Andrew Brill.

And Dr. Varner, there's been comments and statements this morning either stating or implying that perhaps a urogynecologist should be the only individual who should or could be using transvaginal mesh.

How does that sit with SGS, knowing that it's populated by many non-urogynecologists, and how would you respond to that, if in fact it became an issue?

DR. FALCONE: Hit the button there and restate your name.

DR. VARNER: Ed Varner again.

DR. FALCONE: Okay.

DR. VARNER: I would say that any surgeon that is experienced in pelvic prolapse surgery could definitely be credentialed in such. I personally think learning about mesh and how to use it is a lot more than going to a weekend course. And what that is, it probably is a little variable, depending on the person and their judgment in modifying procedures.

DR. FALCONE: Okay, Dr. Rogers.

DR. ROGERS: I have a question for Dr. Nitti. So in your talk you talked about the judicious use in select patients. It's been referred to a number of times throughout the proceedings.

Do you think that we have the data available to determine who

the judicious -- what that patient population looks like? And if not, how would we obtain that information?

DR. NITTI: Vic Nitti.

I do not think that we have that data currently. So currently, if a surgeon and patient decide that this is a select patient or an appropriate patient, it will be based upon the opinion and judgment of the surgeon, and I think the reasons for choosing that should be stated to the patient.

I think that, as we move forward -- and this will not be easy, but I think we have to look specifically at patients who we think the most benefit will be obtained from the use of transvaginal mesh. And those are the patients that really need to be studied.

If there is a general agreement of patients that definitely should not have transvaginal mesh or do not need transvaginal mesh, perhaps that's not the patient population that should be studied, but rather those where we think the most benefit is going to come.

DR. FALCONE: Anything? Yeah, Dr. Dominik.

DR. DOMINIK: Yes, I had a question for Dr. Varner. I think you mentioned that you yourself do not -- that you only use the mesh yourself in select cases.

And can you elaborate a little bit on the situations where you might use mesh?

DR. VARNER: Okay. Ed Varner again.

I do, and to tell you the truth, I use it less than I have at times when I first started using it, but I still will use it in certain situations. I will use it in a patient who has what I term no perivaginal muscle or connective tissue, or very minimal, just like the picture that was shown a while ago, and no ability to pull lateral tissue across. But I always do an apical suspension along with it, if the mesh itself does not perform an apical suspension in patients with anterior prolapse or posterior descent as well.

I modify most of my meshes. I don't do them exactly like the kits say, to tell you the truth. But I use them if I'm pretty sure the patient would fail what I do. For instance, a patient with severe constipation and a very, very large rectocele with very poor lateral and central tissue that included the entire septum there, a native tissue repair is going to create a lot more dyspareunia than a replacement-type mesh procedure in that patient. And I think most of the failures in the posterior meshes occur because the perineum's not approached.

DR. FALCONE: Thank you. Okay. So we're going to have one more question. Yes, go ahead, Dr. Lerner.

DR. LERNER: It's not a question. FDA would like to thank everybody for coming and participating. If you've not left a written or electronic copy of your presentation, we'd appreciate if you do so outside at the table. So thank you again very much.

DR. FALCONE: I'd also like to thank you. And to submit your

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presentation electronically, whether it's your slides or testimonials or anything, you can do so outside or to Shanika Craig, our Federal Officer, so that we can have access to those presentations.

So now we're going to move on. And the next part will be our industry presentations. And let us see. The first will be AdvaMed. So we have an on-time start and that means an on-time finish.

MR. SECUNDA: Good morning, distinguished members of the FDA Advisory Committee and FDA. I'm Jeff Secunda, Vice President of Regulatory Affairs at AdvaMed. AdvaMed is the world's largest medical technology association representing medical device manufacturers.

The majority of surgical mesh device manufacturers have joined together under AdvaMed to create the Transvaginal Mesh Working Group. This working group represents approximately 90 percent of the mesh sold to treat pelvic organ prolapse. Today, this working group will present their perspective on surgical mesh for pelvic organ prolapse.

The manufacturers of transvaginal mesh strongly believe that these devices are safe and effective for treating pelvic organ prolapse, and we are confident that they can continue to be appropriately regulated within Class II and the 510(k) clearance paradigm.

The current regulatory pathway has fostered the development and continued improvement of devices to treat this critical women's health issue. And in the hands of experienced surgeons, these devices are safe and

effective, with clearly established benefit/risk profiles based on clinical data.

We are aligned with most of FDA's recommendations to further clarify the benefit/risk profile for new mesh devices through clinical trials, longer-term postmarketing trials, a continued emphasis on training, and improved patient and physician labeling.

To ensure these are integrated into the regulation, we are further recommending that FDA define these requirements in a special controls document, as allowed by the 510(k) regulation.

I'd like now to outline our presentation. Dr. Suzette Sutherland, a urologist in private practice, who specializes in female urology and pelvic floor reconstruction; Dr. Piet Hinoul, Medical Director for Women's Health and Urology at Ethicon, will discuss the effectiveness and safety data and why we believe it shows a favorable benefit/risk profile for pelvic organ prolapse. Ginger Glaser, Senior Director of Global Quality and Regulatory Affairs at American Medical Systems, will outline device manufacturers' proposals and describe how fully utilizing the existing FDA pathway will allow FDA to enforce these proposals.

Given the limited time we have to speak today, we are not able to go into great detail on some issues. We look forward to answering any questions you may have to further clarify our perspective and proposals on transvaginal mesh.

I would now like to turn over the lectern to

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Dr. Suzette Sutherland.

DR. SUTHERLAND: Good morning. I'm Suzette Sutherland.

Thank you for the opportunity to speak today. My disclosure is that AdvaMed is sponsoring me to be here today. But let me be clear about the reason I'm really here. For the last seven years I've been performing pelvic organ prolapse procedures with mesh. For many women, a mesh procedure is their only chance for a durable repair.

I come here today because I'm concerned that we are mischaracterizing the real risks and benefits of these procedures, and so doing may be inadvertently scaring women away from a procedure that may provide them a real and lasting benefit.

Now, I have no doubt that there are women who have suffered from complications from these procedures, as many that we've heard here today. Just as women, however, have suffered from complications from the other surgical options that we have available today.

Correction of pelvic prolapse is a complex problem. But in the case of mesh repairs, serious complications are very rare and most cases easily manageable in the hands of an experienced surgeon. What's equally as important is that, what I see clinically and based on the data that's available to date, I believe transvaginal mesh procedures will provide a lasting benefit and impact on a woman's life.

As you can imagine from these pictures, pelvic organ prolapse

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is a very distressing condition, and we've heard that from others here today as well. The woman's uterus, bladder, bowel can literally be protruding out of the vagina, causing a wide range of urinary, bowel, and sexual problems, not to mention the sensation of a large bulge or even pain.

From a surgical perspective, adequately treating symptomatic prolapse can be very complicated because not all bulges are alike. Prolapse can occur in a multitude of compartments, the anterior, posterior, apex, or any combination thereof.

In addition to the transvaginal mesh surgeries we have available, we currently have several different types of surgeries to treat prolapse, including simple transvaginal colporrhaphy with a concomitant apical repair, and what's been considered by some to be the gold standard, abdominal sacrocolpopexy, which, I'd like to make very clear, also uses synthetic mesh.

But all women are not appropriate candidates for all procedures. The reason surgeons began reinforcing prolapse repairs with mesh in the first place is because some women simply don't have enough native tissue strong enough to stitch together to provide a lasting and durable repair. For these women, the additional support provided by the mesh may be their only hope for a durable repair.

One of the most important steps, however, in this surgical process is counseling the patient about her condition and her options, taking

into consideration what type of prolapse she has, the degree, the severity thereof, prior surgeries, especially when it comes to prolapse, concomitant pelvic symptoms such as pressure, bulge, any medical comorbidities, age, sexual activity, and so on. There are a lot of variables that go into making the decision of what type of procedure is appropriate for a given woman.

I unfortunately don't have the opportunity and the time allotted to go through how I weigh all of these considerations, but I'd be happy to answer any specific questions you may have later.

Like many surgeons, I've been turning increasingly to mesh surgeries over the years because of unacceptable rates of recurrence that have been seen with traditional surgeries and the high efficacy and durability appreciated thus far with mesh repairs. While this does not seem to be discussed much, the rates of reoperation for recurrence following traditional procedures are unacceptable.

Before transvaginal mesh kits became available, I, like many other surgeons, was cutting my own mesh in order to try to address this problem of recurrence.

The advance of transvaginal mesh kits made these procedures more consistent and allowed surgeons to be more effective in reaching parts of the deeper vagina that were previously a significant challenge. Adequate and safe access through the vagina, rather than abdominally, is less invasive and translates to advantages to the patient with respect to less postoperative

pain and shorter recovery times. The use of standardized tools has been a big advance.

But the issue of improved efficacy with mesh still seems to be in question, as it translates to a decrease in recurrence rates. Recent randomized controlled trials and case series on transvaginal mesh noted anatomical superiority with the use of mesh.

While mesh also demonstrated improvements in quality of life measures, these improvements were, however, equivocal to the non-mesh groups. This may be because most of these studies go out to only one year. Since prolapse is a progressive problem, this is not a sufficient amount of time for evaluation following prolapse procedures.

As a surgeon, I feel strongly that anatomical superiority clearly predicts better future outcomes with better sensitivity. This is not only through continued anatomical success, but through quality of life differences that may be appreciated as the number and degree of the anatomical failures in the non-mesh group increases over time.

Now, there's been a lot of focus on the potential complications of transvaginal mesh. As with any surgical procedure, there is a learning curve. And during my own learning curve, I noted some complications such as vaginal mesh exposures and obstructing symptoms from overly tensioned mesh. But I quickly learned to appreciate the differences in the surgical dissection technique necessary for successful vaginal mesh repair as opposed

to a non-mesh repair.

As with all surgery, there is a skill or an art to performing these vaginal mesh procedures, with the goal of providing support for the vagina while maintaining a functional vaginal space. Appreciating the surgical nuances between mesh and non-mesh repairs helps keep these complications to a minimum.

In my own experience, mesh erosions into the bladder, urethra, or bowel are very rare, and mesh exposures that can't be easily managed are also very rare.

With respect to vaginal mesh exposures through the vaginal wall, most occur within the first year and are associated with poor initial wound healing along the incision lines. Treating this can often be done with simple transvaginal estrogen therapy to promote re-epithelialization over the graft or minor surgical excision of the exposed graft repair.

In the case of mesh erosion into neighboring organs, again, very rare. In experienced hands, these have been able to be managed by minimally invasive means either through transvaginal or endoscopic excision, with resolution of associated symptoms.

In the case of dyspareunia or pelvic pain, severe cases are usually associated with the over-tensioning of the mesh in an attempt to provide maximal support. This can often be addressed through manual vaginal physical therapy or releasing incisions into the mesh to eliminate the

tension.

Again, it's vital for us as surgeons to discuss with women all of the risks of the surgical options. Traditional colporrhaphy, as you see on the left, is associated with a high recurrence and reoperation rate. And compared to the transvaginal techniques, abdominal sacrocolpopexy, displayed on the right, is associated with a higher risk of intraoperative bleeding, bowel, bladder, or ureteral injuries, postoperative small bowel obstruction, postoperative pain, and vaginal mesh exposures deep at the apex that is often much more difficult to excise and repair.

Now, I'm not trying to say that anterior colporrhaphy or sacrocolpopexy are not good procedures, but I'm just trying to put their risks into perspective with the transvaginal mesh risks. These complications of the abdominal sacrocolpopexy, as well as recurrences from the colporrhaphy procedures, have just as much impact on the patient, if not more, than those associated with transvaginal mesh.

In summary, transvaginal mesh kits have brought important new choices to women. For many women, it's the best option for a durable and lasting repair. Of course, each woman's situation is unique and it's up to her and her doctor to decide which type of treatment is really best for her.

While transvaginal mesh kits have helped the surgical community to standardize these procedures, the complexities of pelvic organ prolapse surgery still needs to be respected and should only be done by

experienced surgeons who understand the pelvic anatomy and surgical techniques necessary to successfully work with mesh in the vagina.

There has been great progress made in this area of women's health in a short amount of time. And while I'm not a regulatory expert, I do hope that we don't slow down the medical advances we have seen thus far by putting undue restrictions on these devices that have helped so many women.

We need to give women accurate information about the risks and benefits of every procedure so we ensure that they take advantage of the surgical option that may be in their best interests overall.

Thank you for your time.

DR. HINOUL: Thank you. Good morning. I'm Dr. Piet Hinoul, the Worldwide Medical Affairs Director for Women's Health and Urology of Ethicon. I came to Ethicon two years ago, and up until that time I was a practicing urogynecologic surgeon. I've performed of hundreds of transvaginal mesh procedures and traditional procedures to treat pelvic organ prolapse, and as a result, I have seen firsthand the clinical benefit this treatment option can provide women.

Today, I'm speaking on behalf of the Transvaginal Mesh Working Group through AdvaMed. In the next few minutes I would like to address the question that the FDA asked you to consider. I will highlight the data that demonstrate a favorable benefit/risk profile of transvaginal mesh

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repair for prolapse, and I will also outline the clinical proposals that the working group is suggesting to continue to ensure the safety and effectiveness on both existing products and new products coming to the market.

Device manufacturers have been consistently improving these products and conducting studies on these devices since they first became available. The first five-year studies on transvaginal mesh kits are being reported upon and additional studies are underway. This is, of course, in addition to the rigorous bench and animal testing that occurred before surgeons ever used these meshes.

Today, to help you in your deliberations, we would like to provide context of how these devices are being used, our analysis of the data, as well as our proposals to further the progress that has already been made in this important field in female health.

As Dr. Sutherland has just explained, pelvic organ prolapse is a complex disease involving several anatomic compartments and different levels of disease, which can be addressed through different surgical options, each with their own potential merits and their own potential complications.

Patients and doctors need to consider all the factors we just mentioned, as well as the patient's medical history, the surgeon's training and experience, and available data on intervention, to make an informed decision on which surgical approach is best for that patient.

Transvaginal mesh, like all medical treatments, is not the optimal solution for everyone, but it will be for some.

Starting with the FDA's question on whether there is adequate assurance of effectiveness, current data demonstrate that transvaginal mesh is effective; first, because it demonstrates a statistically significant high anatomic cure rate than traditional surgeries; secondly, there is also significant improvement in quality of life measures that is comparable to traditional surgery.

The first measure of efficacy is anatomic cure, which is measured by the POP-Q score, and that is a measure that the National Institute of Health and multiple medical societies have determined is the most objective outcome measure. And we are aware of the ongoing scientific discussions regarding whether the current staging of pelvic organ prolapse actually correlates with the patient symptoms. Regardless of the outcome of the scientific discussions, anatomic assessment will remain a cornerstone in assessing prolapse.

Now, let's look at the literature addressing anatomic cure rates. Among the randomized controlled trials for pelvic organ prolapse, seven compared transvaginal polypropylene mesh to traditional vaginal surgery. These data clearly show that transvaginal mesh is efficacious in restoring pelvic floor anatomy. In fact, in five of the seven, the difference between the two were statistically significant. Even the two studies, by Dr. Iglesia and

Dr. Carey, that did not reach significance, trended in the same direction, showing higher efficacy for the mesh arm in their studies.

The second measure considered in the studies was quality of life, or often referred to as QoL. The quality of life improvements reported in these studies for mesh were both clinically and statistically significant. And in the studies, where improvement in both groups were compared, the improvements were similar.

Now, I would like to briefly focus on the largest randomized controlled trial conducted to date on transvaginal mesh. This landmark article, recently published in *The New England Journal of Medicine*, specifically addressed women with isolated anterior vault prolapse.

This was a multicenter study that followed 389 women, comparing mesh to traditional colporrhaphy. They used a compound outcome measure for defining success, looking at both anatomic cure as well as the most specific prolapse symptom, the feeling of bulge. This article reports on these endpoints at one-year follow-up.

Women using mesh had an 82 percent anatomic cure rate as opposed to 48 percent cure rate in the traditional native repair arm. Mesh kits were superior for symptomatic outcome as well: 75 percent in favor of mesh versus 62 percent for colporrhaphy. The compound measure thus yielded a significant difference in favor of mesh, with a combined anatomic and functional success of 61 versus 35 percent.

Therefore, this study provides Level I evidence and is a clear indication that transvaginal mesh kits are a valuable treatment option, from both an anatomic as well as a functional viewpoint, for women suffering from anterior vaginal wall prolapse.

So we looked at effectiveness. Now, let's turn our attention to safety.

The FDA poses the question of whether there's adequate assurance of safety of transvaginal mesh for prolapse. The data demonstrates that there is adequate assurance of safety when we consider the two incidents of serious adverse events. Serious adverse events that are mesh-specific are very low.

Looking at the FDA's MAUDE database, which is designed to identify new events and signals, there have been new adverse events related to vaginal mesh identified since the initial introduction of these products. Although rates vary, the types of events remain the same.

We know from the literature that exposures are the most commonly reported adverse events for transvaginal mesh kits. We believe it's important to understand an essential distinction between mesh exposure, where a piece of mesh is exposed into the vagina, and mesh erosion, where we are actually referring to a perforation into a hollow organ by the mesh. Not differentiating between the two may lead one to over-interpret its clinical importance.

Mesh erosion complications are so rare that we learn about them in the literature through case reports. The long-term data we have for sacrocolpopexy, which uses exactly the same material as these mesh kits, has long established this.

For transvaginal meshes, when exposures occur, nearly half can be treated nonsurgically, as shown in a large meta-analysis by the Society of Gynecologic Surgeons, of 10,000 women treated by mesh.

One of the most important questions we need to ask ourselves is also why these adverse events are occurring. And the risk factors for mesh exposures are becoming more and more apparent. Several studies published this year show that hysterectomy, patient age, smoking, diabetes, and surgeon experience predispose patients to mesh exposure. Patient selection and risk factors, appropriately stated in the device's labeling, as well as the surgeon's training, are therefore part of our proposal.

Another adverse event that has attracted the attention is the occurrence of dyspareunia, or painful intercourse. It's important to note that dyspareunia is inherent to the condition of prolapse. And as you can see in the study quoted by Lowman, dyspareunia at baseline and new onset of dyspareunia post-intervention is prevalent for all treatment options.

While there has been a lot of focus on the complications of transvaginal mesh, it is important to note that the total complication rate for traditional repair, sacrocolpopexy, and mesh kits are all very similar, at 15, 17

and 15 percent, respectively, as shown in this meta-analysis on procedures addressing apical support.

Note that the total reoperation rate is indeed higher for the mesh kits, but most of these constitute ambulatory procedures for mesh exposure, while those for traditional repair and sacrocolpopexy are often major in patient operative procedures to treat wound problems, fistula injury, and bleeding.

Let us now turn to the question of whether the benefits of transvaginal mesh outweigh the risks. The data says yes. The benefits are clear in the areas of anatomic restoration and quality of life measures.

Risk is well defined. There have been no new events identified since the introduction of the products, and their rates remain low.

This is a complicated disease with a variety of presentations and available interventions. As I noted earlier, these treatment options are not one size fits all, nor are they each the most appropriate for all patients. It comes down to the surgeon individualizing the patient's care to her specific condition, but also to the patient-specific goals and expectations.

So turning to the FDA's questions regarding whether clinical studies should be performed premarket for transvaginal mesh, our position is yes, because, for transvaginal products, clinical data should continue to be generated for all new products, to assure new products remain as safe and effective as the current interventions.

We also want to make sure, however, that we are clear on what a clinical trial is meant to achieve. The appropriate trial design must be developed in conjunction with surgeons, manufacturers, and FDA because we firmly believe that one trial design will not apply to all new pelvic floor devices. The type of study will depend on the specific question of safety and efficacy asked, depending on the product differences from current products.

The study will also have to address the indication for use and the target population. Equally important can be to confirm whether key claims are met or when specific research questions need to be answered.

For these reasons, we have reservations about the FDA study design proposal because we don't believe that one clinical design can fit all. We agree that multiple efficacy endpoints assessing both functional and anatomical outcomes are needed. However, because of the low rate of adverse events, a trial powered for non-inferiority would require an unacceptably large number of patients in order to meet that endpoint, with little gain in patient protection.

There are also some practical limitations regarding a surgical randomized controlled trial design that we must consider. First, surgeon and patient preference to one type of surgery over another will influence recruitment. Also, ensuring that the control arm, the traditional repair, is performed in a standard fashion is not always easy. And lastly, blinding the assessor has proven to be difficult, as incision size and adverse events reveal

what type of surgery was actually performed.

Therefore, we believe that for the introduction of the majority of new devices, a single-arm, prospective trial with multiple efficacy endpoints assessing functional anatomy will appropriately address the questions regarding continued safety and efficacy.

As I mentioned, we feel the study should be powered to address these multiple efficacy endpoints that assess both anatomy and symptoms.

In conclusion, we believe the benefit/risk profile of transvaginal mesh is comparable to traditional surgeries. In fact, the data demonstrate that transvaginal mesh is superior or equivalent to traditional surgery with respect to anatomy and is comparable in quality of life measures.

Serious adverse events, including mesh erosion, not to be confused with exposures, are rare. And mesh exposure, the most common adverse event, is usually minor and well manageable.

Nevertheless, device manufacturers are committed to collecting long-term data to further elucidate the benefit/risk ratio and to perform premarket clinical trials for new devices for this indication.

As a gynecologic surgeon who has seen firsthand the positive difference these procedures can make in a woman's life, and now as a medical director committed to ensuring safety and efficacy of these products, I want to make sure that this is an option that remains available for the

patients that need it.

I would now like to introduce Ginger Glaser, the Senior Director of Global Quality and Regulatory Affairs at American Medical Systems, to discuss our regulatory proposals in greater detail. Thank you.

MS. GLASER: Thank you, Dr. Hinoul. And good afternoon, everyone. I would like to focus my presentation on the question FDA is posing to you regarding the appropriate regulatory pathway for transvaginal mesh.

As the members of the Advisory Committee have seen from the briefing booklets, due to their evaluation of the literature and MAUDE data, FDA believes additional regulatory controls are needed for this product category.

As Dr. Hinoul described, these devices have been shown to be a safe and effective treatment option for women with prolapse.

We do agree that the early experience with these devices, as is common with all new devices, has identified areas for further study that may facilitate the continued achievement of possible optimal patient outcomes. Thus, we agree that FDA should utilize additional regulatory tools that are available within the Class II 510(k) process to ensure such information is collected and that patients and physicians receive the information that they need to continue to use the product safely and effectively.

In fact, of the types of controls that FDA has referenced, we

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agree with nearly all of them. Specifically, as you just heard, we agree that new products should have premarket clinical trials prior to the product gaining marketing clearance.

We also suggest that the following actions should be required: collecting additional postmarket clinical data on current products; revising the physician labeling for transvaginal mesh to have standardized content that clearly presents the safety and effectiveness information based on clinical evidence, and creating standardized patient labeling that clearly describes the risks and benefits of the devices for patients who are considering mesh repairs; requiring conduct of rigorous and specific preclinical or bench studies that are specific to the intended device use. In addition, device-specific physician training programs should be required.

We are committed to implementing, and in many cases have already implemented, these actions. And although not a topic for FDA controls, we have also committed to working with the certified boards and specialty societies in developing practice guidelines and training programs to assist surgeons using transvaginal mesh.

Our position on regulatory controls differs from that of FDA in only two points, one of which is simply a matter of degree. First, as you heard from Dr. Hinoul, we would like to discuss a more appropriate design for the premarket clinical trials than what's proposed by the FDA in their briefing materials. Second, unlike FDA, we believe that there is no need to reclassify

transvaginal mesh for prolapse repair into Class III because all the necessary controls are available within the Class II 510(k) paradigm.

Based on the data Dr. Hinoul just presented, we have demonstrated that there is sufficient information available to establish these special controls.

Historically, the 510(k) guidance on surgical mesh was applied to transvaginal mesh for prolapse repair as it was the only relevant guidance document available from FDA. This guidance is not specific to the nuances of transvaginal mesh placement for prolapse. Thus, in addition to following this guidance, manufacturers have conducted postmarket clinical trials and offered extensive physician training programs supporting the use of our devices.

We believe there is no need to reclassify transvaginal mesh prior to fully utilizing the many other regulatory mechanisms available within the existing Class II 510(k) regulatory framework.

Fully utilizing the existing framework would have the benefit of providing the information that physicians and FDA are seeking, while at the same time allowing manufacturers an efficient system in which we can provide surgeons and patients with continually improved devices.

As FDA clearly points out in their briefing booklet, the special controls provisions of the regulations give FDA the authority to create very specific regulatory requirements for Class II 510(k) devices. These special

controls may cover a wide range of activities, such as preclinical testing, premarket clinical studies, physician training, labeling requirements, and postmarket activities such as clinical studies, registries, or enhanced surveillance.

Additionally, as FDA also references in their briefing materials, 522 orders that specify postmarket clinical study requirements are also applicable to Class II 510(k) products. The proposed special controls provide sufficient evidence to address the concerns being discussed today.

Although, as we stated earlier, we do not believe a randomized controlled trial versus traditional repair is needed for premarket approval in most cases, such a trial could be required in a special controls document, as described in the regulations for Class II 510(k) devices.

The regulation describes special controls as those steps needed to provide reasonable assurance of the safety and effectiveness of the device. It does not define nor preclude any type of study design or duration either for premarket or postmarket clinical requirements. Neither does it require comparison only to other devices.

Based on the breadth of regulatory controls available for Class II 510(k) products, we believe that transvaginal mesh for the treatment of prolapse should remain in Class II and that special controls and 522 studies should define the requirements that address all of the questions raised by FDA and then ensure the continued safety and effectiveness of both current

and future devices.

From our perspective, the issue isn't that the regulatory framework governing transvaginal mesh is broken and needs to be replaced, but rather that it has not been fully utilized. We have demonstrated our intent to meet and exceed FDA requirements for our devices, and we are committed to continuing to improve our devices, our training, and the information provided in our labeling so that patients and physicians have the best information on which to base a decision on if and when they should use transvaginal mesh.

Finally, on behalf of the members of the Surgical Mesh Working Group, I would like to conclude by thanking you for giving us the opportunity to present the data showing that transvaginal mesh is a safe and effective treatment option that can continue to be regulated under the Class II 510(k) pathway.

We have the data available to create special controls, and we look forward to the opportunity to continue to discuss the proposed controls and clinical trial designs with FDA. Thank you.

DR. FALCONE: Okay, we're going to have the other presentation. Does that conclude your presentation?

MR. SECUNDA: Yes, it does.

DR. FALCONE: Okay. So we're going to go on to hear from Cook Medical, and then we will have questions from the Panel for you.

DR. MARK: Good afternoon, ladies and gentlemen. My name is Dr. Saralyn Mark. I am an Adjunct Associate Professor of Medicine and Obstetrics and Gynecology at both Yale University and Georgetown University Schools of Medicine. Today, I am speaking as a consulting scientific policy advisor for Cook.

Cook is a privately held manufacturer of products for surgery, gynecology, and other medical specialties, with more than 10,000 employees worldwide, including 8,000 employees in North America. For more than 13 years, Cook has been providing biologically derived grafts that are not crosslinked, including grafts for pelvic organ prolapse, also known as POP, in over 10,000 patients. Given its background, Cook respectfully submits the following comments for your consideration.

Surgeons have been using synthetic mesh and biologically derived grafts for over 10 years to improve upon the outcomes associated with standard colporrhaphy. However, FDA's recent report has raised legitimate concerns about these products.

To place the report in context, successful outcome of any implant procedure depends on three factors: (1) assuring that the patient is a suitable candidate; (2) performing the procedure correctly; and (3) choosing the appropriate product.

While the report addresses the safety and effectiveness of different procedures, it only briefly acknowledges that there are significantly

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different types of products.

Although the report mentions both nonabsorbable and absorbable synthetics, it does not distinguish between chemically crosslinked versus non-crosslinked biologic grafts.

As a result, Cook has conducted a thorough review of the literature on POP repair with respect to these four fundamental material types. We reviewed the literature on tissue response and on clinical outcomes. Please note that Cook's products are one of several non-crosslinked biologic grafts on the market. Our review focused on material types, not specific products, as we believe that the analysis by material type is more instructive than analysis by individual product. The literature review has been submitted to FDA and the Panel and is available on FDA's website. The remainder of my presentation summarizes the review and our conclusions.

Most nonabsorbable synthetic mesh for POP repair is made of Type I polypropylene. With Type I polypropylene, compact fibrous tissue surrounds the mesh, which is postulated to provide a strong bond between it and adjacent tissue. However, there is a body of literature that suggests that the ultimate tissue response is that of a foreign body, such as granulation, limited neovascularization, eventual fibrosis, and encapsulation.

Absorbable synthetic mesh has an initial response similar to the response to the nonabsorbable mesh. Unfortunately, the patient's cells

hasten the degradation of the mesh. So absorbable synthetic mesh products do not provide long-term mechanical support and are not in widespread use and will not be discussed further.

