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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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OBSTETRICS AND GYNECOLOGY DEVICES PANEL

+ + +

February 12, 2019
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

PANEL MEMBERS:

KEITH ISAACSON, M.D.	Panel Chair
RICHARD J. CHAPPELL, Ph.D.	Panel Member
JASON T. CONNOR, Ph.D.	Panel Member
MADELINE A. DICK-BIASCOECHEA, M.D.	Panel Member
ELISABETH DUNNE EREKSON, M.D., M.P.H.	Panel Member
DANIEL D. GRUBER, M.D., M.S.	Panel Member
KAY A. HOSKEY, M.D.	Panel Member
FRANK WEN-YUNG LING, M.D.	Panel Member
JERRY L. LOWDER, M.D., M.Sc.	Panel Member
DONNA MAZLOOMDOOST, M.D.	Panel Member
DANIEL M. MORGAN, M.D.	Panel Member
WYATT LISON, ESQ.	Consumer Representative
SHARON L. TIMBERLAKE, M.S.H.S., RAC, CCRA	Industry Representative
BARBARA BERNEY	Patient Representative
EVELLA WASHINGTON	Designated Federal Officer

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Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

BENJAMIN R. FISHER, Ph.D.
Director, Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

SHARON ANDREWS
Chief, Obstetrics and Gynecology Devices Branch
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

ELLEN OLSON, Ph.D.
Division of Analysis and Program Operations
Office of Compliance

DEBORAH KOTZ
Press Contact

FDA PRESENTERS:

KELLY COLDEN, M.D., M.P.H., FACOG
Obstetrics and Gynecology Devices Branch
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

JACQUELINE CUNKELMAN, M.D., M.P.H.
Obstetrics and Gynecology Devices Branch
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

ANGIE LEE, M.D., FACOG
Obstetrics and Gynecology Devices Branch
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

BOSTON SCIENTIFIC SPEAKERS:

RONALD MORTON, JR., M.D., FACS
Vice President, Clinical Sciences
Boston Scientific Corporation

SUZETTE E. SUTHERLAND, M.D., M.S., FPMRS
Director, Female Urology
University of Washington Pelvic Health Center
Associate Professor, Department of Urology
University of Washington School of Medicine

MILES MURPHY, M.D.
Board Certified, Obstetrics, Gynecology, Female Pelvic Medicine, and Reconstructive Surgery
Partner/Associate Medical Director
The Institute for Female Pelvic Medicine and Reconstructive Surgery
Chief, Division of Urogynecology
Department of Obstetrics and Gynecology
Abington-Jefferson Health

COLOPLAST SPEAKERS:

DALE KLOUS
Director, Clinical Science and Office of Medical Affairs
Interventional Urology
Coloplast Corporation

JAN-PAUL ROOVERS
Professor of Urogynecology
Co-Lead Investigator, Restorelle 522 Study
University of Amsterdam
Amsterdam, Netherlands

PROFESSIONAL SOCIETY SPEAKERS:

CHERYL IGLESIA, M.D.
American College of Obstetricians and Gynecologists

GEOFFREY CUNDIFF, M.D.
President
American Urogynecologic Society

MEGAN O. SCHIMPF, M.D.
Society of Gynecologic Surgeons

OPEN PUBLIC HEARING SPEAKERS:

KILA B. BALDWIN, Esq.
Kline & Spector, P.C.

SUZANNE EMMETT (read by Kila B. Baldwin, Esq.)
Patient

NANCY GRETZINGER, Ed.D.
Patient

IRAM LEVIT
Lyra Medical, Ltd.

CHARLES W. NAGER, M.D.
Pelvic Floor Disorders Network

VARUNA SRINIVASAN, M.B.B.S., M.P.H.
Patient, Consumer, and Public Health Coalition

ELIZABETH BROOK BROWN, M.D., M.P.H.
American Urologic Association

LANA KEETON
President/Founder
Truth in Medicine, Incorporated

BARBARA MELLON
Patient

MICHAEL A. CAROME, M.D.
Director, Health Research Group
Public Citizen

DANIEL ELLIOTT, M.D. (read by Michael A. Carome, M.D.)
Mayo Clinic

KATHY HISTAND
Patient

JODIE CALLAHAN, ORT/L
Patient

MADRIS TOMES, M.B.A.
Founder/CEO
Device Events

DIANA ZUCKERMAN, Ph.D.
President
National Center for Health Research

THOMAS GILBERT, Ph.D.
Chief Science Officer
ACell, Inc.

SHERRIE PALM
Founder
Association for Pelvic Organ Prolapse Support

CINDY PEARSON
National Women's Health Network

INDEX

INDEX

INDEX

M E E T I N G

(8:05 a.m.)

DR. ISAACSON: Good morning, everyone. I would like to call this meeting of the Obstetrics and Gynecology Devices Panel to order.

My name is Keith Isaacson. I'm the Chairperson of this Panel. I'm actually a reproductive endocrinologist and not a urogynecologist, and I focus on infertility surgery for things such as endometriosis and fibroids. But it's very much of an honor for me to serve as the Chair of this Panel, and I should be with this Panel for the next 3 years, God willing.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations on information related to the safety and effectiveness of surgical mesh placed transvaginally in the anterior vaginal compartment to treat pelvic organ prolapse.

Before we begin, I'd like to ask our distinguished Panel members and the FDA staff seated at this table to introduce yourself. Please state your name, your area of expertise, your position, and affiliation. And we'll start with Barbara.

MS. BERNEY: I'm Barbara Berney. I am the Patient Representative, and I have lots of areas of expertise, but what I do best is I'm an artist.

MS. TIMBERLAKE: Good morning, I'm Sharon Timberlake. I'm the Industry Rep today. I have 25 years in the medical device industry focusing on clinical affairs, regulatory and quality.

MR. LISON: Good morning, my name is Wyatt Lison. I'm a partner with the law firm of Feinstein Doyle Payne & Kravec in Pittsburgh, Pennsylvania. I'm a consumer advocate sitting on the Panel as the Consumer Representative.

DR. MAZLOOMDOOST: I'm Donna Mazloomdoost. I am a urogynecologist, and I'm also a medical officer at NIH.

DR. DICK-BIASCOECHEA: I'm Dr. Madeline Dick-Biascoechea. I'm a urogynecologist as well, at the University of Maryland Medical Center.

DR. CHAPPELL: I'm Rick Chappell from the Department of Biostatistics and Medical Informatics at the University of Wisconsin Medical School. I'm one of the token techies and medical statistician specializing in clinical trials.

MS. WASHINGTON: My name is Evella Washington. I'm the DFO.

DR. LING: My name is Frank Ling. I'm an OB/GYN practicing physician in Memphis, Tennessee.

DR. EREKSON: My name is Beth Erekson. I'm a urogynecologist and work for Dartmouth-Hitchcock, and I'm the interim chair of the Department of OB/GYN and the service line.

DR. CONNOR: Jason Connor, a statistician and consultant with ConfluenceStat and Assistant Professor of Medical Education at the University of Central Florida College of Medicine.

DR. LOWDER: I'm Jerry Lowder. I'm a urogynecologist at Washington University in St. Louis.

DR. GRUBER: I'm Dan Gruber, urogynecology at the Walter Reed National Military Medical Center.

DR. HOSKEY: Kay Hoskey, urogynecologist, Anne Arundel Medical Center.

DR. MORGAN: My name is Dan Morgan, and I'm a urogynecologist at the University of Michigan in Ann Arbor.

DR. FISHER: Ben Fisher. I'm the Director of the Division of Reproductive, Gastro-Renal, and Urological Devices within the Center of Devices and Radiological Health at FDA.

And I'd like to thank all of the members of the Panel for their willingness to come in despite the weather and sitting on the Panel and serving today. Thank you.

DR. ISAACSON: Thank you. If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Evella Washington, the Designated Federal Officer for the Obstetrics and Gynecology Devices Panel, will make some introductory remarks.

MS. WASHINGTON: I will now read the Conflict of Interest Statement.

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 of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

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

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. 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 placed transvaginally in the anterior vaginal compartment to treat pelvic organ prolapse. The FDA is convening this meeting to seek expert opinion on the evaluation of the risks and benefits of these devices.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Sharon Timberlake, owner of Sharon Timberlake Consulting, LLC, is serving as the Industry Representative, acting on behalf of all related industry.

We would like to remind members and consultants that if the discussions involve 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.

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

A copy of this statement will be made available for review at the registration table during this meeting and will be included as a part of the official transcript. Thank you.

Before I turn the meeting back over to the Chair, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table

outside the meeting room.

You may view the electronic comments that have been submitted for this meeting by going to www.regulation.gov and search for Docket FDA-2018-N-4395.

Additionally, there are some public comments in a binder on the table outside of the room if you would like to view them.

The press contact for today's meeting is Ms. Deborah Kotz. If anyone from the press desires to speak with her, please see Mr. Artair Mallett at the desk outside the meeting room to obtain her contact information.

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

If you are presenting in the Open Public Hearing session today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. Artair Mallett 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 your cell phones and other electronic devices at this time. Thank you very much.

I will now turn the meeting over to the Chair.

DR. ISAACSON: Thank you.

We will now proceed to the FDA's introduction. I would like to invite Ms. Sharon Andrews to approach the podium.

I will 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.

Good morning.

MS. ANDREWS: Good morning, everyone. My name is Sharon Andrews, and I'm the Branch Chief for the Obstetrics and Gynecology Devices Branch in the Office of Device Evaluation in the Center for Devices and Radiological Health. Thank you for joining us today for this meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee.

Today we're holding a general issues Panel meeting to discuss surgical mesh placed in the anterior vaginal compartment to treat pelvic organ prolapse. While the scope of this Panel meeting is limited to anterior compartment repair, FDA notes that anterior compartment prolapse often includes an apical component. Therefore, during today's meeting, apical compartment prolapse will be discussed alongside anterior repair. All other urogynecologic surgical mesh, namely surgical mesh placed transvaginally in the posterior vaginal compartment to treat prolapse, surgical mesh placed abdominally to treat prolapse, and mesh for stress urinary incontinence are outside the scope of today's meeting.

Today's Panel meeting is a follow-up to our September 8th, 2011 Panel meeting to discuss the safety and effectiveness of surgical mesh for prolapse repair. While you'll hear about FDA's regulatory actions related to mesh for transvaginal repair of prolapse in greater detail later today, I want to speak briefly about two major regulatory actions that are the impetus for today's meeting. Following our 2011 Panel meeting, FDA implemented two key recommendations from the Panel. First, we issued a postmarket surveillance study orders, also known as 522 orders, and second, we reclassified mesh for transvaginal repair of prolapse to a higher-risk category, Class II to Class III.

With our first regulatory action, starting in 2012 FDA issued 131 522 study orders to 34 manufacturers of surgical mesh for transvaginal repair of prolapse. The 522 study orders required manufacturers to answer a series of public health questions related to the safety

and effectiveness of their individual surgical mesh devices for transvaginal repair of prolapse. To address these questions, manufacturers conducted studies to evaluate the safety and effectiveness outcomes of their device at 12, 24, and 36 months compared to native tissue repair. FDA informed manufacturers that the 522 studies could be designed to support future PMA applications if FDA reclassified these devices.

I'll note here that 522 studies are typically completed to answer postmarket safety and effectiveness questions, while clinical studies to support PMA applications are designed to provide a reasonable assurance of safety and effectiveness of a device prior to marketing. Therefore, using a 522 study to support a future marketing application as being done here for mesh for transvaginal repair of prolapse is a novel regulatory situation.

With our second regulatory action, reclassification to Class III, FDA changed the regulatory paradigm for surgical mesh placed transvaginally to treat prolapse. As Class II devices, surgical mesh for transvaginal repair were reviewed through the 510(k) pathway. This allowed these devices to be marketed based on a standard of substantial equivalence, meaning that a new device should be as safe and as effective as an already marketed device of the same type.

However, with the reclassification to Class III, surgical mesh for transvaginal repair needs premarket approval to be marketed. This means that each individual device must independently demonstrate that it has a reasonable assurance of safety and effectiveness and cannot rely on information from already marketed devices. Each individual device must establish favorable benefit-risk in its intended patient population to support marketing. Reclassification is an extensive regulatory process, which is why FDA proposed reclassification in 2014, finalized reclassification in 2016, and required submission of PMAs in 2018.

As a result of these regulatory actions, many manufacturers elected to stop

marketing their devices for transvaginal repair of prolapse. Compared to the 131 522 orders issued to 34 manufacturers starting in 2012, there are currently three devices on the market for transvaginal repair of prolapse from two manufacturers: the Boston Scientific Uphold LITE, the Boston Scientific Xenform, and the Coloplast Restorelle DirectFix Anterior. All three of these devices are indicated for anterior/apical compartment repair, and the 522 studies for three marketed devices are currently ongoing.

FDA intends to use the recommendations from the Panel today to help us review the 522 studies for the currently marketed devices. We also plan to use the Panel's recommendations to evaluate future PMA applications for devices of this type. The Panel's recommendations will help us (1) evaluate the safety and effectiveness of individual devices placed in the anterior/apical compartment, and (2) determine if the benefit-risk profile of each device supports premarket approval.

Specifically, we are seeking the Panel's input on the following questions:

1. Should mesh be more effective than native tissue repair and at what time point?
2. Should both anatomic and subjective outcomes be used to assess effectiveness?
3. What are the types of adverse events that should be used to evaluate safety and how should these adverse events be assessed?
4. Should the adverse event profile of mesh be similar to native tissue repair and at what time point?
5. What are the effects of concomitant procedures and a patient's surgical/medical history on safety and effectiveness outcomes?
6. What factors determine whether a patient undergoes a mesh versus native tissue repair?
7. What is the effect of surgeon experience on safety and effectiveness outcomes? And

8. How should FDA assess the overall benefit-risk for surgical mesh placed transvaginally in the anterior vaginal compartment to treat prolapse?

As you'll note from these questions, we are not asking the Panel to determine the safety and effectiveness of currently marketed devices of surgical mesh placed in the anterior vaginal compartment as a device type. We are also not asking the Panel whether surgical mesh placed in the anterior compartment should continue to be on the market.

Today we're asking the Panel how to evaluate surgical mesh placed in the anterior compartment for prolapse repair. What are the important considerations that FDA needs to take into account as it reviews these devices and how well this mesh needs to perform with respect to safety and effectiveness when compared to native tissue repair? In the making your recommendations, FDA requests that the Panel focus their discussion on the general population of women who are candidates for transvaginal surgical repair of prolapse. This patient population is consistent with the labeled indication for the currently marketed devices.

The Panel will be presented with a significant amount of data today; however, it's important to remember that the data presented today are not intended to be representative of the devices on the market or surgical mesh for anterior compartment repair as whole. Rather, the data presented today are intended to give context around how the safety and effectiveness of surgical mesh placed transvaginally in the anterior vaginal compartment are typically assessed in the key considerations that affect these outcomes.

FDA acknowledges that differences in individual device characteristics, such as mesh material, weave, pore size, density, and implantation technique may all play a role in safety and effectiveness outcomes. However, these different characteristics are considered when FDA reviews an individual surgical mesh device. As we noted earlier, surgical mesh for transvaginal repair of prolapse are now Class III PMA devices, and accordingly, they must

each independently demonstrate a reasonable assurance of safety and effectiveness. FDA requests that the Panel keep this specific charge in mind as you progress through the remainder of today.

Throughout the remainder of today, the Panel will hear perspectives from a variety of stakeholders including patients, physicians, industry, professional societies, and the FDA. The Panel should consider the information provided by all stakeholders in making their recommendations today.

To close out my presentation, I would like to walk through our agenda for today. Following this introductory presentation, we will hold our Open Public Hearing. The Open Public Hearing is an opportunity for members of the public to provide their perspective on the devices under consideration today. The Panel may ask questions of the Open Public Hearing speakers after their presentations.

The Open Public Hearing will be followed by presentations from FDA, industry representing the currently marketed devices, and professional societies. Each group will present their assessment of surgical mesh for transvaginal repair of prolapse in the anterior compartment. Following each session, the Panel will have an opportunity to ask each group questions. We will conclude today's meeting with Panel deliberations and the Panel's responses to the questions posed by FDA.

Before I conclude, I would like to thank the FDA team for their hard work and their dedication in putting this Panel meeting together. Their commitment and perseverance has been exemplary and a great testament to the FDA mission to protect and promote public health.

Finally, I would like to thank everyone in attendance today: the patients, physicians, industry, professional societies, and Panel members. We know that many of you are attending at your own expense and on your own time to share your experience and your

expertise with us. On behalf of FDA, we sincerely appreciate your participation in today's meeting, and we look forward to learning and hearing from all of you.

Thank you very much.

(Applause.)

DR. ISAACSON: Thank you, Sharon.

So we'll now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda. Panel members may ask clarifying questions to the speakers after we've finished a group of five speakers. After each group has finished all presentations, I will open the floor for questions. At that time you may raise your hand and identify the speaker to whom your question is directed. Ms. Washington will read the Open Public Hearing disclosure process statement.

MS. WASHINGTON: 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 relationship 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 today. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. However, if you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Finally, if any speaker is reading

for someone else, please state this at the beginning of your statement as well.

FDA has received 16 requests to speak prior to the final date published in the *Federal Register*. Each speaker will be given 5 minutes to speak.

DR. ISAACSON: I just want to remind everyone that it is 5 minutes. I will be trying to keep track of it, and so if I do interrupt you as the time is getting -- as time has expired, please do not take it personally. It's not meant that way. But our first speaker is Ms. Kila Baldwin. Please come forward to the microphone. We ask that all the speakers speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

Ms. Baldwin.

MS. BALDWIN: Thank you. I just want to clarify. I have a statement here of one my clients as well, so I believe I was given 10 minutes; is that correct?

DR. ISAACSON: Is that what you assumed? That's correct.

MS. BALDWIN: Okay, great. Thank you very much. Good morning, everyone, my name is Kila Baldwin, and I am a partner at the law firm of Kline & Specter located in Philadelphia, Pennsylvania. Our law firm currently represents women who were catastrophically injured by polypropylene transvaginal mesh implants manufactured by Boston Scientific, Coloplast, Bard, Ethicon, Johnson & Johnson, and AMS. Over one-third of our 3,000 clients have had mesh placed for anterior prolapse repair. Our firm has tried more of these cases than any other law firm in the country.

The vagina is unlike the abdomen where hernia mesh has been used for years. It has unique bacteria and peroxides that cause excessive scarring and contraction and inflammation around the mesh. Because of this, the mesh stiffens causing vaginal retraction, loss of pelvic elasticity, vaginal deformation, organ dysfunction, erosions, and/or pain. Unlike complications associated with native tissue repairs, mesh complications are

permanent. Once implanted, it's nearly impossible to remove the mesh in its entirety or undo the retraction, deformation, and scarring caused by the mesh. The complications of transvaginal mesh used in the anterior compartment far outweigh the stated benefit of less chance of recurrence. These complications have been well known among mesh manufacturers and the physicians who consulted with those manufacturers for many years.

In February of 2007, Ethicon held an expert meeting regarding meshes for the treatment of pelvic organ prolapse. The unmet needs at that time were recognized as shrinkage, contraction, rigidity, folding, fibrosis leading to dyspareunia, decreased sexual function, and vaginal distortion. Many of the products today on the market for the treatment of anterior prolapse rely on the data from Ethicon's products.

As of 2009 Ethicon recognized that although mesh may reduce the rate of recurrence of prolapse, there are still several complications from the chronic inflammatory response and mesh shrinkage which leads to folding and migration. Chronic severe complications of this kind are virtually unheard of with native tissue repairs.

In 2017, Maher et al. published a Cochrane Review regarding transvaginal mesh grafts compared with native tissue repair for prolapse, examining 37 RCTs involving over 4,000 women. The study concluded that TVM repair may be associated with higher rates of repeat surgery for prolapse, stress incontinence, and erosion, and that the risk-benefit profile means it has limited utility in primary surgery. Additionally, it found that while it is possible that in women with a higher risk of recurrence the benefits may outweigh the risks, there is currently no evidence to support this. The Maher review also stated the quality of evidence ranged from very low to moderate and the main limitations were poor reporting of study methods, inconsistency, and imprecision.

No mesh products should be marketed until adequate long-term studies of the mesh, i.e., greater than 2 years, establishing both efficacy and safety in the vaginal region

are performed.

The amount of polypropylene in sutures is much less than that of mesh and it's inappropriate for manufacturers to rely on data for sutures because there's much less scarring and inflammation Further, because the vagina is physiologically so different from the abdomen, it's not appropriate to rely on data about hernia meshes.