Cross-linked biologic grafts are processed using chemical agents to bond or crosslink collagen fibers together in hopes of inhibiting the rate of degradation. However, the normal infiltration of the body's own cells into the graft is significantly decreased. Studies show that inflammation gradually gives way to a foreign body reaction and encapsulation. The tissue response of chemically crosslinked graft material is much like a synthetic.

Non-crosslinked biologic grafts are minimally processed to remove cells without crosslinking the collagen. They provide both mechanical strength and a collagen scaffold that permits cellular infiltration, proliferation, and remodeling of the patient's tissue. The scaffold is gradually repopulated by the patient's cells. In its final state, the structural defect is repaired and reinforced as the original graft material is replaced by well-organized connective tissue and a normal vascular supply.

Cook reviewed the synthetic mesh products and standard colporrhaphy by examining the references cited in FDA's report. Additionally, Cook reviewed the clinical literature for the past 15 years for articles describing biologic grafts used in POP repair. For every article, the incidence rates of the following five parameters were reviewed: (1) erosion, (2) pain including dyspareunia, (3) graft-related infection, (4) persistence or

recurrence of prolapse based on objective measures such as the POP-Q score, and (5) symptomatic recurrence.

Cook's review presents extensive data on the five parameters for the different material types. However, when comparing different types of materials, three objective measures, erosion, infection, and objective measurement of recurrence, allow for a more standardized comparison than the subjective measures of pain and symptomatic recurrence. Thus, the next three slides focus on erosion, infection, and objective recurrence for the three widely used material types.

Rates are reported as non-weighted averages of the incidence rates reported in the literature. Reports were weighted equally, in part to prevent very large studies from unduly influencing the analysis.

As can be seen, nonabsorbable synthetic mesh products had a 10 percent erosion rate, while crosslinked biologics had 6.2 percent rate. Repairs with non-crosslinked biologic grafts had the lowest erosion rate at 1.2 percent.

Infection rates associated with all three material types were similar to or lower than 4.0 percent infection rate associated with colporrhaphy.

Repairs with all three material types had lower rates of objective recurrence than colporrhaphy. Repairs with nonabsorbable synthetic mesh had the lowest objective recurrence rate. The rate for repair

with non-crosslinked biologic grafts was approximately one-half of the rate for colporrhaphy.

These differences in clinical outcomes between materials are consistent with the body's local tissue response. The histological literature suggests that the body responds to nonabsorbable synthetic mesh and chemically crosslinked biologic grafts as foreign bodies. The body responds to non-crosslinked biologic graft materials by remodeling it into organized tissue, substantially reducing the risk of long-term foreign body response.

The data shows that the different material types have different risk profiles. To illustrate this difference, the next slide compares data on all five outcomes associated with nonabsorbable synthetic mesh products and non-crosslinked biologic grafts.

Both types of materials offer decreased rates of pain, objective recurrence, and symptomatic recurrence compared to colporrhaphy.

Non-crosslinked biologic grafts also offer decreased rates of infection. The clearest difference is in the erosion rates, with repair using nonabsorbable synthetic mesh products having a 10 percent rate and repair using non-crosslinked biologic grafts having a 1.2 percent rate.

It is also important to note the significance to the patient in management of erosion and recurrence. Erosion with a non-crosslinked biologic graft can be managed with topical medical treatment, rather than one or more operative revisions. Recurrence of the prolapse with a

non-crosslinked biologic graft does not involve working around or removing the graft. The graft remodels into organized tissue and the fascial planes are preserved, thus making it easier to perform a surgical revision, if necessary.

In summary, the literature review shows important differences exist in the risk profile among the four types of materials: tissue responses are different; erosion rates are different; recurrence rates are different; management of complications is different.

Cook's review shows that the literature strongly suggests that important differences exist between materials in terms of tissue response and clinical outcome. The literature provides reasonable assurance of safety and effectiveness of non-crosslinked biologic grafts, such as those provided by Cook and other companies.

Therefore, Cook believes that non-crosslinked biologic grafts should remain as Class II devices for the following reasons: the grafts are not permanent implants but are replaced by the patient's organized tissue in less than 12 months; the grafts are not for use in supporting or sustaining human life; any complications associated with grafts can be managed with less risk to the patient; the grafts have a low overall risk profile; the grafts have a improved safety and effectiveness profile compared to colporrhaphy.

So, in summary, Cook urges the FDA and the Panel to consider this information when deliberating on recommendations concerning materials for POP repair.

Thank you for considering our views.

DR. FALCONE: Thank you. So first of all, I'd like thank industry for their thorough presentations.

And I'm going to open it up now to the Panel. It's 12:25, and we have until 12:45, so if there are any questions for any of the industry.

Okay, we'll start with Dr. Brill, as usual.

DR. BRILL: Andrew Brill.

Dr. Hinooul, I have a question for you. Both in the FDA summary as well as statements made by various public presenters today, there's been a question of the denominator, the true number and how we can relate that to incidents or reported events on the MAUDE database.

Can you speak on behalf of the consortium and tell us how many of these products have been placed to this date?

DR. HINOUL: Piet Hinooul.

The working group represents around 80, 90 percent, as we stated, of all the products sold. I want to make clear that we have no issues, or we do not contest what the FDA has stated that they've seen otherwise in the adverse event rates reported through the MAUDE database.

Even for industry, it is difficult for us to see -- to know how many of these procedures have actually been used. We know how many have been sold, approximately, but how many eventually end up into the patient in a certain period of time is not clear for us.

We have done our own analysis of MDRs, and if you would like to look more specifically into those numbers, I would like to call one of our members of industry that can explain those numbers, if we can have access to our backup slides.

Would that be possible, Dr. Falcone?

DR. FALCONE: Yes.

DR. HINOUL: So I call to the lectern Dr. Michael Steinbuch.

DR. STEINBUCH: Michael Steinbuch.

So in this slide we see, for the Transvaginal Mesh Industry Working Group, we pulled together all of the complaint intake information that was submitted to FDA in the form of MDRs, and you can see, across the top we have the information starting in 2005 all the way up to 2010. We have the complication broken out by the various complications, and the details for how those were done were submitted in the AE analysis section of the docket submission.

In the next portion you can see, as Dr. Hinoul said, we have the mesh kits sales. So for mesh kits for POP, we have that. And so the very bottom row indicates the percent of AEs for mesh kits, ranging from 2005 all the way to 2010.

DR. FALCONE: Does that answer your question, Dr. Brill?

DR. BRILL: Yeah. Those are cumulative numbers or those per annum?

DR. STEINBUCH: Per annum.

DR. BRILL: Per annum. Thank you.

DR. FALCONE: Okay, Dr. Fitzgerald.

DR. FITZGERALD: I have a question for the representative from Cook Medical. I'm sorry, I don't know your name.

DR. MARK: I'm Dr. Saralyn Mark.

DR. FITZGERALD: Thank you, Dr. Mark. I have a question for you about the non-crosslinked biological mesh, obviously. You point out how its behavior, the behavior of the mesh portion of the repair, it does differ clinically and statistically from the nonabsorbable meshes.

Can you tell us any information you have about the associated use of trocars or other devices to implant the non-crosslinked biologic mesh? Or is there any difference there?

DR. MARK: Thank you very much for your question. Is it possible also to call up my colleagues as well to the podium, if they were not a speaker?

DR. FALCONE: Yes.

DR. MARK: Okay, I'd like to call Dr. Dan Dillon, as well, so he can provide additional information.

The SIS material helps to provide repair as well as remodeling. The body responds to it. But I'm going to have Dr. Dillon provide that answer.

DR. FITZGERALD: And this is information about the placement

of the trocar?

DR. MARK: Placement of the trocar, yeah.

DR. FALCONE: Are the slides ready and set to go?

DR. MARK: No, he does not have a presentation.

DR. FALCONE: Okay, just a response. Okay, go ahead. Please identify yourself.

MR. DILLON: My name is Dan Dillon, and not only do I not have slides, I'm not a doctor.

We did not analyze for that particular aspect. And let me just double check. I believe that we don't specifically indicate using trocars or any special kits with it. That's up to the surgeon.

DR. FALCONE: Yeah, can you speak in the microphone, please?

MR. DILLON: Yeah. We don't sell any special kits with our products and we didn't analyze for that factor.

DR. FALCONE: Does that answer your question, Dr. Fitzgerald?

DR. FITZGERALD: Thank you.

DR. FALCONE: Okay, before you leave, there's another question for you. Right. Go ahead.

DR. CHAPPELL: Yes. So you made some fairly rosy statements concerning non-crosslinked biologic grafts. Could you tell us, or remind me because I don't recall, how many patients total you have experience with? Although that may relate to the last question. And the kinds of follow-up that

you have.

DR. MARK: Yes. Dr. Saralyn Mark.

We've had over 10,000 patients, we've had clinical study follow-up for up to three years, and we've had no MDRs.

DR. FALCONE: Let's see. Dr. Iglesia.

DR. IGLESIA: Yes, Cheryl Iglesia. I have a question for Dr. Hinoul.

DR. HINOUL: Dr. Hinoul.

DR. IGLESIA: Yes. My question relates to experience and generalizability and just what the industry thinks about that, in that the early -- in experienced hands, the exposure rates that you reported were two percent. But even in experienced hands of the clinical investigators, when they report the longer five-year data, those exposure rates jump up to double digits, 17 percent and whatnot, and I was just wondering what industry's view on that is, in terms of when do you consider making modifications?

DR. HINOUL: Okay, thank you, Dr. Iglesia, for that question.

Well, there's two parts to my question. First, about the exposure rate. I think, in my presentation, I did not quote the rate of two percent. I referred to the Abed paper published this year on 10,000 patients in whom mesh was used, and they quote a rate of around 10 percent, which we agree with. The paper by Diwadkar, I forgot exactly what the exact number is, but it's also much higher than five percent.

We also clearly acknowledge that mesh exposures, even in experienced hands, exists. We don't deny adverse events. What we do disagree with is the clinical importance that the FDA is attaching to it because, indeed, according the FDA's definition of a serious adverse event, any patient that has to be taken back into the hospital or into an operating room is correctly defined as a serious adverse event for regulatory purposes. But I think that many of the clinicians that we've heard today would concur with me that most of them are not a serious adverse event.

And I also agree, and I have a lot of empathy for the patients that I saw today that have got significant morbidity related to it, but we are very clear that what we've learned from the literature and what we've learned from our MDRs, that these are very rare, those very severe instances.

As I also quoted, there seems to be certain populations that are going to have a higher risk of developing an exposure: hysterectomy, diabetics, smokers, recurrent surgery, and then surgeon experience. Does that mean that we have to start restricting it for certain populations? Well, I think that again is going to be an individual decision that a surgeon's got to make between -- you know, the surgeon's got to make with the patient because -- let me give you an example.

Let's say you've got a clearly mid-compartment prolapse. She would be an ideal candidate for sacrocolpopexy because, indeed, if you introduce the mesh abdominally, your mesh exposure rate is going to be

lower because you haven't got a vaginal incision. But if that same patient, you know, is very obese or has a lot of other comorbidities, you know, the anesthesia necessary for an abdominal procedure may still warrant her to choose for a transvaginal procedure.

DR. IGLESIA: But my question really was, do you have a criteria for modification of an implantable device, for potential products? Yes? No? Perhaps?

DR. HINOUL: We do not feel that the exposure rate that is established in the literature at the moment would indicate that, would signal that we should have to modify the mesh.

DR. FALCONE: Okay, Dr. Mattison.

DR. MATTISON: Dr. Hinoul, you indicated that the medical device organization is in favor of premarketing single-arm studies. Would you describe how those would be evaluated?

DR. HINOUL: What our outcome parameters would be? Is that what you mean?

DR. MATTISON: Yeah, what would you evaluate them against, if it's a single-arm study?

DR. HINOUL: Well, as I stated -- and I'll speak on behalf of medical affairs, but I would also like to have our clinical development expert, Dr. Jessica Shen, answer the question in more detail to you.

But we feel that there is robust data out there establishing the

safety and efficacy, and we would compare it to what is out there. But of course, it will depend on what your clinical trial has to answer. And as I said, the clinical trial design will have to be in conjunction with the FDA and the surgeons to answer the appropriate research question.

And I would like to have Dr. Jessica Shen be more detailed about our proposal.

DR. SHEN: Jessica Shen.

First of all, we would like to identify the research questions first. Based on the existing data, what's the remaining research question that would propose an appropriate study design working with the Agency and clinical investigators? And we do agree, a potential -- a primary endpoint could be a composite endpoint, including both anatomic measurement and patient symptom improvement or patient-reported outcome measurement.

So we would also like to propose a longer follow-up, and the primary endpoint could be up to one year for premarketing, and continue to follow the patient out for a long-term outcome, both anatomically and quality of life. And we will also include all the mesh-related adverse events and regular adverse events reporting.

DR. FALCONE: Go ahead.

DR. CHAPPELL: Rick Chappell.

So following up on that same line of questioning and actually repeating what I heard as your original question, because we've heard several

times today that surgeon experience must play a big role in this. And we just heard Dr. Hinoul say that the patients themselves can be quite variable.

The crucial issue is the control. What control group would you use? Suppose you decided on analysis, outcomes, et cetera. To whom would you compare these single-arm studies?

DR. SHEN: That's exactly the challenge for this type of study design, and we would like to really answer that question based on an individual device, what the device proposed indication would be, what the change is compared to the previous generation or other devices on the marketplace. What's the existing evidence we have? What's appropriate or, in theory, what's an appropriate patient population that we can't identify?

Then we narrow down the patient population and hopefully we can standardize the -- if we have proper control, surgical procedure, we can identify the proper surgical standard. And then that would be appropriate to do a randomized controlled study. But that inherently is that surgical standard practice can vary. That really posed a challenge for us. That's why we believe, in lots of settings, a single-arm, well-designed, prospective cohort study would be beneficial to provide long-term data to help patients and clinicians to make an informed decision.

DR. FALCONE: Any rebuttal on that? Let's move on to Dr. Diamond.

DR. DIAMOND: I had two questions, one of which has really

been the topic of these last two, which I guess I'll just make the first question a statement, which is that I share the concern that members of this Panel have had about the idea of a single-arm study, and would actually point the consortium to their own data that you all shared with us in Slide C-27 and C-28.

And for both of the endpoints that you've just mentioned, of anatomical cures as well as quality of life outcomes, you have tremendous variation of the studies that are there, both for the traditional arms and for the mesh arms. And so how you would assess the results that you would get from that study, I think, is a huge, huge challenge.

Now, I do want to say along those same lines that I do also agree, though, with the comments that you all made, that no individual study design is going to be appropriate for all products and that that should be individualized based on specific questions that are going to be assessed and the properties of the product that's going to be evaluated. But, again, to have a single-arm study, I don't see how you can do that and be able to make a comparison.

The question I wanted to ask was, another comment that was made was that there may be patient characteristics which are different. And some have been mentioned, patients who had a hysterectomy or smoking or weight. But I would suspect that those are going to be different, not only for patients who may receive mesh, but for alternative therapies as well. And

one of the comments that Dr. Hinoul -- and I hope I pronounced your name correctly -- made was that mesh may be best for some.

And so the question is, which patients is it best for? I know there are problems that will happen in high-risk groups, but I think they'd probably be high risk for all. Which are the patients for which you think mesh are best for, as you alluded to in your presentation?

DR. HINOUL: Piet Hinoul.

Dr. Diamond, thank you for your question. I think most of the studies have -- and certainly the observational cohorts series have been published upon -- represent your average presentation of prolapse in a clinical setup. However, there's certainly two well-run, well-conducted randomized controlled trials for specific indications, one being the Altman paper on the anterior vagina wall prolapse, showing superiority, and the other is a Dutch research consortium run by Withagen, presented and published in *The Green Journal* earlier this year, looking at recurrent surgery.

So all the patients included in that study have undergone traditional repairs in the past, but in all compartments. And they too show clearly, at one year, superiority from an anatomical perspective and equal outcomes for quality of life.

So we have randomized controlled data available to us for those specific groups, anterior vagina wall prolapse and recurrent surgery. But I think that has been the message throughout the day. It's a very complex

disease. So making these studies very, very specific, they will no longer correlate to the real-life setting that a surgeon is dealing with in his daily practice, and that is why an overall statement or an overall assessment in clinical trials in cohort series seems appropriate. Unless you want to specifically address the question of this is better for posterior or for anterior.

DR. DIAMOND: But you made the comment that mesh was best for some patients. What are those patients for whom mesh is best for? Perhaps I misunderstood you.

DR. HINOUL: No, Dr. Diamond, I tried to explain that the randomized controlled trial data, on which I can base my clear statement on Level I evidence, is for anterior vagina wall prolapse and recurrent surgery.

DR. FALCONE: Okay, we're going to have one last question from Dr. Dominik, and then we're going to break for lunch. There's going to be plenty of time to ask our industry colleagues after the lunch break, but just to keep on time, because it's 12:45.

So go ahead, Dr. Dominik, a final question.

DR. DOMINIK: In part, this is a reiteration of a comment that -- the choice of control group. If you can't identify what would be the appropriate control group for a randomized study, I think it's even harder to say what group of historical controls would provide meaningful comparison.

And I wonder if it's possible that the control arm not just be, you know, defined as one procedure, but that the control arm be a choice of

procedures, depending on the surgeon's judgment, so that the control arm might be a choice among a small number of procedures that are involving native tissue and that don't involve mesh versus the randomized arm that would involve -- you know, the arm that would include the mesh. So rather than say, you know, narrow it down to a very limited option in the one arm, that it be a choice, depending on the particular case.

DR. HINOUL: Yeah, I understand your viewpoint, and I agree with what you're suggesting, but that is why I think that we've got to continue investing in research in this field and take the whole body of the evidence and move forward with that because that isn't going to resolve it.

Let's say, for example, the Altman study is so specific that the criticism from the people looking at that paper say it's too specific. And I rarely see an isolated anterior vault prolapse in my practice, whereas, on the other hand, the Withagen paper, where they allowed in the control arm the surgeons to do the traditional repair they were used to doing, the criticism to that paper is, well, they are comparing apples with oranges.

And that's why I think we've got to continue moving forward, stick to validated outcome measures, both for quality of life and anatomy, and then the bulk of the literature is certainly moving our knowledge and our understanding of this condition, of this significant condition, forward and we've seen great progress, I believe, in the last five years.

DR. FALCONE: If there are any questions on the control group,

I'm going to allow it because this is an important part of what we're going to discuss this afternoon. It's just so we can bring some measure of -- are there any questions? Yeah.

DR. KALOTA: Susan Kalota.

I see the only true option control group is doing it against no mesh, but I think that's going back many years. And that's a personal opinion. But the only true scientific data would be comparing it to a group who do not get mesh, and I think that's an impossible study to do, unless somebody's paying for it.

DR. HINOUL: Piet Hinoul.

But the studies have been done. So the two randomized controlled trials, we're certainly talking about almost -- approximately 600 patients that have been randomized to mesh versus traditional repair.

DR. FALCONE: Okay, Dr. Rogers has a question on control groups.

DR. ROGERS: We've heard it a number of times in the presentations today, about a repair for the anterior compartment or apical or posterior compartment. But the vagina is a continuous organ, right? And I think this is related to the control group issue because of the extreme variation in patient presentation.

But I also agree with my colleagues' comments about the fact that trying to single out an appropriate control group in a nonrandomized

fashion would be almost impossible with the plethora of presentations of prolapse which result in similar symptoms, you know, when we hear presentations about types of prolapse that, you know, I had three out of the five types of prolapse.

So I'm just wondering what's industry's opinion about this compartmentalization piece that was also addressed in the FDA materials that were made available to us, and whether that is the correct way to think about it, and would that inform our choice of control groups for further data?

DR. FALCONE: Hit the button.

DR. HINOUL: Piet Hinoul.

Thank you, Professor Rogers. I think it will -- and this is why we refer to labeling and indications for use or target patient populations. If the mesh device that would be going to the market is specifically addressing anterior vaginal wall prolapse -- and I realize very well that in a lot of the cases there's an apical component to that. But if we stick together with the FDA and the authorities into the field to design that study and the mesh kit is specifically addressing anterior vaginal wall prolapse, then I think that clinical trials should only involve those patients. It shouldn't involve posterior vaginal wall prolapse procedures or concomitant procedures.

If it is a generic kit for prolapse in general, then I think you will have to design the inclusion, that it will include an equal number of anterior, posterior, and middle compartment patients.

But I think that is why we feel let's not settle on one single study design. Let's treat each device and each indication individually and come to a good clinical trial design. We're not going to solve, as industry, all of the problems of urogynecology with the next study that we're going to come up with.

DR. ROGERS: Do you think, though, that -- Rebecca Rogers. Do you think, though, that that would end up with a series of studies focused on small numbers of patients who present with isolated anterior, posterior, or apical problems and not address the multitude of women who present with multi-compartment problems?

DR. HINOUL: I think if you are making a kit that would address multi-compartment prolapse, then that is going to be addressed in that study and the inclusion criteria should be clear on that.

DR. FALCONE: Okay. Well, thank you.

So we're going to break for lunch. And for the panel members, you will all be sequestered together in a room for lunch, at which time you are not to discuss amongst yourselves or any member of the audience the meeting topic. And we'll reconvene in one hour. Yeah, we're going to reconvene in one hour, which should be 1:51. And please take any personal belongings you may want with you.

(Whereupon, at 12:51 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:50 p.m.)

DR. FALCONE: Please take your seats. Go back to your seats so that we can start, so we can resume this Panel meeting.

And first we're going to go ahead with the FDA presentation. And we have four speakers, and I guess we're going to go in the order that's listed, right? Okay.

MS. PRESSLY: Good afternoon. We'll now begin the FDA segment of the Panel meeting, where we will present the FDA perspective. We'll begin with MDR analysis, followed by the systematic literature review, the clinical overview, and then we'll go into the concluding remarks and the Panel questions.

I'm Nancy Pressly. I'm the Associate Director for the Division of Postmarket Surveillance in the Office of Surveillance and Biometrics, and I will be presenting the MDR analysis that was performed by one our staff members. This is the analysis of surgical mesh for POP repair.

I'll begin with a brief overview of the Medical Device Reporting system for those of you who are unfamiliar with MDR. It will then be followed by the search methodology, the limitations of the search, as well as the results.

What is MDR? MDR refers to Medical Device Reporting. MDR

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is required under 21 C.F.R. Part 803. Manufacturers are required to report deaths, injuries, and malfunctions related to their devices to FDA. User facilities are required to report medical device-related deaths to FDA and the manufacturer, and serious injuries to the manufacturer. MDR is a mechanism for FDA and manufacturers to identify and monitor significant adverse events involved with marketed medical devices.

In addition to the mandatory reporting, there's also voluntary reporting. Anyone can file a voluntary report through FDA's MedWatch program, and we encourage clinicians and patients to use this. And the link is included here for anyone's use.

Mandatory and voluntary reports are entered into the Manufacturer and User Facility Device Experience database. This is also referred to as the MAUDE database, so you may hear that term.

In 2010, FDA received more than 300,000 individual MDR reports into the MAUDE database.

MDR reports provide a qualitative snapshot of adverse events for a specific device or device type. They vary in quality and usefulness due to the information that's provided, or the lack of information that's provided. MDR reports include both coding of the problem as well as narrative text. Each individual report may be coded with multiple problem and event codes.

There are numerous limitations of MDRs. We've heard a little bit this morning. As one of the speakers mentioned, there's vast

underreporting of events, and there's really no way of quantifying the underreporting for any specific device type.

Many times the reports include insufficient or inadequate information to draw any types of conclusions. There's often an inability to establish causality between the device and the event that occurred. There's an inability to establish a rate of adverse events. You cannot take the number of adverse events that are in the database and divide it by the devices that have been sold by a manufacturer to come up with a rate. MDRs cannot be used in that manner. Trends in numbers should be interpreted cautiously because of all of these limitations.

We'll now move on to the specifics of the mesh analysis. The search criteria that we used included looking at the two product codes that meshes are classified under by the FDA. And I want to point out that all meshes, at the time the search was done, were procoded under these two procodes. The data entered that we used was between January 1st, 2008 and December 31st, 2010. This gave us all meshes, all reports related to all meshes.

So we had to then remove meshes that we were not interested in. The first group that we took out were all the non-urogynecological meshes. This accounted for about half of the reports that we found during our initial search. These are all hernia meshes, the meshes for male incontinence. There are limited meshes for orthopedic uses. All of those

were removed from what we looked at.

Additionally, we looked for any duplicate reports, reports with unknown device specifications -- these typically came from voluntary reporters who did not know what mesh was implanted in them -- and miscoded reports. Occasionally, reports are given the wrong procode and should not be in that search. Those three final categories were a very small amount of reports that were removed.

The remaining reports were then sorted into pelvic organ prolapse use or stress urinary incontinence use, based on the indicated use of the product that was being reported on in the report. A number of the reports, based on the report narrative, involved both POP and SUI procedures being done. In this case, the report was categorized based on the intended use that the mesh was being reported on. So even though both types of procedures were discussed, we went by how the report was coded.

After we separated these reports into the two types of uses, the following analysis was completed using semantic text mining techniques as well as traditional analytical methods.

I want to point out a few limitations that are specific to this search, in addition to the general limitations that I already mentioned.

In many cases there were multiple procedures in one operation. It's difficult, in that case, to know exactly what part of the operation the adverse event was related to. Again, we went by the device

that was reported on in the MDR report. In some cases, multiple meshes were used, based on the narrative of the text. And, again, we went by how the device was coded, by the way it was submitted to the Agency, for how we looked at that.

There were a number of voluntary reports in which lay terminology was used, which can be confusing and not always match the language and terminology that we are expecting or looking for.

This table provides a breakdown of the number of reports received during each year we looked at. These numbers include all reports received: deaths, injuries, and malfunctions. This is approximately a five-time increase in the number of reports over the previous three-year reporting period, when we had done our previous look in this product area.

But I want to point out that multiple factors can affect the number of MDRs that are received. These can include an increased use of mesh in the clinical community, an increased awareness of the potential adverse events associated with urogynecological surgical mesh after our 2008 Public Health Notification, as well as the increased number of new POP meshes in the marketplace.

There were seven deaths associated with the use of surgical mesh for POP. While deaths have occurred, we understand that surgical complications happen with all surgeries, and we do not believe that this is the main concern regarding these devices.

What we do want focus on is the adverse events that we've seen. This table lists the top 10 adverse events that have been reported. These numbers represent the number of MDR reports that cited a particular adverse event. The total number of adverse events is greater than the number of MDR reports because many MDR reports cited more than one adverse event. Be aware that the percentile listed in the last column is the percent of MDR reports that cited the particular adverse event.

Note that the top two adverse events are erosion and pain, each occurring in about a third of the reports. This is followed by infection, bleeding, dyspareunia, organ perforation, urinary problems, neuromuscular problems, vaginal scarring and shrinkage, and recurrence of prolapse.

The most frequently reported interventions are shown in this table. Please note that in many cases the required intervention was not provided to us in the report, so this just is information for when we were given it. Additionally, there may be some overlap in the groupings listed in the table.

Additional surgical procedure, without specific information on what this included, was the top intervention. Additionally, there were specific reports of mesh explantation as well as general reports just stating hospitalization.

In summary, FDA is seeing a persistent signal related to the use of surgical mesh for pelvic organ prolapse. This includes reports of serious

life-altering adverse events. This MDR signal led the FDA to further evaluation, which included an in-depth literature review.

We will now hear about the literature review from Colin Anderson-Smits.

MR. ANDERSON-SMITS: Thank you, Mrs. Pressly. And good afternoon, distinguished Panel members and audience. My name is Colin Anderson-Smits, and I'm an epidemiologist in the Division of Epidemiology, Office of Surveillance and Biometrics. I will be presenting the epidemiological review and need for postmarket studies of surgical mesh used to treat pelvic organ prolapse.

Today I will be briefly discussing our recent review of the literature on surgical mesh used for the treatment of pelvic organ prolapse, or POP, including our methods and findings. This will be followed by preliminary results on analysis of Medicare data that we have conducted on POP and risk of revision surgery and FDA postmarket regulatory options.

As discussed in depth by Mrs. Pressly, at the time of the 2008 Public Health Notification, the number of adverse events reported to the FDA for the previous three-year period, 2005 to 2007, was listed at over 1,000. Since this assessment, another search in January of 2011 of the MAUDE database, for the time period of 2008 to 2010, identified an additional 2,874 MDRs for urogynecological surgical mesh, with slightly more than half associated with POP repairs.

Based on the MAUDE findings and an effort to establish new policy for review of surgical mesh devices, we have systematically reviewed the scientific literature to review the safety and effectiveness of surgical mesh for urogynecological indications. We have assessed these findings separately for the use of POP and stress urinary incontinence, or SUI.