Long-term studies are also needed because there's a significant problem with underreporting of mesh complications, as documented in the literature. The problems with mesh develop over long periods of time and the problems with mesh are chronic and can occur at any point in a woman's life following implantation. I'm going to keep going if the Panel can hear me, despite the current blinking.

Thus, the studies should be -- I'm sorry. The 2017 -- let's see if we've still got it. There we go. The 2017 Cochrane Review performed by Lundh et al. concluded that sponsorship of drug and device studies by manufacturing companies lead to more favorable efficacy results and conclusions than sponsorship by other sources. Thus, studies should be independent studies without the influence of industry and/or by professional organizations with strong ties to industry. It's a very real fear that if mesh products are marketed on a widespread basis for anterior repair, they will be marketed without proper pre- and postmarket studies and without proper warnings for surgeons in order to prioritize profits.

This diagram is an internal Ethicon document showing where Ethicon placed money versus actual patient needs when it was marketing mesh for POP repair. This was done in 2009 when Ethicon was marketing meshes for POP repair despite an internal document where there was still poor knowledge of the vaginal in vivo response to meshes.

Polypropylene meshes for the treatment of POP are not being marketed in Australia, New Zealand, Scotland, Ireland, and the United Kingdom, and the United States should follow suit.

In 2007 Ethicon was selling the Prolift and Gynemesh for anterior prolapse repair. This 2007 internal slide presentation, titled "When the Implant Worries the Body," states "No mesh is the best mesh." I have thousands of clients who agree.

This is from a February 2008 technical review of Ethicon. It again states that "No mesh is the best mesh." My clients agree.

I urge this Panel to recommend long-term clinical testing on any transvaginal mesh product before it is brought to market or allowed to stay on the market. There is no good, sound evidence supporting the safety of any transvaginal mesh product, and there is not a consensus that mesh is needed to treat women with anterior prolapse or any other pelvic disorder.

I'll now read the words of Suzanne Emmett, my client who recently got a $41 million verdict against Ethicon, including a $25 million award for punitive damages meant to punish and deter reckless conduct. Notably, her case was defended with argument by the defense that her doctor implanted the mesh incorrectly and that she had comorbidities such as a concomitant hysterectomy, obesity, and high blood pressure. The jury still unanimously found the mesh was defective and it was the cause of her harms.

"My name is Suzanne Emmett, I am 57 years old, and I was implanted with the anterior Prolift, Gynemesh, and a TVT-O in May of 2007. Since that time, the mesh implanted for my prolapse has eroded through my vaginal wall 14 times, primarily in the anterior compartment, and I have undergone nine surgical procedures to remove pieces of the mesh. You could read through my voluminous medical records and see the revisions, excisions, injections, silver nitrate treatments, Botox injections in my bladder, endless rounds of antibiotics, UTIs, and PTNS treatments. But what you wouldn't see in those records is the devastating impact all of this has had on my life.

"The marital dysfunctions due to painful intercourse nearly destroyed my marriage

of 27 years in 2011. My husband and I were able to reconcile, but the scarring has made it so painful that we have been unable to have intercourse since our 33rd wedding anniversary in 2017. We weren't able to complete the act that night because it was not only painful for me, but the exposed mesh cut my husband's penis and he likened the sensation to barbed wire.

"My vagina is so badly scarred and deformed from surgeries on the mesh that it is no longer straight, soft, and accommodating. My interior vaginal wall feels like a football, hard and rough. There is no cure, no treatment to fix this. I am 57 years old and I will never again know the pleasure and intimacy of having sex with my husband. This fills me with a sadness so deep I can't put it into words. I have painful bladder contractions on a daily and nightly basis that are random and unpredictable and cause me to leak urine that sometimes isn't contained by the pads I am forced to wear at all times.

"As I sat in the courtroom recently and heard my doctors talk about me and my treatment, I was struck by the matter-of-fact way they spoke. It all sounded so clinical. They truly have no idea what my life is like beyond the confines of their examining room. I want the doctors who treat women like me to do a better job of really listening to us and understanding the devastation that mesh has wreaked in our lives, and the hell our lives have become. Until this is fully explored and understood, the true extent of the problem cannot be known and when the true extent is known, I cannot imagine that any intelligent person of good conscience would believe that these products should be allowed on the market to ruin more lives."

Mrs. Emmett's story, Mrs. Emmett is not alone. Her story is commonplace among my clients. I have a client who lost her leg following a Coloplast implant. I have a client who had her urethra mangled from a mesh implant. I met two women at breakfast just this morning who shared their stories with me.

I urge this Panel to recognize the severity of complications caused by polypropylene transvaginal meshes, the severity and how much greater it is than native tissue, and to recognize the need for quality, long-term data on the safety of meshes before they are put in women, data that is not influenced by industry.

Thank you.

(Applause.)

DR. ISAACSON: Thank you, Ms. Baldwin. We'll have a chance for questions after our group of five. We now call up Nancy Gretzinger. Here? Oh, here.

DR. GRETZINGER: I'm Dr. Nancy Gretzinger, Ed.D., from Phoenix, Arizona. December 19th, 2009 was the worst day of my life. I was assured by the surgeon implanting the two mesh for my condition was a simple procedure she had completed many times with no problems. She did not mention the FDA 2008 notification. Who ensures that the doctors read any FDA notifications? The above had specific recommendations for the physicians including informing physicians about the potential for serious complications and their effect on the quality of life. I might have reconsidered it all if I had got all the facts.

Polypropylene mesh shrinks substantially after implementation by up to 50% after 4 weeks and often requires repeat surgical intervention. Since I was still unable to urinate on my own, surgically 8 weeks later it took her 7 hours to pick out mesh piece by piece. I then went to Dr. Christian Twiss, who had trained with Dr. Raz at UCLA. Dr. Twiss is one of the few urologists in Arizona who has board certification in both urology and female pelvic medicine and reconstructive surgery. In the forward to my book, *Enmeshed*, he wrote, "It was a new era in pelvic floor reconstruction. We have found synthetic vaginal mesh to be the ideal material. A permanent cure in less than 3 hours."

Mesh has been used for the past 20 years because it overcomes the need to harvest native tissue, is less invasive, takes less surgical time, and has been thought to reduce the

risk of recurrent prolapse.

In our initial meeting, Dr. Twiss explained in detail what all could happen. In all my visits, he listened, was thorough, and answered all my questions. Unfortunately, eight surgeries, multiple procedures and drugs, my bladder neck was removed and a suprapubic catheter was inserted into my bladder. Other effects are surfacing: decreased immunity, UTIs, resistance to antibiotics, and additional risks including bladder cancer.

Not all my mesh was removed. In 2013, excision of exposed vaginal mesh was removed. During a cystoscopy in 2018, a piece of mesh was being absorbed into my bladder. I had to retire because I caught everything my special needs inner-city preschool children brought to school. Subbing being the same thing.

My adopted daughter from China missed out on her mother when she needed her the most. I believe and feel both of us were robbed.

This was an elective surgery I should have passed on. What happened was do no harm became profit first. So why did this happen? In 1992 the 510(k) FDA code allowed for clearance without clinical trials after an exchange of paperwork, naming of the predicate devices substantially equivalent of a new device, a few thousand dollars and a wait of about 90 days.

The ProtoGen was the first transvaginal mesh approved which was made from polyester, continued to be used as a predicate for more modern devices even though they were made from polypropylene. And despite that the ProtoGen sling was removed from the market due to defective ways they were harmful to patients, this recall should have been a huge red flag for the FDA, whose job through their approval process is keeping Americans safe. If a predicate device is defective, those that follow should be carefully inspected for the same issues. Very few doctors know about mesh complications and these doctors and others will not listen to the patients that know their bodies and neither know

what to do. The FDA considers that mesh trials have been poorly designed and poorly conducted and have failed to account for variable lengths of patient follow-up. The FDA has been authorized to collect $999.5 million over 5 years that started in October of 2017. This funding is to provide critical resources to the FDA medical device review program.

I've had three mesh implanted for the prolapse organs and incontinence and I speak for hundreds of thousands of women who were victims of mesh.

FDA made its first announcement in 2008, with many communications since, and it's 10 years later. There's been multiple complications from placement with life-altering effects, even death. No research or viable mesh trials have been successful or have taken place. With all that data, it's time to ban polypropylene mesh.

Thank you.

(Applause.)

DR. ISAACSON: Thank you.

We'll next call up Mr. Iram Levit.

MR. LEVIT: Maybe I'll start with the disclosure. My name is Iram Levit. I'm the CEO, co-founder and a shareholder at Lyra Medical, so obviously I have a financial interest in the decisions of this Panel today.

(Off microphone discussion.)

MR. LEVIT: So good morning again. Again, my name is Iram Levit, and I'm the CEO of Lyra Medical. In the last 6 years we've developed a new device for anterior and apical vaginal wall prolapse treatment. I came here today all the way from Israel, hoping to change a little bit your perspective on pelvic organ prolapse treatment options. Taking a very close look at all the safety concerns and various opinions in this field, we note that the entire discussion is limited to mesh or not to mesh, without properly understanding the root cause of all these safety issues and looking for other rather different solutions.

Speaking about the appropriate first-line treatment for a cure-based prolapses, it seems like most of the stakeholders acknowledge that mesh kits are superior efficacy-wise, but at the same time expose patients to significant complications. Since they raised up all these concerns, manufacturers like ourselves made a lot of effort to demonstrate clinical evidence showing that the risks are lower than what originally thought.

On the other end, groups such as the PFDN, pushed the Agency to adopt a different success criteria. Following this change in the criteria, the success rate of native tissue repair was improved, should I say, artificially. This modification was obviously legitimate, especially considering that the alternative treatment, considering the modified criteria, demonstrated insignificant efficacy improvement or significant inferiority safety-wise. Unfortunately, this entire discussion did not take under the consideration that there may be other rather better solutions. The solution is to encourage innovation in this field and aim to a single solution that may offer both safe treatment and high success rate.

As Michelangelo once said, the greater danger of most of us lies not in setting our aim too high and falling short, but rather in setting our aim too low and achieving our mark. Back to the risk-benefit diagram, this is what we need to aim for.

So obviously the optimal solution is one that is safe, easy to use and uses optimal material, which could potentially lead to a high success rate. And actually, looking at it, there is such a device available in the market. It's called the pessary. So our original idea was to create an implant that provides the same benefits without the pessary's limitations. An implant does not block the vaginal canal and allows sexual intercourse, an implant does not cause bothersome vaginal discharge, and an implant does not need to be cleaned or replaced every few weeks.

We called it after its fundamental concept, self-retaining support implant, or the SRS implant. It comprises of two components: an ultra-light 16 g/m^2 surgical mesh coated with

a titanium dioxide surface to enhance its biocompatibility, and a solid frame that retains the mesh by itself without any fixation. We started development 6 years ago, and since then it complies with the highest standards, keeping patient safety as our number one priority.

After two premarket clinical studies, we've just recently initiated sales in Israel and selected European markets. Thus far, we have extremely positive feedback from all involved, surgeons and patients alike.

Our studies included 70 patients who were and still are evaluated for long-term safety and efficacy. They were prospective international studies involving six surgeons at four medical centers. The majority of available data is from 2-years follow-up, but over 30% of our patients reached over 3-years follow-up now, and the results speak for themselves. We have 98 anatomical success and only one symptomatic patient. By the way, using the new FDA criteria at the hymen level, we're reaching close to 100% success. Subjective results also show significant improvement in all treated domains, as well as improvement of sexual functioning. And most importantly, high safety results. We have no pain, no mesh erosions. A single device-related adverse event was due to an oversized implant without performing sufficient dissection. Following this incident, we've discontinued the use of various sizes and since then did not have any issue.

Literature supports the conclusion that mesh fixation is the main reason for complications with current techniques. Our clinical data demonstrated this conclusion by proving that anchorless solutions may provide the anatomical benefits of current available transvaginal mesh kits, while keeping the subjective and safety results as high as native tissue repair option. We believe that future discussions, and especially FDA's decisions, needs to consider that patients may benefit from vaginal approach solutions, solutions which addresses the root cause of known complications which, from our standpoint, is the various anchoring techniques.

Thank you.

(Applause.)

DR. ISAACSON: Thank you.

Our next speaker is Dr. Charles Nager.

DR. NAGER: Good morning, my name is Charlie Nager. I'm the chair of the OB/GYN department at UC San Diego. I'm here today representing the Pelvic Floor Disorders Network, which is a network funded by the NIH and our goal is performing randomized clinical trials to study pelvic floor disorders. The study I'm going to present is called the SUPeR trial, it was seven years in development, and this study received some public-private cooperation from Boston Scientific. Boston Scientific supplied the implants and they provided some funding for our data coordinating center, Research Triangle International, but they were not involved in the design, the implementation, the statistical analysis or the preparation of the manuscript for this study. They also have not funded any of my travel or lodging. Thank you.

The study was a randomized trial of vaginal hysterectomy versus vaginal mesh hysteropexy for uterovaginal prolapse. The pictures on the right describe the two procedures. The top picture is an illustration of a vaginal hysterectomy with the uterosacral ligament suspension and the one on the bottom shows an Uphold mesh hysteropexy for uterine preservation.

In terms of our study, our inclusion criteria were postmenopausal amenorrheic women. This was to allow masking of the studies -- of the subjects. Patients had to have symptomatic prolapse beyond the hymen and they had uterine descent into at least the lower half of the vagina. Patients were excluded if they had any uterine abnormalities. Our primary outcome was -- of treatment failure was a composite measure in which failure could be any of the three following events: either retreatment, any prolapse beyond the

hymen, or a bulge symptom. And these patients were queried every 6 months with the 3-year mark determining our primary outcome.

For our secondary outcomes, we evaluated POP-Q exams by non-surgeons every 6 months. Functional outcomes included numerous validated patient-reported outcomes that were administered by masked study personnel, and we also had specific safety and adverse event outcomes which were queried every 6 months.

This is our CONSORT diagram. Eventually, 87 and 88 patients were included in the two arms and 84 and 86, in other words 96% completed the 36-month follow-up. The study is ongoing and about half of those patients are -- were carried out to 48 months and our first patient will hit the 5-year mark this April.

Our typical patient was in her mid-60s, she typically was white and not Hispanic and not Latino. The baseline demographics of these patients show that they typically had Stage III anterior prolapse, that's what BA means, usually about 3 cm past the introitis, and their uterus or cervix was typically just past the introitis. These are very typical findings when women present with uterovaginal prolapse with the anterior compartment being more prolapsed than the uterus.

This is our primary outcome. You see a survival analysis of the composite primary outcome for the hysterectomy and hysteropexy groups. The blue is the hysterectomy group and the red is the hysteropexy group. Again, all patients were followed for 3 years, but half the patients were followed out to 48 months. Overall, our hysterectomy model at 36 months predicts 62% success and the hysteropexy model at 36 months produces 74%. The adjusted hazard ratio was 0.62. The confidence intervals did overlap one and the conclusion is there was no statistically significant difference between groups with up to 48 months follow-up at a *p* equals 0.06 level.

When we looked at our anatomic adverse events, which we followed again at every

6-month interval, we found that suture exposure rates and excessive granulation tissue rates were higher in the hysterectomy group, and we had an 8% hysteropexy mesh exposure rate. Our masking was quite successful with over three-quarters of patients remaining masked to the treatment arm during that 36 months.

I'm going to show some sexual activity and dyspareunia data. At the beginning of the study, about 40% of our patients were sexually active and this prevalence remained the same at 36 months. Of those in the hysterectomy group, 46% were sexually active had dyspareunia before surgery and the prevalence was 16% at 36 months. In the hysteropexy group, 38% were sexually active and that prevalence decreased to 19%. Of those who were not sexually active because of dyspareunia, the prevalence was 33% before surgery and 11% afterwards. In the hysterectomy group, 33% and 24%.

We used validated PISQ-IR, which is how we obtained these measurements, we had very low rates of de novo dyspareunia in sexually active women and very low rates of women who were not sexually active because of dyspareunia. With our adverse event recording we found that patients -- we had a 2% and 10% rate between the two groups, a higher rate with a significant p-value for the hysteropexy group. We also asked about pelvic pain and daily pelvic pain every 6 months and there was no difference in the two groups in those who had pain or did not or in daily pelvic pain.

In terms of our major findings, we found that hysterectomy and hysteropexy had a comparable primary outcome success rates through 36 months. We are following patients for 60 months and conclusions could change with more extended follow-up. We found mesh exposure rates are approximately 8%, but none of these required any OR management and this has to be compared to the 11 to 20% suture exposure and granulation tissue rates, which also did not require any OR management. There were no differences in our extensive patient-reported outcomes between groups.

Both groups had improvement in sexual function and decreases in dyspareunia and de novo dyspareunia and pelvic pain rates were low with no difference between groups. The strengths of this study included that it was a randomized trial, we had masked participants, we had a minimum 3-year follow-up, we had nine sites which improved generalizability. Our limitations is the study was limited to postmenopausal women and only 40% were sexually active. Limiting dyspareunia outcome assessments may not be generalizable to younger, more sexually active women.

In conclusion, the study suggests that a transvaginal mesh hysteropexy should remain an option for postmenopausal women with uterovaginal prolapse who desire a uterus-preserving vaginal operation.

Thank you very much.

DR. ISAACSON: Thank you.

(Applause.)

DR. ISAACSON: Now I'll call Dr. Varuna Srinivasan.

DR. SRINIVASAN: Good morning. Thank you for the opportunity to speak today. My name is Dr. Varuna Srinivasan, and I am speaking on behalf of members of the Patient, Consumer, and Public Health Coalition. The coalition includes nonprofit organizations representing millions of patients, consumers, and researchers united to ensure that medical treatments are safe and effective. The coalition does not have paid staff and does not accept funding from any outside sources, so I have no conflicts of interest.

Our coalition strongly supports FDA's decision to require a premarket approval review, including clinical trials, to determine the long-term safety and effectiveness of transvaginal mesh for pelvic organ prolapse repair. These products were initially allowed onto the market as substantially equivalent to mesh used in other parts of the body under the 510(k) approval pathway that does not usually require clinical trials or direct scientific

evidence of safety or effectiveness.

Mesh devices used in the repair of pelvic organ prolapse are permanent and are made out of synthetic material that has been proven to sometimes incite a foreign body response. It is likely to shrink over time, which can result in it degrading into the surrounding tissue making it painful as well as impossible to fix. As a result, thousands of women have reported serious injury to the FDA from surgical mesh implanted as a result of POP surgeries using either the anterior or the posterior vaginal compartment.

Almost a hundred submissions by mesh manufacturers between 2008 and 2013 were cleared by the FDA through the 510(k) processes for pelvic organ prolapse repair. Despite these decisions as well as thousands of MAUDE adverse events reports, the FDA has concluded that the risk-benefit profile of mesh has not been well established.

Research studies included in the recent FDA literature review were designed to compare POP surgery with mesh over native tissue repair, but almost all of the studies used a range of primary effectiveness endpoints, most of which only followed patients from 1 to 3 years and many of which did not include quality of life indicators.

When comparing the safety and effectiveness of these surgeries with or without mesh most showed that, on average, mesh surgeries were less safe than native tissue repair. Although the initial surgery with native tissue was somewhat less effective than the initial surgery with mesh, many complications occurred within the initial months of surgery with mesh for which very little data are available on the long-term risks.

The studies included in the FDA review focused on either anterior compartment repair or a combination of anterior and posterior compartment repair. Because the review was not limited to studies of anterior procedures, the FDA could not conclude whether POP surgery with mesh was safe and effective specifically for anterior compartment repair. The data the FDA provided are not sufficient to predict whether there are some women for

whom the benefits of anterior mesh POP procedures are likely to outweigh the risks. The effectiveness summary suggests that mesh may have some advantage over native tissue repair for anatomical POP evaluation and reoperation, but this possible advantage comes with significant risks. Women who undergo POP surgery with mesh are more likely to have numerous reoperations due to serious complications such as mesh erosion and exposure.

A Cochrane Review published in 2016 concluded that anterior POP surgery with mesh was not a better option than native tissue repair. They examined data on the use of different types of mesh in surgical repair of pelvic organ prolapse. The review looked exclusively at 33 randomized controlled trials that included more than 3000 surgeries, comparing traditional native tissue anterior repair versus other surgical options. Sixteen of these studies compared native tissue repair to permanent polypropylene mesh. They concluded that biological graft repair or absorbable mesh provides minimal advantage compared with native tissue repair. The Cochrane scientists pointed out that although women who had native tissue repair had more repeated surgeries for prolapse rectification, they had a much-reduced risk of bladder injury, mesh exposure, and erosion. In summary, they concluded that the evidence does not support the use of mesh for anterior vaginal compartment repair in pelvic organ prolapse.