Our review started with a broad search of the MEDLINE database for randomized controlled trials, observational studies, and systematic reviews or meta-analysis from January 1996 to April 2011, performed in PubMed using extensive terms related to surgical mesh and urogynecological procedures.

For our review of the literature, we decided to keep any RCT with a surgical treatment arm with no restriction on sample size. Observational studies with multiple treatment groups with at least one mesh arm were kept if they had a sample size greater than or equal to 100. Single-arm observational studies evaluating surgical mesh were kept if there were 50 or greater patients.

The initial search yielded 925 articles. Titles and abstracts were reviewed, and a preliminary cut of the 925 articles was made based on the inclusion criteria presented in the previous slide. The remaining studies were then categorized into either POP or SUI indication. There were 75 total articles for POP that were fully assessed. Twenty-two were randomized controlled trials, or RCTs, and 38 were observational studies and are the focus

of this presentation.

It should be noted that upon early review of the RCTs available, substantial methodological limitations were apparent, including unmasked trials, large potential of confounding, such as not recording or adjusting for known confounders, which will be discussed later in this presentation, lack of clearly defined hypothesis-driven trials, and differential loss to follow-up between treatment arms, which indicates that randomization was broken by the time primary endpoints were measured.

While many of the trials were designed as RCTs, we determined that very few were truly executed as such, and therefore we decided to include patients from both RCTs and observational studies in the same evaluation groups as we reviewed the literature.

The quantitative findings of adverse events from treatment groups and RCTs and cohorts in observational studies are presented as weighted mean percentages. The percentage of an adverse event within a study treatment group or cohort was calculated by dividing the number of patients within the cohort who reported the adverse event within the specified time frame of follow-up by the number of patients within the cohort who continued follow-up through the specified time frame. The percentages of each time frame were then averaged across cohorts, weighing the percentage in each cohort according to the number of the patients in the cohort.

There were 115 treatment groups that met our inclusion criteria for POP. The number of treatment groups per study ranged from 1 to 3, and the range of sample sizes in each treatment group was from 13 to 577 patients.

This column graph displays the number of treatment groups or cohorts of patients broken down by the time period of patient evaluation and stratified by the described POP repair, which included apical, anterior, posterior, anterior and posterior, abdominal sacrocolpopexy, unspecified vaginal repair, and other POP, which include more rare surgeries and others that did not fit into the previous categories and in those in which there was no specification of the surgical approach.

As seen in the figure, a large proportion of the studies consisted of unspecified vaginal repair and reported adverse events and outcomes from the perioperative period, which was defined as the intraoperative period to 48 hours postop to 12 months postoperatively. Only five studies reported a follow-up period beyond 12 months.

The two most frequently studied procedures within the literature were anterior prolapse repair and abdominal sacrocolpopexy. Thirty-nine percent of the articles did not indicate a specific surgical approach. The duration of follow-up ranged from perioperative to 48 months postop, and as mentioned in the previous slide, very few followed up patients beyond 12 months.

Erosion can result in serious complications unique to mesh procedures and is not experienced by patients who undergo traditional repair. Mesh erosion may require mesh removal to manage the sequelae. In the published literature, mesh erosion into the vagina was found to be the most common and consistently reported mesh-related complication following vaginal POP repair with mesh.

We found that the weighted average of mesh erosion reported in the literature ranged from 7.7 to 19 percent from six months postop to 36 months postop, respectively. However, there's limited data beyond 12 months of follow-up.

Mesh contraction, causing vaginal shortening, tightening, and/or vaginal pain associated with vaginal POP repair with mesh, is another mesh-specific adverse event that was found to be reported in a small number of studies in the body of literature. However, please note that vaginal scarring and tightening can also occur following traditional repair.

Perioperative complications were consistently reported across the literature for POP repair using mesh. Based on calculations of weighted mean percentages, the most commonly reported adverse events associated with POP procedures using mesh were organ perforation, which included bladder, urethral, vaginal, rectal, occurring at a rate of 2.6 percent, bleeding at 2.4 percent, hematoma at 1.4 percent, pain at 6 percent, and infection at 7.7 percent.

While these findings warrant attention and consideration, it should be noted that all surgical procedures for POP have associated perioperative risks, and other non-mesh procedures are not immune to the complications presented above.

This column graph displays the weighted mean percentage of adverse events across the literature broken down by time period: 6, 12, 24, 36, and 48 months postop.

The weighted averages of adverse events past 24 months of follow-up are subsequently more heavily weighted by select studies and have smaller sample sizes, which can make the estimates less precise. There was one treatment group that had follow-up assessment at 36 months, representing a total of 209 patients. At 48 months there were two mesh treatment groups representing a total of 65 patients. There were no studies past 48-month follow-up that provided a calculable rate of adverse events among patients treated for POP using mesh.

Other postoperative adverse events commonly reported in the literature associated with POP repair in mesh treatment arms were dyspareunia, infection, which included wound, UTI and recurring UTIs, pain related to the mesh or surgical procedure, re-surgery and urinary problems, which include de novo urinary incontinence, de novo SUI, de novo overactive bladder, urinary retention, urgency, frequency, nocturia, and other voiding dysfunctions.

Please note that these adverse events are not mesh-specific related adverse events, such as erosion and contraction, and are also reported in traditional repairs.

Insufficient information exists in the literature to provide quantitative measures of these adverse events among women with non-mesh surgeries.

Later this afternoon you'll be asked to weigh in on the risks associated with vaginal mesh used for POP repair. Given the rates and incidence and severity of adverse events reported in the literature and other information provided to you today, you will be asked to discuss if there's adequate assurance of the safety of vaginally placed mesh for POP repair.

Of the studies evaluating transvaginal colporrhaphy for POP, there were 10 studies that evaluated anterior wall prolapse repair compared to a non-mesh group.

Please note that three studies included were follow-on studies of one trial and used the same dataset. Therefore, 3 of the 10 studies represent outcomes on the same group of patients, just at different follow-up times.

All 10 studies used anatomic benefit as the primary criteria of success. Four of these studies used improvement in the pelvic organ prolapse quality of life questionnaire as a secondary outcome measure. Eight of the eight unmasked studies measuring anatomic benefit showed a statistically

significant improvement in anatomic benefit of mesh compared to non-mesh. Of the two masked studies, one found no difference in anatomic outcomes between groups, while the other found a statistically favorable anatomic improvement in the mesh group.

Of the studies that measured subjective improvement by pelvic organ prolapse quality of life questionnaire as a secondary outcome, none found significant difference in improvements in scores in the mesh group compared to the non-mesh group, despite anatomic benefit.

There were four studies that evaluated posterior wall prolapse repair compared to a non-mesh group, all in conjunction with anterior repair. All of these studies used anatomic benefit as the primary criteria of success. Two unmasked studies found significant improvements in the mesh group; two failed to find a difference, one of which was masked.

Using a strict definition of anatomic success, which will be discussed further by Dr. Brown, it appears that mesh augmentation in the anterior compartment may provide an anatomic benefit compared to non-mesh repair. We believe that the literature provides inconclusive evidence on whether mesh augmentation for posterior repair provides a superior anatomic result compared to traditional repair.

Moreover, with the limited available literature on subjective anatomic outcomes, we believe that patients who undergo traditional repair have similar subjective anatomic improvements in prolapse quality of life,

compared to patients who undergo mesh repairs.

As I will discuss momentarily, however, it is difficult to arrive at conclusions about the impact of mesh or no mesh on outcomes, as many patients underwent concomitant prolapse procedures and could confound results.

In addition to the limitations of the RCTs discussed when I described the methods in our review earlier, there were several themes of limitations identified in the literature, such as the literature on POP repair largely represents studies in which the primary endpoint was ideal anatomic support; the outcome is not based on a correlation with symptomatology; results reflect both primary and repeat prolapse repairs; most studies involved concomitant surgical procedures; adverse events are not the endpoint of interest and are inconsistently reported across the studies; the inclusion and exclusion criteria are incompletely documented; the majority of the studies are not evaluator-masked or adequately powered; and very few studies extend beyond one year.

Considering the safety and effectiveness concerns with these devices, and in context of the limitations within the literature, you will be asked to discuss whether the risks associated with the use of vaginal mesh for POP repair outweigh the benefit.

I would now like to briefly present an ongoing surveillance study we at the Division of Epidemiology have been conducting using

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Medicare administrative billing databases. Using Medicare data, we identified all women, from January 1st, 2006 to December 31st, 2010, that had a transvaginal repair for POP, using CPT, HCSPCS, and ICD-9 codes.

Women were then categorized into two groups, depending on whether there was an additional HCSPCS code indicating mesh was used during the procedure. All women had to be enrolled 180 days prior to the procedure to be included.

We then measured the differences in rates of repeat or additional surgeries for POP among women who have an initial transvaginal surgery for POP using mesh, compared to those who had surgery with no mesh, up to one year after the initial procedure.

There were 212,113 women identified who had a transvaginal POP repair for the indicated time periods. Of these women, 55 percent had traditional repairs without mesh, and 45 percent had mesh used in their initial POP surgery. The majority of women were Caucasian and age 65 to 75 years old at the time of the initial procedure.

Using HCSPCS codes to define the primary outcome of interest, which is repeat for the same surgery, we found that women who were initially treated with mesh underwent re-surgery 2.26 times more often than women who did not have mesh placed. This is after controlling for age, race, hysterectomy, pertinent health risk factors, hospital size, and location.

There are limitations of using Medicare data that must be

noted. First, it's an open cohort where beneficiaries move into and out of the database. Secondly, it's claims based. This presents a possible time lag from the actual day of the procedure until it is captured in the data by the billing date.

Additionally, there exists the potential that patients could've been misclassified as an initial mesh or no-mesh procedure, as billing codes are the only method of classifying the women, and its validity is unknown. Therefore, results from this study could be either underestimates or overestimates of the true risk of repeat surgery within the study population.

We believe that the available scientific literature does not provide evidence that surgical mesh currently on the market and indicated for vaginal POP repair offers a clear improvement in effectiveness compared to traditional repair. Given the rate and severity of the safety concerns raised in the MDRs, literature, and Medicare data, we think further study is warranted for currently marketed devices.

Moreover, for mesh products indicated for POP, there are unanswered questions regarding the safety and effectiveness that for new premarket submissions may be best addressed in new RCTs comparing vaginal POP repair with mesh to traditional non-mesh repair.

Following my presentation, Dr. Jill Brown and Dr. Julia Corrado will provide further information on potential study designs to assess the safety and effectiveness of a new mesh product for vaginal POP repair from a

premarket perspective.

However, as already mentioned, as these devices are currently already legally marketed, the FDA has the option to mandate postmarket surveillance studies under Section 522 of the Act.

We believe postmarket studies are warranted and can more immediately begin to answer questions regarding the long-term safety and effectiveness of vaginal mesh used for POP repair while other premarket regulatory options are explored.

To address the questions under consideration regarding vaginal POP repair using mesh, the FDA may recommend as part of the 522 order a randomized clinical trial or a prospective cohort study or a registry study, all of which could contain a common non-mesh control group through a specified duration of follow-up.

As part of a potential 522 order, each manufacturer of all current mesh products indicated for POP could propose and conduct their own study. Alternatively to traditional study designs, sponsors may also choose to develop a common study or registry to address the questions in collaboration with multiple sponsors or in conjunction with societies.

The FDA would advocate and be amenable to facilitating the creation of a multi-sponsor or society study or registry to address the public health concerns.

The clinical data collected via 522 studies may be part of the

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data submitted for future PMA submissions, if both the 522 and the reclassification options are exercised. In this case, sponsors may choose to nest an RCT within a registry.

Within any study with a non-mesh control group, we would recommend including a population of women who are age 18 years or older with documented pelvic organ prolapse, for whom surgery is scheduled.

Inclusion and adjustment for the following risk factors that have not been adequately captured in the current body of literature, such as level of prolapse, primary versus recurrent prolapse, concomitant surgical procedures, menopausal status, estrogen use, age, lifestyle factors, obesity, obstetric history, modification of the mesh prior to placement, and documentation of the surgical technique or procedure would be encouraged.

Later this afternoon you will be asked if you agree with the FDA that 522 studies are needed to evaluate vaginal mesh products currently on the market. If so, you will be asked to expand on recommendations on the type of clinical study that should be required for these devices and general study objectives.

Here's a list of the RCTs that have evaluated traditional repair to anterior or anterior with posterior repair using surgical mesh that were presented in a previous slide. Details and a complete list of the studies that were evaluated for the review of the literature we have performed can be found in the Executive Summary and Panel Pack. As stated in a previous

slide, two of the above studies are follow-on studies of the Hiltunen et al. study and represent the same dataset.

This concludes my presentation on the epidemiological overview and need for postmarket studies of surgical mesh used to treat pelvic organ prolapse.

I'll now turn the podium over to Dr. Jill Brown, who will provide a detailed clinical perspective. Thank you for your attention.

DR. BROWN: Thank you, Mr. Anderson-Smits. Good afternoon, Panel members and other distinguished guests. I'm Jill Brown, and I'll be presenting a clinical overview of the use of surgical mesh for pelvic organ prolapse

For my presentation, I'll go through a clinical background of the use of mesh for prolapse. I'll discuss some of the safety and effectiveness findings in the literature. Some of this will overlap with what you've just heard, but I'll try to distill the information further and discuss the findings based on the repair compartments and the repair approach. I'll discuss some overall safety findings, the safety and effectiveness findings for abdominal versus vaginal approach for apical repair, and safety and effectiveness findings for the vaginal approach for both anterior and posterior repair. I'll briefly discuss some of the limitations in the literature and our regulatory conclusions.

This schematic you saw earlier today. On the left is the normal

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pelvic anatomy, in the middle is a depiction of anterior vaginal wall prolapse, or cystocele, and on the right is the apical prolapse after hysterectomy. Not pictured is posterior vaginal wall prolapse between the vagina and the rectum.

So prolapse can occur in one or more of these compartments at the same time, and risk factors for prolapse include vaginal delivery, increasing parity, increasing age, and obesity.

As far as the scope of the problem, the NHANES survey data from 2005 included a question about symptoms of vaginal bulge, and approximately three percent of women age 18 to 80 endorse the symptom.

An Australian cohort study from last year found that 19 percent of women underwent surgery for prolapse in their life. This is higher than other estimates and may be considered an upper limit.

There's not a lot of data about repeat surgery for just prolapse. A UK cohort study from 2008 found that there is an 11 percent reoperation rate for prolapse surgery at 11 years. Forty percent of this was in the same compartment, and 60 percent was in a different vaginal compartment.

As far as the reasons for using mesh, surgeons began to use surgical mesh with the goal of increasing the longevity of the repair and decreasing the need for the re-surgery. This is incorporated into clinical practice without clinical validation. However, success with using surgical mesh for mid-urethral slings for stress incontinence served as a promising

precedent.

For the repair approaches, prolapse repair can be done either vaginally or abdominally. For vaginal repair, this can be done via a traditional route, which does not use mesh, or with a mesh-augmented repair to address prolapse in one or more vaginal compartments.

Mesh is attached to the vaginal wall beneath the mucosa, and with the vaginal mesh kits, it's also attached to pelvic floor ligaments. For the mesh kits, these typically come in anterior, posterior, or total repair kits.

For abdominal repair, this is almost exclusively done with mesh, and this is called sacrocolpopexy, and it's intended to address apical prolapse. So for women who have primarily an anterior or posterior wall defect, this would not typically be the recommended surgery.

This is a representation of the estimates of the prolapse surgeries in the U.S. last year. Approximately 300,000 women underwent prolapse surgery last year, and about two-thirds of these were done via traditional approach and the remainder were done with mesh. Of the mesh surgeries, about two-thirds were done vaginally and the remainder were done abdominally.

The next slide includes just the mesh prolapse surgeries. And as you can see in this slide, approximately 65 percent of these were done using vaginal mesh kits last year. Almost all of the vaginal mesh kits are synthetic, although there are some composite products that are synthetic and

non-synthetic. Including the synthetic mesh patches, approximately 80 percent of these surgeries were done with synthetic products, and the remainder were done with non-synthetic patches, which includes the xenografts and allografts.

And as you've heard about earlier today, in 2008, the FDA issued a Public Health Notification regarding serious adverse events associated with the urogynecologic use of surgical mesh. Following the Public Health Notification, there was continued clinical concern, particularly regarding the use of mesh for prolapse.

As part of ongoing surveillance, the FDA performed a new search of the MAUDE database from 2008 to 2010, as you heard about in Ms. Pressly's presentation. This search generated approximately 1500 reports for prolapse. This is a fivefold increase from the previous reporting period from 2005 to 2007, which corresponded to the Public Health Notification.

Mesh erosion was the most often cited adverse event in these reports. This is also called exposure, extrusion, or protrusion. I will use the term erosion because this is the most commonly used term in the reports and in the literature.

And as you've also just heard about, the FDA performed a systematic review of the published literature, concurrent with a search of the MAUDE database, to evaluate the reported safety and effectiveness of

surgical mesh for urogynecologic indications. Our goals were to assess the rate and severity of adverse events in the literature and the clinical benefit compared to traditional repair.

So now I'm going to talk about some safety findings from the literature.

Mesh erosion is the most common and consistently reported adverse event in the literature. This is a depiction of mesh coming through the anterior vaginal wall.

Some of the risk factors for erosion cited in the literature include surgical factors such as concomitant hysterectomy, use of an inverted T colpotomy or vaginal incision, surgeon experience, and patient factors such as age, smoking, and diabetes. However, it's important to note that it's unclear how much each of these factors contributes to the risk of mesh erosion. Mesh factors also contribute to this risk, such as the mesh material and the design of the mesh. Most synthetic products are now monofilament macroporous, as these tend to have the most favorable risk profile.

As far as the risk of mesh erosion for mesh placed vaginally, Abed estimated -- excuse me -- reported a summary incidence of 10.3 percent from 110 studies including almost 12,000 women. Erosion was diagnosed from 6 weeks to 12 months postoperatively, and the rate of erosion following use of nonabsorbable synthetic products and non-synthetic products was similar, at 10.3 and 10.1 percent.

As far as the management of erosion for mesh placed vaginally, for studies that reported management of nonabsorbable synthetic mesh erosions, 11 percent of women were treated with excision in the office; 56 percent required surgical excision in the operating room; some women required two to three surgeries to repair this complication; and as you've heard about earlier today, the sequelae, like pain, may continue despite mesh removal.

There's little reported in the literature about management of erosion following use of non-synthetic materials. This is only reported on 35 women, and half of these women responded to topical treatment, and for the remainder, treatment was not stated.

For sacrocolpopexy, Jia reported a summary instance of mesh erosion of four percent. This is from 27 studies including almost 3,000 women. The median follow-up for these studies was 23 months. For those that reported management of the erosion, 3.5 percent of women required surgery to manage this complication.

The likelihood of erosion following use of non-synthetic materials was lower, a reported median of zero percent, compared to the erosion following use of nonabsorbable synthetic materials, with a median of four percent.

Mesh contraction is another mesh-specific adverse event reported on the literature. This is when the mesh becomes taut and it may

cause severe pain. There's not a lot of information about this complication in the literature, but one large series by Caquant reported a 12 percent incidence. In this series, three percent of women required surgical treatment to manage this complication.

As far as overall complications requiring re-surgery, Diwadkar reported that the rate of re-surgery following vaginal mesh repair was highest comparing to sacrocolpopexy and traditional repair, at 7.2 percent, despite the shortest duration of mean follow-up at 17 months. The rate following sacrocolpopexy was 4.8 percent, with a mean follow-up at 26 months, and 1.9 percent following traditional repair, with a mean follow-up of 32 months.

Additional adverse events reported in the literature include de novo stress urinary incontinence. This was reportedly higher in one randomized controlled trial following anterior repair with mesh compared to traditional repair. However, this difference was not seen in three other trials.

Other commonly reported adverse events include pain, infection, and dyspareunia. However, the information we have to date cannot tell whether these rates are higher with mesh compared to non-mesh surgeries. For surgeries that looked at dyspareunia postoperatively, comparing mesh and non-mesh surgeries, did not find a difference.

Moving on to effectiveness, as you've heard about earlier, most studies have used an endpoint of ideal pelvic support, which is a POP-Q stage of zero or one, and corresponds to prolapse that's at least a centimeter above

the hymen. However, there were several limitations to this outcome measure, including that it's not correlated with prolapse symptoms or patient assessment of improvement. Whiteside also found that it suffers from interobserver variability, with 68 percent agreement in the central anterior wall. This is a kappa of .35.

Other outcome measures that can be used in these trials include absence of prolapse beyond the hymen. Swift found that the average number of prolapse symptoms increases when the prolapse extends beyond the hymen; also, improvement in prolapse quality of life, re-surgery for recurrence, and absence of bulge symptoms.

Barber found that when comparing anatomic outcomes, re-surgery, and absence of bulge symptoms, that absence of bulge symptoms was most associated with patient assessment of improvement and the greatest difference of prolapse quality of life between the different outcome measures.

Next, I'd like to talk about sacrocolpopexy. I already talked about the risks of mesh erosion and complications requiring re-surgery. So for effectiveness, Nygaard reported on success rates from 63 studies including approximately 3500 women. Using a definition of lack of apical prolapse postoperatively, success was defined as 78 to 100 percent. Using the definition of no postoperative prolapse in any compartment, success was found in 58 to 100 percent.

There have been three trials which directly compared sacrocolpopexy to traditional vaginal repair. All three of these found superior anatomic results with sacrocolpopexy. One of them also looked at symptomatic results and found that the sacrocolpopexy group also did better symptomatically.

As far as re-surgery for recurrent prolapse, Diwadkar reported on these rates after sacrocolpopexy, vaginal mesh, and traditional repair, and these rates were similar between groups. However, their rates -- excuse me -- the duration of follow-ups were different between groups.

For sacrocolpopexy, the average rate was 2.3 percent, with a mean follow-up of 26 months. For vaginal mesh repair, the average rate was 1.3 percent, but this a 17-month mean follow-up. A recently published series by De Landsheere, with a longer mean follow-up of 38 months, found a rate of 3 percent of re-surgery for recurrent prolapse. Following traditional repair, the average rate of re-surgery was 3.9 percent, with 32-month follow-up.

Our conclusions for sacrocolpopexy are that it leads to lower rates of mesh complications compared to vaginal repair with mesh, leads to better anatomic outcomes than traditional repair, and low rates of repeat surgery for recurrent prolapse.

Please note that we will be asking the Panel to weigh in on this conclusion as part of our discussion questions.

So moving on to vaginal apical repair with mesh, for

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effectiveness, there have been multiple case series which have shown that vaginal repair with mesh often restores anatomy. However, there have only been two randomized controlled trials which have directly compared the mesh repair to traditional repair for the apex. These are both multi-compartment repairs that included the apex, neither of which found a difference in anatomic outcomes between groups. Mesh erosion was reported at 15.6 and 17 percent in these trials.

So our conclusions for vaginal apical repair with mesh are that it can lead to high rates of mesh erosion and offers no clinical improvement in effectiveness over a similar non-mesh repair.

For posterior repair with mesh, there's been one randomized controlled trial which evaluated a single compartment posterior repair with mesh compared to traditional repair. And this actually found that the anatomic outcomes were better with a traditional repair.

There have been four randomized controlled trials which evaluate a multi-compartment repair, including the posterior compartment. Three of these found no significant improvement using mesh. One of them did find a significant improvement with mesh. However, in this study, women who received mesh had less prolapse at baseline.

As far as the risk of mesh erosion, this was reported up to 17 percent, and it should be noted that, in the posterior compartment, mesh erosion can lead to serious sequelae, like rectovaginal fistula and the need for

a diverting colostomy.

Our conclusions for posterior repair with mesh are that it can lead to high rates of mesh erosion, with a potential for serious sequelae, and offers no clinical improvement in effectiveness over similar non-mesh repair.

Moving on to anterior repair with mesh, there is a lot more data for this use. And this is often cited as the overall body of literature to support the use of mesh for prolapse repair.

There have been 11 randomized controlled trials comparing traditional repair -- excuse me -- comparing mesh repair to traditional repair with one-year follow-up. Eight of these used an outcome of ideal pelvic support, eight of them were also unmasked, and seven out of eight unmasked studies found an anatomic benefit to using mesh. Of the three evaluator-masked studies, two out of three did not find an additional anatomic benefit to using mesh. Four of these studies reported on quality of life outcomes, and none of them found that there is an additional quality of life benefit to using mesh.

As I discussed, that most of these studies have used an outcome of ideal pelvic support, Chmielewski recently published an outcome reanalysis of an earlier published randomized controlled trial using success as less than or equal to Stage I prolapse, which found that there were lower reported success rates for traditional anterior repair compared to anterior repair with mesh.

Using a definition of prolapse above or below the hymen, and for this definition, women with Stage II prolapse would be considered successes, they found that there were high rates of success, anatomically, for both the traditional repair and the mesh group. There was also no difference in prolapse symptoms or reoperation for recurrence between groups.

As far as mesh erosion, this was reported up to 17 percent at one year in these trials.

Next, I'd like to spend a few minutes talking about the Altman trial, which you heard about earlier today. This was a large trial looking at anterior prolapse compared to traditional repair with one-year follow-up. The study success was a little different than the other trials. They looked at a composite measure of objective and subjective cure. Objective cure was defined as less or equal to Stage I prolapse, and subjective cure was defined as no complaint of vaginal bulge.

For the mesh group, study success was found in 61 percent of patients compared to 35 percent in the non-mesh group. The mesh group also did better, looking just a bulge symptoms, with 75 percent meeting the definition of success, compared to 62 percent in the non-mesh group. And this is statistically significant, although you can see the difference is less pronounced than the overall study success. They also found that there was no difference in prolapse quality of life outcomes between groups.

Perioperative complications in this trial were also greater in the

mesh group, to include longer operative times, greater mean blood loss, and more bladder perforations. The mesh group also had significantly more de novo incontinence at one year. Doctors did not report a total mesh erosion rate. They did report the percentage of women who required re-surgery for erosion.

So looking at all causes for re-surgery at one year in this trial, in the non-mesh group, the rate was .6 percent. And this is for one repeat anterior repair. In the mesh group, the rate was 5.9 percent, with half of these for SUI surgery and half for a mesh complication. So this overall rate of 5.9 to .6 percent is statistically significant.

There's been one randomized controlled trial with three-year follow-up. This was published by Nieminen et al. They found that, at three years, there continued to be better anatomic results in the mesh group, but there was no difference in symptomatic recurrence between groups. He also found a 19 percent mesh erosion in the mesh group and that 13.5 percent of women required mesh resection for mesh erosion within three years.

As far as overall reasons for re-surgery at three years in this trial, in the non-mesh group, women underwent repeat surgery for repeat anterior repair, other prolapse surgery, stress urinary incontinence surgery, for a total rate of 19.8 percent. In the mesh group, women underwent repeat surgery for other prolapse surgery, SUI, or a mesh complication, for a total rate of 24 percent. Although this trend is higher in the mesh group, it's not

statistically significant.

Our conclusions for anterior repair with mesh are that it can lead to high rates in mesh erosion and possibly de novo incontinence. It likely results in a better anatomic result. However, there's mixed data on symptomatic results, and there's no apparent difference in quality of life outcomes. There's also likely an increase in re-surgery compared to a non-mesh repair.

As you've heard about earlier, there are several limitations to this data, including the outcome measure used in most trials, most trials did not use masked evaluations, most trials included primary and repeat surgeries and multiple concomitant procedures, adverse events were reported inconsistently, we only have a data for a subset of products, and we have lack of long-term follow-up.

So our overall conclusions from the literature are that the vaginal repair with mesh is our main of concern. We find that the serious adverse events are not rare, contrary to what was stated in the 2008 Public Health Notification. Effectiveness does not appear to be superior to traditional repair, with a possible exception for anterior repair with the caveats just discussed. There's little known about the long-term implications. So, overall, we feel that the safety and effectiveness is in question for this use.

We find the data for sacrocolpopexy less concerning, as there

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are lower rates of mesh complications, excellent anatomic outcomes, and low rates of repeat surgery for recurrent prolapse. So we feel that the safety and effectiveness has been demonstrated in the literature for this use.

As far as our regulatory concern for new mesh products for vaginal prolapse repair, we feel that we need to establish an acceptable safety profile and clinical benefit in comparison to a similar non-mesh repair. However, these products are currently evaluated under the 510(k) pathway, which calls for comparison to a legally marketed predicate device. So in order to allow for the appropriate comparison, we feel that up-classification to Class III is necessary.

For currently marketed products, we also feel that additional data is necessary. Up-classification to Class III and PMA requirements, including clinical data requirements, would apply to these products. However, independent of up-classification, we feel that postmarket surveillance studies are warranted and should start now. If these studies are designed properly, they could satisfy future PMAs.

In our discussion questions we'll be asking the Panel to weigh in on our conclusions based on the literature and our proposed regulatory strategy.

Next, Dr. Corrado will discuss the regulatory considerations further.

DR. CAREY-CORRADO: Thank you, Dr. Brown. And thank you to

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the audience and the Panel members for your continued attention on this long day.

I'm going to very briefly recap the last three speakers. I'm going to review regulatory considerations for moving forward in our review of mesh for prolapse. I'm going to present our new regulatory strategy and ask your input on it for later this afternoon, and introduce the Panel questions.

So we've heard from Nancy Pressly what the MAUDE database tells us regarding mesh for prolapse. The key findings from Nancy's presentation are that the MDR reports increased between the reporting period from '05 to '07 to the reporting period of '08 through '10. The number of MDR reports on prolapse mesh increased fivefold from the first to the second reporting period, and we identified a new type of adverse event, which is vaginal contraction, also called shrinkage, that was previously unreported.

Colin Anderson-Smiths provided the Division of Epidemiology review of the literature for vaginal prolapse. His key findings are that there is serious morbidity which is unique to mesh for prolapse, there are limited long-term outcomes data for both safety and effectiveness, and that postmarket studies are needed to fill in information gaps.

Dr. Brown provided FDA's clinical review. Her key findings are that there are high rates of serious adverse events that are unique to mesh, for example -- well, the prime example of which is vaginal mesh exposure.

Mesh augmentation does not improve clinical outcomes. And that is obviously an area where we're seeing data differently compared to the industry. And the long-term safety and effectiveness of mesh for prolapse are unknown.

We also heard this morning from Marjorie Shulman about medical device classification. So basically there are three classes of medical devices: Class I, which is usually exempt from 510(k), Class II, which usually requires a 510(k) -- and vaginal mesh are classified in Class II -- and then there is Class III, which usually requires a PMA and clinical data.

So where is FDA today in terms of getting submissions and reviewing submissions for vaginal mesh for prolapse? Since approximately 2002, we've cleared over 100 510(k)s for mesh products indicated for prolapse. None of these devices were cleared based on original clinical data, that is, FDA did not require clinical data for any of these submissions. Published studies now indicate serious risks and, in our opinion, no clinical benefit compared to non-mesh repair.

So based on the literature and going forward, we feel that we need to know whether the use of mesh improves clinical effectiveness compared to traditional non-mesh repair, and is that improvement in effectiveness sufficient to outweigh the additional risks introduced by mesh? We believe that a randomized clinical trial could help answer this question.

So as you all know, one of the topics for later this afternoon is

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the issue of reclassification. And so before we talk about Class III, we need to ask, in Class II, can we get the information we need?

So let's talk about -- and we heard a little bit this morning about special regulatory controls that are available for Class II devices. And examples are, as listed in the Federal Food, Drug and Cosmetic Act, performance standards, examples of which are testing for material and electrical safety, postmarket surveillance, patient registries, and guidelines that FDA issues, setting out for industry what information they need to include in a submission. And this can include clinical data, but the clinical data that can be requested under Class II needs to be appropriate within Class II. And I'm going to talk about that in the next slide.

So we've heard one perspective from industry, that clinical data can be obtained under the current Class II special controls rules. The problem that we see is that the 510(k) standard for evaluating a device for marketing is the question of is it substantially equivalent to another legally marketed device? So what that means is a new device only needs to be as good as a device on the market, and we are concerned that that is not good enough for these devices.

So where do we go from here? A clinical trial showing substantial equivalence, we don't feel, is sufficient to ensure safety and effectiveness of mesh for prolapse. We feel that reclassification of prolapse mesh from Class II to Class III would allow for assessment of reasonable

assurance of safety and effectiveness via a randomized controlled trial with a non-mesh control arm. We believe that that is the most appropriate type of study to answer this key question. And we're going to be talking about that. We're asking the Panel, do you agree with us? And that's why we're all here today.

But unlike a Class II device, it's important that everybody appreciate that a Class III device, Class III vaginal mesh for prolapse, has to stand on its own in terms of safety and effectiveness. It's not good enough to say that is essentially equivalent to something else on the market. So each of these devices would have to pass a standalone test in Class III.

So what kind of clinical trial do we believe is needed? As I mentioned, as I alluded, we believe randomized controlled trials with a non-mesh control arm is appropriate. But at a minimum, we believe that we need an appropriately targeted patient population, clinically meaningful endpoints, adequate length of patient follow-up, and the right research question. And I've talked about FDA's thoughts along those lines.

I would like to make a special note, however, that although we need -- although we believe we should reclassify, because that would enable us to ask for what we believe are the appropriate clinical trials, it's important to say that just because a device is in Class III, it does not mean that the clinical trial must be a randomized controlled trial. So we're using the RCT to argue for Class III. It's really to argue for our ability to ask for an RCT, not that

it must be an RCT.

So going forward, if we do reclassify, FDA would assess the data requirements on a case-by-case basis, and that assessment would drive the type of study we would ask for.

So, in summary, we have a two-part strategy for going forward that we are hoping to get your input on today. Our premarket strategy would be to reclassify vaginal mesh kits for pelvic organ prolapse from Class II to Class III premarket approval. This process would probably take two to three years to complete. When finalized, these Class III requirements will apply to both new devices and devices that have already been cleared and are currently legally marketed. However, during the interim, the cleared products will continue to be available as Class II devices.

Our postmarket strategy is to issue 522 orders to manufacturers of surgical mesh to conduct postmarket studies. The 522 order, unlike the reclassification, would only apply to products already marketed.

And that concludes my presentation. And I'm going to briefly go through a synopsis version of our Panel discussion questions, but I would like to pause right now in case there are any questions.

DR. FALCONE: Dr. Brill.

DR. BRILL: Andrew Brill.

Dr. Corrado, Section 522 of the Act, does that not allow us or

allow the FDA to request a randomized controlled trial from a device company?

DR. CAREY-CORRADO: My understanding is that FDA cannot dictate the trial design, but I'm going to defer. Mary Beth Ritchey is nodding that that is correct. We can't dictate the trial design under the 522 section.

DR. FALCONE: Okay. But you can if you reclassify?

DR. CAREY-CORRADO: Yes.

DR. FALCONE: To dictate the randomized clinical trial.

DR. CAREY-CORRADO: Correct.

DR. FALCONE: Dr. Diamond.

DR. DIAMOND: When Mr. Anderson-Smits was presenting the Medicare data, he indicated that there was 2.26-fold increase in the patients that receive mesh. But I don't think you mentioned what the actual rates were in the two groups. So what was the actual incidence in the mesh population and the non-mesh population? Not the fold increase.

MR. ANDERSON-SMITS: I don't have those --

DR. FALCONE: The absolute increase.

MR. ANDERSON-SMITS: -- numbers off the top of my head. I can get them and provide them to you in a few minutes.

DR. DIAMOND: That'd be great.

DR. FALCONE: Go ahead.

DR. DIAMOND: I had one other question and it was, is there

any data in the literature which talks about patients who have mesh placed, who undergo revisions, as to what their subsequent efficacy is? Of the procedure after revision, what is their clinical outcome, as far as their symptoms after mesh revision? Has that been reported in the literature?

MR. ANDERSON-SMITS: Well, most of the literature is a mix of both primary and repeat in their outcomes. So that is reported.

DR. DIAMOND: But the latter is not specifically reported?

MR. ANDERSON-SMITS: Exactly.

DR. FALCONE: Dr. Iglesia.

DR. CAREY-CORRADO: Dr. Brown is going to respond.

DR. BROWN: I don't really have much to add except for I don't think that has been reported in the literature.

DR. DIAMOND: Thank you.

DR. IGLESIA: Okay. Cheryl Iglesia.

My question is just on -- I need a clarification on the ramifications of reclassification versus a potential alternative as keeping it in Class II special controls and issuing a 522. So can you clarify it for me in terms of what it means for existing products? I think I understand it with the new ones moving forward and at Class III, but I'm not really quite understanding the 522 special control keeping and what would happen to the existing products and what -- if I wanted a registry, for example, would that suffice in a 522, keeping it as a special control?

DR. CAREY-CORRADO: I'll try to answer. The first thing I would say is the key difference between Class II and Class III, of course, is the substantial equivalence test that applies to Class II. We can't raise the bar on a Class II product, if that makes sense. We can't ask for a Class II product to stand on its own in terms of safety and effectiveness.

Under a 522 order, as you heard from our Division of Epidemiology, there is a variety of types of studies, including registries and RCTs nested in registries, that could occur under 522. The information that we would derive from a 522 study would help inform us, patients, physicians, between now and when a classification occurs. An appropriately designed 522 study could be the clinical data submitted with a PMA if reclassification happens.

So there's a lot of potential to get a lot of valuable results from conducting 522 studies. It could obviate the need for a new RCT to support a PMA, depending on how it were designed.

DR. IGLESIA: Okay.

DR. FALCONE: Would the 522 studies be sufficient going forward, or does the FDA feel that you really need to reclassify?

DR. CAREY-CORRADO: I guess maybe what you're asking is, can we ask for an RCT that essentially describes a standalone study for safety and effectiveness?

DR. FALCONE: Yeah.

DR. CAREY-CORRADO: And I think that I'm going to defer to epidemiology on that. I think that that is a great question, and I'm not sure that I can give you the right answer on that.

DR. FALCONE: Please identify yourselves.

MR. POLLARD: Colin Pollard, Branch Chief for the OB-GYN Devices Branch. And Dr. Ritchey is going to speak in a moment and tell you more about the 522 study.

But the one thing I wanted to clarify with respect to what the 522 study can do versus what reclassification can do is that the 522 study is only going to speak to products that are either on the market or go on the market in the future; whereas, a reclassification would essentially mean that new products that reach the market would need to do a clinical trial and get premarket approval before they go on the market; whereas, the 522 would only apply after something's on the market. So you could argue that the horse is already out of the barn in that kind of scenario, so to speak.

DR. RITCHEY: Mary Beth Ritchey.

I would like to add that the 522 is different from special controls. Special controls is a device class sort of thing. The 522 is something that we can issue at any point during the postmarket. It's not something that's built in as part of what we're typically doing for that device.

DR. FALCONE: Thank you. All right, on this side now. I think Dr. Sears was first. No? Okay, moving on to Dr. Rogers.

DR. ROGERS: I have a question for this panel. So there have been 100 devices that have been cleared. I'm curious. How many of them are represented in the clinical data that you were able to gather? And the epidemiological data. So how many of those devices are represented in those studies?

And a corollary question. Is there enough variability between the devices and the delivery systems?

So clarifying my understanding of, if the classification piece, if the Panel makes a decision that it stays at the same classification, then we're treating all 100 of those devices similarly versus saying that there are differences between the devices. So I know it's a long question, so I apologize for that.

DR. BROWN: I'm Jill Brown.

The first question. The trials represent a very small number of the cleared mesh products. I don't know exactly how many, however. The second question, could you say it again?

DR. ROGERS: So the second question had to do with, if they stay as a Class II device versus going to a Class III device, clarifying for me whether that means that we treat that whole group of 100 devices with the same regulatory process. And I also had -- a piece of that question was the FDA's reviewed those devices. Is there a lot of variability in them?

DR. BROWN: Jill Brown.

So if the devices are reclassified to Class III, then each device would have to have its own clinical data to support that device, instead of the situation now, they're compared to other devices. So I think we can speak up to you, but there is a significant amount of variability between different devices. There are a lot that kind of are evolving from similar devices, perhaps within a particular company, but from one company to the next, they can be significantly different.

DR. CAREY-CORRADO: This is Julia Corrado.

And one other note is that although we've cleared over 100 510(k)s, that doesn't mean that there are 100 unique devices that are being currently marketed under those clearances. Some of the clearances are for modifications to devices. We have only guesstimated. We don't have hard data, but we're guessing that the number among that 100, the number currently marketed is probably closer to 20, possibly.

DR. FALCONE: Dr. Lerner.

DR. CAREY-CORRADO: We're guessing.

DR. LERNER: I think Dr. Corrado just --

DR. FALCONE: Answered it.

DR. LERNER: -- answered that question.

DR. FALCONE: Okay. Okay, Dr. Flesh, I think you had a question. Push the button.

DR. FLESH: I'm sorry. George Flesh.

I wanted to ask if the FDA has some awareness of the weaknesses of randomized controlled trials because I think there's this underlying premise that a randomized controlled trial is solid gold, not to be questioned, and to be assumed to be the gospel truth. And I just want to point out a few potential difficulties.

The first one, there's an assumption, I think, that the people who are doing the surgery are neutral about which arm is better. And I think that this is in reality almost never the case. The people who are doing the surgery have a significant feeling about which arm is better. Not only that, but they also have often significantly more experience and more expertise in one of the two arms. And this, from the start, skews this kind of study.

The second thing has to do with details of technique. I read through in detail all of the randomized controlled studies, and I can tell you that, at minimum, two of them are using techniques which nobody would use anymore. And specifically the Hiltunen study and the Nieminen study. What they did, they started out by splitting the endopelvic fascia from the vaginal mucosa, doing a traditional repair and then laying the mesh over the traditional repair.

Now, this is an invitation to a high erosion rate, and this high erosion rate skews all of the meta-analyses, which have way too high erosion rates because techniques were used which are simply obsolete, completely obsolete. And everybody who does this surgery knows that they're obsolete.

Number three. I don't see anywhere a distinction being made between procedures which require the use of long trocars stuck through the obturator framing versus procedures, which I personally have been using and many others have been using, which don't use any long trocars and have a much less traumatic and difficult manner of attaching the mesh in the pelvis. And if this distinction is not made, I think that we're going to get a very false idea of what the real results are.

Number three [sic]. The randomized controlled trial, although it may make some general conclusions, it cannot by its very nature distinguish individual cases done by individual surgeons in certain circumstances which require a specific product. I'll give you one very concrete example.

I very rarely use mesh in posterior repair. However, two months ago I had a patient 70 years old with a posterior prolapse the size of a football. Now, I can assure you, there was no way to fix that without mesh. And I can also assure you that that one case would've made no difference in a randomized controlled trial. It's only one case.

So the randomized controlled trial misses out on specific cases and also specific surgeons who have specific expertise that may be different or better, or at least different, than the general surgeon doing this kind of repair.

So I'm just saying all of this to point out that a randomized controlled trial, of course it's of value and of course we all love to read them,

but let's not assume that they're just solid gold and that cohort trials are meaningless, or even single surgeon observational trials are not meaningful. I think they are. I read them with great interest.

DR. FALCONE: Would you like to respond on the strengths of a randomized clinical trial and specifically surgical trials?

DR. CAREY-CORRADO: This is Julia Corrado.

We all appreciate your thoughtful comments and we respect them. And as I noted, even within Class III, FDA doesn't always require a randomized controlled trial. So we don't want to be misunderstood to say that is -- that no other type of clinical trial design would contribute to us understanding and appreciating the risk/benefit profile for any device in general.

We've put a lot of thought into this, and we for several reasons think an RCT is the appropriate way to go, at least initially. However, the purpose of this meeting is to receive feedback from you, precisely as you've just given us.

But just very briefly, we saw a signal of mesh-specific complications that are over and above complications associated with non-mesh repair for prolapse. And although we've heard a perspective today, that only a subset of mesh erosion is clinically significant, we believe we need to take seriously all reported cases of vaginal mesh exposure or erosion, whether or not you have to go back to the OR, because potentially,

potentially, they can be harmful.

The Panel may disagree with this, and I understand industry disagrees with that. But from our perspective, the additional risk forces us to look more closely at effectiveness, and our review of the literature, as presented by Dr. Brown, leads us to conclude that clinical benefit versus native tissue repair has not been demonstrated. And we want your input on that perspective as well.

DR. FALCONE: I think Dr. Gadaleta had a question.

DR. GADALETA: Well, I have a statement more than a question.

DR. FALCONE: Okay.

DR. GADALETA: So as we enter the deliberation section of this meeting, I think it's important for us to review a couple of items that are going to be germane to the questions that we're being asked.

And so in some of the questions, I think they ask the individuals to make a comment on safety and effectiveness of the device, and I think it's important to understand that there is a definition of safety and a definition of effectiveness that we should work with, and I just wanted to sort of go through that, so that as we think about the answers to the questions, we use the construct that FDA has established.

And so I'll just read what our definition of safety is so that we can understand how we should apply the data relative to safety. So it's 21 C.F.R. 860.7. And I'm going to -- rather than read all of it, it just indicates that

safety is --

DR. LERNER: Excuse me, Dr. Gadaleta, could you do this when we ask the questions about safety and effectiveness?

DR. GADALETA: Sure, that's completely fine.

DR. LERNER: I think we have more discussion at this point.

DR. GADALETA: That's fine.

DR. LERNER: So we could do that a little bit later. But thank you for bringing that up.

DR. BROWN: May I address Dr. Flesh's points?

DR. FALCONE: Sure, go ahead.

DR. BROWN: This is Jill Brown.

DR. FALCONE: This is specifically the question about randomized clinical trials? Or which one?

DR. BROWN: It was the follow-on comments to that, really.

DR. FALCONE: Okay. We just want to make sure what question you're answering.

DR. BROWN: Yeah, I'll try to -- so what Dr. Flesh was commenting on about how we don't have a distinguishing -- distinction -- excuse me -- between the trocars and the patches, I think, is sort of what you're talking about as far as safety outcomes. And I think that's true, but to me the problem is we don't have enough information. And so getting more information from the devices that are in the market, that use those type of

techniques, I think, will help to answer those questions.

The second piece was that you had mentioned the case with the large rectocele. I just wanted to comment that, you know, that to me is a practice of a medicine type of thing, and that's not something that we're necessarily here to regulate or talk about.

DR. FALCONE: Yes, Dr. Chappell.

DR. CHAPEL: Rick Chappell. I have a question and a statement for the FDA, and it'll become clear which is which.

In discussion of randomized clinical trials, I'm reminded of the request on page 23 of the Executive Summary to the Committee. Considering the safety and effectiveness concerns associated with these devices, the Panel will be asked to discuss whether the risks associated with use of vaginal mesh for POP repair outweigh the benefit. And then I certainly won't read all that follows, but there's a request for a randomized clinical trial. And then, in order to claim study success, vaginal POP with the new mesh products should be superior to prolapse repair surgery without mesh, in terms of effectiveness, and non-inferior in terms of safety.

So suppose the safety outcomes were already determined, percentage of some adverse event, group of adverse events, which is well defined. How do you define non-inferior? And that's an important question because five percent worse, up to five percent worse in the mesh arm, or up to double in the mesh arm -- those are just examples -- and five percent

would require a very large sample size, for example, much more than 10 percent.

So my question is, does the FDA want us to specify a non-inferiority margin, and non-inferior by how much?

And my statement is, you really ought to because that's going to be a real bear if not.

DR. BROWN: This is Jill Brown.

I don't think we're asking you to provide a non-inferior margin for us, but that is something that we would discuss and come to an agreement about before these trials are initiated.

DR. CAREY-CORRADO: What we'd really like the Panel to tell us today is whether you agree with us that we need to know whether the addition of mesh offers the clinical benefit and whether -- and if we do need to know that, whether you agree that an RCT comparing mesh repair to a non-mesh repair is the appropriate way to answer the question.

DR. FALCONE: Dr. Brill, were you going to ask a question?

DR. BRILL: Well, I would like to address the group at the table at present. You know, we're looking for tools in order to provide this advisement and I was just --

DR. FALCONE: Not to interrupt you, but -- because these are questions directed to the FDA, because then we'll have hours to talk to each other.

DR. BRILL: Yeah, and I appreciate that.

DR. FALCONE: And I think it's going to be hours.

DR. BRILL: And I would just like to know where you see the deficit or decrement of going with a Section 522 versus reclassification, because the implications are very significant. So where would it not satisfy what you see as the essential needs that you have gleaned from what's been a sophisticated analysis of the data?

DR. BROWN: This is Jill Brown.

I think that's part of what Colin Pollard mentioned earlier, that the postmarket surveillance studies only allow us to collect data once a device is on the market. So we won't know, when we clear a product, how it performs clinically. So we feel that that's important to know before introducing these products to the market.

DR. FALCONE: Okay, Dr. Duerhring.

DR. DUERHRING: Maybe you guys can clarify something that I have here. If you reclassify the device as a III, that's anything coming in to the FDA from this point forward? No? That's everything?

DR. CAREY-CORRADO: That would apply to both currently marketed products as well as the new products.

DR. DUERHRING: Okay. So if you did a 522, that would give us -- you could require a certain amount of data, like a registry, and all of this so that we can actually see what the injuries and the adverse reports are all

about, right, that's already current. And you can do that through a 522, but you can't ask for specific types of statistical testing, right, or data collection unless we reclassify? Is that what you're trying to say?

DR. CAREY-CORRADO: No. I guess what I tried to say was that we can't dictate a clinical trial design under the 522 order.

DR. FALCONE: Can you introduce a device with the 522 attached to it, clear the device with -- you can say, You're cleared, but you've got to do this?

MR. POLLARD: So I would try to answer that question, but I am actually going to go back to what I was saying before, and Dr. Brown was saying, is that I think it's important to recognize that the 522 studies will not change fundamentally the premarket clearance of a product or the premarket approval of it.

Back to your point. Sure, we could issue a 522 study every time we cleared a new product. That's kind of an unusual way to go about doing things. So that's why what we're suggesting that needs to be done is we need to change we how we do our premarket evaluation of these products and that, as you've heard before, we think that the current 510(k) substantial equivalence paradigm doesn't work because we don't feel like we know enough about the fundamental safety and effectiveness of vaginal mesh for POP repair. And the way that we could do it is to see, in a clinical trial, how it fares vis-à-vis a traditional non-mesh repair.

I would just also like to say that, typically, 522 studies, they're not going to affect that product in terms of how it gets on the market or whether it stays on the market. You know, when the 522 study is done, typically what that does, it affects some labeling for that product.

DR. FALCONE: Yeah, go ahead, you can follow up. Good luck.

(Laughter.)

DR. DUERHRING: I'm not so sure I want to now.

(Laughter.)

DR. RITCHEY: Mary Beth Ritchey.

The 522 is something that we do when there's a question that comes up. If there is something going on premarket and we have a question in the premarket that needs to be addressed in the premarket, the 522 is not an appropriate vehicle for that. And a 522 cannot be issued as a condition of clearance, except under pediatric provisions. So here, if it's a premarket question, then a 522 would not be an appropriate vehicle.

DR. FALCONE: Yeah, go ahead. State your name again.

DR. DUERHRING: This is Dr. Gary Duerhring.

If you people actually reclassify it to a III, what that will do is it will require independent studies that would demonstrate that they are better than or not just equivalent to, because we don't know what the current product is all about, right? We don't have enough information to really have a risk/benefit ratio, correct?

DR. LERNER: They wouldn't be better than. They would have to stand on their own to show that they're safe and effective.

DR. DUERHRING: Okay, all right.

DR. LERNER: But the current paradigm is that they have to just be equivalent to something that's already on the marketplace.

DR. DUERHRING: Okay.

DR. LERNER: So it could be a paper description of the two different products.

DR. DUERHRING: Okay. Now, the products that are already on the market would remain on the market, but they would have to provide a standalone, also?

DR. LERNER: So if we reclassify and order 522 studies, once the data from the 522 studies are in, yes, the devices would stay on the market now. We would get the data from the 522 studies. At that point all the mesh that's on the market would then have to submit, if we up-classify, a new PMA and they could use the data from the 522 study to support their safety and effectiveness for that specific device.

DR. DUERHRING: Okay, thank you very much. That answered my question.

DR. FALCONE: Dr. Diamond, go ahead.

DR. DIAMOND: During the second portion of the industry presentation, the non-consortium portion, there was a presentation which

tried to make the point that non-crosslinked biological materials may be different than other forms of mesh. And now that the FDA has had a chance to see that in preparation for today, I didn't hear that as part of anybody's presentation and wonder if you'd like to make a comment about that and give us some guidance of FDA's thoughts in that regard.

DR. BROWN: Yeah, I can make some comments. This is Jill Brown.

So the data that was included in that presentation was limited, in our perspective, and there is a total of about 400 women and this is looking at using all different types of the non-crosslinked products. There was one randomized controlled trial in that group which was small and had 30 women in each arm. There are a couple of other case-control studies, comparative, retrospective studies. There's very little prospective data there.

The erosion rates reported amongst those women seem to be favorable. But the other question that's not really addressed in that data is the clinical benefit. The one randomized controlled trial that was there, the women in that trial who received the -- in that case it was Surgisis -- they did have higher perioperative complication rates. There was an anatomic benefit in that group, but again it leads back to our discussion previously about whether an anatomic benefit alone is really adequate. And I guess I'll stop there.

DR. FALCONE: Does that answer your question?

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DR. DIAMOND: Yes, thank you.

DR. FALCONE: Okay. Go ahead.

DR. CHAPPELL: Rick Chappell.

I'm sorry, I'm confused now. You said 400 patients' experience with non-crosslinked material, mesh. And then I asked Dr. Mark, from Cook, that question. She said greater than 10,000 patients, with up to three years follow-up and no MDRs.

DR. BROWN: Right.

DR. CHAPPELL: That sounds different to me.

DR. BROWN: I'm not going to speak for Dr. Mark, but the studies that were presented in their packet included 400 women. I think what she was talking about is overall experience with the product in the marketplace, if I'm not mistaken. She was not referring to their data on 10,000 women.

DR. FALCONE: Well, we will have opportunity to ask them directly during the discussion period, so that between ourselves we can call up anybody that spoke beforehand and ask them again to clarify that point. I just wanted to make the questions now clear for the FDA.

All right, go ahead, Cheryl. Dr. Iglesia.

DR. IGLESIA: Yes, Cheryl Iglesia.

A question for Julia Corrado. And it really relates to the practical nature of conducting trials and the feasibility of RCTs. While they,

you know, do provide a significant amount of information, in terms of feasibility, I have some concerns about the ability to recruit for this kind of trial in this current climate.

The second concern is that you're chasing a moving target, which relates to my other question to industry, in that you're saying a device that, you know, two months -- I mean, two years later is no longer in existence because they've made modifications. We've moved on from large mesh to smaller meshes, from trocar based to non-trocar based. So there's some little practical concerns, although I really understand the glory of an RCT.

So my question relates to like in terms of using something like a multi-society or a multi-specialty registry. I think you can get some valuable information in terms of -- or do you agree, in terms of figuring out if there are outliers. And the outliers would be, are there certain products that, when implanted in patients, are not performing very well compared to the others? Or, God forbid, are there certain products placed in certain surgeons' hands that are outliers compared to, you know, the average person?

DR. FALCONE: Please respond.

DR. CAREY-CORRADO: So my response would be that it's possible we're being naive about the ability to recruit, but we understand, from estimates provided by industry, that there's still a substantial percentage of procedures being performed on native tissue. And so we

accepted that and we are assuming that there are surgeons who would be available to perform those procedures, who wouldn't object to performing those procedures.

Regarding the moving target device, it applies to a generic issue, it applies across all devices FDA looks at. The fact that improvement in design and manufacture, you know, is part of progress, that doesn't obviate the need for us to have data on which to conclude that the products we're clearing or approving for market are safe and effective.

We have already been talking about, as you know, the issue of a registry. We need to be careful in terms of identifying issues with particular products and surgeons. The products, certainly, we have to look at, but FDA doesn't regulate the practice of medicine, doesn't police physicians, and so there's only so much that we can do.

DR. FALCONE: Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

I'm persuaded, as I listen to this, about the moving target aspect and Dr. Iglesia and Dr. Diamond's comment. Has there been any reports on rejection? Some of the patient issues that we heard a little earlier today don't seem to be just a minor erosion. And so might there be something on rejection? I didn't hear that from industry either, but since we're talking about moving targets.

DR. BROWN: This is Jill Brown.

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Are you talking about mesh rejection?

DR. CODDINGTON: Yes.

DR. BROWN: About factors that would contribute to mesh rejection, is that --

DR. CODDINGTON: No, not factors, but just in the fact of a difference between seeing a little bit of an erosion is one thing. To hear a young lady talk to me about where she's had seven surgeries and there seems to have been a granuloma to process, et cetera and so forth, you know. And then, as we've kind of discussed, we've evolved and had a number of different products, really, that have totally changed on the market.

Has that had any -- is that a different product than, for instance, that individual had or is there an issue there kind of underlying all of this that are small but may be significant?

DR. BROWN: Yeah, this is Jill Brown.

All I can say about that is there has been some trial and error over time with different mesh products that people really don't use as much anymore because their profiles were worse. So as I mentioned in my presentation, that most of the synthetic products are the monofilament macroporous mesh.

And as far as the mesh components, other than that that contribute to rejection, there's not a lot of information about that. I don't think we really know enough to answer those questions. There are other

factors that we've been talking about, like surgical experience, vaginal incisions, patient factors, that contribute to erosion risk, but it does not appear that these have been clearly identified.