Concurrently, other regulatory agencies such as Health Canada concluded that POP procedures have a higher risk of complications compared to native tissue repair and mesh placed abdominally.

I'm just going to skip ahead because I have 18 seconds, but we want to be clear that we're on the side of evidence-based medicine. If specific companies can provide irrefutable scientific evidence that the benefits outweigh the risks of using mesh for POP surgery, then we will support POP mesh surgeries if patients are provided with informed consent ensuring that they know that the adverse events can result in chronic, life-changing pain. While the

FDA is focusing on how to evaluate and review postmarket surveillance from three companies, we urge the FDA to ensure that the POP mesh research must include long-term studies which have reliable and validated quality of life indicators.

As a doctor, I strongly believe that doctors owe it to their patients to ensure that devices being implanted in their bodies are safe and that adequate prior preclinical testing has been conducted. I hope you all will agree. Thank you.

DR. ISAACSON: Thank you.

(Applause.)

DR. ISAACSON: Thank you very much to all the public hearing speakers.

The Panel now has an opportunity to ask questions to any of these Open Public Hearing speakers. Please address the speaker by name so they can come up to the podium. Does the Panel have any questions?

MS. KEETON: Excuse me, my name is Lana Keeton, and I don't know if I missed my time. I'm a public speaker.

DR. ISAACSON: No, not yet.

MS. KEETON: Okay, thank you.

DR. ISAACSON: Dan.

DR. MORGAN: Yeah. Dan Morgan. I have a question for Ms. Baldwin. With respect to the devices that we're looking at today, do you have any experience with clients that have reported problems with the devices specific to today?

MS. BALDWIN: Yeah. My firm represents, as I said, a myriad of clients, but we do have clients who have been implanted with the products that are still on the market that you are looking at today.

DR. MORGAN: Have they had problems with the devices?

MS. BALDWIN: Yeah. Our firm screens our clients before we take them on and they

have had serious complications. The exact specifics I'm not at liberty to get into because their cases haven't been resolved yet, but they have experienced things, the likes of which I discussed in generalities here today. Thank you.

DR. ISAACSON: Any other questions from the Panel?

DR. MORGAN: This is for Dr. Nager. Since one of the questions is about training, I'd just be curious to hear about your ideas about the ops physician training at the nine different sites and how you guys addressed that.

DR. NAGER: Yes. So this was the Pelvic Floor Disorders Network. It was nine sites who were all in this NIH clinical trial. The procedures were being done by about 38 different surgeons, but they were all FPMRS specialists, subspecialists who were qualified for this. When we designed the study, all the practitioners were well experienced with vaginal hysterectomy and uterosacral ligament suspension, but nevertheless we required them all to watch a video and document that they had completed so many in their career and so many in the last 6 months.

We also had the same requirements for the Uphold hysteropexy as a newer procedure for everyone, but they all had to have completed a number, and I believe it was about 10 sacrospinous ligament suspensions through the anterior approach, they had to have several in the last previous year, and they had to have at least five experiences with the Uphold mesh. We felt when we designed the study that there could be a potential bias against the hysteropexy because this was the less experienced study, so we particularly wanted to try to reduce that bias when we designed it.

DR. ISAACSON: Thank you.

DR. CHAPPELL: I have a question for Iram Levit, the representative from Leera, from Lita?

MR. LEVIT: Lyra.

DR. CHAPPELL: Lyra, thank you. You mentioned, specifically mentioned, the very light weight of your mesh.

MR. LEVIT: Um-hum.

DR. CHAPPELL: Could you briefly tell me why that has come to be an issue and why you -- it sounds like you were bragging about it as an advantage, so why that should be true?

MR. LEVIT: Yeah. I mean numerous studies showed in all recent years, 15 years back, shows that as light as the mesh is, the less complications. So actually, we -- our device is 16 g per -- it is 16 g. I mean, some manufacturers, what they did in order to decrease the light or the weight of the mesh, just opened the pores a little bit. Ours is 65 µm of fiber, which is very delicately knitted. Actually, you cannot use this kind of mesh because it's too light and too delicate without -- to use that without a frame. The frame retains it by itself and providing mechanical properties without causing the mesh of being folded and buckled, but usually that's the root cause of erosions and therefore we don't see any mesh erosions. It's not by chance, it's by design.

DR. CHAPPELL: But you say that you do have clinical studies that correlate lighter mesh weight with fewer complications. Did you say that?

MR. LEVIT: Not studies that we sponsored but a lot of the clinical data that is available, yes.

DR. CHAPPELL: Thank you.

DR. ISAACSON: Yes, Sharon.

MS. TIMBERLAKE: Hi. Yes, I have a question for Ms. Baldwin. Thank you for your presentation.

MS. BALDWIN: You're welcome.

MS. TIMBERLAKE: During the presentation you made several references to Ethicon.

I was wondering if you could talk to the differences between the Ethicon mesh used in your cases that you've entailed over the years versus the remaining mesh on the market that's available today.

MS. BALDWIN: Sure, no problem. So the documents that I showed you were related to Ethicon's pelvic mesh products which, just for background, would be the Gynemesh, the cut-to-fit sheets for anterior or posterior colporrhaphies, and then they obviously had the Prolift product which came in a total as well as an anterior. Now, this was a heavyweight, smaller pore mesh, which is evidenced by their own documents. A lot of meshes that are currently on the market, as I said, relied on the data about this, which was one of the earlier meshes out there for POP repair. The current meshes, admittedly, are larger pore and somewhat lighter weight. However, based on the documents that I have seen internally, and I just didn't have enough time in 10 minutes to present them here, we're seeing the same type of complications.

So what I've seen, based on my experience, is that there seems to be a lot of argument about, admittedly, the weight and the actual technical size of the pore. But the real issue becomes the amount of inflammatory response that is incited to any foreign body being put specifically in the vagina, because it differs so much from the abdomen or other areas of the body, and the same meshes that are on the market now, the three that we talked about earlier are inciting the same type of chronic inflammatory response, this foreign-body response that's chronic, never ending and the fibrotic ridging and the reaction that created is almost identical to Gynemesh and Ethicon and these earlier products, which is why I think there is a need for long-term data because I think there's been a focus for far too long on actually just erosions, right? You can't get a mesh erosion without mesh. But the real issue that you need to look at is the retraction, the deformation and the chronic inflammation, because those are the conditions that are going to lead to chronic pain, to

chronic dyspareunia and to chronic debilitating loss of function of the organs, and we're seeing those exact same problems with the current meshes that are on the market despite the fact that they do have a slightly larger pore size, slightly less heavy weight; it's the same response, and that's really the heart of the matter.

So although there are some technical differences that you can look at with the minutia of millimeters about weight or actual pore size, it's the overall response. And respectfully, to the good man from Lyra who presented his product, I had some questions myself about, you know, what kind of biocompatibility testing have you done in the long term in a vaginal environment, and that's really my question because I'm not seeing it out there and available with the meshes that are out there on the market.

MS. TIMBERLAKE: Thank you. I'm sure the manufacturers will cover that information this afternoon --

MS. BALDWIN: Right.

MS. TIMBERLAKE: -- as well as the 522 studies that they're conducting and evaluating with the Agency. A question. You also mentioned something about 50% shrinkage of the mesh.

MS. BALDWIN: I'm sorry, I couldn't quite hear you.

MS. TIMBERLAKE: I'm sorry, you also mentioned a point about shrinkage of the mesh.

MS. BALDWIN: I believe that was -- the woman seated next to me gave a rate of 50. I've seen rates in -- I'm sorry to interrupt you. Go ahead. Go ahead.

MS. TIMBERLAKE: I was just going to ask that maybe Coloplast and Boston Scientific can address that question as well as the physicians on the Panel today. It sounds like there might be some sort of impact versus what was available on the market with the older generation of meshes versus what's available today on the market and perhaps they can

talk to some of that information to better understand the properties and differences between the polypropylene and other meshes on the market today.

MS. BALDWIN: A good point. I think that's a great well-received point. The number that was cited by one of the ladies seated next to me was 50%. I've seen rates much lower than that and again, the problem is that any contraction that I've seen, based on my experience, my discussions with surgeons and clients, is that the vagina needs to remain elastic. So if you've got any shrinkage whatsoever, it's going to create a problem, and so we've got this issue, have you done the ultrasound testing to see if it's shrinking, to see if the scar tissue around it is contracting.

DR. ISAACSON: Yeah, thank you very much.

Dr. Fisher.

DR. FISHER: I was just going to say, in the interest of time, I wanted to go ahead --

DR. ISAACSON: Right.

DR. FISHER: -- if we could. So I know that there's a lot of interest in specific mesh characteristics. We've been talking about pore size and biocompatibility and I would just like to say, as Class III devices, each one of these submissions has got to stand on its own and the FDA requires extensive biocompatibility testing regardless of pore size or composition of the mesh itself. So I don't want to get too granular in that area, but if we can move to the -- I just want to make sure that everybody has an opportunity to -- for the Open Public Hearing.

Thank you.

DR. ISAACSON: Thank you.

We'll continue on with the Open Public Hearing speakers.

Ms. Leslie Hill.

(No response.)

DR. ISAACSON: Ms. Hill is not here. Is Dr. Brook Brown available? Dr. Brown? Here she comes.

DR. BROWN: Hi, thank you. I am Dr. Brown, and I am speaking on behalf of the American Urologic Association today. I have no disclosures. I have been asked by the AUA board of directors to read the recently reaffirmed AUA position statement on the use of vaginal mesh for the repair of pelvic organ prolapse.

Pelvic organ prolapse is a highly prevalent condition. Many effective treatments exist for this condition, including pelvic floor exercises, support devices such as pessaries, and surgery. Surgical techniques have evolved over time in an effort to treat pelvic organ prolapse in an effective, safe, and durable manner. Synthetic mesh has been utilized by many surgeons as an adjunctive technique to improve the long-term results of surgical repair.

Like all surgical techniques, the incorporation of mesh into surgical prolapse repair has potential advantages and disadvantages. Mesh may improve long-term anatomic results of surgery as compared to non-mesh repairs for some types of prolapse. Certain patients may benefit from mesh techniques, and the use of mesh techniques should be a choice that is made after a careful discussion between the surgeon and the patient. Better data are needed to determine the appropriate role of vaginal mesh techniques in the treatment of prolapse.

Vaginal mesh placement for prolapse is associated with risks to the patient including vaginal extrusion, erosion, sexual dysfunction, urinary tract injury, pain, and other complications. Like with all surgeries, these complications may be due to surgical technique, the materials utilized, patient anatomy, or a combination of factors. It is also important to recognize that many of these complications are not unique to mesh surgeries and are known to occur with non-mesh prolapse procedures as well. In patients with

postoperative symptoms that are not clearly caused by a mesh complication, removal of vaginal mesh may not improve the symptoms and, in fact, may worsen their condition.

Many women undergo prolapse repairs without complications. There is no convincing evidence that vaginal mesh placement can cause an autoimmune response and there is no reason to remove vaginal mesh in asymptomatic patients. In patients who have had vaginal mesh surgery for pelvic organ prolapse and are satisfied with their results, there is no need to take any action other than routine check-ups and follow-up care.

Vaginal mesh may be used for the surgical treatment of stress urinary incontinence or pelvic organ prolapse. The AUA believes that it is critically important to distinguish between these two uses of vaginal mesh. Extensive data exists to support the use of contemporary synthetic mesh slings to treat stress urinary incontinence with minimal morbidity compared with alternative surgical techniques. Mesh-related complications from sling placement are typically easier to address than those related to prolapse repair. The AUA Guideline for the Surgical Management of Stress Urinary Incontinence in 2017 concluded that synthetic slings are an appropriate treatment for women with stress incontinence with similar efficacy but less morbidity than conventional non-mesh sling techniques.

The AUA strongly agrees with the FDA that a thorough informed consent should be conducted prior to the use of mesh products for pelvic organ prolapse. The AUA also agrees with the FDA statement that surgeons who wish to utilize mesh techniques for pelvic organ prolapse should undergo rigorous training in the principles of pelvic anatomy and pelvic surgery, be properly trained in specific mesh implantation techniques, and be able to recognize and manage complications associated with vaginal mesh.

Thank you for your time.

(Applause.)

DR. ISAACSON: Thank you, Dr. Brown.

Ms. Lana Keeton.

MS. KEETON: Good morning, my name is Lana Keeton. I'm the president and founder of Truth in Medicine, Incorporated. It was created in 2008 following my own personal experience with flesh-eating bacteria from the implantation of a Gynecare TVT polypropylene sling. Since that day, I would try to figure out, like, what happened to me, but nobody knew. Well, I can promise you there's a lot of lies related to mesh. It starts with the manufacturers and it goes to the plaintiffs' attorneys that are representing over 104,000 women in one court alone in West Virginia. If there's 104,000 women injured by mesh for any reason, it should not be on the market. If tomatoes are killing people, they take it off the market.

So just so that you understand my experience, I'm not just -- I'm not a nonprofessional, I am a medical device expert. I have spent over 10,000 hours researching polymers. I have 30 years experience as a steel broker and I understood the physical and chemical properties of steel, so I related that to physical and chemical properties of polypropylene. I assure you that it is defective. I'm sure that you have not heard the word post-crystallization and if you have heard that word, then you might understand it's not inert and it always shrinks. It's an inherent defect in the manufacturing process. So, for years there's been a misapprehension that mesh is inert. Well, why do they have to have additives, antioxidants, and surfactants to protect the mesh itself? If they didn't, then maybe it would be inert; it's not.

So my focus is to get mesh off the market. I've been focused on it for over 12 years and the reason is it causes severe harm to so many hundreds of thousands of women. This is worldwide. Other countries are taking it off the market, and I call for the FDA to take mesh off the market for any pelvic use, including bladder slings.

Now, you've got to consider there are certain things that are inherent in every single product. Number one, all of it goes through a post-crystallization process and it shrinks. The manufacturers have no control, they don't have an inventory control process, so they can't tell you when it's going to shrink, sitting in the package, implanted in the person, 5 years after in a person, but it shrinks.

The other thing that's really very important is no matter where you put this a person, a human, the tissue weakens with time as a person becomes older. So the mesh is not going to weaken and so it's going to tear away. It's like bed sheets that are weak. If you place a patch on a weak bed sheet, it's going to tear around the edges.

The other thing is the biofilm infections that are killing women all over the world, they cannot be stopped, they cannot be cured. Biofilm infection is inherent with this product.

I'm probably not dead because following the surgery to remove a 3-inch portion of my stomach, they gave me a million units of antibiotics of every spectrum, every 2 hours for 4 days and I used to think oh, that's awful, but I'll tell you something, that's probably why I don't have a biofilm infection today. I don't know how many surgeries I've had. Probably 14 or 15. I want to tell you something, it consumes our lives and -- but I'm not a victim, I'm a victor and there is going to be a victory over mesh because this is -- it's barbaric and it's medieval and to think that you have to cut a woman open and put a piece of mesh in her is ridiculous. Probably what you need to do is not do surgery, particularly if it's asymptomatic. You have to reconsider your entire position. You know, we have this lovely discussion, but they're meaningless because you have a product and you name it and say all of these things about it and then you put it in a human and say this is going -- how it's going to act. That is not true. No matter what we say as humans and how we now define the product, the body and the product make the decision of what happens when it gets into the body.

The surfactant that they use on polypropylene and most other meshes, it's a non-ionic surfactant. It has an estrogen effect, and it causes thymocyte apoptosis. Hundreds of thousands of people are developing the autoimmune disease because there's a cascade of -- you know, in a body as this continues, the process continues. So purposely it's put in place through scarring, through inflammation. So there's I don't know how many millions of people who take, you know, anti-inflammatory products or cholesterol and things like that, but you to take the whole patient sector and you put a product in them that causes inflammation, what is wrong with that picture? You need to look at the person as a whole person.

So, again, there's 104,000 lawsuits in West Virginia. The plaintiffs' attorneys are lying to the core. They say it's the pore size and the weight. That is ridiculous. There's like 14 or 15 chemical and physical properties of mesh. It's not the weight and it's not the pore size because you can take a piece of mesh just like a windscreen and just scrunch it up. Well, you think that doesn't happen in a body? This also is a one-size-fits all. A woman's vagina is small and there's various sizes and you take this one-size-fits all and put it in women that are 5 feet tall and women that are 6 feet tall and just can't keep cramming mesh into a woman's vagina. I'm sorry, it's really, really wrong.

As a patient advocate I've dealt with over 2,000 people worldwide helping to find medical help. It's not available. There are not skilled surgeons, there's no -- nothing in the instructions for use on how to locate it in the body. There's nothing in the instructions for use on how to remove it. There's no protocol. Where's the protocol? We're discussing well, where are we going to place it? Where's the protocol to find it in the human body? Where's the protocol to remove it? That's what the manufacturer is supposed to have the instructions for use when they sell the product.

And at any rate, it is such a flawed -- it's completely flawed. This product should not

be in humans, it shouldn't be in humans for incontinence, for hernia or for pelvic organ prolapse, unless there's no tissue available. That's the only time it should be used. Bassini did hernia repair in the '50s -- one second -- and he could repair 90% of all hernias without mesh. But once the companies started selling mesh --

(Microphone turned off.)

DR. ISAACSON: Yeah.

MS. KEETON: And I want to say thank you to Dr. Shuren, the Director of the Center for Devices, for having me. I want to say thank you to Dr. Fisher. I want to say thank you to Dr. Isaacson and I want to say thank you to Ms. Washington, and I want to say thank you --

DR. ISAACSON: I'm sorry, we have to move on. Thank you very much.

MS. KEETON: And, listen, I want to thank you, and I hope you will take into consideration taking it off the market. Thank you.

(Applause.)

DR. ISAACSON: I'd like to call up next Ms. Barbara Mellon. Barbara? Oh, okay.

MS. MELLON: We should have long-term studies on it because a lot of people like me, I did have it erode through within 1 year and have to have another, but they never even told me I was having plastic implanted in me and I was already allergic to heated plastic, which was found out at a Puget and -- plastics plant. They had to all an ambulance three times for me because I had anaphylactic shock. And this was still put in me without telling me that plastic was implanted.

DR. ISAACSON: Barbara, before you continue, would you introduce yourself and what you're representing? Thanks.

MS. MELLON: Okay, I'm Barbara Lynne Mellon, and I'd like to tell you everything I represent, but my records were -- I was told were destroyed for a couple years and I tried to get them and it wasn't until went to the Attorney General to get them that they finally got

them within 3 weeks and certain things had been changed and the implant stickers were not there, they removed them or didn't have them, but they were supposed to. The doctor that was going to -- I was wanting to go to Dr. Raz, but I had sepsis five times and couldn't travel, but I didn't want to go to the same place that had put them in, but I ended up having to because I almost died over and over. I had been put in the hospital every time I was scheduled to have the mesh removal, and when I had told one of the doctors that was doing the removal, that she had an orthopedic surgeon also because I had to have titanium things pulled out of my pelvic bone that had to be chiseled out because they don't have a way to just pop them out and I lost bone in there.

And, anyway, I saw disease doctors, I was running fevers for years, I was showing up in emergency rooms from a year after I had had the surgery. It was less than a year that it eroded through and they did a second surgery, and I had blood in my urine continually and I found out, when I did get my records, my bladder had been punctured twice because they had used -- when they did it they did a blind procedure that keeps them from seeing where they're going, so they could put it anywhere. They go into your liver or wherever. They punctured my bladder twice. I was never told. But I kind of understood now how bad I was sick afterwards and the infections that I continue to get.

Anyway, it's destroyed my sex life. I have a zero sex life with my husband. There are times where I've given in where I take pain medicine, turn lights off, and lay there and cry because there are so many women who have had their husbands leave when they could no longer -- I'm almost 20 years married this August, and I had a good sex life with my husband. It's been destroyed. I was active and I rock climbed, I went boating, jet skiing, horseback riding, ballroom dancing. Everything has been destroyed, and it's not just me. People that I've gotten to know in our group have died. They've committed suicide from pain that's not being controlled. There are other people that have died from infections, like

Chrissie, and that means her two little boys grow up with no mom. This is affecting lives and it's major and nobody is really listening to us.

When I went to the emergency rooms with all these problems, I kept being told it wasn't the mesh, that I just had a bladder infection or maybe I had kidney stones. None of this stuff was ever found, except I would be put on antibiotics, which would make me get better for a week or two and then it was back. And I was constantly having pain. I couldn't go to my kids' school things because you have to sit on benches and I was starting to get nerve pain that was going into my legs and into my groin, and the hard benches.