DR. FALCONE: Okay, Dr. Gadaleta.

DR. GADALETA: I'd like to go back to Dr. Brill's comment and question, and that is why a Section 522 can't address this. So in recent history there's been at least one or two examples of Section 522s proposed on certain device classes to address issues like we're talking about today. So one example is positive displacement valves and the perceived increased infection rate. Another is spinal screws. So they have been used previously to address issues like this.

So what makes this particular example not aligned with the Section 522 like it has been applied to spinal screws and positive displacement valves?

DR. RITCHEY: Mary Beth Ritchey.

So a good example here is the dynamic stabilization systems. There, for the postmarket, we had 522s for everything that was on the market, but then a randomized clinical trial is needed for anything else to come to market.

DR. GADALETA: Are those Class III now or are they still --

DR. RITCHEY: No, those are Class II.

DR. GADALETA: Right. So there is an ability to do the

Section 522 and do a randomized controlled trial, like you just said.

DR. RITCHEY: With a control that is substantially equivalent.

DR. GADALETA: Okay. So there is a modality of doing it under a Class II, like you just said, or no?

DR. RITCHEY: There are several 522s that are for Class II products, yes.

DR. GADALETA: Yes, but you then said that the spinal screws then were required to do clinical studies as part of the 510(k) process.

DR. RITCHEY: They are required to do clinical studies --

DR. GADALETA: Um-hum.

DR. RITCHEY: -- as part of the 510(k) process, yes.

DR. GADALETA: Right.

DR. RITCHEY: And those clinical studies --

DR. GADALETA: Um-hum.

DR. RITCHEY: -- it's a randomized controlled trial.

DR. GADALETA: Right.

DR. RITCHEY: It's randomized to a control --

DR. GADALETA: Right.

DR. RITCHEY: -- that is what the device is substantially equivalent to.

DR. GADALETA: And what is that, if you know?

DR. RITCHEY: It's a rigid fixation.

DR. GADALETA: Okay.

DR. FALCONE: I think the point, though, is, is always that it's the control is something that's equivalent, you know. So up front you're loading it.

But I was going to go here to other questions. Go ahead, Dr. Rogers. Then we'll move around.

Just to make it clear, it's the questions to the FDA panel because we'll have lots of time to talk to ourselves. But I just want to make sure that the FDA -- and the most important thing for all the Panel members to get this clear, this up-classification versus 522, although they will be around to answer the same question in a different way.

DR. ROGERS: So I was just curious, with the literature review, if there was any mention of postoperative maintenance of the graft. So it's been my experience that when I use a mesh material, that I recommend the use of topical estrogen cream after the surgery. And we've had some discussions today about using it for treatment of erosion or difficulties following implantation. But we haven't really talked about what the recommendations have been for during these trials or actual practices, in terms of graft maintenance. So, you know, I guess I'm kind of thinking of it as analogous to battery changes or something like that.

But it seems to me, from my personal experience, that most surgeons are recommending the estrogen follow-up, and I'm curious to know

if you've found that that was true, and do you feel that this should factor into our decisions about these products?

DR. BROWN: Jill Brown. And I'll let you answer too, if you have something to add.

We do not comprehensively evaluate that in the literature, as to whether that component was addressed in the trial. Just generally speaking, I know that some of the trials do incorporate that. For example, for women who are postmenopausal, they may have required that they used topical estrogen for a period of time before the surgery. But we did not comprehensively evaluate that in our review.

MR. ANDERSON-SMITS: And I would just say it was in anecdotal reports of postsurgical protocol, but very infrequently.

DR. ROGERS: So both pre- and postsurgical protocols --

MR. ANDERSON-SMITS: Yes.

DR. ROGERS: -- had those requirements? And was there any range of time for the postsurgical?

MR. ANDERSON-SMITS: I don't know off the top of my head.

DR. ROGERS: Okay. So my second part of that question is, do you think that that is something that we should be considering, as it is a common use for maintenance of the device, or no?

DR. BROWN: Jill Brown.

I think that's something that we would be interested to hear

from the Panel. We're certainly open to that sort of discussion.

DR. FALCONE: Yeah, okay, thank you. Dr. Fitzgerald.

DR. FITZGERALD: One of the highly emotional issues for the industry and for patients and for ourselves is that, you know, in hindsight, some of these meshes just appear unsuitable and, you know, they quietly went away.

With the current FDA 510(k) process, is it possible that, say, a microporous transvaginal mesh could be -- could come to be approved to be marketed because it is equivalent to a currently approved microporous mesh? No, micro. Could a Gore-Tex mesh be --

DR. FALCONE: Be cleared or approved?

DR. FITZGERALD: Cleared, cleared.

DR. FALCONE: Cleared.

DR. FITZGERALD: Sorry.

DR. BROWN: Jill Brown.

I would say it's unlikely but not impossible. So, you know, if there is data out there in the literature that shows a specific adverse event profile with a specific type of mesh, we certainly consider that in our process. So in that regard, I think it would be very unlikely, but I just can't say for sure.

DR. FALCONE: Dr. Davis.

DR. CAREY-CORRADO: It's Julia Corrado. I just want to make one additional comment.

When we receive a 510(k) submission, we routinely go through one or two review cycles where we issue requests for additional information from companies. For a device such as you have described, we would cite the evidence of adverse experience associated with that type of mesh, and we would say, please provide a justification as to why we should expect this to perform safely and effectively.

DR. DAVIS: Ann Davis.

I have some questions related to patient factors and your review of the literature and what I would call serious adverse events.

Was there any literature that pointed towards those patients who were seen by a physician who maybe wasn't the primary surgeon, or a physician who did not have experience with the possible complications on multiple occasions, before going back to someone who had experience? Or perhaps a patient who had socioeconomic factors that made it impossible to get to another location? Was there any information on that?

DR. BROWN: Jill Brown.

I would say, not really. Anecdotally, we certainly know of cases like that, that we've had interactions with patients who have described those type of scenarios. But I don't think this has been captured in the literature. I'll defer to --

MR. ANDERSON-SMITS: Colin Anderson-Smits.

I would second that, but it's definitely something that's not

currently captured.

DR. FALCONE: Dr. Hillard.

DR. HILLARD: So during the public commentary we heard a couple of comments about recall of devices, and we're also discussing now that there may be specific devices that are either generally not used or even perhaps specific indications where the risks are higher.

Just for my information, what would be involved -- I'm understanding that a reclassification does not -- remaining Class II would not remove any products from the market.

DR. CAREY-CORRADO: It's Julia Corrado.

It's correct that the devices that have already been legally cleared for market would not be removed from market. It is possible, for cause, for FDA to rescind a 510(k) clearance. And there are also -- there is a whole group of types of recalls that FDA's Office of Compliance carries out. But a recall can have many meanings, and it does not necessarily mean you would rescind a 510(k). A 510(k) rescission is a separate process. But for good cause, it is possible to rescind clearances of Class II devices.

DR. FALCONE: Do you want add to that?

DR. LERNER: No, I don't. I just think that we're falling way, way behind, and a lot of these points could be brought up in the discussion of the questions.

DR. FALCONE: I just want to make sure that the Panel

understands everything completely. And I understand that. But if it's a direct question to the FDA panel, I think that I'm going to allow it.

Go ahead.

DR. DIAMOND: When Mr. Anderson-Smiths gave his presentation and described how you identify the studies that you included in the review, you identified that you excluded the non-urogynecology procedures and that that accounted to about half of the mesh reports that were in the MAUDE literature.

But as I look at the top adverse events from the urogynecology group, which were erosion and pain and infection and bleeding, I would envision that those can be things that would be potential complications at other sites also, in the presence of mesh.

And so either from looking at those reports that you excluded or from FDA's other analyses of mesh, have those been common types of events with mesh, which has a larger class sort of effect of an agent, that the Panel should be aware of?

MS. PRESSLY: Actually, that was my presentation on the MDR data. We have looked at the MDR data for other mesh uses such as hernia repair. It is not as thorough at this point as the review that we did for the urogynecological uses.

Yes, there is some overlap in the types of adverse events that we see for those other uses of mesh, but I really can't state specifically what

the rate is that we've seen in the MDR for erosion and hernia, or specifically what those other percentages are for hernia use right now.

DR. FALCONE: Okay. So I think that we may consider a break at this moment, rather than having the FDA questions to the Panel. Maybe we need to take a break and then you can present the questions.

MR. ANDERSON-SMITS: I just wanted to -- this is Colin Anderson-Smits -- provide the information that Dr. Diamond asked about the re-surgery for the same surgery. It was 2.4 percent for no mesh and 5.1 percent for mesh.

DR. DIAMOND: Thank you.

DR. FALCONE: Okay, thank you. A 10-minute break, so that means 3:53.

(Off the record.)

(On the record.)

DR. FALCONE: Please take your seats and we're going to proceed to this, but beforehand -- we're going to proceed to the FDA questions. I think, Dr. Lerner, did you want to say a few more words about clarifying some unclarified points?

DR. LERNER: Yes, thank you very much.

So there seems to be some confusion about 522 studies, clinical trials, and what the requirements would be for each. So before we get into the questions, just a very brief clarification.

A 522 study can be ordered for any device in the postmarket setting. As was outlined earlier today, it could be that they can take the form of any one of a number of trial designs. It could also be a collaboration between several companies to put together some -- to get enough data to support a marketing application for whichever pathway the devices end up in. No, this is for postmarket.

For premarket, if we're going to ask for -- if we're going to up-classify, then the data from those postmarket studies could be used to support a new PMA application with that dataset.

But I also want to make it clear that that doesn't mean that forever every new mesh device coming in for POP repair would require a full-fledged PMA study. Once time has gone on and we've seen some of these, we can modify the requirements for clinical data. So it wouldn't necessarily follow for the lifetime of these device groups.

Additionally, we could also use collaborative data to support PMA applications, although that would be a little tricky to work through with how we would separate the data for each study group for each specific device.

So we're trying to be, in our lingo, least burdensome, and we're trying to make the point that we can use mandated postmarket data to get to a premarket arena.

So does that make more sense?

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DR. FALCONE: Yeah, I think it makes sense. I think, if I can summarize, essentially you clear then study, as compared to study then approve?

DR. LERNER: The cleared devices that are on the market --

DR. FALCONE: Yeah, and then you study them.

DR. LERNER: -- we could be studying in a mandated 522. And that data could be used to approve for premarket.

DR. FALCONE: Yeah, but you clear and then study them.

DR. LERNER: Right.

DR. FALCONE: And then if you up-classify, you study then approve.

DR. LERNER: Then approve, right.

DR. FALCONE: Okay, got to keep it simple.

DR. LERNER: The old devices will stay on the market.

DR. FALCONE: All right. So are you going to give us -- what are you going to give us, the questions now? Is that what you're going to do? Okay.

MR. POLLARD: I was going to do two things.

DR. FALCONE: Okay.

MR. POLLARD: Mr. Gadaleta had wanted us to remind everybody of what the definitions of safety and effectiveness are, so I was going to do that.

DR. FALCONE: Excellent.

MR. POLLARD: I've got a slide up here that captures it right from the Code of Federal Regulations, and I'll just read it briefly just to imbed that in your brains.

DR. FALCONE: Yes, please do.

MR. POLLARD: Safety. And we've kind of got underlined here some of the key aspects. There is a reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence -- and we went through that in our training yesterday -- that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.

And the definition of effectiveness is: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, again, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

And so those are the standards that would be applied.

Number one, in the case of a Class III premarket approval application, the applicant would need to show that the device is safe and effective. With a 510(k) premarket notification, the applicant needs to show

FDA that the device is substantially equivalent, in terms of safety and effectiveness, to the predicate device.

DR. FALCONE: Great. There are four questions. I think --

MR. POLLARD: Yeah.

DR. FALCONE: -- Colin is going to bring up the four questions. So I just want to make it clear, there are four questions, you know, with two and a half pages, and therefore what's critical here is that -- and we're going to answer these questions. And what we're going to do is we're going to, in fact, go around the room and I'm going to ask, in response to the actual question, which I'll reread, is to give me your focused opinion because, as it stands now, we can debate forever.

We have received the information, and certainly when it's your turn to give me a very short, focused opinion, if you wish to give it, you can of course, you know, ask other questions to whoever you want to ask. The FDA is here and everybody else. So to make sure that absolutely everyone in this room gets a chance to give their focused opinion, that's what we're going to do and we're going to start -- we'll probably start on the left to right.

But we're going to get the whole question. In fact, the only piece you'll be asked to comment on, focused opinion, very brief, state your name, then your opinion, or pass if you don't want to, and then we can move on and try to complete the task at hand. Is that acceptable? All right.

MR. POLLARD: Thank you. And I would just add that since

we've begun this part of the Panel meeting, to the degree you have questions and discussion, that you try to contain it to yourselves. That's the purpose of this situation. If you absolutely need to ask FDA for help or otherwise, you know, at the Panel's discretion, you can allow that.

So the painful truth is I've got to read the entire question, although we've got it paraphrased up here, and I'm going to read it in parts as you go through it.

So there's four questions. Question 1 deals with the risk/benefit. Question 2 deals with the reclassification aspect. Question 3 deals with the 522 need for postmarket studies. And Question 4 deals with ASC.

So I'm going to read to you Question 1a. So we're talking in this portion Question 1 and Question 2, we're talking about vaginal placement of surgical mesh for POP repair.

1. Medical devices are classified (i.e., Class I, Class II, and Class III) according to their risk and the level of regulatory control necessary to provide adequate assurance of their safety and effectiveness. The following questions are intended to assist the FDA in identifying the safety or effectiveness concerns associated with vaginal mesh used for POP repair and determining whether the evidence shows that the clinical benefits outweigh the risks.

Risk/benefit of vaginal mesh for POP repair.

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- a. Safety of vaginal mesh used for POP repair. Based on a review of the published literature and an evaluation of the MAUDE database, FDA has identified numerous perioperative and long-term risks associated with vaginal mesh for POP repair.

Peri-Operative Risks

- Organ perforation
- Bleeding (including hemorrhage/hematoma)

Long-Term Risks

- Mesh exposure into the vagina. Clinical sequelae including pelvic pain, infection, dyspareunia (painful sex for patient or partner), vaginal bleeding, vaginal discharge, and the need for additional corrective surgeries.
- Mesh erosion into the bladder or rectum. Clinical sequelae including pelvic pain, infection, dyspareunia, fistula formation, need for additional corrective surgeries (possibly including suprapubic catheter, diverting colostomy).
- And other risks that can occur without mesh erosion. These risks include pelvic pain, infection, dyspareunia, urinary problems, vaginal

scarring/shrinkage, recurrent prolapse,  
neuromuscular problems.

And here's the crux of the question:

Please comment on the accuracy of this list and whether it captures the most serious risks associated with vaginal mesh used for POP repair. Discuss the incidence and severity of these adverse events. Please discuss if there is reasonable assurance of the safety of vaginal mesh for POP repair.

And in answering this question, please consider the following factors: pelvic compartment for repair, i.e., anterior, posterior, apical, or multi-compartment, previous and concomitant surgeries, patient factors, surgical technique and expertise, limited patient follow-up, which is typically no more than six months to a year.

So that's Question 1a.

DR. FALCONE: For Question 1a, basically, to summarize -- you can answer all or part of this -- is the list of risks prepared by the FDA complete and accurate? And given the available evidence on the incidence of severity, is there reasonable assurance of the safety of vaginal mesh for POP repair?

Can we start on my left here? Dr. Chappell, focused opinion, please, if you may. Or you can --

DR. CHAPPELL: I'll pass on that one, but I'll make it up later.

DR. FALCONE: Yeah, I'm sure you will.

Dr. Brill, state your name and then give me your focused opinion.

DR. BRILL: Andrew Brill.

I think the list is exhaustively complete. I would mention, though, that certain categories perhaps deserve more mention. So such as mesh exposure, in the context of whether this is an adverse event, this is a severe adverse event, or this is a non-consequential event, I think, would be more helpful ultimately when this list is compiled.

DR. FALCONE: Okay, Dr. Sears.

DR. SEARS: Dr. Sears.

I think that the list is complete.

DR. FALCONE: Dr. Fitzgerald.

DR. FITZGERALD: Just to clarify, are we to confine ourselves to whether the list is complete or also to comment on the expert --

DR. FALCONE: Those two questions right there.

DR. FITZGERALD: Oh, sorry.

DR. FALCONE: Is the list prepared by FDA complete and accurate? And given the available evidence on the incidence and severity of these adverse events, is there reasonable assurance of the safety of vaginal mesh for POP repair?

DR. FITZGERALD: Thank you. One complication that I don't see

listed here that is clinically not rare would be leg pain. You just have pelvic pain. I think leg pain clinically significant. Other than that, I think it's an accurate list.

The question was about the incidence and severity of the adverse events. Clinically, there is a qualitative difference in reoperating for recurrence of prolapse to reoperating for a severe adverse event that can occur with some -- that it can be unique to mesh. Certainly I have seen severe adverse events from native tissue repairs and also from mesh repairs.

The severe and long, long-lasting adverse events with mesh seem to be qualitatively different in the clinical setting, and the number of repeat surgeries, I would say, would be -- I've never heard of, you know, many surgeries, return surgeries for a native repair.

As to whether we have reasonable assurance of the safety of vaginal mesh at the moment, the main reason I think we don't have that is we don't know about -- we don't have enough data on native repairs to compare the safety. So I think we simply don't have enough data to say whether the meshes are safer.

DR. FALCONE: Thank you. I'm actually going to go back to Dr. Brill because he didn't answer the second question and he does want to answer it, I think.

DR. BRILL: Thank you for the clarification.

I think, from the data that's been presented, albeit limited by

what's been discussed by many presenters today, the actual incidence of adverse events in the context of number of procedures is acceptably small, especially in the context of traditional surgeries. That's of course a random number because we don't know the true denominator. So ultimately a post-surveillance study and/or a randomized controlled trial will be necessary to answer this question.

DR. FALCONE: Very well, thank you. Dr. Rogers.

DR. ROGERS: I believe that the list of risks that the FDA has compiled is complete and accurate. I would agree with Dr. Fitzgerald about the addition of other leg or lower extremity pain syndromes which are seen at times with these types of repairs.

I think that when I think of safety, I think of, you know, the tradeoffs between a native tissue repair versus a mesh repair and would concur with my colleague that we do not -- have not fully characterized the risks of native tissue repairs.

But would also add that I think that, at times in rare examples, the nature of these complications with mesh lead to a qualitatively different degree of complications that at least I have experienced or, in speaking with my colleagues, they have experienced with native tissue repairs. So there's a qualitative difference in our ability to address some of these rare, to agree with Dr. Brill, complications.

I think that the other piece that is missing is long-term data. So

long-term safety data, including maintenance of the graft or its acceptability in vaginal tissues, is not well characterized, it is not well studied, and it is unknown. And I think that the potential exists for there to be serious sequelae that have just not appeared yet.

DR. FALCONE: Thank you. Dr. Flesh.

DR. FLESH: The first part of the question, I think the list of risks and complications is complete. For the second part of the question, I have to give a very qualified answer.

First, the general answer is I would have to say yes, that the safety has been demonstrated to a reasonable degree. However, the question really cannot be answered in the way that it's stated at all. Number one, compared to what? Compared to what kinds of other repairs? Number two, in which particular kinds of cases, big prolapse, medium prolapse, little prolapse?

For example, a lot of the randomized controlled studies, they include almost 50 percent Stage II. To me, this makes the non-mesh repairs much more likely to be successful. If they only use Stage III and Stage IV, I think we'd see much more dramatically different results.

Next, by which surgeon and using which techniques? I think there's a false assumption that all of these numbers mean the same thing. They don't. It depends on who's doing the surgery, how much training they have, whether they understand the details of technique that are essential to

avoid complications.

Next, by which version of mesh? The meshes that we're using now are quite different from what we were using eight years ago. The meshes are softer, they're more porous, they're more elastic.

Next, with or without trocars? And my heart breaks when I hear these horrendous complications of bladder injury and bowel injury. I think virtually all of these are from misplacement of trocars. I do not believe that they're related to erosion of mesh. I don't think that monofilament mesh does that. People are sticking the mesh into the wrong place and then five months later they're discovering it and calling it an erosion because it's not as embarrassing as admitting that you stuck it there in the first place.

Now, just a couple more things. And I'm sorry to take up so much time. I looked at my own data between July 1st, 2008 and July 1st, 2011. I did a total of 364 cases using polypropylene mesh, not counting mid-urethral slings. About three-fourths of those also involved sacrospinous suspension, which was also done with mesh. Out of those 364 cases in the last three years, I took five patients back to the operating room for erosion. All of these cases involved erosions of 1/2 to 1.5 centimeters. They were at the incision line. All cases were resolved with a 15-minute outpatient surgery.

I also had six cases where small erosions were seen in the office. These were almost all asymptomatic. They were treated with

estrogen cream and in some cases with snipping a few fibers.

The total erosion rate that I have had, then, is about 3 percent, and the number of erosions that actually required a serious intervention, meaning 15 minutes in the operating room, was 1.4 percent.

Now, I can tell you one explanation for these statistics, which I know for sure is not the correct explanation, and that is that I'm surgeon genius and everybody else is stupid.

(Laughter.)

DR. FLESH: That's not the correct explanation. The correct explanation is, just like with Dr. Stanford, who said basically the same thing, we do certain things with certain details of technique which minimize erosion. And I think that the FDA panel is focused on the wrong issue. The problem, in my opinion, it is not the material itself; it is how the material is being used and by whom and in what kinds of cases.

DR. FALCONE: Thank you. Ms. Berney.

MS. BERNEY: Barbara Berney. I'll pass.

DR. FALCONE: Okay.

DR. GADALETA: Sergio Gadaleta.

I think the list is complete. I would make one proposal, though. I would ask that we clarify which of those adverse events are related to surgery in general versus those that are related to the mesh specifically.

On the comment of safety, I agree with Dr. Flesh that the

probable benefits outweigh the probable risks in the hands of a trained surgeon.

DR. FALCONE: The question: Is there a reasonable assurance of safety of the vaginal mesh? We'll get to the effectiveness and then --

DR. GADALETA: Oh, I'm sorry, did I say effectiveness?

DR. FALCONE: Yeah, I thought I heard --

DR. GADALETA: I meant safety. Sorry, sir, I meant safety.

DR. FALCONE: Okay, thank you. Dr. Duerhring.

DR. DUERHRING: This is Gary Duerhring.

Do I think that the list of risks is complete? Yes, I do. Do I feel that we have reasonable assurance of the safety of vaginal mesh in a POP procedure? It's like, does the gun kill or is it the person who's holding the gun? I feel that the mesh has been proven to be safe, but there's a lot of things that we don't know and I think that there has to be postmarket evaluation, without a doubt. But I would have to answer, I would agree with Dr. Flesh.

DR. FALCONE: Thank you. Right, Dr. Davis.

DR. DAVIS: I think that it is safe in the hands of an experienced surgeon who is an excellent counselor and able to judiciously choose the appropriate patient. My problem is that the surgeons, who I have great respect for today, that have given us data do not represent all of the people that may well be doing this procedure, and in their hands I do not think that it

is safe.

DR. FALCONE: Thank you. Dr. Hillard.

DR. HILLARD: Paula Hillard.

I agree with Dr. Davis and with the previous comment, but I also have additional concerns about mesh-specific complications, specifically erosion and exposure, that have the really significant life-altering potential risks. And so I do not believe that it is safe.

DR. FALCONE: Dr. Diamond.

DR. DIAMOND: I think there are probably a couple of things that could be added to the risks that would be assessed. Those include impact on quality of life measures. Secondly, dyspareunia is measured, as mentioned, as a long-term risk, but sexual function as a whole is not, and I think there ought to be more of an assessment of sexual function in its entirety.

Long-term risks I think we do not know a lot about. And specifically, as a subgroup of that, patients who have had revisions or removal of mesh and their subsequent long-term outcome, I don't think we know the answers to that.

We may know things about rehospitalization rates, but I don't think we have a real good grasp of repeat procedures or follow-up procedures that are done in the office, and in future studies I would think that would be something that should be captured as well.

I share Dr. Davis' concern about who's doing the procedures and what is the general use going to be as far as safety of these procedures, how those are compared to the rates that we've seen in the hands of the experts.

And, lastly, the FDA has asked us to consider these thoughts in the terms of patient factors, and in this day and age of burgeoning personalized medicine, I don't think we know anything about innate characteristics of individuals and who will or will not be better candidates for the use of mesh, and would think that would be something also for the future, to learn more about.

DR. FALCONE: Thank you. Dr. Dominik.

DR. DOMINIK: Based on the data provided, I think everything that's on the list belongs on the list. I don't know if additional things should be added to that list.

Although I expect that the use of the mesh may be safe, relative to approaches that do not use the mesh, when used by the right hands, I don't think we have the data to support that statement yet.

And I also think the comment earlier about there's a qualitative nature, although you might see the same kinds of events when the mesh is used versus when the mesh is not used, there's a qualitative nature, perhaps, that is different and important to better understand. And there may be a quantitative difference as well.

I think very often it's been said today that we see the same types of events in native tissue repair, but there hasn't been a lot of discussion about the differences in rates between those same types of events in native versus mesh repair.

DR. FALCONE: Thank you. Dr. Iglesia.

DR. IGLESIA: Okay, Cheryl Iglesia.

For the first question, I do think that the FDA did a good job in outlining the lists of risks, and I like the fact that you did parse it out between complications specific to mesh and those that are just specific to undergoing prolapse surgery in general.

But perhaps under the one specific to mesh, with regard to the vaginal scarring and contracture, I do think that we need much more evidence on how we're defining that and what parameters we're using. You know, I know ultrasound, I know there's just been clear measurements, but we need to understand, you know, how that shrinking and contracture effect is really affecting women.

And as for the leg issues, I think that that classification of neuromuscular kind of maybe incorporates that to some degree.

But under urinary symptoms, the problems, I think that you can't just say urinary problems in general. But this question of de novo stress incontinence, which can be a problem with over-tensioning of mesh and really flattening out that anterior wall so that, you know, the bladder just

starts leaking, I think that, in addition to voiding dysfunction and detrusor overactivity, kind of has to be separated out a little bit more as well because there have been some studies reporting on some of these de novo complications, but particularly relative to stress incontinence. Those are my two cents on the lists of risks.

With regard to the available evidence on whether or not this is safe, I feel, in general, in appropriate hands and appropriate patients it's safe. But I just don't think it was ready for prime time in generalizability. So I'm just going to have to say, overall, there's insufficient data and we need to focus a lot on the training and on looking at the dedicated practices for physicians who can appropriately counsel with regards to no mesh procedures versus mesh procedures versus nonsurgical options, and also be able to handle the complications. Because, you know, what we see in my practice, as a referring practice, is that a lot of patients don't go back to the same doctor who had the complication.

So while we would love to track and feel like we have zero complications -- and I think that, you know, even of myself, if someone had a complication, they may not want to come back. Maybe they'll come back once, but you know, I may not ever hear from them again, and we don't know about it. And I really feel like we need to get a better handle on that. So I'm going to say insufficient.

DR. FALCONE: Thank you. Dr. Coddington.

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DR. CODDINGTON: Charles Coddington.

In looking at Question 1, I think Question 1 is complete with the additions that have been there, assuming that, as mentioned, the chance for rejection is small.

Also, in looking at Question 2, I agree with Dr. Flesh and Davis that there are a lot of aspects -- and Dr. Iglesia -- of where we do not have the data. But I think the proper hands managing the patient properly with problems, I think that the mesh is safe.

DR. FALCONE: Very well. Dr. Mattison.

DR. MATTISON: Don Mattison.

I think that the list prepared is good, with the additions noted and with two caveats. One deals with the fact that most of the risks have come from short-term follow-up as opposed to longer-term follow-up, and that's been noted by other panelists in the past.

The other is I'm getting a sense from the way that the data is evolving that as the follow-up of these patients is evaluated more closely, additional risks or adverse events are being identified. So I think that that's something that may be an evolving concern in terms of the risks.

Given evidence on the adverse events, reasonable appearance of safety, I think the comparison with the native tissue repair needs to be done. I believe that the heterogeneity and the quality of the studies that have tried to assess safety is such that there is no reasonable assurance of

safety for vaginal mesh.

DR. FALCONE: Thank you. Dr. Kalota.

DR. KALOTA: Susan Kalota.

I think the list of the risks --

DR. FALCONE: The list that just disappeared.

DR. KALOTA: Exactly. I think that along with the -- it's appropriate. As far as the way -- I think we've focused a lot on the erosion into the vagina. I don't see that that is a significant problem. Where the isolated risk with the mesh that is really significant is the pain. I think that occurs very infrequently, but I can tell you, every single one of the patients that I've ever had come back for pain were the erosion. Most of the older patients, it's a nonissue.