And then when I had the surgery to remove it, like I said, it took forever, I thought I would die before then because I kept being put in before they could get the surgery there and then they removed it and they gave me MRSA that started at the pelvic bone, and it spread through my body and all my bones, it was osteomyelitis, and I was sent home because they didn't know they'd given it to me, but I was folding up like this and there had to be an orthopedic surgeon along with a bladder reconstruction surgeon and then they had people help.

Anyway, I got sent home 4 days later and I kept -- I told them I couldn't -- it wasn't 4 days later I got sent home, but when I got home I was there 4 days. I couldn't walk when I was leaving and I'm a person who hates hospitals, I would have left on my own accord if I could. I told the doctor I couldn't walk, there's something really wrong. And there was. It was an abscess that it's rolled up like this on my pubic bone and when I was rushed back in because all of a sudden my fever was sky high and I was peeing in a bucket, laying on the couch in my living room because I could only stand to squat, which would take me forever over this bucket that somebody would have go empty because I couldn't go to my bed using stairs.

And when I went back and they told me vancomycin was the last option, I had all the

antibiotics to get rid of it and nothing would work, it was a hospital one that was immune to all the antibiotics. They told me if vancomycin didn't work, that there wasn't any more they could do. So when I got sent home that time I was in, like, months, like I'd be in there so many weeks on IVs and then sent home and then come back. And so when I started swelling again --

(Microphone turned off.)

DR. ISAACSON: I'm sorry, thank you for sharing your story, but we must move on. I appreciate it.

(Off microphone comment.)

(Applause.)

DR. ISAACSON: And, again, I'd just remind everyone, I'm going to try to be a little more proactive in trying to stick to the 5 minutes because we're running so far behind and we want to hear from a lot of different people.

The next is Dr. Michael Carome.

DR. CAROME: I'm Dr. Michael Carome, Director of Public Citizen's Health Research Group. Public Citizen and I have no conflicts of interest.

In 2011 Public Citizen petitioned the FDA to ban and recall all non-absorbable surgical mesh products labeled for transvaginal repair of POP because these devices offer no clinically significant benefits in comparison with non-mesh repair of POP and have high rates of serious complications. The Agency denied our petition in 2014.

Surgical mesh for transvaginal POP repair is a quintessential example of the fundamental deficiencies in the FDA's oversight of medical devices, particularly those that are permanently implanted. From 2002 to 2011, numerous such mesh products were cleared under the 510(k) process without clinical testing. By 2011, after thousands of women had been injured by these devices, the FDA concluded that serious complications

associated with surgical mesh for transvaginal repair of POP are not rare and that it was not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair.

In May 2014, nearly 5 years ago, the FDA issued a proposed order to reclassify these products as Class III devices based in part on this Panel's conclusion that a favorable benefit-risk profile for surgical mesh used for transvaginal POP repair has not been well established. That order was finalized in 2016. Nevertheless, the Agency allowed these products to remain on the market pending submission of PMAs, resulting in avoidable harm to many more women.

In terms of benefit, most women who have POP are asymptomatic and do not require treatment. For symptomatic women, this non-life threatening condition, the goal of treatment is symptom relief. Thus, the assessment of the benefits of surgical POP repair procedures necessarily must focus on symptom relief rather than anatomic outcomes. We disagree with the FDA that a combination of objective and subjective outcomes is needed to adequately evaluate the effectiveness of surgical mesh placed in the anterior vaginal compartment against native tissue POP repair.

The FDA's review of the literature reveals that although transvaginal POP repair in the anterior vaginal compartment with mesh results in lower rates of objectively documented prolapse post-op, in comparison with non-mesh procedures, the use of mesh in general does not provide better outcomes in terms of relief of prolapse symptoms and quality of life measures.

Importantly, the FDA also stated that when considering reoperation for either prolapse recurrence or mesh erosion and exposure, mesh patients had greater odds of reoperation. Of note, the 522 clinical studies evaluating Boston Scientific's Uphold LITE and Xenform transvaginal mesh products, which were non-randomized and unblinded,

increasing the likelihood of bias, these studies revealed that use of these products did not result in better subjective success rates than native tissue repair at 1, 2, or 3 years.

In terms of risk, on the other hand, a review of the literature demonstrates that the use of mesh leads to high rates of serious complications, many of which require additional surgical intervention and some of which are not amenable to surgical correction and result in permanent life-altering harm to women. Mesh erosion and exposure and/or extrusion are common significant adverse effects unique to the use of mesh in transvaginal POP repair in the anterior vaginal compartment occurring in 3 to 15% of patients across studies in the first 3 to 5 years post-surgery.

The FDA highlighted the following regarding this adverse effect: The FDA believes that the risk profile for surgical mesh placed in the anterior vaginal compartment is greater than that of native tissue repair. This is because mesh erosion and exposure, which can be serious and potentially debilitating, is associated only with surgical mesh and not native tissue repair. Management of mesh erosion may not be uncomplicated, may require multiple additional surgeries to address, and may remain unresolved despite treatment.

The FDA search of the MAUDE database has documented more than 11,000 reports of all transvaginal POP mesh products over the past decade, including more than 10,000 reports of serious injury and 77 reports of death. The top 10 problems from the reports are listed in Table 1 in the briefing document and are shown here. Many of these same adverse effects are also reported for the transvaginal mesh products still marketed by Boston Scientific and Coloplast.

In conclusion, because of the FDA's recklessly inadequate actions regarding surgical mesh for transvaginal POP repair over nearly a decade, thousands of women have been unnecessarily harmed, many permanently. To prevent further harm to women, Public Citizen urges the FDA to reject the PMAs submitted for the three mesh products still on the

market, thus effectively banning them. Thank you for your attention.

(Applause.)

DR. ISAACSON: Thank you.

We'll call on Ms. -- oh, you're speaking for Dr. Elliott as well? Okay, so please continue.

DR. CAROME: Thank you. I'm speaking on behalf of Dr. Daniel Elliott. I will note, for transparency, that he was a co-petitioner on our 2011 petition, the Citizen petition to the FDA.

"I'm Dr. Daniel Elliott, Professor of Urology, Section of Pelvic and Reconstructive Surgery, and a urologic pelvic reconstructive surgeon specializing in, and specifically credentialed in female pelvic and reconstructive surgery at the Mayo Clinic in Rochester, Minnesota. I have no commercial or industry involvement.

"Personally, I have refused to use any transvaginal mesh kits for pelvic organ prolapse because the medical literature failed to demonstrate any consistent and significant advantage over traditional safer and cheaper POP repairs. However, daily, I am in direct contact with referral patients who have been previously treated with pelvic meshes. As a result of treating literally hundreds of patients with mesh complications, I am fully aware these complications, their management and their potentially life-long ramifications including, but not limited to, irreparable pelvic pain, vaginal scarring, and permanent dyspareunia.

"As a result of my own personal surgical experience at Mayo and patient consultation and surgery, and following a careful review of the available literature, and because of my attendance at national and international surgical meetings and taking into account the outstanding waste of medical insurance and Medicare dollars to repair the complications resulting from mesh use, I think the data clearly shows that the use of non-

absorbable mesh for transvaginal POP repair should, at a minimum, be banned until further data is derived from multiple, independent, non-industry supported research groups that prove a clear benefit without unwarranted risk. Thank you."

(Applause.)

DR. ISAACSON: Thank you.

Ms. Kathy Histand.

MS. HISTAND: Good morning, and thank you for hearing my story. It's unlike -- thank you for hearing my story. It's pretty much unlike what you've heard formerly. My name is Kathy Histand from Pennsylvania, and I've been compensated for my trip down here only, the roundtrip.

I'm 78 years old and have given birth to eight children between the years of 1962 and 1982. My last child was born at my age of 42. My pregnancies were all normal and without any complications. I have been healthy and active all my life and very well able to carry on a lifestyle of hard work more than the average woman of today. I went through the normal menopause stage at the age of 52.

Approximately 5 years ago at the age of 74, I began to notice a protrusion coming from my vagina which I hadn't felt previously. After 2 years, I decided it was not getting better in spite of doing various Kegel and other abdominal exercises, which I had learned about through my Internet search. Therefore, I saw a local gynecologist who suggested it would be best to have a hysterectomy. I wasn't interested in such an extreme surgery at that point in time, so I continued on with the aforementioned exercises in addition to yoga classes at the suggestion of the doctor at my second visit with him. I continued to live with this discomfort. More than 2 years later I was still suffering from this pelvic organ prolapse, the term which I later learned. My symptoms continued, a feeling of heaviness while in a standing position; urinary leakage during coughing and sneezing and other things; difficulty

with cleanliness and discomfort during sexual relations.

I finally learned of another doctor, a urogynecologist, Dr. Murphy, who I visited in the fall of 2017. With pictures and diagrams, he explained to my husband and I what procedures he considered necessary to correct or alleviate this continual problem of the uterine prolapse: drop bladder, rectum, and uterus which, in layman's terms, is what I had. He very carefully and concisely explained how he would use a mesh to support my bladder. At that time he suggested that it would be best to do another repair at the same time by using a bladder sling designed to treat stress incontinence during coughing and sneezing. In other words, in this consultation, he suggested that the best procedure would be to have a uterine lift and a bladder sling.

Hearing the word mesh conjured up concerns which my husband and I had regarding ads on TV suggesting recalls and warnings about the dangers of transvaginal mesh. But this doctor clearly and calmly set us at ease by explaining how the TV communications had been misconstrued as a recall. He also explained the risks of mesh possibly eroding through the vagina. He followed by telling us the percentages of risks involved, which are low, and that the complication of risks are far outweighed by the potential benefits of the mesh, such as a more durable and in some cases, a less invasive repair. It would allow me to preserve my uterus and to not need general anesthesia. He gave us paperwork on safety communications which the FDA recommends, also with a list of questions and answers. It was easy for us to understand.

With this consultation, my husband and I both felt relief in knowing there was help for my problem and I was willing to finally have the surgical repair on November 30th, 2017. After an uneventful hospital stay overnight, I was discharged the following day. The doctor's advice at that time was to refrain from stooping, not to lift more than eight pounds for the first 6 weeks and for this, I was careful as possible, although there were times that

I'd forget as I was feeling very well. At my next appointment 6 weeks later, he was pleased with my healing progress and he had upgraded my lifting limits to 30 pounds for the next 6 to 12 weeks after surgery. Having the lifestyle that I do, I nevertheless found myself lifting more than that sometimes and going about as I had been previous to surgery. By that time and until now, I have had no ill effects from the surgery. I no longer have urinary leakage, no heaviness while standing and I'm able to have normal sexual relations --

(Microphone turned off.)

DR. ISAACSON: And the time is up, so they turned off the microphone. That's okay. Thank you very much, I appreciate it.

(Applause.)

DR. ISAACSON: So thank you, Ms. Histand.

So the Panel now has an opportunity to ask questions of these Open Public Hearing speakers. Does the Panel have any questions? And please address -- Panel, any questions at all?

(No response.)

DR. ISAACSON: If not, we'll move on to the next set of speakers. Thank you. So we'd like to call, next, Ms. Jodie Callahan.

MS. CALLAHAN: Okay. Good morning, my name is Jodie Callahan. I am one of over a hundred thousand women who have been severely and permanently harmed by the devastating complications from anterior transvaginal mesh. My story echoes that of many other women with complications such as this. I'm here as a mother who has had four boys, a wife, a daughter, a friend, and human being. I am an occupational therapist and have been for over 25 years. Over the last 9 years I have done my fair share of research on this topic, but I'm really here to discuss it today from the patient perspective. I'm sure by looking at me you would not realize that I have endured 9 long years of dealing with

extreme pain and life-altering complications that this device has had on my health and my life, but it has. I had my mesh implanted in April of 2010 at the age of 45 for POP and SUI, which I didn't really have an SUI, but the doctor convinced me that I needed to have that as well. The anterior vaginal mesh eroded at 6 weeks, it was causing severe pain, reoccurring UTIs, vaginal infections, chronic constipation, inflammation, bloating, I had difficulty urinating and painful sexual intercourse with my husband. It also started to cause some autoimmune issues that I didn't have prior to the surgery.

These symptoms are consistent with a lot of other things and a lot of other experiences that other mesh patients have had. This changed my life and caused me to limit a lot of activities with my family. I have to deal a lot of times with laying in bed with heating pads and trying to find pain relief wherever I could. I went to nine different specialists, all trying to find someone to help me deal with this. Most doctors were ill-informed of how to help with those issues and left me feeling hopeless, depressed, and anxious as well as isolated.

On February 12th of 2012, a revision surgery was performed by a board certified urogyn to extract eroding mesh near my cervix. My symptoms continued and even exacerbated after the revision. My decreased energy and unbearable pain was too much to endure. So I spoke to the revision surgeon about an explant. His recommendation was to just sew up my vagina because my organs would be falling out. It was pretty much devastating words. Many degrading words have been heard by a lot of women and a lot of mesh patients with this. The medical community has no answers to give.

In November of 2013 an extensive surgery was performed by Dr. Raz for a full removal at UCLA. During the procedure, I experienced life-threatening complications due to the extensive lengths to extract the mesh. The doctor reported that the mesh had eroded to my bladder, attached to my bowels, my nerves and my muscles, as well as stress urinary

incontinence sling had twisted my urethra, so voiding was almost nearly impossible at times. They also extracted a large gelatinous cyst that was removed from my cervix and was engulfed and intertwined with the mesh.

As of January of this year, 21st, I recently went to my primary doctor for a physical. During the female exam, she visibly noticed and palpated more mesh inside my vagina. After almost 5 years the insidious mesh had resurfaced. I have to endure another procedure. My fortitude will again be tested as I will have to mentally, physically and emotionally prepare for a painful surgery and extensive rehab, hopefully without any life-altering impairment and eradication of the mesh. I'm scared, frustrated, and devastated that I will have to do this again.

I strongly believe putting in permanent devices made out of polypropylene, a synthetic plastic material that is toxic and is an estrogen disrupter, causes systemic inflammatory responses, its sharp edges placed in a highly sensitive, highly enervated area with vital organs in an active woman, or even one that's inactive, causes grave physical functional impairments. This is reckless, destructive and shortsighted as to the catastrophic impact this has. An unsuccessful transvaginal mesh procedure not only affects a woman's body, but her essence of being a woman. It impacts the entire woman as a whole. The pain is beyond excruciating. The shame and humiliation to discuss the topic is embarrassing and because it impacts the very intimate part of a woman, she deals with it in isolation. It destroys a woman from the inside out, with lasting effects of depression and anxiety as well as complex PTSD response.

So women sometimes get to the point that the pain is so unbearable that some of them have felt that the last resort is suicide. I do believe the use of toxic synthetic mesh causes nerve and muscle injury and organ damage as well as autoimmune response. Mesh implants must stop, period. It has no place in the human body, its complications far

outweigh the risks when it fails. Even if it fails at 10 or 20 years afterwards, it is not worth someone's life.

In closing, I'd like to thank you all, and I appreciate your time and attention to this matter and I truly hope the FDA is serious about addressing the research, development, training as well as adequate oversight for future medical devices. It is imperative that the medical community have specific guidance for supporting women both physically and emotionally with complications now and in the future.

Thank you.

DR. ISAACSON: Thank you, Ms. Callahan.

(Applause.)

DR. ISAACSON: Ms. Madris Tomes. Tomess?

MS. TOMES: My name is Madris Tomes, and I'm going to share a little about me so that you understand why I'm here today. I have created a company called Device Events but essentially, it's all FDA data that I'm going to be presenting today. It comes from the MAUDE adverse event reporting system. I'm also involved with the MDEpiNet public-private partnership, but that's unpaid.

I wanted to do a quick slide for you to show you, overall, how many mesh adverse events there are. When I worked at the FDA I was supposed to be replacing the MAUDE system. That was replaced internally, but not externally for the public, so they're still using a system that can only show about 500 reports at a time. Within a few seconds I was able to pull up 139,000 adverse event reports for mesh and there were over 1,000 patient deaths . When I then narrowed in because I realized today that we're not covering all types of mesh, there were 64,000 injury reports and 393 deaths.

If you want to look at the bottom, you can see the search details that I used, so I made sure that these cover stress urinary incontinence or hernia.

Of those reports, I wanted to point out that the majority of the reports are from the manufacturers, 66,000, and user facility reports are typically hospitals or ambulatory surgery centers.

Typically, reports to the FDA, only 17% of them are from physicians and that's globally across all devices. With this type of mesh, that number increased to 26%. There are over 17,000 physician reports about this device. I'm not sure how many of you are physicians, but most physicians don't have a lot of time to do adverse event reporting and they're not mandated to do so. So when I see this number of adverse events, I have to think that the issues are fairly serious. There were only 18, not 18%, 18 reports total from the medical device company sales representatives.

Another thing that I want to point out about the MAUDE data, there are a lot of things that aren't public, publicly available, but that data is available internally to the FDA. One of the things that I can view, as just a person on the street -- and consequently, I do not have mesh, just so you know, I'm a data advocate. The most commonly coded device problem was that there was no known device problem. But because I searched the narrative of the reports rather than just looking for the device problems, there you can see material erosion shows up 1,236 times. When I do a search on erosion, it returned 17,000 reports. So that shows that the coding is not correctly done. I didn't want to pick on any one company, but I sort of had to for a moment, but I'm showing a good and a bad example of coding.

So an example of a coded report is this first one. You can see that it lists the problem as material erosion. The second one does not list material erosion and it did not get coded at all, but you can see that erosion is listed in the narrative.

So since 2008, mesh manufacturers have been submitting adverse events to the FDA in a different format other than medical device reports, the typical MDR. For every 100

reports, MDRs that come in, the OIG estimates that 66 reports additionally are submitted by summary report and are not publicly available to view.

An example of a mesh summary report that reveals the number of summarized events, you can see up on the screen, this one report lists 1,175 events; it would count as one MDR.

I also wanted to point out that the FDA redacts many of those reports. If you're familiar with the Freedom of Information Act, there are two codes that are typically used. B-6 is for protected health information, so hospital names, doctors' names, patients' names are redacted, which makes perfect sense. But B-4 indicates that the -- it's being redacted as a trade secret. And so many times the injury and the detail in the narrative is redacted as before. Sometimes you don't see anything at all.

DR. ISAACSON: Sorry, we have to stick to the 5 minutes because we're running short of time, but I appreciate your presentation.

And we will call up next Dr. Diana Zuckerman.

(Applause.)

DR. ZUCKERMAN: Thank you very much. I'm Dr. Diana Zuckerman. I'm president of the National Center for Health Research. The center does not accept funding from companies that make medical products, so I have no conflicts of interest that way, but I will mention, personally, my father worked for Johnson & Johnson most of his career and I inherited stock from him. However, I will not be saying anything nice about Johnson & Johnson mesh, I promise.

The National Center for Health Research conducts research and scrutinizes research and we focus primarily on the safety and effectiveness of medical products of all types. I'm going to start out by, oh, just saying that my training is in epidemiology and public health and I was trained as a researcher and conducted research at Yale and Harvard before

coming to Washington. Next slide, please, or do I do it myself? There we go. There we are.

All right, I'm sorry this isn't larger, but this is just a simplified version of a chart from the Cochrane Review which was done in 2016, these are specifically comparing anterior prolapse repair, mesh versus native tissue. If you look at it you can see that, somewhat similar to the FDA review -- and I should say this is specifically focused only on randomized clinical trials. It does show more failures with mesh compared to native tissue initially, but more problems later on. And these were fairly short-term studies, so this -- they could only review the studies that had already been conducted.

So the big question is how relevant are these studies, the FDA studies of the review as well as these Cochrane studies? How relevant are they to the new PMAs? And that's the big issue here. We know that mesh has changed over time, the results and the outcomes can change as a result, and that's exactly why these premarket studies are so important and that's what I really want to emphasize today, that when FDA is looking at these PMA studies, these studies have to be done really well because postmarket studies aren't going to really provide the information we need because these meshes change over time.

I don't usually like to use the term nightmare when I'm talking to a professional group, but I don't think you could describe the problems that some of these women have been having in any other term. These are really terrible outcomes for some women. And the only thing we don't know is how many women, but we have heard some very important statistics from the MAUDE database, looking at it more carefully, as Madris Tomes has, how there could be well over 60,000 adverse event reports already and as we all know, it's voluntary and so that really can be the tip of the iceberg.

So, really, the only uncertainty is how often it happens and how many years it takes. I mentioned on this nightmare scenario 5 to 10 surgeries, but you've heard today already that it can be many, many more than 10. And that's the reason -- and you've also heard

that sometimes these symptoms appear after 5 years, so these 1-year studies are just inadequate and even a 3-year study isn't adequate. We need a longer-term study to really know what's going on.

Okay, so what kind of research is needed? We also think that we should be looking at whether there could be autoimmune issues where women who already have autoimmune diseases or a family history might be more susceptible. We don't know, we don't have research like that. We need long-term research at least 3 to 5 years, but really longer. And we also need subgroup analyses looking at women of different ages, BMI, race, and many other variables that could potentially affect outcome.

And then just to say that registries are not the answer for the simple reason that the registries for mesh as well as many other device registries, really focus on reoperations and what you've heard today is that there are many, many complications that are not related only to reoperations and if you only count reoperations, you don't get that subjective data that is so important in terms of how women's lives have been totally changed and, in some cases, ruined as a result.

The other big problem with registries is that they almost always focus on one particular medical specialty. You don't get the data from other doctors that may be seeing these patients. Thanks.

DR. ISAACSON: Thank you very much, Dr. Zuckerman.

(Applause.)

DR. ISAACSON: Dr. Thomas Gilbert.

DR. GILBERT: In terms of disclosure, my name is Thomas Gilbert. I'm the chief science officer for ACell. ACell is a medical device company principally in the wound care and general surgery space. We had just been entering the market at the time of the 522 order, have engaged in the 522 registry, but recently exited the market. So the decisions of

this Panel will impact our decisions about how to proceed moving forward in this market. And I've got slides. I'm sorry, I had submitted slides on Friday, but I'll speak to the points if they're not available.

So we've heard a lot about the polypropylene meshes which are, perhaps, the most prevalent products in this space. However, there are other technologies that are being currently used that are among the products that are currently still available, including dermis and other biologically derived materials. It's important to recognize that the risks associated with these different types of materials are different and so not to have a one-size-fits-all approach to the studies or the risk factors that are being evaluated. So in the slides, what I describe are really four categories of materials that are based upon the processing, the origin of the material, and the longevity of -- and the longevity in the body.

And so the polypropylene meshes are a synthetic material that's a durable, permanent material. There's another class of synthetic absorbable materials that is really not a part of the discussion here, at least for the products available today. There are durable biologically derived grafts, principally dermis and fascia lata today, and then there's a separate class of biologically derived resorbable grafts that include products like Urinary Bladder Matrix which ACell commercializes in other spaces.

There's animal data for the resorbable biologically derived grafts in primate models that show that the -- and particularly in direct comparison to the polypropylene mesh, that the effects on the vaginal tissue, which is so critical to our discussions today, are very different. There is not the pro-inflammatory environment that you see with the synthetic mesh. The thickness of the vaginal wall is retained. There's much less cell apoptosis. Furthermore, in transvaginal pelvic organ prolapse repair models in primates, the resorbable grafts, even though they're completely resorbed over a period of just a few months, are providing the body the opportunity to deposit mechanically robust tissue that

is able to provide durable repairs in the long term.

So I'm not here to advocate for, you know, anything. You know, we're in the Class III world and that's something that we recognize. However, as was pointed out earlier, each product has to stand on its own merits and it's a risk-benefit profile, and I think, unfortunately, we are now in a period where products that are very different from the permanent synthetic mesh are being viewed in the same way as those materials. And so I just suggest and hope that this Panel will recommend that, you know, a one-size-fits-all approach is not the best path forward in terms of innovation and providing options for surgeons and for patients in the future.

So thank you.

(Applause.)

DR. ISAACSON: Thank you very much.

Ms. Sherrie Palm. Sherrie Palm.

MS. PALM: Thank you. I'm Sherrie Palm, the founder of the Association for Pelvic Organ Prolapse Support, and I have no conflicts of interest to disclose, and neither does APOPS.

I would like to share with the Committee that I am an 11 years past successful transvaginal mesh surgery. I had grade three cysto-rectoenterocele, mesh was used for both the bladder and the rectum repairs. I've had no complications.

Pelvic organ prolapse is not an American women's health issue. It is a global women's health pandemic. Since 2010 APOPS has been networking with women, healthcare, academics, research, industry, and policymakers trying to increase awareness of and address issues related to pelvic organ prolapse and over the time that we have been around, we have captured connections in 177 countries. So we truly are a global voice for women with POP. That includes women with both mesh success and mesh complications.

The women we serve are mid-teens to end of life and they're navigating every diverse POP issue that exists and that includes the mesh versus native tissue debate. APOPS has a considerable following in both the UK and Australia in zones that are very volatile right now, and obviously, mesh comes up regularly in our space.

I submitted documents to the Committee, but I also wanted to be here today to be the voice for the voiceless, those women that have had success with mesh and then move on with their lives. The majority of women in our space who've had mesh are happy with their procedures and rather than engage in the hostile energy that is very, very common in mesh-bashing forums because, obviously, they have complications, they have a right to be upset. And also with the media, there is very little attention paid to the success side of this equation.

Everyone attending this meeting is aware that POP has pandemic-like prevalence of between 40 and 50%. The stigma of pelvic organ prolapse symptoms continues to shroud POP in silence despite nearly 4,000 years on medical record. I implore the Committee to analyze the mesh controversy through a progressive lens. Millions of women experience POP, millions will need surgery in coming years and I assure that behind our curtain, women are becoming very empowered and quite vocal. They deserve treatment options.

Please consider the ramifications of POP awareness going mainstream as a result of media exposure clarifying POP problems, symptoms, and quality of life impact on programs such as 20/20. What's going to happen then? Consider the ramifications to healthcare, the insurance industry, policy, and women's wellness protocol that will arise if 30% of the millions of women having surgery need repeat procedures because mesh is no longer an option. And consider the ramifications of women needing repeat surgery but who choose to forego it because they don't want to replicate the discomfort, expense, and downtime of prior failed procedures. And note I said procedures, plural, not single. We hear about that

a lot in our space.

With the evolution of healthcare typically follows a long and winding road and it's often under construction. Unfortunately, in medicine, we don't know what we don't know. And the nature of healthcare, as in any other system, is to evolve step by step. It is imperative, throughout this process, that the patient voice continues to be enabled and respected to effectively and efficiently identify issues that must be addressed and that includes voices on both sides of the mesh debate.

As I mentioned at the FDA meeting in 2011, my heart goes out to women that have complications, they suffer horribly, they truly do. We have, as I mentioned, women in our space who have had complications and we do the best we can to guide them and that's why we don't allow mesh bashing in our space, but we do try and nurture them because they need support as well. And ruining beneficial procedures, however, from POP treatment options that benefit the majority of women is not the answer. We must not let overseas energy influence due process stateside. The health status of millions of women hangs in the balance of decisions made by this Committee. I implore the Committee to consider the voices of the silent majority and to recognize that as a country we have and should continue to move forward addressing issues, leading the global charge to evolve best practices. There's no doubt, the next significant evolution of women's health screening, treatment and wellness directives looms large.

In APOPS's opinion, and in my humble opinion, transvaginal mesh, including for cystocele repair, should continue to be an option on the table. And I just want to give a quick nod to the fact that it's imperative that subspecialists only are doing these procedures and patient screening is critical.

Thank you.

(Applause.)

DR. ISAACSON: Thank you very much, Ms. Palm.

And our last speaker for this session is Ms. Cindy Pearson.

MS. PEARSON: Thanks. I'm Cindy Pearson. I'm the executive director of the National Women's Health Network. We bring the voices of women consumers to tables where regulatory and policy decisions are made. By choice, we don't accept any funding from medical device, pharmaceutical, insurance companies or others with a direct financial interest in healthcare.

In 2011, like some but not all patient and consumer organizations that the FDA heard from, we called for the recall of vaginal mesh products until their safety could be established. Your predecessors on this Committee disagreed, although you did -- your earlier version of your Committee recommended more stringent regulatory oversight of vaginal mesh products. The FDA agreed and what seems to consumers a long process, finally classified vaginal mesh products as -- in the PMA category.

But in the meantime, postmarket surveillance studies had started and the FDA gave permission to the companies who have now submitted those PMA studies to use postmarket surveillance studies as PMA studies. Now, that might seem fair to the companies who were told they could do that, which is apparently what the FDA told us this morning, but as the FDA speaker said this morning, it's a novel approach. We think it's the wrong approach and while it may be fair to companies who make business decisions on the assurance that a postmarket surveillance study could be used in lieu of a PMA study, it's not fair to women. PMA studies for products that are used chronically, particularly in people who do not have a life-threatening condition, are typically randomized, large, long-term, have blinded assessment and very scrupulous follow-up to ensure a low lost-to-follow-up rate. Postmarket surveillance studies don't meet those standards in general nor do they in this case.

Boston Scientific has presented their version of their 12-month results from their postmarket surveillance study in the background materials, which have been publicly available since Friday, so we've had a chance to look at those.

You know, when the FDA reclassified vaginal mesh devices as PMA devices we thought well, at least it's a step in the right direction. At least we'll get more information than we've ever had before, clinical information. The decision, the so-called novel decision to accept postmarket surveillance studies as PMA studies, made us feel doubtful that women would get the information they deserve and then when we found in the background materials for this meeting on Friday morning, that the questions to the Committee are not about those data, but about how stringently should the FDA look at those data, it was very disheartening.

It appears to those of us who are sort of seasoned activists and attend a lot of FDA meetings on a lot of topics, that the FDA may be trying to sort of back away from the already lesser requirements that they negotiated with sponsors in the time in between 2011 and 2016.

So we know that they are asking you to answer eight questions and a well-managed committee won't deviate from the questions that the FDA asks and the Chair's nodding at me, yeah, that's the way it's going to go this afternoon. You all will discuss and respond to those eight questions. Three of them are yes/no, where the answer really has to be yes, an emphatic yes. That yes, those data are required. Yes, women need those data. One, for example, is on whether patient-reported data, which is being called subjective data, needs to be included. Absolutely. Women won't get the information they need unless you emphatically say yes to all the yes/no questions.

But five of the eight questions are what, how, maybe. You know, do the best you can to tell the FDA that these studies need to be analyzed in a way that's as close as

possible to PMA standards, even if that would lead to a failed PMA application. I know you've heard from patients for whom products have worked. That's a real experience, it's valid. However, this is the FDA is engaged in the PMA moment and they need to hear from you that PMA standards are what women deserve.

Thank you.

(Applause.)

DR. ISAACSON: Thank you, Ms. Pearson.

So the Panel now has the opportunity to ask questions to any of these six Open Public Hearing speakers. Again, I'll remind you to address the speaker by name so they can come up to the platform.

(No response.)

DR. ISAACSON: So we have no questions, and so what we have now we are scheduled for a break at 10:00 and to come back at 10:15. We're a little bit past that at 10:25 now, so how about a 6-minute break. Everybody rush to the restrooms in 6 minutes, and we'll start the FDA presentation promptly at 10:30.

(Off the record at 10:25 a.m.)

(On the record at 10:31 a.m.)

DR. ISAACSON: Everyone, if you would take your seat. And we'd like to call this meeting back to order. So, again, thank you. I'm sorry for such a short break and just -- we just have a tremendous agenda and we'd like to get it all presented, and a lot of speakers. So the FDA will now give their presentation. I'd like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The FDA will have 60 minutes to present and would you please begin your presentation? Thank you.

DR. COLDEN: Good morning. Welcome back. I'm Kelly Colden, an OB/GYN generalist in the Office of Device Evaluation at FDA. First, before we get started with the FDA presentation, I would like to thank the speakers in the audience who have shared their personal experiences through their testimony. Your stories are an important component of our discussion for today's Panel meeting.

We will continue the meeting with the FDA presentation which will be divided into three raw discussion topics. Each discussion will be presented by an OB/GYN medical officer on the team. I will be providing the background. My presentation will be followed by a discussion on the medical device reports and published literature. In closing, we will focus on the benefit-risk assessment.

In my discussion of the background, I will focus on the clinical overview, device description, and regulatory history.

First, to start with a very general overview of the condition. Pelvic organ prolapse occurs when the tissue and muscles of the pelvic floor no longer support the pelvic organs, resulting in prolapse of the pelvic organs from their normal position. Depending on where weakness occurs, prolapse can occur in one or more compartments of the vagina. In this Panel meeting, we will focus on transvaginal surgical repair of anterior vaginal wall prolapse. This type of repair is used to treat cystocele or prolapse of the bladder, as depicted on the slide, and may also include an apical prolapse repair.

The Pelvic Organ Prolapse Quantification System is an objective tool utilized for describing and staging pelvic organ prolapse. It describes and measures specific points on the vaginal surface in relation to the hymen. The degree of prolapse is described in stages from 0 to IV, with higher numbers indicating more severe prolapse.

On physical exam, some degree of prolapse is present in 41 to 50% of women; however, only around 3% of women report symptoms. Although women of all ages are

affected, advancing age is a risk factor with a peak in prevalence of 5% between 60 to 69 years of age. Other risk factors include previous vaginal delivery, obesity, race, and ethnicity, with white and Hispanic women being more affected. Previous hysterectomy or prolapse surgery are additional risk factors. I'll move on to briefly discuss symptoms and treatment.

Most prolapse is asymptomatic. Symptoms, when present, can vary and include sensation of bulge, pain, urinary symptoms, or sexual dysfunction. Treatment is indicated for women with symptoms and depends on type and severity of symptoms, compartment affected as well as the stage of prolapse. Age is also a factor to consider when discussing treatment options.

Conservative management may be a treatment option. For instance, pelvic floor muscle training may improve symptoms. Vaginal pessaries can be an effective nonsurgical treatment for women with prolapse. Surgical options include transvaginal and abdominal approaches. Transvaginal repair of pelvic organ prolapse can be augmented with mesh or may be performed with tissue plication and suture only, otherwise known as native tissue repair. For this presentation, we will be doing an in-depth assessment on transvaginal repair for pelvic organ prolapse using mesh augmentation.

Surgical mesh for pelvic organ prolapse repair is intended to provide mechanical support and surgical repairs. It consists of a thin sheet or netted material and is available in either a non-configured form, which often comes in a variety of sizes to be trimmed and sutured by the surgeon to meet an individual patient's needs or a pre-configured form to match the specific anatomic defect.

Surgical mesh is divided into four general categories: non-absorbable synthetic mesh, absorbable synthetic mesh, biologic, or composite, which is a combination of the three. Non-absorbable synthetic mesh are described by type and classified by weave and

density. Recently and currently marketed mesh for anterior repair are considered lightweight or ultra-lightweight. Surgical mesh from biologic materials differ in their source species, tissue source, and whether or not chemical cross-linking is used in the processing of material.

The currently marketed synthetic surgical mesh products for anterior repair of pelvic organ prolapse are Boston Scientific Uphold LITE and Coloplast Restorelle DirectFix Anterior. Both are made of Type I polypropylene. Boston Scientific Xenform is a non-cross-linked mesh from fetal bovine material.

For perspective, I will provide a brief summary of the regulatory history of surgical mesh.

Surgical mesh was placed into Class II or a low-to-moderate risk classification in 1988. Since the 1950s, surgical mesh has been used to repair abdominal hernias. Beginning in the 1970s, gynecologists began using surgical mesh indicated for hernia repair for abdominal repair of pelvic organ prolapse, and in the 1990s began using that mesh transvaginally. Over time, manufacturers responded to this clinical practice by developing mesh products specifically designed for pelvic organ prolapse repair.

In 1996 the Surgical Fabrics device, or the ProteGen Sling manufactured by Boston Scientific Corporation, became the first surgical mesh cleared through the 510(k) pathway for vaginal pelvic organ prolapse repair. In 2002 the first pre-configured surgical mesh product for pelvic organ prolapse repair was cleared. Surgical mesh products then evolved into kits that included tools to aid in the delivery or insertion of the mesh. The first kits for pelvic organ prolapse, both manufactured by American Medical Systems, were cleared in 2008 -- 2004, excuse me. I'll move on to briefly discuss specific FDA regulatory actions.

Between 2005 and 2007, FDA received more than 1,000 medical device reports for surgical mesh. Based on these medical device reports, published literature, and concerns

from the public and clinical community, FDA issued a public health notification in October of 2008.

Based on an analysis of medical device reports received between 2008 and 2010, with slightly more than half associated with pelvic organ prolapse repairs, FDA issued a safety communication on July 13th, 2011. At the same time, FDA issued a white paper to advise the public and medical community of complications related to vaginal pelvic organ prolapse repair with mesh.

In September of 2011, FDA convened the Obstetrics and Gynecology Devices Panel to discuss the safety and effectiveness of surgical mesh to treat pelvic organ prolapse and stress urinary incontinence.

The Panel consensus was that the safety of surgical mesh for transvaginal pelvic organ prolapse repair had not been well established and, depending on the repair compartment, may not be more effective than native tissue repair. The recommendation from the Panel was that devices be reclassified to a higher risk category, from Class II to Class III, as the risk-benefit profile was not well established. Reclassification of these devices would change the regulatory paradigm for this device type, which would now include new data requirements to support safety and effectiveness. The Panel also recommended that FDA issue postmarket study orders to conduct safety and -- to collect safety and effectiveness information for these devices.

Following the Panel meeting, in January 2012, FDA ordered manufacturers of urogynecologic surgical mesh devices to conduct postmarket surveillance studies, or 522 studies, to address specific safety and effectiveness concerns related to surgical mesh for transvaginal repair of pelvic organ prolapse. FDA informed manufacturers that 522 studies could be designed to support future PMA applications if devices were reclassified.

Most manufacturers elected to stop marketing surgical mesh for transvaginal repair

of pelvic organ prolapse after receiving their 522 orders. Currently, there are four ongoing 522 studies for five surgical mesh devices placed transvaginally to treat pelvic organ prolapse.

For the 522 studies, FDA requested that manufacturers conduct either randomized controlled studies or parallel cohort studies comparing the subject device to native tissue repair. The requested effectiveness endpoints included an assessment of the anatomic success, subjective success, and retreatment for prolapse. Safety endpoints included all device- and procedure-related adverse events as well as the rate of individual adverse events of interest. Data collection in the 522 studies is occurring every 6 months out to 24 months and then again at 36 months. FDA will use the results of the 522 studies in addition to other information to evaluate the safety and effectiveness of individual surgical mesh devices placed in the anterior vaginal compartment to treat pelvic organ prolapse and determine if the benefit-risk profile of each device supports continued marketing.

In April of 2014, FDA proposed reclassifying surgical mesh for pelvic organ prolapse repairs from Class II to Class III and proposed requiring the filing of a premarket approval application. In January of 2016, the final orders were issued.

As a consequence of reclassification, manufacturers were required to file premarket approval applications by July 5th, 2018, to allow continued marketing of devices. To reiterate what was discussed during the introduction this morning, premarket approval is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. It is the most stringent type of marketing application required by FDA. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use.

In addition to regulatory actions taken here in the United States, Canada, Australia,

the United Kingdom, Ireland, and Scotland have also taken action. Some actions, such as removal of devices from the market by the Australian Therapeutic Goods Administration, were based on published literature. Other actions, such as the pause on the use of transvaginally placed mesh for pelvic organ prolapse and stress urinary incontinence, taken in the UK and Ireland, were based on concerns raised by advocacy groups and not on new scientific or clinical evidence.

Following FDA regulatory actions, many professional societies released position statements or guidance documents for providers who treat women diagnosed with pelvic organ prolapse.

After release of the FDA safety communication and white paper, the American Urogynecologic Society, or AUGS, the largest professional society representing female medicine and reconstructive surgery specialists, issued a guideline document in 2012. This guideline document was issued to provide recommendations for privileging and credentialing of physicians planning to implement or continue using transvaginally placed mesh for pelvic organ prolapse in the clinical practice setting. In our discussion of the published literature and in our benefit-risk discussion, we will touch on the topic of surgeon training. For the Panel, please note that we will request your feedback on this topic.

Following the guideline publication, AUGS published a position statement in March of 2013. This statement was published in response to restrictions on the use of transvaginal mesh for pelvic organ prolapse made by some healthcare systems or insurance companies. One key message is that there may be a population of women for whom transvaginal mesh for pelvic organ prolapse may be the most appropriate option.

In 2017 AUGS published a best practice statement to provide guidance for clinicians on the evaluation and counseling of women with pelvic organ prolapse.

Also, in 2017, the American College of Obstetricians and Gynecologists and AUGS

issued two joint publications. One key message in the committee opinion, published in April of 2017, is there is no role for intervention or removal of mesh in women who are asymptomatic. A practice bulletin titled "Pelvic Organ Prolapse," initially published in April of 2017, was updated in November of the same year to reflect a recent systematic review of evidence on the use of biologic and synthetic mesh for the repair of anterior pelvic organ prolapse.

In our next focused presentation, we will include a discussion on the published literature. This discussion on professional society positions concludes the background section of the FDA presentation. Later in the agenda, individual professional organizations will have the opportunity to speak.

I will now hand off to my colleague, Dr. Jacqueline Cunkelman. Thank you.

(Applause.)