Comparing it to the repairs without mesh, we're not going back immediately and doing surgery on those patients who have problems. But maybe their prolapse doesn't come back. But there's as many women in the past who had no mesh, whose vagina was shortened, narrowed, became nonfunctional, and it wasn't a product. So they can complain, but there's not much they can do about it, and there's a lot more women who had nonfunctional vaginas when we were doing non-mesh repair. And you have to bring up that part, too. As far as complications, we're not seeing that as much with the mesh.

The shrinkage we may see, but I see that much less often than

what I used to see. After my colleagues in private practice would do these repairs, I'd help them and we'd end up with a small, small vagina in a young woman.

So the complications associated with mesh I think are there. They're important. But comparing to what else is out there, I don't know that that would preclude the use of it at all.

DR. FALCONE: Very well, thank you. So I'd like to -- no, I'm going to ask, if you abstained, if they want to give an opinion. Dr. Chappell and Ms. Berney, if you want to give your opinion before we have Colin come up and give us part (b) of Question 1.

DR. CHAPPELL: No, thanks. You'll hear from me.

DR. FALCONE: Okay, I'm sure I will.

Ms. Berney, would you like to --

MS. BERNEY: Yes.

DR. FALCONE: Okay, please go ahead.

MS. BERNEY: As the patient who has to live with this miserable mess, it's 20 years now. They didn't use mesh when I had surgery. And I can tell you, the complications that I've had are every bit as awful sounding to me as anything I've heard of with the mesh.

However, because of the experience I had and because of my other experience with products that were approved and have been difficult, I'm very hesitant to say that I think it's completely safe because we don't

have enough data. There just isn't a long enough history. Things happen after 10, 15 years and women's bodies change, and for younger women who have surgery with mesh, their bodies are going to change a lot. So we don't really know what will happen. And until there's something to compare it to and a history, it's hard to say whether it's actually safe and effective.

I also agree that in the hands of the proper surgeon, a well-trained surgeon, that you probably have a better chance. But I also know that even the best surgeons, who are the most careful, the most judicious and cautious, also have disasters. So is it the surgeon or is it the mesh? I just don't think we have enough information, so I'd have to say that I have to reserve judgment as to whether it's safe or not.

DR. FALCONE: Thank you very much.

I think, to summarize, it appears that -- the only thing that I can summarize from this is that preponderance of the group feel that they require more evidence to actually answer those questions, more than anything else.

So Colin, part (b).

MR. POLLARD: So part (b) asks you to look at the effectiveness of vaginal mesh for POP repair.

The FDA believes the available scientific evidence does not demonstrate that vaginal mesh used for POP repair provides clinical benefit compared to surgical repair of POP without using mesh. In light of the

scientific evidence, please discuss if there is a reasonable assurance of effectiveness for vaginal mesh for POP repair.

And in answering this question, please consider the following factors:

- pelvic compartment for repair, i.e., anterior, posterior, apical, or multi-compartment
- clinical relevance of anatomical outcomes (e.g., the POP-Q score, or prolapse above and below the hymen) in relation to patient satisfaction outcomes (such as the QoL instrument)
- whether use in certain subpopulations (e.g., higher stage prolapse or recurrent prolapse) changes the clinical benefit profile
- the duration of patient follow-up
- synthetic versus non-synthetic.

And maybe there are some other factors that you think should be considered.

DR. FALCONE: Okay, now I get to start on my right. Dr. Davis. So considering the available evidence, is there a reasonable assurance that vaginal mesh for POP repair is effective? And, again, I just need a focused opinion.

DR. DAVIS: Right.

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DR. FALCONE: It doesn't have to be very long and you can cover any or none of those things.

DR. DAVIS: Okay. I think that there is evidence that it is effective in some circumstances, which I'm sure some of my colleagues will elucidate on, and in terms of quality of life. But it certainly has not been proven to be superior to the native tissues.

I also wanted to comment that there, of course, is a problem in terms of actually defining and recognizing some benefit related to the target populations because we don't know how to define those target populations.

DR. FALCONE: Thank you. Dr. Hillard.

DR. HILLARD: So I think we're hearing that this can be effective or potentially as effective as traditional procedures, except that we're not so sure and we certainly are not seeing lots of benefits over the traditional procedures. And I'm hearing as well that there may be more benefit in certain compartments than others. And, again, I'll let my colleagues comment about that.

There's been comment about assessment with POP-Q, and I think that's an objective measurement and I think that can be helpful. But I don't think it should be the only measurement or even the most important one, and additional weight should be given to quality of life assessments.

And in addition, as Dr. Diamond had mentioned, assessment of sexual function overall, I think, is also important.

In addition, comments about the duration of study are also important.

DR. FALCONE: Thank you. Dr. Diamond.

DR. DIAMOND: My thoughts with regard to proven effectiveness of the vaginal mesh is that, overall, I think we still need additional information and particularly in comparison to other non-mesh uses.

With individual articles perhaps notwithstanding, the general embodiment of the literature that group had to review, I don't think leads to a clear picture demonstrating efficacy.

A couple of specific things regarding efficacy, which I mentioned before. As has been stated, I don't think that the anatomical POP-Q score in and of itself should probably be the efficacy endpoint. That may be one component. Let the follow-up be considered. And, again, I would make pitch for including innate characteristics of individuals and how they respond as part of that assessment, so that we can better determine treatment approaches in the future, which will be able to be individualized for individual patients.

DR. FALCONE: Thank you. Dr. Dominik.

DR. DOMINIK: Can I pass and come back, please?

DR. FALCONE: I'm sure Dr. Iglesia is ready already.

(Laughter.)

DR. IGLESIA: Okay. So I would say that after considering all the available evidence, that the only compartment where there seems to be some effectiveness is the anterior compartment. We have insufficient data from the apex for the posterior compartment and certainly for multi-compartment use.

As for outcome, I do think that composite scores are very important, that meaning inclusion of objective anatomical improvement as well as subjective relief of bulge and the quality of life symptoms. That is important as well in the evidence, as well as looking at the rate of reoperation, reoperations not only for recurrence but reoperation for other mesh-related complications.

And I think that as these evolve, hopefully we'll be able to give some guidance so that we can understand in what patients, you know, this is most useful for, the patients that have recurrences, the patients with the more advanced prolapse, Stage III's and IV's, and maybe who have major medical morbidities that an abdominal or laparoscopic, robotic or other procedure really is not easy to perform and may have a higher potential of complications associated with it.

So, you know, what to do with the younger, sexually active patients is also important. And I think that we need to look at this long term.

DR. FALCONE: Very well, thanks. Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

I think I agree with Dr. Iglesia that this -- the anterior compartment, there is some data suggesting effectiveness; posterior, apical, and multi-component, it doesn't seem to be there. Clinical relevance of anatomic outcomes, pre- and postmenopausal, I think, are going to make a significant difference. You're already alluded to the sexual functioning.

I find there's no data on certain subpopulations, particularly in relation to the higher stage for recurrent prolapse. Short durations, less than two years, or two years or less, make it very hard for long-term follow-up, and there doesn't seem to me to be any compelling data on synthetic versus non-synthetic.

Other than that one area, I don't find that there's effectiveness proven.

DR. FALCONE: Thank you. Dr. Mattison.

DR. MATTISON: Well, there have been more studies looking at the mesh in repair of anterior compartment prolapse. I'm not persuaded that the data across all of the studies strongly supports effectiveness. And given the paucity of data in the other areas, it would have to assert that there is -- I don't believe that there's reasonable assurance that using mesh for POP is effective.

DR. FALCONE: Thank you. Dr. Kalota.

DR. KALOTA: Susan Kalota.

My interpretation of the data, of course, may be biased by my

own personal preferences. I thought the data did show efficacy.

In my personal experience, I think that in the smaller degrees of prolapse, that probably the non-mesh is possibly even better, but it's at least equal. But in the big degrees of prolapse, anterior and posterior, I actually love the mesh for the posterior. I think we get a much nicer repair and maintaining the vaginal length and width. I think the greater degree of prolapse, the more likelihood that we're going shorten and narrow the vagina if we don't use mesh. That's been my experience.

DR. FALCONE: Thank you. On my left, Dr. Chappell, are you going to pass?

DR. CHAPPELL: Not this time.

DR. FALCONE: Okay.

DR. CHAPPELL: So concerning no evidence of efficacy, if there does seem to be some evidence, I don't know what reasonable means in this context, and I think that Drs. Iglesia and Mattison have -- sorry -- Kalota have presented the evidence better than I can.

The second issue is something that Dr. Hillard mentioned concerning outcomes. You have to define efficacy with respect to the outcome.

For research, I will have suggestions when the research question comes up.

But I really don't know how to answer this question without

knowing what they mean, what the questioners mean by efficacy. Surely when there was -- when we discussed some positive results, it almost always seemed to be anatomic, not quality of life. And so later on I'll present some requests for how we're relating the two so we can translate one into the other or see if we can translate them.

DR. FALCONE: Dr. Brill.

DR. BRILL: Well, I think we've heard how confounded all the data is that exists for us to evaluate, and in that context, I think there is demonstrable, but not necessarily definitive, data for anterior augmentation with mesh. And I think the question is out for the rest of the compartments.

Of course one of the problems also in designing the future studies is trying to make these more site-specific rather than multi-site, and as we've heard from my colleagues here, larger-stage defects may in fact be another creature altogether in the context of surgical needs.

I think follow-up is key. That's one of our weaknesses. In all of our data, the average study is 12 months. I think 36 months or more is minimal to determine the outcome of these procedures.

It's interesting that the FDA presented the Altman paper toward the end of the presentation this morning. It was very different than what Dr. Hinoul presented. The FDA presented that there really wasn't very much difference between the groups, and Dr. Hinoul, you presented that with transvaginal mesh the anatomy was 82 percent, the anterior repair was 48

percent, and for the quality of life, it was 76 percent versus 62 percent.

And I bring this up just because, you know, it depends on what we're going to look at as to our standard as to how we're going to interpret these studies, and you have here radically divergent opinions based on simply the modicum that was used to evaluate the endpoint.

So I agree with Cheryl. We need complex instruments, we need validated instruments for sexuality, for quality of life that have to be added to these anatomical milestones that are looked at postoperatively.

No one, I don't think, has mentioned synthetic versus non-synthetic. I think we also heard several presentations on that. One presentation was, I believe, a 1.6 percent, from industry, erosion rate, and then I believe the FDA had a 10 percent erosion rate in their data.

So I'm not sure about which way to turn on this, but we obviously have mixed information. I think that's all I have to say.

DR. FALCONE: Thank you. Dr. Sears.

DR. SEARS: Thank you. In general, I would completely agree with what's already been said, particularly by Dr. Iglesia.

The one thing that I would say slightly differently is my reading of the literature on the posterior compartment is actually that I think that the literature says no mesh in the posterior compartment. The body of literature either shows no benefit or potentially even decreased outcomes in the posterior compartment, and with the exception obviously of specific cases,

which I think we do all see where things are very hard, people have very hard stool, they're chronically constipated, we try to control that and just can't.

So I would actually be even more -- state stronger that I think there is not good evidence in the posterior compartment and potentially there's evidence that mesh-based repairs are worse than native tissue-based repairs in most cases in the posterior compartment, with the exception of those outliers which have been mentioned. Otherwise, I completely agree with everything that's been said.

DR. FALCONE: Thank you. Dr. Fitzgerald.

DR. FITZGERALD: I agree with the findings. The SGS review and the FDA review again confirms that the data supports efficacy in the anterior compartment for synthetic mesh. I think the evidence of effectiveness for the non-crosslinked biological grafts is minimal. Probably, when you're considering effectiveness, those need to be separated out. I concur with all the other requests for longer data we just don't know.

One thing that has been thrown out a few times and not really addressed again is the notion that the reoperation rate for native tissue repairs is unacceptably high, to quote one of the speakers. Actually, in the native tissue case series, sacrospinous, uterosacral, the reoperation rate is nearly always four or five percent. The prolapse recurrence rate is higher, but the reoperation rate is low. And we heard some evidence today that it may even be a higher reoperation rate for prolapse in that Medicare group,

with all the limitations of that data. Thank you.

DR. FALCONE: Thank you. Dr. Rogers.

DR. ROGERS: With regard to the compartment of repair, I agree with my colleagues that the evidence would support that in the anterior compartment there may be benefit in mesh-augmented repair.

However, I would still caution the FDA to think of the vagina as a continuous organ and that perhaps -- and this is also linked to surgeon experience and technique -- that the reason that there is almost, as presented today, a two times higher rate of reoperation for prolapse is neglect of other compartments in the same patient, or appearance of "new prolapse" in that patient.

So that said, I think that we're a little off base just saying that the anterior compartment, although that is the compartment that most often recurs as the presenting organ of prolapse, is part of a global pelvic problem and should be addressed as such, whether anatomy and function obviously are intimately related and one follows the other.

But the direct linkage between those two in the case of prolapse, to my knowledge, is undefined and data were not presented to tell us that if the prolapse, for example, the apex, is moving down the vagina, we're just not seeing quality of life changes or not. And what that all means in terms of a perfectly anatomically supported vagina or a nearly perfectly supported vagina, if that makes a real difference to the patient, is not known.

So the outcome measures, the other colleagues have talked about that, the definition of the importance and the quality of the outcome measure has yet to be defined.

I would agree about the mesh types, that the efficacy for biologic grafts has very limited data, although the numbers of patients that were presented in the FDA report, 400 patients, is really too small, in my opinion, to make a decision about efficacy.

And then, finally, I think that we have heard a couple of themes here about the efficacy for certain patients and, in certain hands, will vary, and that when we make decisions regarding efficacy, that we cannot disregard the importance of those variables in the decision making and outcomes.

DR. FALCONE: Thank you. Dr. Flesh.

DR. FLESH: Again, a qualified answer which has to be in several parts.

First, with regard to anterior colporrhaphy, I think there's already excellent evidence that the anatomic results are better with mesh repairs. There are now five or perhaps it's six randomized controlled studies that show clear superiority of mesh repairs with anatomic result.

Secondly, there are two studies, also randomized studies, which show superior subjective results. One of them is the Altman study from *The New England Journal* this year, with composite objective and

subjective success with mesh was 60-some percent and without mesh it was 38 percent. I believe those are correct numbers.

Next, the stage of the anterior vaginal wall prolapse will determine significantly whether the mesh is going to be helpful or not. And it's a big mistake, I think, that all of these studies that I read combined Stage II, Stage III, Stage IV. And in my own practice, Stage II, most of them I wouldn't operate on at all. But the few that I would operate on, I would almost never use mesh. Stage III and IV is a different story completely.

I would also like to emphasize my very strong agreement with Dr. Kalota who points out that, before we had these mesh materials, we were seeing all of these constricted, shortened vaginas because the only way you could fix the prolapse is by tightening everything up. And now we can fix the prolapse without tightening everything up.

Along these lines, Dietz did an ultrasound study, which was published this year, which showed in 40 patients, an average of 18 months postop, by ultrasound study, there was no shortening of the vagina in mesh repairs. And I believe that this whole issue of contraction, it's really a mistake.

Number two, the types of mesh arm tightening that is seen, I think this is not tightening. The problem is people put in the arms too tightly to begin with and they just don't understand the importance of keeping the arms loose. All right, I'll finish in a second.

Posterior prolapse, overall, the few studies that we have show no superiority for mesh. However, as Dr. Kalota said, there are cases of big prolapse where there is no other good way to fix it. And any study, randomized or otherwise, that led the FDA to make the conclusion that mesh should not be used in posterior repair, this would be a mistake. This has to be left to the individual judgment of the surgeon.

The final thing. The one thing that I think is the most critical need in terms of future studies, we need to have a study comparing bilateral vaginal sacrospinous suspension done with mesh without using trocars, compared to abdominal sacrocolpopexy, either laparoscopically, robotically, whatever you want. Dr. Iglesia presented, I believe, at AUGS. Am I correct? Or was it somebody else?

DR. FALCONE: We will be discussing research.

DR. FLESH: Okay.

DR. FALCONE: Okay, great. Thank you. Ms. Berney.

MS. BERNEY: I have a very definite opinion on this.

DR. FALCONE: And we want to hear them.

MS. BERNEY: I want to start by saying that, for all of you who are doctors, anatomical success does not mean a successful surgery. I am reminded of the saying that the operation was a success, but the patient died.

There are so many subjective factors from the patient point of

view. You can look at my surgery and say, Oh man, your stitches look great. Oh, there's no prolapse. But I am in so much pain, I don't know what to do with it.

So I'm not seeing in any of these data anything that convinces me that anatomical success equals efficacy. Maybe it looks like it's fixed, but if it doesn't feel like it's fixed or it causes some other problem, to me, that's not effective.

As far as the long term, once again, I don't think there's enough data.

DR. FALCONE: Thank you. Dr. Gadaleta.

DR. GADALETA: Sergio Gadaleta.

I think the data that we saw this morning, provided by AdvaMed and FDA, demonstrated that a significant portion of the target population saw a clinically significant result. Whether or not that result was superior for mesh over traditional repair is a different question. But based on that definition of effectiveness, I believe that the product is effective.

DR. FALCONE: Okay, Dr. Duerhring.

DR. DUERHRING: Gary Duerhring.

I would like to think that it's effective in certain populations, but I don't think that we've proven that at all. I would have to say that no, I have no reasonable assurance that it is an effective repair at this point.

DR. FALCONE: Thank you. Did you want to, Dr. Dominik?

DR. DOMINIK: Sure. I believe there's some evidence of -- that's limited to the effectiveness, with respect to the anatomical success rate at one year, and that's limited to the anterior compartment and for synthetic mesh, and that we don't know really the true meaning of the anatomical effectiveness.

DR. FALCONE: Thank you. All right, Colin. Part (c), Question 1.

MR. POLLARD: So we're doing the last part of Question 1, which is actually asking you to pool together your discussion of part (a) and part (b).

And it's asking you, Based on your assessment of the safety and effectiveness of these devices -- and we're talking about vaginal mesh for POP repair -- please discuss whether the evidence shows that the clinical benefits of using vaginal mesh for POP repair outweigh the risks associated with its use.

DR. FALCONE: Okay. So basically, do the benefits outweigh the risks? You don't have to expand if you don't want to, or you can just say, yes, they do, and no, they don't. And if you want, you can of course give a more focused opinion, but you can certainly just, you know, give a brief, straightforward yes.

Okay, we can start with you, Dr. Kalota.

DR. KALOTA: Susan Kalota.

Yes, I'd love to see more studies, I love data, but I think that --

DR. FALCONE: The benefits --

DR. KALOTA: The benefits.

DR. FALCONE: Dr. Mattison.

DR. MATTISON: No.

DR. FALCONE: Thank you. Dr. Coddington.

DR. CODDINGTON: No.

DR. FALCONE: Dr. Iglesia.

DR. IGLESIA: Yes, only for the anterior. Overall, no, and long term, no.

DR. FALCONE: Dr. Dominik.

DR. DOMINIK: No.

DR. FALCONE: Dr. Diamond.

DR. DIAMOND: Consistent with the quotes that I took down from some of the speakers this morning, from AUGS and ACOG and AUA and SGS, I would say there's a need for more information, so no.

DR. FALCONE: Thank you. Dr. Hillard.

DR. HILLARD: No.

DR. FALCONE: Dr. Davis.

DR. DAVIS: No.

DR. FALCONE: Dr. Chappell.

DR. CHAPPELL: No, but given the evidence presented today, I think we need to have more studies on situations where it might -- the risks

might not outweigh the benefit.

DR. FALCONE: Thank you. Dr. Brill.

DR. BRILL: We are needy of evidence and appropriate studies, but I would complete the answer with saying, in the hands of experienced surgeons, yes.

DR. FALCONE: Thank you. Dr. Sears.

DR. SEARS: In most cases, no.

DR. FALCONE: Dr. Fitzgerald.

DR. FITZGERALD: I think for the use of mesh for routine use for all stages of prolapse, that the clinical benefits do not outweigh the risks. I liked the way Dr. Varner put it for the SGS. Their use should not be widespread.

DR. FALCONE: Dr. Rogers.

DR. ROGERS: I think that I would concur with my colleague, Dr. Fitzgerald, about that in selective cases there may be -- the benefit may outweigh the risks. But for generalized use, the benefits do not outweigh the risks.

DR. FALCONE: Dr. Flesh.

DR. FLESH: Yes, the benefits outweigh the risks in selected cases, by specific surgeons, and compared to the alternatives available.

DR. FALCONE: Thank you. Ms. Berney.

MS. BERNEY: In cases where there is not quality native tissue

repair and that's not feasible and there seems no other alternative, I would say yes. Otherwise no.

DR. GADALETA: I agree with Drs. Brill and Flesh. Yes, in the hands of the right surgeon, with the right procedures.

DR. FALCONE: Dr. Duerhring.

DR. DUERHRING: Gary Duerhring.

I do believe that in the specific situations they may be effective and safe, but I don't believe that I've seen enough evidence to say that that blankets all situations.

DR. FALCONE: Thank you. Okay, Colin, we're going to Question 2.

MR. POLLARD: Yes, I'd just like to clarify, as we noticed almost as soon as I went back to my chair, that the question on the slide does not exactly match the question in your handout, and I'm presuming that the answer that we heard along this line was, do we believe the benefits outweigh the risks?

DR. FALCONE: Benefits outweigh the risks, yes.

MR. POLLARD: Right, right. So just to clarify that for that record.

DR. FALCONE: Yes.

DR. CHAPPELL: My answer was whether the benefits outweigh the risk, and then after I turned off my mike, I looked in alarm at the

question, so I wanted to correct it.

DR. FALCONE: No, it's the benefits outweigh the risks. That's the problem with asking the question; we forgot what the question is by the time we get to the end.

(Laughter.)

MR. POLLARD: Right. So we apologize for that.

So now we're turning to Question 2 and we're getting at one of the core questions for why we have you here today. We're going to be talking about the reclassification of vaginal mesh for POP repair.

And Question 2a starts out -- this question, there's three parts to it.

Given what is known about the safety and effectiveness of vaginal mesh for POP repair, should clinical studies be required for premarket evaluation? And if yes, please describe the appropriate study design, including patient selection/exclusion, outcome measures, follow-up duration, and especially what type of control arm, if any, is needed.

DR. FALCONE: Very well. So just to make it clear, are clinical studies needed for premarket evaluation of vaginal mesh products for POP repair? And that can be a straightforward one. If yes, what type of clinical studies? Again, a focused opinion would be nice, rather than an application for an NIH grant, at this moment.

(Laughter.)

DR. FALCONE: All right, are you applying? Dr. Davis.

DR. DAVIS: Oh, my goodness. I would support reclassification to Class III. I will say that my opinion would be markedly different if I could somehow control that this would be utilized by experienced surgeons.

Like Dr. Varner said this morning, I agree strongly that this does not mean just training in a weekend course. You'll know that I work for a medical school when I note this word, but it should be competency-based, not training-based.

And if we could control something that many of the patients, who remarked this morning, brought up, that they truly had interactive counseling in a language that was understandable to them so that they could make sense out of the benefits and risks, I would change my opinion.

DR. FALCONE: So just to clarify --

DR. DAVIS: Oh, did I not answer?

DR. FALCONE: Well, it's actually part (c) of Question 2 which will ask you specifically whether you want to reclassify. Is that right, Colin?

MR. POLLARD: Yes.

DR. DAVIS: Oh, I'm sorry, I thought we were to do that.

DR. FALCONE: That's okay. Right here, all we need is, do you want premarket evaluation and what type of clinical studies? And I guess it would be -- go ahead.

DR. DAVIS: Yes, I would like a study. And the exact design of

that study I would leave up to the FDA, but it likely would be similar to a randomized controlled trial, unless they could define great control subjects.

DR. FALCONE: Thank you. Dr. Hillard.

DR. HILLARD: Paula Hillard.

I agree with Dr. Davis, and that some sort of a randomized clinical trial would be appropriate. I do not think that a single-arm, prospective clinical trial is sufficient.

DR. FALCONE: Thank you. And Dr. Diamond.

DR. DIAMOND: Are clinical studies needed? I think they are. And the components of what I would like to see within those clinical studies are comparative studies that -- well, let's not say comparative studies. I think there should be an opportunity to individualize those studies based on the specific question that's being addressed, as well as the specific product that's being tested, that they probably should be for a minimum of one year that's being reported out initially, with subsequent follow-up of two to four years. And there probably needs to be consideration, at least for some products, for location of the prolapse and the stage of the prolapse as part of the study design.

DR. FALCONE: Thank you. Dr. Dominik.

DR. DOMINIK: I think a randomized controlled --

DR. FALCONE: What, I messed up again?

MR. POLLARD: No, I just want to highlight. A key part of the

question is if the Panel thinks a control arm is needed, and if so, what type of control? And I'm not hearing the discussion really providing any input on that.

DR. FALCONE: I think that they asked for controls. I just don't know if they're going to be able to answer without a lot of late debate. But if you wanted --

MR. POLLARD: Well, I would say that that's important. It's going to become important as we get into the second and third part of Question 2.

DR. FALCONE: Okay.

DR. DIAMOND: Let me amend my response.

DR. FALCONE: Okay.

DR. DIAMOND: So yes, I think there needs to be controls, and I think there ought to be native tissue controls.

DR. FALCONE: Dr. Davis and Dr. Hillard, do you want native tissue controls or you don't want them? Yes, okay. So is that what you wanted to hear? Okay. The type of controls, yeah.

Okay, Dr. Dominik.

DR. DOMINIK: Yes, I think preclinical -- premarket studies are needed and that they should be randomized controlled trials involving native controls. But I think the control arm may be different and the primary outcomes may be different, depending on the mesh of interest.

DR. FALCONE: Okay, thank you. Dr. Iglesia.

DR. IGLESIA: Yes, I would welcome comparative data. As for what type, again, I really feel that there are some limitations in conducting randomized clinical trials and that we can glean a lot of evidence on comparative trials looking at prospective cohorts of vaginal mesh repairs versus native tissue repairs, as well as trials comparing vaginal mesh to robotic laparoscopic or abdominally placed mesh.

I think these are the answers that women need. And we want to say, Do you want to give an informed consent? But quite frankly, given the evidence that we have, we can't give a really good informed consent because the data is not all there. And, you know, that's no matter in what hands. Obviously even in your own hands is important as well. But, you know, in an ideal world and practicality, randomized clinical trials are great. I think prospective cohorts can get a lot of information.

DR. FALCONE: Thank you. Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

I think the answer is yes, I think native tissue controls, I think, in some of the unique situations described by Dr. Flesh and Dr. Kalota, that we may have to resort to cohorts. But I think there can be a number of randomized trials done. And follow-up would be probably three to four years, and I think the stage of prolapse would definitely be important.

DR. FALCONE: Thank you. Dr. Mattison.

DR. MATTISON: Don Mattison.

Yes, I believe clinical studies are needed for premarket evaluation, and agree with the need for randomized trials that compare the mesh with native tissue. I also agree with the longer-term follow-up, three to four years, and really careful staging and thinking about how differences in staging across the patient groups would impact the study design.

DR. FALCONE: Thank you. Dr. Kalota.

DR. KALOTA: Susan Kalota.

I would love to see the studies. I would hate that my patients would have to go through the studies. I think that through the years that we've all practiced, we understand what works well in our hands with our patients, and to subject some of these patients to a non-mesh repair, I would think that that's not what I want to offer my patients.

DR. FALCONE: Thank you. Dr. Chappell.

DR. CHAPPELL: Yes, with randomized controls where it's considered ethical and in situations, as Dr. Kalota just mentioned, where it is not considered ethical in one extreme to use mesh, then a registry for a one-arm trial for those patients. On the other extreme, where it's not considered ethical to withhold mesh, then also a one-arm study. Those are better than nothing. But on the middle ground, which may be larger than many suspect, a randomized control.

Here's what I'll caution in just a minute or two because now

we're talking about research, and there's two issues that have received very heavy play today. One is that a surgeon -- variation of surgeon ability and technique.

For example, the industry support group -- let's see, I know what it is. Exhibit I, the prolapse surgeons network, cites a study, a multicenter clinical trial in which there are so-called 0 percent to 100 percent center-specific success rates, and my explanation for 0 percent and 100 percent center-specific success rate in the same multicenter study is that you have some centers with patient sample sizes of one, where there has to be 0 percent or 100 percent. It could be that there's 100 patients with 0 percent and 100 patients in another center with 100 percent, but I really doubt it. I mean, there could be variation, but it's probably due to very small sample sizes, which force that kind of variation. So I would ignore those kinds of data.

However, there's an alternative. And in many trials I have seen -- in which there are large centers. That is, suppose there's a center with 50 patients in a trial. You can look at the progress of the trend in results, either toxicity or efficacy, or certainly both, over those 50 patients. They may not be from the surgeon, but surgeons talk and they watch each other and study each other's examples. If the surgeons start off extremely experienced, you might not see much of a trend. But if they start off less experienced, you would see a trend, and I have seen that in many situations. It isn't perfect,

but it's better than the current kinds of analyses.