DR. CUNKELMAN: Good morning, my name is Jacqueline Cunkelman, and I'm a medical officer OB/GYN in the Office of Device Evaluation. I'm going to give an overview of the clinical evidence. This includes medical device reports as well as the literature review conducted by FDA.

The FDA reviewed MDRs submitted for adverse events related to surgical mesh placed transvaginally in the anterior compartment to treat pelvic organ prolapse. The FDA requests the Panel's input on the types of adverse events that should be used to evaluate safety and how those adverse events should be assessed. The following MDR analysis is intended to provide real-world evidence to complement the FDA literature review.

Reports submitted from January 1st of 2008 through September 30th of 2018 were reviewed. This date range is consistent with the literature review and covers the full time period of FDA regulatory actions and communications related to urogynecologic mesh, which was a significant driver in the adverse event reports. We were looking at reports that

were specific to anterior and apical repairs. We found 11,274 reports. Of these, 10,391 were serious injuries, 806 were device malfunctions, and there were 77 reports of deaths.

Following FDA's regulatory actions in 2011 and 2012, 3,881 MDR reports were noted in 2013. This high may be in response to those actions while the drop in MDRs after 2013 may be the result of many manufacturers electing to stop marketing their devices upon issuance of the 522 orders. FDA also notes that the timing of an MDR report does not necessarily correspond with the timing of an adverse event.

This table depicts the top 10 patient problems for reports that included an identifiable patient problem. This list is not all inclusive and more than one patient problem code is often found in a single MDR. The most common patient problems reported in MDRs were consistent with those observed in the published literature. The differences are in terminology, and none of the top 10 MDR patient problems were missing in the literature. While FDA is unable to calculate rates from the MDRs due to a lack of a denominator, these data provide real-world evidence that adverse events associated with these devices are not rare.

Let's review Panel Question Number 3, which you will be asked to comment on later in this meeting. The following adverse events have been associated with mesh and/or native tissue repair and are being collected in the 522 studies:

- Pelvic pain
- Erosion and exposure
- Dyspareunia
- De novo voiding dysfunction
- Infection
- Vaginal shortening
- Atypical vaginal discharge

- Neuromuscular problems
- Vaginal scarring
- De novo vaginal bleeding
- Fistula formation

We're going to ask that the Committee discuss these adverse events and consider their importance, their potential to be debilitating, how they should be assessed, when they should be assessed, and key considerations related to the mesh material or other mesh characteristics. We also ask that the Panel comment on any important adverse events that may be missing from this list.

The limitations of this MDR analysis are that while MDR reports can be used to monitor device performance or alert FDA to potential safety signals, this is a passive surveillance system and it's prone to reporting that may be incomplete, inaccurate, unverified or biased. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with these devices.

So as I mentioned, in preparation for this Panel, the FDA conducted a systematic literature review to provide an overview of the published literature from 2008 through 2018. The current PMAs under review pertain to mesh or graft-augmented repair of the anterior or anterior/apical compartment. This literature review focused on anterior repair and/or apical repair.

And I will be going over the methods and limitations, the effectiveness data, safety data, and then we'll go on to discuss concomitant procedures, patient characteristics and surgeon characteristics.

So consistent with the MDR review, the search dates were January 1st of 2008 through November 1st of 2018. Our search terms were pelvic organ prolapse, surgical

mesh, transvaginal mesh, or vaginal mesh.

In order to be included in the literature review, the study had to be in English and had to be relevant to transvaginal mesh, any brand or type used for anterior and/or apical pelvic organ prolapse repair. Mesh repairs for posterior prolapse must include an anterior/apical component to be included.

We looked at clinical research studies with live human participants or meta-analyses of randomized controlled trials. These studies included had clinical outcome data, either safety and/or effectiveness, for at least 12 months of follow-up with a cohort of at least 25 patients. The cohort studies prospectively collected data relevant to at least one of the devices of interest we collected. We identified 1,339 results in PubMed, 1,267 of the papers were excluded, and we reviewed 73 papers for this literature review.

Some limitations include variability in the length of follow-up in the papers, as well as heterogeneity of study design and that includes inclusion and exclusion criteria, age of the patients, concomitant procedures, definitions of success, classifications of adverse events, and the devices evaluated, not all of which are currently available in the United States.

Looking at the literature review effectiveness data, I'm going to review the FDA position in Panel Question Number 1 for you to keep in mind as you're looking at this data.

In light of the increased risks compared to native tissue repair, to demonstrate reasonable assurance of effectiveness, the FDA believes that surgical mesh used in the anterior or anterior/apical vaginal compartments for transvaginal prolapse repair should be superior to native tissue repair. If the Panel agrees with this statement, we're interested in their input on what time point superiority should be demonstrated. And if they disagree, how should effectiveness of mesh compare to native tissue repair and at what time point should that effectiveness be assessed?

I'm also going to review Panel Question Number 2, which states that the FDA literature review identified that while objective outcomes generally favor mesh, subjective outcomes demonstrate similar effectiveness for mesh and for native tissue repair. The FDA believes that both objective and subjective outcomes should be used to assess the effectiveness of transvaginal anterior or anterior/apical prolapse repair compared to native tissue.

We'd like to know whether the Panel agrees that both objective and subjective outcomes should be used to assess effectiveness. And should improvement in both outcomes be required to consider a patient a success? Should the assessment of objective outcomes be completed by a blinded evaluator? FDA also believes that improvement or resolution of patient symptoms are an important component demonstrating effectiveness of treatment. And we'd like the Panel to address how symptoms should be measured.

- How should we assess whether the patient has a meaningful improvement? For example, what if a patient has symptoms but says she's not bothered by those symptoms?
- How is the patient's assessment of her symptoms affected by sexual activity or other patient factors? And
- When patients are not blinded to their treatment, how might that affect their assessment of their symptoms?

So we looked at multiple types of studies and we're going to review them in the order of meta-analyses, database studies, RCTs, prospective cohort studies, and some Markov analyses. And then we'll look at data on effectiveness by time points and material and then some brief conclusions.

So based on these meta-analyses, effectiveness outcomes of surgery for recurrent prolapse and objective cure were generally more favorable for surgical mesh patients

compared to native tissue repair patients. However, subjective outcomes such as satisfaction, quality of life variables and sexual function were generally similar between surgical mesh and native tissue repair. When mesh erosion or exposure was included in the reoperation outcome, along with pelvic organ prolapse recurrence, the native tissue repair group had more favorable outcomes in two meta-analyses, as patients are not at risk for mesh erosion or exposure after a native tissue repair procedure.

There were mixed effectiveness results reported by the database studies. Seven studies compared reoperation or reintervention rates for mesh versus native tissue repair. Of these, five reported more favorable results for the native tissue repair group, one reported more favorable results for the mesh group, and one reported similar rates between the groups. Overall, mesh patients tended to have higher risks of reoperation for pelvic organ prolapse or mesh complications than native tissue repair subjects. The rate of reoperation for pelvic organ prolapse mesh complications is consistent with about 5 to 6% between 1 and 5 years of follow-up with the exception of one study that reported a reoperation rate closer to 10%.

A study using the MarketScan data demonstrated a greater 5-year cumulative risk for mesh patients compared to native tissue repair for any repeat surgery. That's either POP or mesh complications, but similar risks for surgery for recurrent prolapse.

And then most of these studies focused on objective endpoints. There was a Swedish registry which reported results for the subjective outcomes of patient-reported cure, satisfaction, improvement, and feeling of protrusion. This study found more favorable subjective outcomes for the mesh group compared to the native tissue group.

There were 30 RCTs with variable lengths of follow-up. Regarding objective outcomes, all studies reported either statistically significant favorable results for the mesh group compared to the native tissue repair group, or no statistically significant differences

between the two groups. Regarding subjective outcomes, most studies reported no statistically significant difference between the groups. The largest RCT was the NIHR-funded PROSPECT trial, which was performed in the UK, and this study found no statistically significant differences in POP-Q stage or reoperation rates at 1 year for either synthetic or biologic mesh when compared to native tissue repair.

As noted previously, the literature review only included prospective cohort studies that were specific to one of the devices currently under PMA review or a previous iteration of that product. The FDA notes that the Boston Scientific Uphold and Uphold LITE are different products, with the Uphold having a higher mesh density than the Uphold LITE and the Uphold is no longer marketed in the United States.

For the Uphold and Uphold LITE products, there were four studies. These demonstrated an objective cure rate of 94 to 97%, a composite cure rate of 74 to 97%, reoperation rates ranging from 1 to 7%, and in the one study that compared the mesh product to native tissue repair, there was no difference. In the one study on Xenform, there was an improvement in objective and subjective outcomes at 12 months.

And then moving on to Restorelle, Restorelle is the broader Coloplast product line of urogynecologic surgical mesh. The DirectFix Anterior is the only Restorelle product that is currently marketed for transvaginal repair of anterior compartment prolapse. The remaining Restorelle products that are currently marketed are indicated for abdominal repair of prolapse; however, some Restorelle products were previously indicated for transvaginal repair. And of the two studies on Restorelle, there was an objective cure rate ranging from 92 to 95% with a reoperation rate of 8.5%.

Dieter performed a Markov analysis in 2015 using published studies and meta-analyses to compute theoretical probability of reoperation for recurrent apical prolapse. They tested four different analytical approaches and concluded that there is at least a 30%

likelihood that TVM repair would result in a greater likelihood of undergoing surgery for recurrent prolapse over 24 months with this likelihood increasing to 70% using the most robust analysis method. This conclusion is consistent with the other evidence reviewed.

The Cochrane Review meta-analysis by Maher in 2017 for anterior repair reported that there is a minimal advantage for biologic graft or for polypropylene mesh compared to native tissue repair based on outcomes of awareness of prolapse, repeat surgery for prolapse, or recurrent prolapse. However, the risk ratios compared to native tissue repair were more favorable for polypropylene and biologic graft, indicating that synthetic mesh may have better effectiveness. The authors reported that there was little data available for absorbable mesh.

No major differences were noted by time point for mesh versus native tissue repair in the time point analysis. Due to limited data with longer follow-up, conclusions are fairly limited past 3 years of follow-up. The database study with the longest follow-up, which presented 5-year results for apical repair patients in the Truven MarketScan and Medicare databases, reported no significant differences in reoperation for recurrent prolapse between mesh and native tissue repair at 5 years. The finding was confirmed by a different study also using the MarketScan data and this study reported that patients receiving anterior repair had a higher risk of reoperation due to mesh complications.

These data suggest that mesh outcomes are similar to those of native tissue repair out to 5 years regarding prolapse recurrence and reoperation, but mesh complications lead to additional reoperations for mesh patients. Reoperations appear to occur throughout at least 3 years of post-operation. The New York SPARCS dataset showed that the reintervention rate increased from 4% at 1 year to 6.3% at 3 years of follow-up, and Kaplan-Meier curves indicated that reintervention occurred throughout the 3-year period. Therefore, reinterventions were not limited to the first year following implantation.

FDA is again seeking the Panel's input on the appropriate time point at which effectiveness should be evaluated.

So, in conclusion, between 1 and 3 years of follow-up, mesh may have some advantage over native tissue repair for objective, but not necessarily subjective, outcomes.

Mesh outcomes are similar to native tissue repair over 5 years, but mesh complications may lead to higher rates of reoperation.

Looking at the safety, again, FDA requests the Panel's input on the types of adverse events that should be used to evaluate safety, how these adverse events should be assessed, and the duration of follow-up needed to adequately assess these outcomes.

I'm just going to review Panel Question Number 4 that you'll be asked to comment on later. To demonstrate reasonable assurance of safety, the FDA believes the adverse event profile for mesh placed in the anterior or anterior/apical vaginal compartment should be comparable to native tissue repair, or that any increase in risk should be offset by a corresponding improvement in effectiveness. The FDA also believes that all adverse events (not just those adjudicated as device- or procedure-related adverse events or serious adverse events) should be considered, along with their severity and seriousness, timing, resolution, and relatedness to the device and/or procedure used to evaluate the safety of mesh compared to native tissue repair.

We ask whether the Panel agrees with this question and what are the effectiveness scenarios where an increased safety risk may be acceptable? At what time point should comparable safety be demonstrated? And then any additional comments from the Panel on this endpoint.

So specifically we reviewed the literature for data on erosion and exposure, de novo SUI, de novo dyspareunia, other adverse events, and then we'll look at safety by time point and material and some brief conclusions.

As noted previously, events related to exposure and erosion continue at least through 3 years of follow-up, and the FDA literature review found the rates to be between 3 and 15%. Thus, this is not an uncommon adverse event.

Looking at the Cochrane Review for the anterior repair, there was an 11.3% rate of erosion and exposure with a higher rate of 18% for apical repairs. Many studies did not differentiate between persistent stress urinary incontinence and de novo stress urinary incontinence. The Cochrane Review meta-analysis by Maher for anterior vaginal repair reported that polypropylene mesh was not associated with a higher risk of de novo stress urinary incontinence than the native tissue repair. There was also no difference for biologic graft versus native tissue repair when comparing overall stress urinary incontinence, but not enough evidence to compare de novo stress incontinence. There was not enough evidence to compare absorbable mesh versus native tissue repair.

However, the Cochrane Review of mesh for all compartment repairs, anterior, apical and posterior, reported that there was a higher rate of stress urinary incontinence for mesh versus native tissue repair. Among the RCTs and database studies reviewed, there were mixed results for between-group differences in de novo stress urinary incontinence.

For the outcome of dyspareunia, the meta-analyses indicated that there were no significant between-group differences in dyspareunia and de novo dyspareunia. There was one RCT that reported a small but significant difference in dyspareunia at 1 year and that was 2.7% for the mesh patients versus none in the native tissue repair patients. Other papers were mixed with other not significant results or just outcome not being tested specifically.

We looked for data on other safety outcomes that have been reported in the MDR reports, including

- Vaginal discharge

- Scarring
- Neuromuscular problems
- De novo vaginal bleeding
- Vaginal shortening/restriction
- Fistula formation

And we found no consistent data in the literature reviewed and of note, the 522 studies are specifically gathering data on these outcomes.

The RCT results are presented by 1, 2, and 3 years of follow-up respectively, and at all three time points, most studies favored the native tissue repair arm with regards to safety outcomes. This conclusion is primarily driven by the mesh exposure and erosion rates for the mesh arm. However, statistically significantly higher rates of de novo dyspareunia and de novo stress incontinence were also observed in the mesh arm. Database studies had up to 5 years of follow-up with no obvious patterns emerging regarding the timing of adverse events.

So the evidence suggests that patients who receive synthetic polypropylene mesh are at a greater risk for mesh erosion than patients who receive biologic graft, partially absorbable mesh, or native tissue repair. Biologic graft seems to be associated with erosions at a rate that is similar to native tissue repair.

So, in conclusion, for safety endpoints, all time points favor the native tissue repair. Complications seem to continue beyond the first year of follow-up and through 5 years of follow-up. Mesh complications are more common for synthetic mesh than for biologic grafts, and the risks of using mesh in the anterior vaginal compartments are greater than native tissue repair, particularly with respect to reoperation for all indications.

I'll hand it off to my colleague, Angie Lee.

DR. LEE: Good morning, Panel. Thank you for your continued attention. Thank you,

audience members. We'll be discussing in this third and final portion of our FDA presentation, the clinical factors and the benefit-risk. My name is Angie Lee. I am a generalist OB/GYN and medical officer in the OB/GYN devices group.

So we'll begin by discussing related factors to the patient, the patient population and characteristics, moving on to surgeon characteristics and then finishing up with our benefit-risk assessment.

So let's start with the patient population discussion and as we do, Panel, we'd like for you to look at Question 5, which is the FDA literature review identified some procedures and surgical/medical history, which we are about to walk through, that may affect the safety or effectiveness outcomes of these repairs.

So Question a: Do you agree with these identified procedures and surgical/medical history?

b. Which additional procedures or surgical/medical history should we consider?

And c: How should FDA factor these in, in the evaluation of study results, thinking about trying to keep a balance between these characteristics, between the study arms, and assessing adverse events?

So we're going to take a moment to talk about concomitant procedures because, as we all know, the pelvic floor problem that's requiring that prolapse surgery often requires an additional procedure to fully address the issue and that additional surgery or a concomitant procedure may affect the safety and effectiveness outcomes. And to be frank, in the literature review, it's kind of challenging to distinguish which of the adverse events or outcomes are due to that primary repair and which of those adverse events are due to the concomitant procedure.

So there was no information available in the literature about how do surgeons use what's known about safety and effectiveness to decide which patient gets which surgery

and why. There were some brief mentions that certain women prefer a uterine-sparing procedure and so those women would obviously elect a hysterectomy. The two most common concomitant procedures are midurethral sling for stress urinary incontinence and hysterectomy.

So let's start with a brief discussion of the midurethral sling. So the purpose of this slide here is bulleted for you at the bottom, that concomitant sling at the time of pelvic organ prolapse surgery is fairly common.

So if you look at this first slide here, this slide, we have three studies that are represented. So the first two studies here, they looked at concomitant sling in those undergoing a mesh repair and found these percentages and then compared that to the percentage of women undergoing a native tissue repair and then that percentage that had a concomitant sling. So these two studies showed that the concomitant sling in a mesh prolapse repair is not uncommon.

The third study, the Anger study here, looked at all comers whether they were having a mesh prolapse repair or a non-mesh repair and found that 15%. And then when they broke it out to just looking at that subset that had a mesh repair, then that concomitant sling percentage was 48%. So, again, not uncommon.

So having established that a concomitant midurethral sling is performed not uncommonly, then what is that implication in terms of erosions and reoperations? So we looked at this Chughtai -- oh, sorry, wrong way. Okay, so -- oh, here. Okay, I'm going to the wrong way. Okay, here we go. Sorry. Okay, so we looked at this -- oh, my goodness, I'm pushing the wrong button, that's why. Okay. There was a dry run, yes. Okay.

(Laughter.)

DR. LEE: Okay, here's the right button. Okay, so in the Chughtai study there were two relationships that were looked at, the erosions and reoperations, and the comparison

was made with concomitant sling and then the percentage having erosions was slightly less when you looked at those that had the POP repair only and not the concomitant sling. Again, that same relationship was borne out with reoperations, that concomitant sling had a reoperation rate of 5.6% and slightly less when no sling was performed at the same time. Therefore, the conclusion is, at the bottom, that the high rates of mesh erosion and reoperation are seen with a concomitant sling.

So moving on to hysterectomy. The concomitant hysterectomy, the purpose of this slide again is bulleted for you at the bottom, that these surgeries are fairly common at the time of pelvic organ prolapse surgery. So these three studies represented, all had the same relationship. They compared the concomitant hysterectomy rate in those undergoing mesh and looked at the concomitant hysterectomy rate in those undergoing native tissue repair. And you can see here that they do occur not uncommonly and perhaps a little more commonly in those that are undergoing the native tissue repair.

So, again, having established that the concomitant hysterectomy is not uncommon, then what are those implications for mesh erosion and mesh exposure? So a Deng meta-analysis in 2016 showed that there were more mesh erosions at a rate of 1.46-fold. There were also more mesh exposures at a rate of 3.8-fold in the Farthmann publication. The terms erosion and exposure are the terms that are used by the author in their publication. The third study referenced here showed that there were no significant differences in 3-year reintervention rates.

So there's a variety of patient factors that we want to discuss because these characteristics can influence the safety and the effectiveness of these repairs, and so we're going to talk through some of these factors that have been identified by the FDA literature review.

So we'll start with the related Panel question, which is Question 6. In non-

randomized studies, selection bias can influence safety and effectiveness outcomes, and FDA believes that these factors can influence whether a patient is undergoing a mesh or a native tissue repair and that is the patient herself; her own medical/surgical history; the procedure, whether a concomitant procedure is necessary; the clinical site, is it a mesh-only site or a native tissue repair-only site? And then the surgeon, the surgeon's own experience with mesh or native tissue repair, and then also the surgeon's preference that's individualized for that particular patient. So please discuss these factors or any other factors that might bias the safety and effectiveness outcomes.

So our first characteristic is age and so on the right-hand side of this slide here of this balance, we see that the Deng meta-analysis reported that women that were younger than age 60 to 70 were slightly less likely to develop mesh erosions. On the opposite side, conversely, Farthmann's study found that younger age was actually a risk factor for mesh erosion -- sorry, for mesh exposure. And then weighing in the middle were these two studies where they did not find any significant differences when stratifying for age. Ultimately, our conclusion is that there is some mixed evidence, not strong evidence, that age can affect treatment outcomes.

The next characteristic is obesity. And so specific to mesh erosion and mesh exposure, there were no significant differences when stratifying for BMI and that's based on those two publications that we've referenced on the slide.

The next characteristic is sexual activity level. And so there were no studies that limited enrollment just on the patient's sexual activity level. There were some that reported out just the de novo dyspareunia rates in those women who reported to be sexually active. However, ultimately, our review did not identify evidence that the level of sexual activity affects outcomes.

And then there was this meta-analysis, the Deng 2016 publication, that identified

these potential risk factors for mesh erosion and those are notably going around the circle, parity, premenopausal estrogen therapy, diabetes, and smoking.

And so as we wrap up these patient characteristics, Panel, we ask you to think about that Question 6, about which factors determine whether a patient undergoes the mesh or the native tissue repair.

And as we recap our patient characteristics, we have discussed how the patient's surgical/medical history, concomitant procedures, how that can affect the safety and effectiveness outcomes. We've also identified the parity, premenopausal estrogen therapy, diabetes, and smoking as potential risk factors for mesh erosion.

And so Panel members, we ask you to think back to -- circle back to Question 5 and that recognizing that these concomitant procedures, patient factors, that they can affect the safety and effectiveness outcomes, how should FDA evaluate study results? How important is it for those characteristics to be balanced between the two arms, and what's recommended when they're not?

So just as patient characteristics are important in effectiveness -- safety and effectiveness, so too are surgeon characteristics. So we'll look at the related Panel question, which is Question 7. The FDA literature review indicated that surgeon experience may affect safety and effectiveness outcomes.

a. Please comment on a physician's level of experience and how that affects the safety and effectiveness.
b. How should FDA incorporate that level of experience of the clinical investigators, and the need for a comparable experience between the two study arms and realizing that the clinical study results may not reflect real-world results?

So the purpose of this slide here is to show you that surgeon experience does matter. So the table here showed Eilber's results from 2015. She used CMS data and

looked at the top 25 percentile to demarcate where that high-volume surgeon line should be drawn and that was drawn at three cases per year, three or more mesh cases per year. The conclusion was that low-volume surgeons, those performing one case per year, had higher reoperation rates, about double, 6% versus 3%, when -- so those lower-volume mesh surgeons having higher reoperation rates.

And then the second bullet point, it's interesting to note that more than half of the procedures were performed by low-volume surgeons. Fifty-three percent of those procedures were performed by those low-volume surgeons, which is reflective and potentially relevant for real-world application. The reoperation rate was similar for both gynecologists and urologists.

Therefore, the conclusion was that we observed lower reoperation rates among high-volume surgeons and propose that increased surgeon experience has an influential role in the outcomes of vaginal surgery with mesh.

The senior surgeons having lower mesh erosions was also borne out in this Deng meta-analysis where the erosion risk was significantly lower when patients had their surgery performed by a senior surgeon as compared to a junior surgeon.

So to recap the surgeon characteristics, so more experienced surgeons, they do have better outcomes with the mesh and so again, we just ask the Panel to think about Question Number 7, which is about the surgeon's level of experience.

And finally to the good stuff, this is the benefit-risk assessment and that leads us to our final question, 8. Surgical mesh for transvaginal repair of POP is an implant and its benefit-risk profile may change over time.

a. What's the appropriate expectation for the durability?

b. How quickly should the data demonstrate the benefit?

c. We're asking you what's the most appropriate time point to assess that benefit-

risk to support a marketing application? And that's in that -- by asking you that, we want to give you the background that a device subject to PMA, it's approved for marketing when that benefit-risk profile is favorable for the proposed indications for use, and then again demonstrating a reasonable assurance of safety and effectiveness. So what's the right time point to make that assessment?

d. What is the appropriate duration of follow-up, premarket and postmarket? And

e. What additional comments do you have related to mesh material?

So let's start in our assessment here with two basic building blocks that would be foundational ideally to a benefit-risk assessment for this device type. The first is the top block, that the comparison should be made to native tissue repair, and that's either through a randomized controlled trial or a parallel cohort study.

Secondly, the use of surgical mesh should offer some sort of advantage over the same repair without the use of mesh, and that the advantage should be over the lifetime of the repair or it might just be specific to a certain patient population.

And so before we get into what's complex about this decision, let's start with what's more straightforward, and so we start with the left-hand side of the slide, that the evidence from the randomized controlled trials, they do favor the safety outcomes of native tissue repair and that's at 12, 24, and 36 months. Moving to the right side of the slide, the mesh risk profile is less favorable than native tissue repair. The erosions and the exposures, they do occur and then when they do occur, they may require further surgery. Some adverse events happening at an increased rate over time and some occurring not as -- some occurring as late as 3 years.

So to those two building blocks that we've just discussed of an ideal benefit-risk assessment, we also want to add a third and that's the -- that all adverse events should be

considered, not just those that have been adjudicated as device or procedure related. But we want to -- in the totality of the evidence, we want to look at the severity, timing, resolution, and relatedness of the -- to the device and/or the procedure. And so the reason for this is, a quick example, an adverse event that is adjudicated by a company as being not related to a procedure. Once FDA reviews the data, then FDA may actually come to a different conclusion that there was actually relatedness to the procedure. So in this way, we want to comprehensively look for any trends even among the unexpected.

So let's look at the components of a benefit-risk assessment. There are three major parts. The first is on the left side, that overall, that we want to establish a favorable benefit-risk profile. We'd like for the benefits to outweigh the risks. And as mesh does have increased risks, then we would like for that mesh placed in that anterior vaginal compartment to be more efficacious in some way, to have more effectiveness. And then we need to establish effectiveness, both anatomic and subjective outcomes should be considered, and when a retreatment is necessary for prolapse, that should also factor into the effectiveness calculation.

Thirdly, we want to establish safety. Adverse events for mesh, they should be comparable to native tissue repair and when they are not, that increased risk should be offset by some sort of corresponding benefits, some sort of improvement in effectiveness.

So FDA understands that as a patient and a physician, and her physician, they're having that informed consent discussion. Then, at the end of that discussion, then the patient may decide that she's willing to take on the greater safety risks for some sort of improved outcome in terms of effectiveness. So, for example, a woman with a recurrent prolapse, she might be willing to take on those greater risks of a reoperation in order to have the benefit of the effectiveness of that reoperation.

And because this device type is a permanent implant, FDA believes that that

favorable benefit-risk, it really needs to be established long term. The safety and effectiveness outcomes beyond 12 months are necessary, and continued postmarket follow-up is necessary to follow those long-term adverse events, to follow that durability of the repair. And currently, there are limited long-term data, particularly beyond 3 years. And so Panel members, this is what FDA believes and we are here to hear what you think. So specifically, looking back to Question 8c, recalling that that device is approved for marketing when that benefit-risk profile is favorable, when is the right time to make that assessment?

So next, let's discuss some of the challenges that we have encountered in the literature and studies that make this benefit-risk determination so complex. We'll start with the top of the slide and that is the first cog wheel there, the lack of blinding for anatomic outcome assessment. So, for example, the surgeon who has performed the surgery on the patient obviously knows which surgery the patient had, not blinded, and then -- so that patient may be having the anatomic outcome assessment performed by that same surgeon. So in that case, when that POP-Q is performed, then obviously there's that lack of blinding and in those situations, bias can be introduced into a study.

The second cog there is the different surgeon experience. We've talked about how the level of the surgeon's experience does matter. Again, if those are not well balanced between study arms, then that could certainly impact outcomes of a study. And then also that thinking about the study results, again, are not necessarily reflective of what's happening in the real world.

And our third cog wheel here is the different patient characteristics between the mesh and the native tissue repair arms. When those characteristics are not well balanced, you can see those items, some potential items we have in the right lower corner, the severity of prolapse, that's pretty clear, if those are not well balanced between the study

arms, then that can certainly affect the outcomes. And the other items listed there as well, can certainly affect the outcomes, the safety and effectiveness outcomes.

And that's not all. There are further challenges to this device assessment. So recalling our 522 studies that are being performed, that these are not randomized controlled trials, these are parallel cohort studies. So there are differences, there may be differences in how the patients are assigned to mesh or native tissue repair and then the lack of collection of the adverse events, of all of the adverse events and the inconsistent adjudication of these events also can be quite challenging. The potential for site selection bias.

Some of those complex cases, they do get sent to the tertiary centers to get those better outcomes for those patients. Obviously, that can affect outcomes of a study as well. The potential for, again, the real-world use may not be reflective, not as good as the study outcomes. And, finally, there can be a significant loss to follow-up and that is particularly important if that follow-up is not similar between the two arms of a study, and especially so if the adverse events are the reason that the patients are dropping out of a study.

So these are all complex considerations that make this benefit-risk assessment so challenging. And so our conclusion in light of all of these challenging factors, Panel members, that is why we've asked you here, we're requesting your expertise and your input so that we can best evaluate the benefit-risk for mesh placed in the anterior vaginal compartment to treat POP.

Thank you.

(Applause.)

DR. ISAACSON: Thank you very much. And I'd like to thank all the FDA speakers for their presentation, and we do have some time -- yeah, let's give it about 15 minutes, if we can, for the Panel to ask clarifying questions to any of the FDA presenters. Are you

presenting now?

MS. ANDREWS: No, I'm just here to help answer questions.

DR. ISAACSON: Oh, good. All right, that's fine.

Panel have any questions for the FDA?

Dan.

DR. MORGAN: Thank you.

There's been a lot of discussion about the decision to follow the -- have the postmarket surveillance studies look like the PMAs that were required in 2018. Can you just clarify a little bit about -- so we should consider the postmarket surveillance studies to be of the same rigor as a premarket approval study. I guess, you know, just trying to interpret how the decision was made back in 2012 or '13 to issue those orders and to ask companies to do those studies and, you know, now should we -- and there's been comments that we should look at them in the light of the premarket approvals that are requiring guidance on, you know, how we should look at that. It just seems like there was -- they're responding is something and --

MS. ANDREWS: Um-hum.

DR. MORGAN: -- I'd just be curious to hear that.

MS. ANDREWS: Sure. So the 522 orders were issued in 2012 shortly after our 2011 Panel meeting. One of the recommendations from our 2011 Panel was that we should consider reclassifying mesh placed transvaginally. So in light of that recommendation, when we issued the 522 orders, we informed the manufacturers that we may reclassify these devices, and if that happened, they could potentially use their 522 study to support a future premarket approval application, and if that was the case, they should inform us at the time they submitted their initial 522 protocol and FDA would review that protocol to make sure it assessed both the questions that were raised in the 522 order as well as

determining whether it would be sufficient to support a future premarket approval application if FDA reclassified the devices. So we did review the 522 studies with the intent that they might one day need to support a premarket approval application and so we believe that they were designed for that dual purpose and that if designed and conducted appropriately, they could potentially demonstrate reasonable assurance of safety and effectiveness. Of course, when a study is conducted there are, perhaps, questions that come up regarding the study execution, of course, the results, but taking all of that together, you know, we will look at that in the PMA application.

DR. ISAACSON: Great. Before I call on you, Jason, let me ask one quick question. As far as the methods for obtaining -- looking at the literature, the eligibility criteria, can you explain why you selected only papers written in English? Number one. And number two, you have some literature that included the posterior prolapse, even if they did have the anterior, which certainly could skew. Can you just explain why you elected to include those two or limited it to that?

MS. ANDREWS: Sure. So in terms of why we included papers that potentially included posterior repair, we wanted to be as comprehensive as possible. However, we did not include any papers that were specific to posterior repair. They had to include information on both anterior and -- excuse me, anterior and apical repairs and it was data specific to anterior/apical repair that was presented in the literature review. We did not present data related to posterior repair. With respect to why we included papers that were only in English, I think that was just more a function of what we would be able to review internally.

DR. ISAACSON: Okay. Jason.

DR. CONNOR: I think Professor Chappell was first, if you want to start with him.

DR. ISAACSON: What's that? Oh, go ahead.

DR. CHAPPELL: Thank you.

Especially since I have two questions. The first is to Drs. Cunkelman and/or Lee. In regards to a statement by Iram Levit, the Lyra representative, that there were clinical studies correlating mesh weight with adverse events, that is, lower mesh weight with lower adverse events, I didn't see them in my literature review and I wanted to ask you if you saw such studies.

MS. ANDREWS: So I can take a stab at that question. We did present data that are specific to the marketed devices and I believe that those devices would be considered lightweight or ultra-lightweight mesh. But I think you can see from our literature review, there were really only a handful of studies on the devices of interest and there was only one comparative study. So I think we would say that based on our review of the published literature, there are limited data on mesh that are considered lightweight or ultra-lightweight.

DR. CHAPPELL: And perhaps none comparing the light or ultra-lightweight versus the older medium or heavyweight meshes?

MS. ANDREWS: We did not identify any articles that compared the heavier weight to the lightweight in our lit review.

DR. CHAPPELL: Thanks.

So my second question is how do you define subjective versus objective endpoints? Since you asked us to opine on that.

DR. CUNKELMAN: Hi. So for objective endpoints, we were looking for things that could be assessed by a clinician and using a methodology that could be repeated and hopefully find the same outcomes, so for example, POP-Q stage as an objective outcome and that's a standardized method of measuring prolapse and it is repeatable among different clinicians. So if I examine a patient and you examine a patient, we would most

likely come to the same conclusion regarding her stage of prolapse. Subjective outcomes were the important patient piece where they talked about quality of life, did they feel better, how is their sexual function, did they feel that they had prolapse or a sensation of bulge, things that are also very important but have to come from the patient herself and what bothers one patient may not bother another one, so there's a subjective component to that.

DR. CHAPPELL: Okay, thank you.

DR. CUNKELMAN: Um-hum.

DR. CONNOR: Jason Connor. I have two, I think, an easy one and a hard one. So for reoperation for mesh patients, it seems like, you know, you have reoperation because surgeries don't meet their surgical objective, you know, the prolapse wasn't fixed and so there's reoperation both for mesh and natural tissue. But also there's reoperations due to mesh failure and AEs that it caused. So for the reoperations is there data breaking those two things out, which are caused because the surgery didn't work and which would caused because, you know, there is an AE with the mesh that required intervention for the mesh, not to treat the original medical problem?

DR. CUNKELMAN: So I think we tried to highlight sometimes that's not clear and sometimes the study did not report on both. Some included all reoperations for either failure or persistent prolapse that needed to be addressed, and they lumped those together with reoperations because she had exposure or erosions. Some didn't include that, and where I had that information I tried to highlight it in my slides, but that goes to one of the limitations of this type of a review in that everybody kind of defines things differently and their endpoints are different. So where we could we broke that out, but that wasn't always if information was available to us.

DR. CONNOR: Okay, thank you.

And then my second question, you know, we see AEs and it's typical in any device or drug case to see AEs broken out by type. But I think what it comes down to here, I guess, especially in terms of informed consent and conversations patients have with their doctors, is to understand, like, the probability of a devastating AE, right? And so is there any literature on -- I mean, many of whom we heard from today are devastating AEs and it seems that that's what a patient needs to know, is that 1 in 1,000? Is that 1 in 10,000?

You know, we understand what is reoperation, what are these things but you know, to really decide whether you want this, it seems like a patient needs to understand the probability that, you know, a devastating event has caused this because it works in whom it works. So to weigh that benefit-risk, is there any data that really tries to quantify or capture what would qualify as a devastating AE?

DR. CUNKELMAN: So I don't think we actually have that information and I think one of the issues with mesh is that when you look at a category, for example, erosion/exposure, in one patient it might be something in the office where you're trimming or kind of over-sewing it and for another patient that can be the devastating outcome.

DR. CONNOR: Right.

DR. CUNKELMAN: So it very much is impacted by specific patient characteristics such as sexual activity, you know, the quality of her tissue, if she has other comorbidities that may make healing difficult for her. So I think that's a very important question, but it's a very difficult one to answer because, in general, the data that we looked at grouped it by, you know, erosion/exposure, pain, things like that. So, again, that's where the subjective comes into it and that's -- you know, an erosion in one woman might be absolutely devastating. In another one it could be an inconvenience that's easily fixed.

DR. CONNOR: Right. So is that even, like, understood to an order of magnitude where that is? Is it 1 in 10,000? Is it greater than that?

DR. CUNKELMAN: In terms of devastating, I don't know that.

DR. CONNOR: Okay.

DR. CUNKELMAN: I'm sorry.

DR. CONNOR: Thanks.

DR. ISAACSON: Go ahead.

DR. EREKSON: So I have two questions. The first one, I think, is just a terminology question, and it goes to the categorizations that were shown between apical and anterior and I'm just trying to make sure or understand, are you considering apical a transvaginal mesh kit that uses the sacrospinous ligament, or is apical a different definition?

DR. CUNKELMAN: I would actually have to defer to our person who did the literature review and we can ask her about that later this afternoon.

DR. EREKSON: Okay. And then the second question I have more goes to Dr. Lee about the adjudication of the adverse events. So when the studies are designed for the adverse events and there's no adjudication, are we going off of the list that's provided in Slide Number 37, which is the top 10 adverse events? Are there other adverse events that get included? How does that get defined?

DR. CUNKELMAN: So the list that we have from the top MDR reports included everything. There was nothing in the literature that we didn't see in this list of MDR report adverse events.

DR. EREKSON: If the complication is one of those adverse events, does it have to be included, or if the adjudication says this wasn't from the device, so it doesn't have to be included?

DR. CUNKELMAN: For MDR reports? I'm sorry.

DR. EREKSON: So what we were just hearing from Dr. Lee about the question of how we classify the adverse events, I'm just wondering if the adverse event is one of those 10,

does it have to be included?

DR. LEE: So I think, for the adverse events, the adjudications, that's talking about the 522 study results and we haven't specifically addressed the results from that -- those clinical 522 studies. We just discussed things that we found in our literature review.

MS. ANDREWS: I will just add to that, that in Panel Question Number 3 we've identified a series of adverse events. Those are the adverse events that we requested the manufacturers collect in the 522 orders. So when we speak to adverse event collection, the 522 mandated that they collect those types of adverse events, but perhaps there might be other adverse events that occur that may or may not be related to the device or procedure and whether it's those adverse events that we've identified in our question or other adverse events not identified, there can be questions that come up as to whether it's related to the device or the procedure and there may be disagreement in terms of how those are adjudicated. I think that's what we were speaking to.

DR. ISAACSON: A question, Madeline? Introduce yourself, please.

DR. DICK-BIASCOECHEA: Dr. Madeline Dick.

I just have one question in terms of the patient datasets that looked at the risk of premenopausal estrogen. I'm not exactly sure what that means.

DR. LEE: So women who had been treated premenopausally with estrogen therapy, then that was actually found in that Deng meta-analysis to be a risk factor for erosion.

DR. DICK-BIASCOECHEA: That have not gone through menopause?

DR. LEE: I will have to get back to you on that detail. We'll look at it during the break.

DR. ISAACSON: Great. So we will now break for lunch. Thank you all for your presentations. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room

at 12:30. Please take any personal belongings with you at this time. The room will be secured by the FDA staff during the lunch break. You will not be allowed back into the room until we reconvene at 12:30. Thank you very much.

(Whereupon, a lunch recess was taken.)

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

(12:40 p.m.)

DR. ISAACSON: Good afternoon, everyone. As I said, we'll start right on time at 12:30. So it's 12:40. It must be 12:30 somewhere. And we want to first -- there were two questions that were asked of the FDA that they said they would respond with answers after lunch and so those two questions, one related -- I don't know where Madeline is. It was her question, so we'll skip that one. The other -- well, we'll come back to it. The other was comment on studying the anterior mesh in conjunction with the apical and possibly the posterior that was included in the data. So if the FDA has a response to that.

DR. CUNKELMAN: So in response to Dr. Erekson's question with the apical prolapse and how that was defined, so when we were looking -- I'm assuming this was pertaining to the literature review and how it was defined in those studies, we looked at papers that self-defined having done an apical prolapse and when we went back through them, there were a variety of procedures that they had done, so some were uterosacral, some were sacrospinous. There wasn't a standardized procedure. And then if they included a mesh component to that, it was usually a mesh product that had an apical component to it, so it wasn't just an anterior wall repair, it was something that also affixed to the ligaments to provide that apical support as a piece of it. They were very heterogeneous, but that's in general what we were looking at.

DR. EREKSON: But they weren't sacrocolpopexies?

DR. CUNKELMAN: No, they were not sacrocolpopexies, so that -- yeah, we removed anything that was a sacrocolpopexy, so it was some form of ligament suspension.

DR. ISAACSON: And then the other question related to the estrogen therapy pre-menopause, I think. Does the FDA have a response?

DR. LEE: So this is in response to Dr. Dick's question and so we did go back to look at

the -- the question was about the risk of -- the risk for mesh erosion with premenopausal and estrogen therapy and so we did go back and look at the study and "the unadjusted odds ratios of premenopausal or estrogen replacement therapy for mesh erosion after pelvic floor reconstruction could be extracted or calculated from 12 studies. No heterogeneity was found in the 12 studies and premenopausal estrogen replacement therapy appeared to be a significant risk factor for mesh erosion." So that was the extent of the explanation that we were able to find.