So what I hear from all of my medical colleagues is it's crucial to take into account the experience of those who are doing the procedures. And when I hear take into account, I think quantitatively.

And so my suggestion to the FDA is to try to figure out, perhaps based on my suggestion, how to quantify a surgeon's experience and relate outcomes, efficacy or safety, to a surgeon's experience. And that can be done with data already, and it can be done prospectively on data that are to be collected. And I don't think there's ethical problems at all. I think that's fairly simple and easy, to the extent that the data exists. And to the extent they don't exist, it's simple and easy to collect.

The second subject which has received an awful lot of play today, besides surgeon experience, is the outcomes. And that's why I've been uncomfortable talking about efficacy because I don't really know what we're talking about with respect to efficacy. We seem to have a choice between the outcomes of greatest importance to the patients, reoperation rates, clinical symptoms, long-term quality of life. I love those. They take maybe, I've heard, three years. Industry might not like those, and they have a good reason. And the patients might not like those because that means the treatment is withheld from them for that long, while these studies are being done.

On the other hand we have anatomic outcomes, which tend to

be short-term, cheaper, less delay. It's the plastic surrogate variable, equivalent to blood pressure versus waiting for strokes. Not quite of that magnitude. But still, we would like to use a short-term outcome.

Again, these data seem to exist, but I haven't seen a graph plotting short-term outcomes, anatomic outcomes, versus these long-term clinical outcomes. Is one predictive of the other?

We've heard from various people that yes, they are.

Dr. Hinoul, I believe, said they were. We've heard from patients that know they are not. They can't be perfectly predictive. I hope they're somewhat predictive, but surely it could be relevant. If they're highly predictive, maybe we could shorten the process of the clinical trials that we're recommending, because I do want clinical trials, but I do sympathize with those who don't want them to take forever and break the bank. So thank you.

DR. FALCONE: Thank you. Dr. Brill.

DR. BRILL: Well, I wholeheartedly agree with everything Richard said. And of course you definitely highlighted the two areas we've talked quite a bit about.

I agree also with my colleagues that we need to have clinical studies, of course, for premarket approval.

I think looking at higher stages of uterovaginal prolapse might get to the issue faster, although in theory it could confound the information and it should be sufficiently powered to look at those elements, because I

think we've heard, both in the public hearing and also from the panel, that the more severe defects may in fact be of greater benefit with these devices.

Follow-up, the longer the better, although I think it puts a significant constriction on the reality of creating the study and conducting the study. But I think we're going to have to do something for long-term outcome. Cohort studies at least answer some of the questions.

Follow-up. I mean, I think we're kind of stuck on anatomy versus, you know, quality of life, and I have to vote for quality of life over anatomy, just because that's the reality of our patients and how they report their outcomes when it comes to, you know, day-to-day reality.

I mean, we look at the story of incontinence and we have positive pad tests, but we also have patients who are totally satisfied with their bladder function, and I think it's important, you know, what we look at. So I look forward to those clinical studies.

DR. FALCONE: Thank you. Dr. Sears.

DR. SEARS: Chris Sears.

Yes to clinical studies. I think, again, the randomized controlled trial would be nice. However, apically I think that's going to be very problematic and, therefore, in the anterior compartment, since a lot of anterior compartment prolapse is also apical prolapse, I think that's going to be very challenging.

There's a whole generation, really, of people who are pelvic

medicine specialists who have done very, very few sacrospinous ligament fixations and uterosacral ligament suspensions, so very, very few tissue-based apical repairs.

And so having a real randomized trial looking at tissue-based repairs only may be very challenging and it may be more beneficial, especially for the apical compartment, for the middle compartment, to look at transabdominal laparoscopic or robotic sacrocolpopexy as the comparison arm, even though that does involve mesh. And that's all I have.

DR. FALCONE: Thank you. Dr. Fitzgerald.

DR. FITZGERALD: Yes, I do think that we need clinical data prior to market approval. Also, in regard to a comparison arm, I think the Cochrane Reviews would support sacrocolpopexy, minimally performed, would make this feasible -- sacrocolpopexy as the gold standard, and if done minimally invasively, it could be the comparison arm.

DR. ROGERS: I believe we need premarket data. I believe that those studies should be comparative. Ideally, for procedures that have shown efficacy either in prior randomized trials or in cohort studies, you know, single randomized trials to confirm differences observed, I would argue for randomized trials in the compartments where efficacy has -- the data are much more sparse. I'm a little concerned about the randomized trial.

I also share Dr. Iglesia's concerns with recruitment of patients, not to the tissue repair, which I believe one of our discussants mentioned, but

more to the mesh repair, given the higher scrutiny. And I would look forward to that information to help guide patient decision making.

DR. FALCONE: Thank you. Dr. Flesh.

DR. FLESH: I think that we do need to require premarket studies. I think the only realistic way they can be done with controls is with cohorts. And there are a number of problems with randomized controlled trials, which I alluded to before, not the least of which, again, as what Dr. Kalota said, that anybody who has been doing this a long time, there's no way that they would consign a Stage III/Stage IV prolapse to a non-mesh repair.

So I think the only way is you have one group of surgeons that's willing to do that, and one group that thinks that mesh repair is better, and you compare the two. And that's reasonable.

In the anterior compartment, in my mind, there's already compelling evidence. I'm really not sure whether it should be repeated.

In the posterior compartment, there's probably already enough evidence that, for the typical kind of rectocele, we don't need mesh. But I think for large rectocele we do need mesh. And, again, the only way this can be done is in a cohort, comparative, prospective trial.

Finally, the study that I think needs to be done more than any other is comparing bilateral sacrospinous suspension done through the vagina without trocars. There are two different ways to do that now. To suspend

the apex and compare it to any kind of abdominal sacrocolpopexy you want, robotic, laparoscopic, open, I have personally no doubt about the result, and I would be delighted to see that study done.

DR. FALCONE: Thank you. Ms. Berney.

MS. BERNEY: Yes, I do believe we need premarket evaluation studies. I am, however, not qualified to comment and pass on that.

DR. GADALETA: I agree that we do need premarket clinical studies, although I don't know how to answer the question about design and patient selection without understanding what specific issue that we're trying to address, so I'm going to abstain on that.

DR. FALCONE: Dr. Duerhring.

DR. DUERHRING: Gary Duerhring.

I do believe that we need studies done. I believe that the data is already there. I don't know if the design shouldn't be a registry. There's how many thousands of women who have had POPs done with or without? When I hear the term comparative studies, because of the individualism of the patient and the surgeon, how do I compare one woman to another woman, unless I do two surgeries on the same woman? How do I compare the two things? I have a real problem when I hear the word is comparative. Well, it's comparative to what? Because individual situations differ with every individual. That's just too hard for me to understand.

The other issue was brought up by Dr. Chappell. I think the

ethical dilemma that we have of withholding something that I feel the patient really can benefit from, I would hate to be put into that situation. But I do believe that there are a lot of cases out there. If we can find out who has had surgeries and evaluate them over a long period of time, that's how we're going to come up with are they safe, are they effective? What's the long-term effects of doing this or not doing it? Are they comfortable symptomatically or anatomically? That has to come from data that's already there.

DR. FALCONE: Thank you. I think we're ready for part (b).

MR. POLLARD: I wanted to ask, did you want to summarize that sort of discussion there? Is there a consensus there or --

DR. FALCONE: So to define consensus is a difficult situation.

(Laughter.)

DR. FALCONE: But if we define it as what the majority seem to be saying, is that they do want -- everyone wants -- well, the majority want premarket evaluation. And I'm not sure if that implies almost as a response for the subsequent question. But anyways, the majority -- so, in summary, the majority want premarket evaluation, and the type of clinical studies, although complex, seem to involve some type of control group in a majority of respondents.

Okay, part (b).

MR. POLLARD: So part (b) asks you in the same context of this

notion that we're going through. And considering what you just discussed in part (a), please discuss whether one or more of Class II special controls listed below would provide reasonable assurance of the safety and effectiveness of vaginal mesh for POP repair.

And special controls in the statute are listed as performance standards, postmarket surveillance, patient registry, and guidelines. And that could include guidelines for submitting clinical data or focused labeling.

And we add the note here, in the caveat that we tried to make in the FDA presentation, that if the Panel does recommend a premarket clinical study, in the context of a special controls guideline, this study must conform to the 510(k) regulatory standard of substantial equivalence and the notion of a predicate device.

DR. FALCONE: So just to expand on this, because the idea of special controls, are they sufficient, you're saying is that -- Colin or Dr. Lerner, does this imply, within the concept of 510(k), it can only be -- the controls can only be with someone with another device?

MR. POLLARD: That's correct. That's exactly correct. I think that's the thing we were trying to make.

DR. FALCONE: But comparing one device to another?

MR. POLLARD: Right. If you were comparing one device to another, a predicate device --

DR. FALCONE: Yeah.

MR. POLLARD: -- you could do that.

DR. FALCONE: Within the context of the 510(k)?

DR. FALCONE: But not with a Class II special control. But if you were to believe that a native tissue repair were the appropriate control arm, we didn't believe we could do that as Class II special control.

DR. FALCONE: So you'll have your chance. So the only thing here is that I'm trying to make this question so that they can have a focused opinion.

(Laughter.)

DR. FALCONE: So I'm trying to extract, because, you know, a lot of them have already answered what type of controls they want. So I mean, what, they're just going to repeat what they said? Because a lot of them said native tissue, for example. That implies that this is not sufficient.

MR. POLLARD: Yeah. We feel it's important to --

DR. FALCONE: For them to say it again.

MR. POLLARD: As sort of a gut check.

DR. FALCONE: Okay. So the controls. Again, we're going to do this again. What type of controls is the type that you want? So essentially, maybe we can kernel it this way. If you're going to stick to a 510(k), you cannot choose anything but another device; is that correct?

MR. POLLARD: I would ask you to look at the question the way it's written. The question to you is, do you believe one or more special

controls, that is, Class II special controls, would be adequate to ensure the safety and effectiveness of vaginal mesh for POP?

DR. FALCONE: Okay. So the controls that are listed?

MR. POLLARD: Yes.

DR. FALCONE: All right. Okay, it's simple, then. Are these controls sufficient, yes or no, for you? Is that okay?

MR. POLLARD: Right. And recognizing that, in the context of the clinical study, you know, if you're talking about a native tissue repair --

DR. FALCONE: It's a no. That would be the logical way. If it's a native tissue repair, it's a no, and if it's not a native tissue repair, you can expand for a focused opinion.

DR. DAVIS: No.

DR. HILLARD: Paula Hillard.

No.

DR. FALCONE: State your name so that they can --

DR. DAVIS: Sorry. Hey, I messed up again. Ann Davis.

No.

DR. FALCONE: That means it's a no to the special controls.

They want a native -- I'm trying to make it --

MR. POLLARD: I think we'd prefer to hear a no with a little bit of explanation on the no.

(Laughter.)

DR. DAVIS: No, I would want native tissue. Although again, as I said, I would leave it to the FDA or someone else to figure whether it's a prospective cohort or a randomized controlled trial.

DR. FALCONE: Thank you.

DR. HILLARD: Paula Hillard.

Can I say ditto?

DR. FALCONE: Is that okay, ditto? Okay, Dr. Diamond.

DR. DIAMOND: Michael Diamond.

While I think the individual special controls may be complementary, I do not think that the Class II special controls in and of themselves are sufficient. We'd want to see more.

DR. FALCONE: Dr. Dominik.

DR. DOMINIK: No, because the clinical studies that are needed require the native tissue control.

DR. FALCONE: Dr. Iglesia.

DR. IGLESIA: Can I be difficult and say I want both?

DR. FALCONE: Sure you can.

DR. IGLESIA: I want them.

DR. FALCONE: Nothing's binding here.

DR. IGLESIA: Okay. I mean, obviously I want some comparative group, whether it be a randomized trial or a prospective cohort, with native tissue because it's vaginal to vaginal, and in some patients, you know, the

vaginal route is probably the way to go.

But understanding that Class II special controls could possibly include an arm of mesh placed abdominally, whether open, laparoscopic, or robotic, that would be very intriguing information as well, correct? To be able to compare the mesh kits to another gold standard, is that -- that's an option?

DR. FALCONE: Yeah, sure, if that's what you suggest.

DR. IGLESIA: Well, I think that would be very interesting data to look at.

DR. FALCONE: Thank you. Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

No. And the same kind of ditto for Dr. Davis' no.

DR. FALCONE: Okay, Dr. Mattison.

DR. MATTISON: Don Mattison.

No, because I'd like the studies to be done prior to marketing, which allows that opportunity to do a more detailed evaluation of comparative safety and effectiveness.

DR. FALCONE: Dr. Kalota.

DR. KALOTA: Susan Kalota.

No. Ditto.

DR. FALCONE: Not enough?

MR. POLLARD: I just want to clarify. Dr. Mattison said no

because he wanted preclinical data, but that really is not the core of that question.

DR. FALCONE: Yeah.

MR. POLLARD: The question is whether or not Class II special controls would be sufficient.

DR. FALCONE: Yeah. Are these controls sufficient or not?

DR. MATTISON: No, they're not.

DR. GADALETA: Well, I think we need to clarify something because I heard you say that you wanted premarket clinical studies, and special controls --

DR. MATTISON: That's correct.

DR. GADALETA: -- would allow you to have premarket clinical studies. So if that's the driver, then premarket clinical studies can be part of special controls.

MR. POLLARD: Right, exactly. So what you need to do is take that notion one step farther and ask, in that preclinical study that you're envisioning that's needed for a premarket evaluation --

DR. FALCONE: Are these sufficient?

MR. POLLARD: -- should we have a control arm and what is the nature of that control arm? And depending on your answer to that question, you can answer the question about whether special controls would be sufficient.

DR. MATTISON: Right, it would need a control arm, and as we've talked about previously and as I think I've commented, there should be risk-adjusted comparison groups with the comparison being at least a native tissue repair.

DR. FALCONE: Which, by definition, native tissue repair means no to the --

DR. GADALETA: Can I make a comment about that now or would you like me to wait until --

DR. FALCONE: As soon as I get to your turn, you can talk as long as you want. How about that?

(Laughter.)

DR. FALCONE: For a focused opinion.

Is everybody fine on this side of the room? Okay, good. And FDA's fine with how they responded? All right, to my left.

DR. CHAPPELL: Rick Chappell.

I earlier called for randomized clinical trials with the control group being native tissue repair, when that was ethical, and then single-arm cohort studies again comparing to native tissue repair when randomization was not feasible. And based on that and my interpretation of the statutes that you've laid out to me, I have to say no.

DR. FALCONE: Dr. Brill.

DR. BRILL: Andrew Brill.

I would like to find some way to utilize 522 of the Act. However, we're still going to have to go to a predicate device, which doesn't answer the question. So we are compelled, I think, to only defer to a non-522 native tissue model.

DR. FALCONE: Thank you. Dr. Sears.

DR. SEARS: Chris Sears.

No, for the same reasons that have been mentioned.

DR. FITZGERALD: No, in general. I wonder if there may be some, for example, mesh without arms that might be suitable for assurance through this mechanism, or perhaps the biological tissue. So there may be some currently marketed devices that may be approvable. But in general, I think no.

DR. FALCONE: Dr. Rogers.

DR. ROGERS: I would say no, for all the reasons elucidated earlier.

I would also just like to say that I do not think that the comparative trial for premarket approval would take the place of all of these other regulatory pieces, including guidelines for consent, explanation, patient selection, follow-up, and registries.

So I would not like the no to mean that we are expunging these other methods of collecting data, which I think are vitally important to the ultimate decisions regarding safety and efficacy for our patients.

DR. FALCONE: Well, I think the point is that they're not sufficient for what you want, but you want these, too. You want all of it.

DR. ROGERS: That's correct.

DR. FALCONE: Good. I just wanted to make it clear.

Dr. Flesh.

DR. FLESH: I would say yes, for most devices, but not all. The devices that I'm personally worried about, and that I think deserve possibly to get reclassified, are the ones that use long trocars. Number one.

Number two, I think that a distinction needs to be made between anterior prolapse, where I think the evidence is pretty clear, versus other areas.

And number three, I'm very concerned their reclassification to Class III is going to slow down the incredible progress that's been made in the last seven years.

DR. FALCONE: That's Question (c). Sorry.

DR. FLESH: Okay.

DR. FALCONE: Okay, sorry.

MS. BERNEY: Barbara Berney.

No, I don't think they're sufficient, and I would agree with Dr. Rogers that we need it all.

DR. FALCONE: Thank you. Now it's your turn.

DR. GADALETA: And I have unlimited time.

DR. FALCONE: Yeah, of course.

(Laughter.)

DR. FALCONE: In the space-time continuum, that's three minutes.

(Laughter.)

DR. GADALETA: So I'm not sure I understand nor agree with the fact that if we choose to do a tissue-based control, that there is no -- that we're automatically forced to Class III because the tissue control uses a device, as I understand it, to achieve the approximation. No? Suture. Suture is bringing stuff together, correct? And so if we're comparing --

DR. FALCONE: Is suture defined as a device by the FDA?

DR. GADALETA: Yes.

DR. FALCONE: Oh, there you go.

DR. GADALETA: So if that's the case, I'm not sure how that automatically brings us to Class III. So I'd like to have a little bit of a discussion to understand why that opportunity doesn't exist.

DR. FALCONE: As the Chair, I would invite the FDA.

MR. POLLARD: So I'm just trying to relive multiple conversations and discussions and probably months of analysis on this. And then, as I said, we ultimately thought about asking this kind of question in a 510(k) context and ran this through our legal folks, and basically the decision was that we couldn't do that in a 510(k) special controls context.

DR. GADALETA: Couldn't do what?

MR. POLLARD: Couldn't require manufacturers to submit a premarket clinical study of mesh versus no mesh. You know, we can take another look. We did not see that as a relevant predicate device in that context.

DR. GADALETA: Isn't that what the original predicate device was, was suture for mesh?

MR. POLLARD: No, the predicate device was mesh, pre-amendments mesh.

DR. GADALETA: So then I'm even more confused, then. So if suture is used in the procedure that would be the comparator, why couldn't we then do the study to compare mesh to suture to demonstrate that it's reasonably -- we've got reasonable assurance of safety and effectiveness?

MR. POLLARD: Yeah, I hear that question.

DR. FALCONE: Dr. Diamond maybe has --

DR. DIAMOND: I think the issue may be that while suture is approved by FDA, it's approved not with an indication of -- not with that indication. It is not a predicate device. The material may be when it's in other configurations, but suture per se is not a predicate device for anterior vaginal repair or the other types of prolapse that we're talking. I think that may be the distinction.

MR. POLLARD: You know what I would like to do, to tell you

the truth, is I'd like to take a 10-minute break. That sounds kind of --

DR. FALCONE: Reasonable.

MR. POLLARD: -- the thing to do -- well, reasonable maybe. I don't know. It's quarter to 6:00 and I know we want to get finished. But I want to give the best answer I can to that, and it's a legitimate question, and I'd just like to talk to folks here.

DR. FALCONE: Yes, a 10-minute break. Thank you.

(Off the record.)

(On the record.)

DR. FALCONE: And Colin is going to --

MR. POLLARD: Thank you. And to answer Dr. Gadaleta's question, the reason we don't consider that a viable approach to go is simply that we think that's stretching the extreme on predicate in the context of the intended use of the product and the technology.

DR. GADALETA: That's fair. So you also mentioned, though, that mesh was a pre-amendments device. And so under the pre-amendments piece, then we don't really need to have a predicate, we have that predicate as a pre-amendments device predicate.

So, again, I think either way you look at this, there is an opportunity to develop the data that I think we all agree that we need under the 510(k) route, and simply saying that if you're choosing --

MR. POLLARD: But I think what we would say about the

pre-amendments device is the intended use is quite different.

DR. GADALETA: Of mesh?

MR. POLLARD: Yes.

DR. GADALETA: I'm confused. So when you said that the mesh is a pre-amendments --

MR. POLLARD: The intended use of mesh was --

DR. GADALETA: Pre-amendments.

MR. POLLARD: -- hernia and I think some very limited --

DR. GADALETA: I think it was to bridge --

MR. POLLARD: -- orthopedic use.

DR. FALCONE: I thought it was hernia.

DR. GADALETA: I'm sorry.

MR. POLLARD: Yeah.

DR. FALCONE: According to the documents you gave us.

MR. POLLARD: Right.

DR. GADALETA: Yeah. But I believe that the intended uses are to bridge soft tissue where weakness exists, which I think is what we're doing here.

MR. POLLARD: Yes.

DR. GADALETA: So I think the pre-amendments piece --

MR. POLLARD: Yeah.

DR. GADALETA: -- and the post-amendments piece --

MR. POLLARD: Yeah, we've looked at them. I think we would say that that was not what mesh was being used for, pre-amendments.

DR. GADALETA: So surgeons weren't cutting it and using it in these particular --

MR. POLLARD: In terms of pre-amendments, we talk about legally marketed, we talk about what was it actually being marketed for.

DR. GADALETA: Okay.

MR. POLLARD: And it was not being marketed for urogynecologic indications.

DR. GADALETA: Okay. So what we're saying is that if the choice of the -- the choice of the control arm is determining the classification of the product as opposed to the risks associated with the product.

MR. POLLARD: When we look at a 510(k), as I know you know -- to everybody, we look fundamentally at the intended use of the product, and then if we can say that it has the same intended use, which we talk about mesh for POP repair versus suture, we would say you've gone from a general to a specific and we would say it doesn't have the same intended use anymore.

You next look at -- even you got past that, you would be looking at the technology, and we would say the technology itself is much different. That raises different types of safety and effectiveness questions.

So what we're saying is that's just taking that substantial

equivalence -- that notion of predicate device and substantial equivalence to sort of the extreme beyond which we think has any kind of real value.

DR. GADALETA: All right. So suffice it to say that we're going to disagree on it. So I just wanted to make a comment then, to say I believe that -- just to answer the question, that Class II special controls are appropriate to show reasonable assurance of safety and effectiveness, given the fact that we can establish performance standards, we can do postmarket surveillance in the form of Section 522, we can establish registries to understand what the issues are and dig down into the registry data, and create guidelines in the form of preclinical studies and clinical studies to establish reasonable reassurance of safety and effectiveness.

DR. FALCONE: Thank you. Dr. Duerhring.

DR. DUERHRING: No.

DR. FALCONE: Oh, thank you very much.

(Laughter.)

DR. DUERHRING: I just want to echo Dr. Rogers. I think that we should see all of these things, but I don't think that's quite enough.

DR. FALCONE: Thank you. Part (c). Question 2, part (c). Only two questions and a part to go.

MR. POLLARD: So in the context of your answers to part (a) and part (b), Question 2c is asking you to please discuss whether vaginal mesh for POP repair should remain in Class II with special controls or be

reclassified into Class III with premarket approval.

DR. FALCONE: Okay. So for this question, again, you can just say reclassify and leave it as such. But obviously this is the crux, so if you wish to expand, you know, certainly you can do so as well, but you don't have to.

Dr. Davis.

DR. DAVIS: Reclassify, based on the need for tissue control.

DR. FALCONE: Thank you. Dr. Hillard.

DR. HILLARD: Paula Hillard.

Reclassify.

DR. FALCONE: Dr. Diamond.

DR. DIAMOND: Reclassify.

DR. FALCONE: Dr. Dominik.

DR. DOMINIK: Reclassify.

DR. FALCONE: Dr. Iglesia.

DR. IGLESIA: I just have concerns about the burdensomeness, in the effort of trying to be least burdensome, and I'm looking at the sales data on the 79,000 of these kits that were sold, 520 in the year 2010. That's a hell of a lot of kits.

Now, I don't know what are implanted, but I think that if we put some guidance in there with regard to the training and indications highlighting recurrences, the more advanced and the complicated patients, as

well as invoke the postmarket surveillance and the registries that are involving societies and the sponsors, you know, anybody who has any kind of skin in the game, I think that we can get a lot of valuable information and be the least burdensome.

So I guess my short answer would have to say Class II special controls.

DR. FALCONE: All right, leave with Class II special controls.

Dr. Coddington.

DR. CODDINGTON: Reclassify.

DR. FALCONE: Dr. Mattison.

DR. MATTISON: Given what I perceive as the paucity of data describing the safety and effectiveness in this context, I think that it should be reclassified.

DR. FALCONE: Thank you. Dr. Kalota.

DR. KALOTA: Susan Kalota.

I think this time I'm going to agree with Dr. Iglesia. I have concerns about --

DR. FALCONE: So you'd keep it as Class II special controls?

DR. KALOTA: Right.

DR. FALCONE: Okay, thank you. Where will I start? Over here. No, not with him. Dr. Chappell.

DR. CHAPPELL: My interpretation of what I hear the

regulations to be is, given that my answer to part (b) was no, I have to say yes to part (c).

DR. FALCONE: Meaning reclassify?

DR. CHAPPELL: Yes.

DR. FALCONE: Okay.

DR. CHAPPELL: This was Rick Chappell.

DR. FALCONE: Yeah.

DR. BRILL: Andrew Brill.

DR. FALCONE: I want to make sure everyone knows.

Dr. Brill.

DR. BRILL: Yeah, I feel like we're in a Class III blackmail. I don't say that heavy in heart, but just metaphorically. Because in my sense, if I were to respond affirmatively, it would be concerned that there is a greater need to establish safety. There's a risk profile that has been underestimated. Something has come up about the product that arouses me for further evaluation and regulation. And if it was not, you know, for the hitch in the 522, we could do it as a Class II. We're stuck with the predicate, as it is.

So I have no choice but to say Class III because there's no other way to have the predicate be something other than presently existing devices.

DR. FALCONE: Thank you. Dr. Sears.

DR. SEARS: I agree, reclassify. I think that I say that with more of a heavy heart than my colleague, Dr. Brill, next to me because I think that that does potentially put me, as a surgeon, now at risk because I will likely be free-cutting mesh for other indications when necessary.

And so I think, if anything -- unfortunately I think that's going to put a lot of subspecialists potentially kind of a little bit out on a limb. But I do think given the 522 issue, that that's what I need to recommend.

DR. FALCONE: But even if it's reclassified, the product is still on the market, right? Yeah. Okay, I just wanted to clarify.

Dr. Fitzgerald.

DR. FITZGERALD: Yes, I agree that, in general, the class needs to be reclassified, but there may be -- please be careful, there may be exceptions within the currently approved devices that don't merit that. I don't know what they are. A few of us have called out certain kits, maybe, that are of more concern to us clinically, but we haven't gone through all of the devices in detail.

DR. FALCONE: Dr. Rogers.

DR. ROGERS: Can I ask for some clarification, please?

DR. FALCONE: From whom?

DR. ROGERS: From you or whomever it would be.

DR. FALCONE: Me? No. Colin.

DR. ROGERS: So we're just talking about prolapse devices.

DR. FALCONE: That's correct.

DR. ROGERS: So this discussion will have no bearing --

DR. FALCONE: On tomorrow?

DR. ROGERS: -- on the stress incontinence devices; is that correct?

DR. FALCONE: Go ahead.

MR. POLLARD: Absolutely. Tomorrow we're talking about mesh used for SUI. Today, and in the context of this question, we're not even talking about all mesh for POP; we're talking about vaginal mesh for POP repair.

And then the one other thing I wanted to answer your question, it was more or less a practical logistics question about what would happen to products.

DR. FALCONE: Yeah.

MR. POLLARD: I mean, there's a whole due diligence process to a reclassification, which we didn't go into in great detail in our FDA presentation. First of all, there's a lot of input that you all have given us today. We would have to look at that and study that carefully and look at where that drives us.

If we were to decide to reclassify vaginal mesh for POP or some subset of that product, depending on the conversation, we would have to put that out as a proposed rule. That proposed rule would have to have a

comment period. We would have to then look at all of those comments and analyze and figure out where they leave us.

If we still felt that we needed to move forward with that action, we would put that out as a final rule. But they would both be accompanied with a guidance document for that PMA, which would be a draft guidance for comment as well. And then that final rule and guidance document would have an effective date.

So during that entire time period, which, in the best of all worlds, would probably be 18 months to 2 years, but could easily be 2 to 3 years -- it's really hard to judge exactly how long it takes companies -- it would still be a Class II product and still be governed under, you know, the Class II controls, 510(k), et cetera, which is also why there's a Question 3.

DR. FALCONE: Yeah, we're looking forward to it.

(Laughter.)

DR. FALCONE: The interesting thing about the -- what's important is that this is not a vote. Okay, just so you understand, this is simply your opinion about reclassification or not, as they ask. But remember we're not voting and it's actually up to the -- we're an Advisory Panel and the FDA will make the decision.

Dr. Lerner wants to make a comment.

DR. LERNER: I'd also like to comment that I hear concerns that there won't be product, or new products coming down the pike. During this

entire process, which as Colin said can take several years, if industry submits new 510(k)s for modifications of their devices, we will put them through the system as we currently do. So until we have a final rule that says they're going to be Class III, essentially nothing changes.

DR. FALCONE: Okay. So with that, Dr. Rogers, did you answer?

DR. ROGERS: Because of the need for a native tissue comparator, I would have to say reclassify.

DR. FALCONE: Okay, thank you. Dr. Flesh.

DR. FLESH: I think these products should remain Class II with special controls. And I think Dr. Iglesia is correct. Yes, we need more information, we need better training programs, we need better labeling about indications. I think all of these things can be done quite well with the Class II special control process.

And, third, despite what Dr. Lerner said, I'm very concerned that making these products Class III is going to slow down the incredible progress that's occurred in the last six to eight years. The meshes have gotten better every couple years. The attachment of the meshes has gotten much safer. Everything keeps getting better, and I think it's because industry is able to listen to doctors who are using these devices, make their improvements, and get them on the market reasonably quickly. And I think if we go to Class III, improvements are going to slow down to a crawl.

DR. FALCONE: Thank you. Ms. Berney.

MS. BERNEY: Based on my earlier comments, I would say reclassify.

DR. FALCONE: Thank you.

DR. GADALETA: As I mentioned earlier, I think that the Class II paradigm allows us to address all of the issues that we're trying to address here, including postmarket studies, physician training, preclinical -- I'm sorry -- premarket clinical studies. So I would recommend that we go with Class II.

DR. FALCONE: Thank you. Dr. Duerhring.

DR. DUERHRING: I would go with reclassify.

DR. FALCONE: Thank you. Okay, we're done with this part.

We'll go to Question 3.

MR. POLLARD: So Question 3 speaks to mesh products that are on the market today or would come onto the market in the near future, and it speaks to postmarket studies.

And the question reads: The FDA is concerned that the safety and effectiveness of currently marketed vaginal mesh for POP repair are not adequately understood. The FDA believes that manufacturers of such products should conduct 522 postmarket surveillance studies of devices on the market to address these outstanding concerns.

And there's a note: Mandating postmarket surveillance studies could begin in parallel with the reclassification process from Class II to Class III, but could still be implemented if these devices remain in Class II. If

reclassification occurs, FDA believes that the postmarket surveillance studies could be designed to satisfy the requirements of future PMAs.

DR. FALCONE: Isn't there --

MR. POLLARD: There's more.

DR. FALCONE: Yeah, is there more? Yeah. It was just too good to be true.

(Laughter.)

MR. POLLARD: Please state if you agree with the FDA's assessment. If you agree, please discuss the type of clinical study that should be required for vaginal mesh for POP repair already on the market and consider the following below:

- a. How should the study address important co-factors such as whether it's primary or recurrent prolapse, the stage of prolapse, concomitant surgeries, the anatomic compartment repaired, surgeon experience, and other patient selection criteria?
- b. What are the most important outcome measures to evaluate, primary and secondary?
- c. What is the appropriate duration for patient follow-up?
- d. Should these studies have a control arm, and if so, what are the optimal comparators (e.g., mesh-to-mesh, mesh-to-no mesh, vaginal-to-vaginal, vaginal-to-abdominal,

etc.)? If a control arm is needed, should the study be randomized?

DR. FALCONE: Didn't we sort of answer this, Colin? How many times can we say the same thing?

All right. Dr. Davis. So basically the question, if you want to keep it simple, Are the 522 postmarket studies needed on the current meshes? And what type of study do you think you would recommend? And you can keep this quite simple.

DR. DAVIS: Yes, I would recommend -- we've already said this -- the entire list and the ones listed in 2(b) above. And I do feel like we've answered the other ones, but certainly we would want to look at all the co-factors that we could, that have been mentioned throughout our remarks.

DR. FALCONE: Okay, Dr. Hillard.

DR. HILLARD: Paula Hillard.

Yes, I agree with the FDA, and I have nothing further to add beyond what's already been said.

DR. FALCONE: Thank you. Dr. Diamond.

DR. DIAMOND: I would agree with the FDA for the need for 522 studies for products that are already on the market. I would think that the issues they address in (a) of their specific question, about co-factors to consider, are things that the sponsor and FDA ought to be looking at for each individual trial, in order to answer the specific hypothesis that's being posed

for the product that's being evaluated, and it may be that some groups of patients with prolapse that are studied for those specific indications as opposed to all comers.

I think we've addressed the issues of primary and secondary outcome before in Question 1a and 1b, so I don't think I would add anything there. Similarly, we've addressed the issues, at that point, about duration of patient follow-up.

With regard to the control arm, yes, I think the vast majority of these studies probably should have a control arm, and what that should be and how it is done, I think, again, it would need to be individualized. I think in many cases it should be a randomized clinical trial. Cohorts, as has been suggested by some of the other members of the Panel, I think have values in certain situations, but there are many potential biases that are introduced by that, which would have to be very carefully considered in that study design so that the results that are obtained are of value.

DR. FALCONE: Thank you. Dr. Dominik.

DR. DOMINIK: Yes, I think we need -- the same sorts of studies that we discussed would be needed for premarket approval.

DR. FALCONE: Dr. Iglesia.

DR. IGLESIA: Okay. So I feel like this is a good, happy medium because you do get the best of both worlds, in that, for the current devices, postmarket studies are needed via the 522 process. However, you know, we

can start that immediately, and even if you reclassify this to a Class III, then, to be least burdensome, the data obtained from these registries can be applicable for the premarket approval process under the Class III. I think that's a really nice compromise.

With regards to moving forward, the kinds of studies that would be of clinical interest to me, I think that -- and sort of providing the guidance, I think that, you know, some of the big bugaboos are the patients who have recurrences and the patients who have the more advanced prolapse, as I said before. Although I would like to see some data on this as primary once we've determine some safety and efficacy in those higher-risk populations and those who have the medical comorbidities.

Moving forward, I'd like to see some comparative data on the gold standard of sacrocolpopexy versus these vaginal meshes as well.

I think the need for other concomitant surgeries, particularly surgeries with respect to stress incontinence and slings, I think that's an extremely important question in figuring out who needs these patients and if they should be done at the same time or not, or staged.

And the multi-compartment issue seems to be the area that has the most -- the least is known about it. I think we've got some superiority on the anterior. I think we've got some pretty good data, as Dr. Sears was saying, that, you know, posterior repairs without mesh, except in some really significant cases, does pretty well. But it's this whole multi-compartment, the

whole vagina as a whole, that needs some kind of question.

And then the outcomes that I would be most interested in are the composite outcomes, so that you include the patient's subjective quality of life data, symptoms of a bulge, and the objective data because, you know, I don't think women want perfect, they want no bulge and they want function, they want functional, and we need to see that out three years.

And Colin, I thank you for giving us the question as an option because now I feel a little more comfortable with the process.

DR. FALCONE: Thank you. Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

Let's see. Yes, with the FDA assessment. I think the co-factors that they've elucidated are good ones and have been mentioned previously.

Quality of life and anatomic factors as outcomes, I would say, start at the two-year mark and then progress on from there. So if you did that, you could gather a year of data and, in a year and a half, two years, have another gathering of this wonderful group.

And then, yes, as the cohort -- as the control arm and the same as I've commented before on the cohort and randomized trial as possible.

DR. FALCONE: Thank you. Dr. Mattison.

DR. MATTISON: Don Mattison.

Yes, I agree with the FDA's assessment and concur with the suggestions of Drs. Coddington, Diamond, and Iglesia.

DR. FALCONE: Thank you. Dr. Kalota.

DR. KALOTA: Susan Kalota.

I think we do need the continued follow-up, the registries. I completely agree with Dr. Flesh. I think we're making great progress. I think industry is listening to us. I don't think we have the perfect mesh. I don't think we have the perfect situation identified. I don't think where we came from is perfect either. And ideally, not only do we have a registry of the mesh repairs, but we have a registry of the non-mesh repairs, and that of course would be much more difficult to get, but that's what we really need, and to keep with the progress so that some day we will get the perfect solution.

DR. FALCONE: Thank you. Dr. Chappell.

DR. CHAPPELL: Rick Chappell.

My intellect has expired for the day, and I could give a more coherent answer tomorrow morning.

(Laughter.)

DR. CHAPPELL: But barring that welcome development, my answer would have to be that I agree with the FDA's assessment, and for the same reasons I gave with a response to Question 2a, to which I gave a lengthy answer. So I would ask the court reporter to copy my answer from 2a to here and let that stand.

DR. FALCONE: Well said. Dr. Brill.

DR. BRILL: Andrew Brill.

I concur with the FDA's recommendation. Also Dr. Diamond's suggestions elegantly rephrased and restated all of my feelings. So the court reporter can also repeat those.

I do have a question for Dr. Pollard. Colin, I just want to ask you, is there anything that the FDA can do without data to at least put on the record that training is an issue with these devices? Are there any tools available?

MR. POLLARD: Yeah, there are some tools. They're not as strong tools as some --

DR. BRILL: Yeah.

MR. POLLARD: -- of our other regulatory tools, and we definitely have heard almost across the board from the entire Panel that we need to look carefully at that. I think it will probably be something along the lines of the tools that we've got, as well as some kind of collaboration with the industry and with the clinical groups and figure out some way of looking at that question. And maybe it's a little bit of regulation, but maybe it's more a little bit of encouragement and some other kinds of things that we can do.

DR. FALCONE: Thank you, thank you. Dr. Sears.

DR. SEARS: I agree with the FDA's assessment. And my only other additional comment to my colleagues is that one of the other outcome measures I would add would be more a physical therapy type of a question of what is the one thing that you wish to improve in your function, or what is

the one thing you wish to do that you cannot currently do preoperatively, and then postoperatively, that one thing, is that one thing better? Yes or no. And that could be on a Likert scale or whatever. But I think that that's very, very important when taking care of these women.

DR. FALCONE: Thank you.

DR. FITZGERALD: Mary Fitzgerald.

I do think that 522 postmarket studies are needed for the existing devices. What they would look like, I think it would be -- it's critical at this point to separate out primary and recurrent prolapses into different studies and also to have a study that's on advance prolapse. I don't know if there's much utility in the other studies, but at least advanced and not advanced, however you describe that.

And for scales and outcomes, you could consider looking at the NIH-sponsored networks, the Urinary Incontinence Treatment Network and the Pelvic Floor Disorders Network, who have done quite a bit of work on scales, outcomes, and their responsiveness. And you don't have to do that work again.

DR. ROGERS: This is Rebecca Rogers.

My understanding is that, previously, I asked a question about how many of the devices that were currently on the market, and it was something like 20. My guess is that some of those devices are very similar to each other, and I don't know that postmarket -- I'm wondering if the

postmarket surveillance things can be done in groups, if they're very similar to each other.

I know this gets into the whole predicate device, but I would hate to see a Type I polypropylene mesh, that's a free mesh, having the same study repeated over and over and over again because different companies are marketing the exact same kind of mesh.

That said, clearly there are devices, as Dr. Flesh has said, that are completely different, that are trocar driven versus biologic.

So I know that I'm making you very uncomfortable with this long, long answer, but I think that postmarket surveillance, I would agree, is needed. I don't know that each and every device needs to prove in a postmarket surveillance the issues that we've been discussing, and I would like to see there to be some kind of grouping of these devices. I think that would be good for both patients and providers.

I think a composite outcome measure is important. I think that there is work that has been done along composite outcome measures, although that has not really determined what is the most clinically significant of those composite measures. I think the appropriate duration is longer than one year. And I think that given the variability and indications, surgeons, patients, that a control arm is essential.

DR. FALCONE: Did you want to answer the matching part?

DR. LERNER: Yes. I think that the FDA would encourage

batching of these devices so that we don't have to get multiple trials to answer the same question. So we would be interested to work with everybody to get those accomplished.

MR. POLLARD: And I would just add, first of all, to echo that there is, in the context of 522 studies -- and Mary Beth will correct me if I have this wrong, but that there is the possibility for companies to collaborate and so not reinvent the wheel five times.

The one thing that we probably would have to work out is sort of, as we laid out the regulatory strategy, there's sort of a reclassification PMA component that might not kick in for two, three, whatever years. 522 studies would start much sooner than that, and if designed properly would satisfy the PMA requirements. We'd probably have to figure out a way to sort of make those two objectives align.

DR. ROGERS: The only other thing I would add that hasn't been mentioned by my colleagues and I think was part of our earlier presentations and conversations was this issue of patient consent, and that I would look to the FDA to give some guidance beyond what is in the notifications regarding how that occurs.

DR. FALCONE: Thank you. Dr. Flesh.

DR. FLESH: I agree that there should be 522 postmarket studies. As far as outcome measure, I think it needs to be a composite of strict anatomic result plus subjective feeling of no more bulge coming out of

there. I think that's the main subjective result that patients want. Of course, adverse events have to be considered, all of the ones that we've been talking about. I don't need to list them all.

Control arm. If these arms are required, I think that cohort studies are more realistic than randomized studies, for all the reasons I've already said. And duration of follow-up, I think it needs to be at least three years.

DR. FALCONE: Thank you. Ms. Berney.

MS. BERNEY: Barbara Berney.

Yes, I do agree with the FDA's assessment. I'm not really qualified to answer the other questions, although I do believe that subjective results need to be taken into account and that the length of the follow-up needs to be longer. Three years is probably realistic.

DR. FALCONE: Thank you.

DR. GADALETA: So I think the idea of up-classifying the product and doing Section 522s is slightly redundant. If we play this out a little bit, we're going to do the Section 522 studies for a duration of three years. We're going to get that data. We might find that there's really not that big of an issue as we think there is, and now we've already made the decision to reclassify. And so I'm a little bit skeptical of this dual path of PMA and 522.

I think the concept of grouping multiple companies and submitting that data as your PMA data are mutually exclusive. I don't think

that's going to work. So I think we need to think through this particular aspect really carefully because I fear that there's going to be 20 Section 522 studies done, 20 different PMAs done, all with similar data.

So I don't know how to answer the question, but I would say that either we do the Section 522 and when we design the study we have an upfront agreement with the Agency that this design fulfills the PMA requirements, so that we do the clinical study once to answer the questions, rather than doing two clinical studies to answer ostensibly the same question.

DR. FALCONE: Okay, thank you. Dr. Duerhring.

DR. DUERHRING: Gary Duerhring.

I do agree with the FDA on the need for postmarket studies. I do agree with their note here: Mandating postmarket surveillance studies could begin in parallel with.

Now, to debate with the Industry Rep, if they don't collaborate and get the information together and they want to do 20 studies and absorb that cost, you know, that -- I'm talking from the consumer, and as a consumer, if my wife were to be in a situation where she would need this, I want her to understand the data that is out there so she can make an informed consent.

I'm not sure what data is out there and what data we know as far as like appropriate duration. Well, if these have been implanted for the last six, seven years, there should be some long-term information out there

that they can glean. And I think industry owes that to the consumer who's buying or utilizing their product.

DR. FALCONE: Thank you. So off to Question 4.

MR. POLLARD: So this is the last question, and it's addressing abdominal sacrocolpopexy.

The FDA believes that the safety and effectiveness of abdominal placement of surgical mesh for POP repair, e.g., sacrocolpopexy for apical prolapse, is well-established. Please state if you agree with FDA's assessment. If not, please discuss the following:

- a. Should future premarket submissions for mesh products indicated for abdominal sacrocolpopexy be supported with clinical performance data? If yes, please discuss the type of clinical performance data that should be requested. Please consider patient selection/exclusion criteria (e.g., concomitant surgeries), consider outcome measures, follow-up duration, and controls.
- b. Should manufacturers of currently marketed mesh products indicated for sacrocolpopexy conduct 522 postmarket surveillance studies? If yes, please discuss the type of clinical study that should be conducted. Please consider patient selection/exclusion criteria (e.g., concomitant surgeries), outcome measures, follow-up

duration, and controls.

DR. FALCONE: So there are obviously two parts, and we're going to take them both, right?

MR. POLLARD: That's your discretion of whether you want to take them both or go through them individually.

DR. FALCONE: Do you want to do it one at a time?

MR. POLLARD: There's actually an opening paragraph and then an (a) and a (b), depending on --

DR. FALCONE: Yeah, but before the (a) there's a preamble question.

MR. POLLARD: Right.

DR. FALCONE: So we have to agree --

MR. POLLARD: Or not.

DR. FALCONE: -- or not. Okay, that's straightforward. And then we'll go to (a). Put up the (a) question. Only if not, we go to (a)?

MR. POLLARD: Right.

DR. FALCONE: Is that correct?

MR. POLLARD: Correct.

DR. FALCONE: Go to the (a) question.

MR. POLLARD: So it says, if you don't agree that the safety and effectiveness is well established --

DR. FALCONE: Okay.

MR. POLLARD: -- then you look at (a). Should new products be supported by clinical --

DR. FALCONE: No, I understand that. I get it. But what I'm saying is if someone says no, do they answer to (a) and (b) immediately.

MR. POLLARD: In terms of how you want to go around the room?

DR. FALCONE: Yeah, yeah.

MR. POLLARD: I'm going to leave that to your discretion.

DR. FALCONE: Okay. So the question is going to be, Are the safety and effectiveness of abdominal placement of surgical mesh for POP repair of apical well established? If you say agree, then you move on. And if you don't agree, we'll show you Question (a) and (b) and keep you here. How about that?

(Laughter.)

DR. FALCONE: Yes, Dr. Rogers.

DR. ROGERS: We're having a little question that's arisen here. So what we're discussing is the mesh used for sacrocolpopexy. And really the question is about whether or not other meshes could be introduced. If we said sacrocolpopexy is not part of this debate, then it would stay as a Class II, and other meshes could be introduced as predicate devices without showing safety and efficacy. They would just have to be compared to -- well, they don't have to do -- I mean, it could be anything, right?

MR. POLLARD: Well, no, they would have to identify an appropriate predicate device and compare their device to that mesh product for ASC and demonstrate to our satisfaction that it's substantially equivalent.

DR. ROGERS: But that would be if you required preclinical studies?

MR. POLLARD: Well, 4a is asking if you think clinical studies are needed for new mesh products for ASC.

DR. FALCONE: But I was under the impression --

MR. POLLARD: Today we don't typically ask for clinical studies for mesh products for ASC, and we're saying that, in general, maybe there are some outlier issues or whatever. In general, we're not uncomfortable with that, but we are looking to your expertise to enrich our appreciation of safety and effectiveness of mesh for that indication.

DR. GADALETA: Can I ask a clarifying question in order to facilitate the discussion?

DR. FALCONE: Yeah, yeah. I just want to make sure Dr. Rogers had her question answered, that's all.

DR. ROGERS: Well, I'm just trying to separate the procedure from the device used to do the procedure because there are already quite a number of variable products as well as, you know, a harvested fascia from the patient that can be done for a sacrocolpopexy.

MR. POLLARD: So we're talking about mesh, just mesh.

DR. ROGERS: Mesh products --

MR. POLLARD: Yeah.

DR. ROGERS: -- for sacrocolpopexy.

MR. POLLARD: Yeah.

DR. ROGERS: And yeah, I think I understand.

DR. FALCONE: Okay.

DR. GADALETA: Can I ask a question to make sure I do?

DR. FALCONE: Sure.

DR. GADALETA: So given how the question is written, it's -- yes, it's for you, Colin. I'm sorry -- it suggests that you're comfortable with the data that supports the safety and effectiveness of mesh used in this particular procedure, and therefore you guys aren't recommending up-classifying mesh for this procedure; is that correct?

MR. POLLARD: Correct.

DR. GADALETA: Perfect, thank you.

DR. DIAMOND: Can I ask a clarification also?

DR. FALCONE: Yes, please, Dr. Diamond.

DR. DIAMOND: Colin, I'm sorry, this is for you as well. If FDA does accept that they are comfortable with the meshes that are currently cleared for use, why would you not want to -- why are you limiting the (a) portion to a no answer for the general question? In other words, for future meshes that are introduced, you would not want our opinion as to whether

or not a clinical study --

MR. POLLARD: Yeah.

DR. DIAMOND: -- should be done for that?

MR. POLLARD: I think you ask a good question, and you know, in the spirit of that question, I think if you thought, you know, that the product in general is well established, but new products should require a clinical study, I think we would listen to that argument and study that and figure out what does that mean in the context of what we're trying to accomplish. It wasn't the general trajectory of this question, but I would not discourage discussion like that.

DR. FALCONE: So you can, in fact, agree and then go on and give your opinion about what the next mesh, you feel, should be compared to and everything.

MR. POLLARD: Yeah. I mean, that's not the real trajectory of that.

DR. FALCONE: That's not the intent. Yeah, yeah.

MR. POLLARD: But I don't think we would discourage that kind of discussion.

DR. FALCONE: Okay. Very well. Dr. Davis.

DR. DAVIS: Ann Davis.

Yes, I agree with the FDA. Parenthetically, I have one concern. Since we're saying that this is -- has well-established safety and efficacy, is

there a chance that we could drive certain surgeons to an abdominal approach when their patients read that?

DR. FALCONE: Okay.

DR. HILLARD: Paula Hillard.

I agree with the FDA and I don't have an answer to (a).

DR. FALCONE: Dr. Diamond.

DR. DIAMOND: I feel, from the data that's been provided to us and with the discussions that have been held, that there is a better assessment of safety and effectiveness of mesh for this purpose. But for future products that would be brought to FDA, I would think that there ought to at least be a consideration, particularly depending on the variation from preexisting products, as to whether or not clinical data would be of value in the assessment of those new devices.

DR. FALCONE: Another clarification?

MR. POLLARD: Yeah, exactly. And hearing your point of view is really what we're talking about. So Question 4a was really talking about, across the board, should we require?

But FDA always reserves the right on something new that comes down the road, and there's something really new and different about it that begs a new question. We could in that scenario, on a case-by-case basis, decide that a clinical study is needed. This Question 4a was more of a general, across-the-board type of question.

DR. FALCONE: Dr. Dominik. With that clarification.

DR. DOMINIK: Exactly. With that clarification, I say yes.

DR. IGLESIA: Okay. So I would say, in general, the data is well supported, but there are many caveats about sacrocolpopexy, in that the data seems to favor synthetic polypropylene Type I monofilament mesh over biologics and certainly over microporous or multifilament types of meshes, for which there is some native data, particularly on, you know, microporous; but limited data and some negative data as well on the biologic performance when placed abdominally.

The second thing is that the route of placement for sacrocolpopexy is important as well because there have been new descriptions of mesh being placed vaginally but being sutured to the sacro. And so that classifies it as a different kind of thing. So, you know, there may be some scenarios where future premarket submissions would be indicated in something such as that.

And, you know, there is one randomized clinical trial that was conducted in Australia by Chris Maher that looked at laparoscopic sacrocolpopexy versus vaginal mesh.

I think that, you know, that's a very difficult study to do on two procedures that are very dichotomous. You know, it's a different kind of operation, and you can't be blinded because patients would know if they have incisions on their abdomen. But the point is some kind of comparison

for safety and effectiveness, and maybe in those scenarios the prospective cohorts for those dichotomously different kinds of operations may be more feasible.

With regard to the 522, you know, I'm interested in this because if you do have some type of registry, then not only -- then you could get that data of the abdominally placed mesh to the vaginally placed mesh into some kind of comparison as well, in the form of these nested or whatever type of registry. So more data is better.

DR. FALCONE: Thank you. Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

Yes.

DR. FALCONE: Dr. Mattison.

DR. MATTISON: Don Mattison.

Yes.

DR. FALCONE: Dr. Kalota.

DR. KALOTA: Susan Kalota.

Yes.

DR. FALCONE: On my left, Dr. Chappell.

DR. CHAPPELL: Rick Chappell.

Yes. And since I can answer Question (a), I would reiterate that the same points that I made regarding transvaginal mesh also apply, with very little expense, pain, and no patient sacrifice, to abdominal surgery; that is, a

correlation of different kinds of endpoints would be useful, and the determination is to the extent that the surgeon's experience plays in success would also be useful, based on existing data and could be built into any prospective studies from now on.

DR. FALCONE: Dr. Brill.

DR. BRILL: Andrew Brill.

I agree. I surely would hope that if there's any changes in the biomechanical behavior of a material, that would provoke an absolute need for clinical evaluation. And I assume that's the case with the FDA. I also think that what Dr. Rogers said when she was trying to clarify some issues here is important in the context of differentiating between procedure and material.

And one of the problems that the FDA probably had in the sequence of approvals, 510(k) approvals of the POP mesh kits, was perhaps not looking enough at the difference between delivery and also of biomechanical qualities. So you may have equivalence with the biomechanical, you know, cell-to-cell basis, histologically. But in fact the delivery mechanism is so profoundly different that that's why you have a different complication profile. So I think that differentiating between those two categories will be very important now and in the future.

DR. FALCONE: Dr. Sears.

DR. SEARS: Chris Sears.

Yes.

DR. FALCONE: Dr. Fitzgerald.

DR. FITZGERALD: I think that safety and effectiveness of abdominal sacrocolpopexy has really only been well established in the permanent synthetic meshes and it has not been well established -- well enough established for the smaller-pore meshes and the biologic grafts.

So I think a new -- the FDA might consider splitting the class up again and requiring at least postmarket surveillance or registries for those that I mentioned.

DR. FALCONE: Thank you. Dr. Rogers.

DR. ROGERS: I think that the safety and efficacy of sacrocolpopexy has been established for permanent mesh that's abdominally placed. Other meshes, it has not been established, as Dr. Fitzgerald has said. And there are composite applications of the mesh, meaning a vaginal application of the mesh, which is then sutured to the sacrum, whose safety and efficacy I do not believe has been established.

I would think that new meshes that were introduced would need human data prior to premarket, before market, and that postoperative surveillance is needed for these procedures in order to meet all of the other requirements that we've been talking about and helping patients make an informed decision about how to proceed.

DR. FALCONE: Thank you. Dr. Flesh.

DR. FLESH: The efficacy of abdominal sacrocolpopexy with

monofilament polypropylene mesh has been very nicely very well established. The safety, most emphatically, has not. And I would like to review from the Nygaard review, which is part of the FDA white papers reference list.

According to the Nygaard review, the median risk of hemorrhage and transfusion is 4 percent, ranging up to 17 percent; bladder injury, 3 percent, ranging up to 16 percent; deep venous thrombosis or pulmonary embolus, 3 percent; bowel injury, 2 percent; ureteral injury, 1 percent; laparotomy for bowel obstruction, 1 percent, ranging up to 9 percent; incisional hernia repair, 5 percent; in addition, rare cases of femoral nerve injury, obturator nerve injury, vertebral osteomyelitis, and necrotizing myofasciitis. In addition, according to Brubaker, the erosion rate is 3.4 percent.

If you add up all of these complications, the total sum of the complications is 19.5 percent. And we're talking about serious. We're not talking about a little erosion in the vagina that takes 15 minutes to fix.

So I think one cannot say that this is shown to be a safe procedure. I think it's essential that postmarket studies be done.

And although it's true that the Nygaard review includes a lot of obsolete techniques, it seems that the FDA had no problem whatsoever in including obsolete techniques in its review of vaginal mesh.

DR. FALCONE: Okay, thank you. Ms. Berney.

MS. BERNEY: I'll take a pass on this.

DR. FALCONE: Thank you.

DR. GADALETA: I have a question for Colin. So is the plan then to change the indications for use statements for the mesh that are on the market for this specific procedure, or will you leave the indications for use for those products that are already cleared as they are?

MR. POLLARD: So I don't think our plan was to -- well, to be honest with you, I think we're hearing a lot of different input here. I think one of the things that we will look at just across the board are the statements of indication for use and whether they really, you know, carefully and appropriately define, you know, what that mesh is used for.

DR. GADALETA: Okay. So the reason I ask is a sharp regulatory professional might then say this is the appropriate predicate for those other uses that we can -- that we're planning to up-classify. So we should probably think a little bit more about how we do this.

MR. POLLARD: So I thank you for that advice.

DR. FALCONE: Thank you. Dr. Duerhring.

DR. DUERHRING: Yes.

DR. FALCONE: Thank you. Colin, are you done with your questions? Thank you very much.

MR. POLLARD: I would just say, yeah, we're finished with the questions.

And I know this has been a really long day, and I just want to

thank all of you, the audience, the folks who have come individually, the industry folks who've enriched the discussion, and we are very, very appreciative of all of that.

DR. FALCONE: Thank you. Thank you very much to everyone.

For the panelists, you see this blue thing here? Okay, either you put your name on it, right, put your name on it and we'll pick it up over here or leave here. Everything without a name gets thrown into the garbage; is that correct? All right. So you either take it with you and bring it back tomorrow, or if you want to leave it here, then you have to put your name on it and give it to Shanika. If not, you can take all the stuff, anything left on the table, garbage.

Thank you very much. See you all tomorrow morning for more fun.

(Whereupon, at 7:00 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

OBSTETRICS AND GYNECOLOGY MEDICAL DEVICES PANEL

September 8, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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