DR. ISAACSON: Thank you very much.

So we'll move on now to -- proceed to the manufacturers' presentations. I assume that Boston Scientific is already up here, and there you are.

DR. MORTON: Yes.

DR. ISAACSON: I'll 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.

And you may begin your presentation. Thank you.

DR. MORTON: Thank you, Dr. Isaacson.

I would like to thank the FDA for the opportunity to present to the Panel today. My name is Dr. Ronald Morton. I am the vice president of clinical sciences for the urology division at Boston Scientific. Today, before I address the Panel, I would like to address the members of the audience.

(Off microphone comment.)

DR. MORTON: It takes great courage to come to a meeting like this and present about your problems and on behalf of Boston Scientific and myself, as a physician, I want to express my deepest sympathy and my sincere empathy for those women who have been harmed by surgical mesh therapies. Boston Scientific is purposeful and is committed to

providing medical devices that are safe and effective, that are supported by clinical evidence, that are supported by physician training, and that will allow for the best possible clinical outcomes. Today we will be discussing the continued need for transvaginal mesh as a treatment for surgical organ prolapse.

Our agenda is as follows. I will give a brief introduction and we will talk about the therapeutic options for pelvic organ prolapse, the clinical evidence for transvaginal mesh, and we will discuss our 522 data before entering into discussions of how this impacts risk-benefit discussions.

These are the issues that we will address throughout the course of this presentation, and they are consistent with those issues that have been raised by FDA when determining benefit-risk for transvaginal mesh.

Today I am joined by several colleagues from Boston Scientific as well as three noted female pelvic surgery specialists, Dr. Suzette Southerland, Dr. Miles Murphy, and Dr. Michael Kennelly, and they will be helping with this -- me with this presentation as well as with entertaining questions and comments from the Panel.

Boston Scientific markets two devices for pelvic organ prolapse: Uphold LITE and Xenform. Each has been cleared by the 510(k) process, have been distributed and implanted worldwide in thousands of women, and is now pending PMA applications with the FDA.

Uphold LITE is a second-generation knitted Type 1 mesh. It is anatomically sized, it has adjustable legs for sacrospinous ligament attachment, and those legs are allowing and facilitating proper graft placement. It can provide both anterior and apical support, can be delivered through a single incision and is delivered generally with the -- and is affixed generally with the Capio SLIM device. It is of note, and has been noted previously by FDA, that Uphold LITE is a different product than Uphold, which is no longer on the market.

Xenform is a biologic material that is non-cross-linked, can be trimmed to fit patient anatomy, and is also capable of providing both anterior and apical support.

We'd now like to allow Dr. Suzette Sutherland to come up and address therapies for mesh and clinical data supporting transvaginal mesh.

DR. SUTHERLAND: Thank you. I'm Dr. Suzette Sutherland, Director of Female Urology at the University of Washington in Seattle. I do serve as a consultant for Boston Scientific, but in spite of that, I don't have any financial interests in the outcome of this meeting. I do have a keen clinical interest, however, as I always try to find the safest and most efficacious and durable prolapse repairs for my patients.

There are over three and a half million women in the United States that have prolapse, and many of those are searching for some type of treatment. We do have some nonsurgical conservative treatments available, pelvic floor exercises, physical therapy as well as pessaries, which are vaginal inserts that just mechanically hold the prolapse up. Both of these types of therapies require some ongoing commitment from the patient and they usually are also mostly successful in milder cases.

For those patients that need or either desire surgical intervention, we do have a number of options available. The goal of all of those options, though, regardless of what type of approach we take, is to restore the anatomical support and then through that, restore the function of the organ that's prolapsing. So the approaches are abdominal approaches as well as transvaginal approaches, which are more minimally invasive. Both can be done with or without the use of mesh. The considerations for which approach is appropriate for what type of patient or prolapse includes the adequacy of the support that's deemed achievable and then the anticipated durability of that repair.

Transvaginal mesh was introduced into the algorithm due to the high recurrence rates that we saw with native tissue repair, so the whole goal is to try and increase the

durability of the repair so that a woman doesn't have a recurrence of her prolapse requiring yet a secondary operation. As a treating provider, I see a recurrence within a short time span requiring another surgery as a complication of that surgery.

Sorry, I'm looking for the right -- oh, the space bar, okay. So the surgical options can fall into one of these four categories. We have the abdominal sacrocolpopexy, we have the hysteropexy, a uterine-sparing approach; transvaginal native tissue repairs, and then transvaginal mesh.

For the sacrocolpopexy, that's optimally termed the gold standard for durability for the apical prolapse, but that's also been a gold standard because it was the only one that had 5-year data in our literature at that time, not because the 5-year results were really that stellar. Keep in mind that it does use permanent polypropylene mesh about the vagina with permanent sutures to secure that mesh and it's just introduced through the abdomen. So the risk of mesh exposure, erosion, or mesh-related pain can happen in this scenario as well. It is an abdominal procedure, so it takes a longer time to do and it requires general anesthesia and also susceptible to a plethora of potential intra-abdominal complications that can occur because you're entering that peritoneal space.

For the hysteropexy, it can be done either abdominally or transvaginally, again uses permanent polypropylene mesh and/or permanent suture. So, again, the risks of foreign body, the permanent suture or mesh, apply here as well.

For the native tissue repairs for the anterior compartment, we're specifically talking about the anterior colporrhaphy or that plication technique, and for the apex we're talking about the sacrospinous ligament or uterosacral ligament suspension. Keep in mind, most sacrospinous ligaments and uterosacral ligament suspension procedures are done with permanent Prolene suture. The only one that doesn't use permanent material is really the anterior colporrhaphy. With both of these we've seen very high rates of prolapse

recurrence, both anteriorally and apical, and we see that clinically as well as in our literature.

Most recently, the Maher Cochrane Review, which has been discussed here already, showed that the failure rate at 2 years for the anterior repair was between 27 and 42%. And when we looked at another study that was recently published, called the OPTIMAL study, in *JAMA* 2018 that looked at the apical repairs which are deemed native tissue repairs, the uterosacral ligation -- ligament, I mean, and the sacrospinous ligament fixation at 2 years, the rate of failure was 40% and at five, you can see it's 60 to 70%. So that's really very high. The retreatment rate at 5 years was still only about 10%, but we know there are a lot of factors that go into the decision for a woman to make that she's going to have yet another prolapse procedure. And, again, I want to drill home the point that the sacrospinous ligament as well as uterosacral ligament suspensions usually use some permanent Prolene suture.

And then for the transvaginal mesh approach, of course, you're using mesh through the vagina, and the advantage of using a transvaginal approach, you're going to address the anterior, posterior, and apical compartment all at the same time. We do know from our literature that the use of transvaginal mesh increases the anatomical durability, but what we don't know and it hasn't been borne out in the literature yet, is that that makes subjective improvements. We do think that as the data that we have matures and goes on beyond 2, 3, 4, and 5 years, we'll start to see more of those native tissue repairs coming down even further beyond the hymen such that they are more symptomatic, yet the mesh-supported repair is staying up nicely. So, of course, we have to weigh the benefit of durability with some of the mesh-related complications.

But, again, I want to point out to you, in each one of these categories, either polypropylene permanent mesh or permanent Prolene suture is being used, so the risks

associated with that foreign body are real in each one of these categories.

So we can't talk about transvaginal mesh products without talking about the evolution of the transvaginal mesh products with respect to the materials, the design as well as the surgical technique. The earlier transvaginal mesh products were associated with higher complication rates as well as poor efficacy and recurrences of those prolapse repairs because of a number of factors that are listed here. The first is that it was a larger mesh footprint, the mesh itself was a higher density, thicker mesh, and it was often used initially as a mesh inlay technique that you can see here where a piece of mesh was just placed on top of the bladder allowing that to incorporate without any anchoring and hoping that that would solve the problem.

A split thickness dissection plane was often used, which means -- which is the traditional dissection done for an anterior colporrhaphy and then the mesh laid there. But this leaves the vaginal epithelium almost de-vascularized and very susceptible to poor healing which then leaves that mesh susceptible to exposure. I want to be really clear about this point. This transvaginal mesh technique, or all the transvaginal mesh techniques, were never designed to be used with a split thickness dissection. It's always been taught to be done with a full thickness dissection. You take the dissection through the vaginal epithelium down to the fascia, and you place that mesh between that plane between the bladder and the fascia. That allows that vaginal epithelium to be very well vascularized still, and it can heal nicely to reduce your rate of mesh exposure.

The prior devices also had implantations with multiple incisions and trocars that were placed in a blind fashion, so the current ones don't do that anymore and they also addressed only the anterior wall and did not address the apex even when it was involved. So no longer are any of these pieces considered standard of practice when we're talking about the contemporary devices that we have today.

So, in comparison, the contemporary devices, the Uphold LITE being one of those, is a low-density, large-pore mesh product. It's implanted through a single incision and without the use of these trocars. It utilizes a Capio device, now it's a Capio SLIM, much narrower in dimension, but that accesses the sacrospinous ligament. For the urogynecologists or gynecologists on the Panel here, they're very familiar with the Capio device, and it's been around a long time, so most people who do vaginal surgery are very comfortable with that device. And the other aspect is that is also provides not only support to the anterior vagina, but also that apex, and we know clinically how important that is. So many of our prior failures were due to the fact that just the anterior compartment was addressed and not the apex.

Isolated anterior or apical prolapse is extremely rare. When one of those compartments is coming down, the others are usually coming down with it. We do have reports in our literature now that also shows that the cystocele stage, it actually predicts the apical prolapse. So with a Stage III prolapse, 85% of the time the POP-Q is coming down to the negative three-point for their apex. And Stage IV, it's 100% of the time. So we absolutely know that in order to get a good, durable prolapse repair we have to treat both compartments. And the current devices, with their designs and surgical techniques, they do that, and they're designed to reduce complications as well as improve the outcomes with respect to efficacy and long-term durability.

So now let's look quickly at some of the really contemporary literature that describes the Boston Scientific Uphold LITE device.

So this is a study that you just heard about. Dr. Charlie Nager from San Diego was here and discussed this with you, a prospective randomized trial again comparing mesh hysteropexy done through the vagina with the Uphold LITE versus the vaginal hysterectomy removing the uterus and doing what's called an apical native tissue repair for the apex, but

keep in mind, Prolene sutures are used for that apical suspension. And what we saw was no difference in composite success through 48 months. The anterior wall, however, was a bit better supported with the Uphold LITE device than it was with the hysterectomy group. No difference in patient reports of pain, dyspareunia, or sexual function. The operative time was less in the order of about 45 minutes. The mesh exposure rate was 8%, he alluded to that, and also said they were all mild, none required any subsequent surgery.

But I really wanted to highlight this, too, and he pointed it out, the suture exposure rate from that Prolene suture up at the apex was 20%, even higher than the mesh exposure rate as well as excessive granulation tissue up at that apex from that hysterectomy. Both of these are issues that although it didn't require surgical intervention, they do require some intervention, especially if the woman is sexually active. So the Uphold LITE does show durable, at least, long-term 3-year success with a uterine-sparing hysteropexy with very low risk.

This next study is a 1-year prospective multicenter trial looking again at transvaginal Uphold for a hysteropexy and now comparing it to what we think is minimally invasive laparoscopic hysteropexy utilizing a sacrocolpopexy-like technique. The operative time here was much shorter in the transvaginal group, less than 2 hours compared to 4 hours for the laparoscopic group. And so those of you on the Panel who do laparoscopy know that steep trend down for 4 hours, that can have some cardiovascular compromises. Patient selection, or satisfaction was very high, 95% in both groups, and the mesh exposure was seen in both groups, but within realistic limits. So, overall, we see comparable efficacy between these two methods, but certainly a more minimally invasive approach with the transvaginal approach and leaving the uterus in and not getting into that peritoneal space.

And the last study is a 5-year prospective study looking at the Uphold device. Success was defined here as a POP-Q stage less than 2, so for those of you who are familiar

with the POP, it's not less than or equal to 2, which includes down at the hymen, but it's above, 1 cm above the hymen or higher. So it's a much stricter criteria here and of course, no vaginal bulge sensation from the woman. The objective and subjective success were very high in this, 83% and 78%, and the mesh exposure rate, 1.4%. None of these required any subsequent surgery and this number is really what we see more in our current literature overall, and certainly with physicians who have a lot of experience with mesh.

So, in summary, for the contemporary literature, we see great anatomic success between 80 and 95% with very low exposure rates, 0 to 8% overall. So these exposure rates are lower than that which was described by the FDA's report of 11 to 18%, but this is also the exposure rates associated with the newest-generation type of devices, not incorporating some of the data from the older-generation devices utilizing different mesh and different techniques.

And then lastly, again, here we're comparing the anatomical success high with the subjective success, 91 to 95% based on validated questionnaires. So there's our symptom evaluation there.

So, overall, we do see, when you're looking at the data for the contemporary devices, we see a much different picture than the picture that was painted from the literature that describes those devices which are older-generation devices and are no longer available.

Thank you for your attention.

DR. MORTON: Thank you, Dr. Sutherland.

We'd now like to turn the Panel's attention to our Boston Scientific 522 data. Boston Scientific is now conducting prospective studies in response to the 522 orders that have been spoken about earlier this morning. It's important to note that these study protocols were vetted with FDA prior to initiation of the studies, and it was deemed that these studies

would be acceptable and satisfy the requirements for a PMA in the event that the devices were up-classified.

Each study is a parallel cohort design with comparison to native tissue repair for both Uphold LITE and Xenform. You can see that a number of both tertiary academic sites and private practice sites are involved in each academic -- in each study, and we believe that this distribution of studies is representative of where women achieve their care for pelvic organ prolapse. The initial study designs were out to 36 months, and they are currently ongoing. At FDA's request, we have submitted our PMAs based on predefined hypothesis testing at 12 months and it's the 12-month data that I'll be going over today.

The study population is quite diverse and, I believe, representative of women who are treated for pelvic organ prolapse; various stages of disease, smokers, diabetics, women who are having a secondary repair, women who are undergoing concomitant procedures. As noted, these were not prospective randomized trials. In order to allow for -- the potential imbalances in baseline characteristics would not be -- could be accounted for in the assessment of the data. Propensity score stratification that was pre-specified and vetted with FDA was used in order to perform the assessments of these data.

A co-primary efficacy and safety endpoint was used for the studies. The safety endpoint is serious device- and/or serious procedure-related adverse events. And there is a composite efficacy endpoint including objective success with the leading edge of prolapse at or above the hymen in the operated compartment. Subjective success, as has been mentioned earlier today, with no symptoms of bulge or bothersome bulge perceived by the women, and no retreatment for pelvic organ prolapse.

There are a number of secondary endpoints in this study. But a key secondary endpoint was a secondary efficacy endpoint that is similar to the primary efficacy endpoint with the exception that it is a little bit more stringent in that objective success was defined

as "above the hymen" as opposed to "at or above the hymen."

I'll begin with some Uphold LITE data. You can see that across the components of the efficacy endpoint at 12 months, objective success, subjective success, and no retreatment for POP, that there is good performance for both Uphold LITE and native tissue repair. The objective success rates are very high in both the anterior and apical compartments and notably, in the anterior compartment, Uphold LITE is numerically higher in terms of efficacy when compared to native tissue repair, 98.5% compared with 93.5%.

Not surprisingly, when one looks at the non-inferiority, we see that Uphold LITE, in all populations that were predefined in the protocol, including the intent-to-treat population, is non-inferiority to native tissue repair, 91.6% in the intent-to-treat population for Uphold LITE in terms of efficacy compared to 87.3% for native tissue repair.

When we look at the more stringent secondary efficacy endpoint of "above the hymen," even at 12 months Uphold LITE showed greater success than native tissue repair. I would note that the p-values and confidence intervals here are not adjusted for multiplicity.

As has been previously stated, the studies are designed to go out to 36 months, but the PMA was required based on 12-month data. At the time of submission of our PMA data, we also looked at efficacy out to 36 months, the caveat being that obviously we have limited numbers of subjects who have crossed that time point. But what we do see is that there is numerically higher success for Uphold LITE compared to native tissue repair; notably at 36 months, 83.3% in the Uphold LITE arm compared to 73.8% in the native tissue repair arm, suggesting benefit over time and durability of response.

Baseline pain scores were comparable, and the improvement in baseline pain scores were comparable in both arms, and the TOMUS pain score was used to assess pain. We looked at a number of patient-reported outcomes that are validated instruments to assess quality of life and we showed that there was comparable improvements in quality of life

between the native tissue repair arms and the Uphold LITE arm.

Turning our attention to safety, there are comparable rates of serious adverse events at 12 months. The overall adverse event rate was also comparable between the two arms. As was stated earlier, there are adverse events that are of particular interest in women undergoing pelvic organ prolapse surgery and you can see those here across this graph and you can see that Uphold LITE, in dark blue, versus native tissue repair, in light blue, had very comparable rates of all of these adverse events. We acknowledge that the introduction of transvaginal mesh results in mesh-specific complications, and it was important in these studies to look at these complications critically.

There were no reported visceral mesh erosions observed in the Uphold LITE versus native tissue repair study. Mesh exposures in the first 12 months that are included the PMA submission were in four subjects at 1.8%. We have looked at the remainder of exposure events that we have seen thus far, and to date, there have been 11 events in 9 subjects. Ten of these events have fully resolved, and we'll talk about these events in just a second. We used this data to develop a Kaplan-Meier estimate of our exposure rate at 36 months, and it comes out to 6.2%. Of these exposure events, approximately half have required either no intervention or mild to moderate office procedures in order to resolve them. Half have also required surgical intervention.

When we look at the specific events for surgical intervention for these mesh exposures, these events or these descriptions come from the narratives provided by the physicians who manage the patients. No subjects required complete removal of their mesh. Five subjects were taken to the operating room and were treated for dime-size or less than 1 cm mesh exposures with mesh trimming. Two subjects had less than 1 cm mesh exposures trimmed in the office under local anesthesia and in three patients, the mesh exposure resolved without intervention. There is one exposure event that is yet to resolve,

it is of 206 days duration at this time, it has been described as palpable but not visible on physical examination and is being managed conservatively.

The Uphold LITE and Xenform studies are very similar in study design and I'll briefly go over data from the Xenform study. The same primary efficacy endpoint was used for Xenform and we note that in all protocol-defined populations, Xenform is non-inferior to native tissue repair for efficacy using a net composite endpoint at 12 months. We did look at Xenform compared to native tissue repair for the most stringent secondary efficacy endpoint at 12 months and Xenform was non-inferior to native tissue repair using that endpoint, unlike Uphold LITE, which was -- showed higher efficacy at 12 months.

Similarly to how we looked at Uphold LITE over 36 months, we've looked at our limited data of Xenform out to 36 months. We note that it is numerically higher in terms of efficacy when compared to native tissue repair, 81.9% compared to 73.8%.

The same quality of life and pain scores were developed in the Xenform study as were used for the Uphold LITE study. Baseline pain scores were comparable in both arms and improvement was comparable as well. And using the same patient-reported outcomes, we saw no difference in the improvement in quality of life in the Xenform arm compared to the native tissue repair arm, again, at 12 months.

There were comparable rates of serious adverse events in the native tissue repair arm at 12 months. However, when looking at those same adverse events specific to pelvic organ prolapse surgery, we did note that in the Xenform arm there was a higher rate of postoperative obstructive voiding symptoms when compared to native tissue repair, 11% versus 3%. All other of those previously described adverse events were comparable when compared between the Xenform and native tissue repair arms.

In order to better understand the potential impact that this would have on quality of life, the Urinary Distress Inventory, UDI-6, instrument was used to measure quality of life

and we looked at patients in the Xenform arm who had de novo voiding dysfunction and compared them to those who did not. And you can see, based on the graph here, that over the course of 36 months there is no appreciable difference between the patients with de novo voiding dysfunction compared to those without, suggesting that while this difference was observed, it may have had no impact on quality of life.

With respect to graft safety, there were no reported visceral graft erosions. There were two graft exposure cases seen at 12 months and these are the only two graft exposure cases seen in the Xenform arm, each with a small incisional dehiscence and each did not require any surgical or other intervention for resolution. Thus, graft exposures were rare and mild and without lasting sequelae in the Xenform study.

In summary, pelvic organ prolapse treatment with Uphold LITE and Xenform achieved a high rate of objective and subjective success. Each was non-inferior to native tissue repair at 12 months on the composite efficacy outcome.

Objective success rates were numerically higher for Uphold LITE compared to native tissue repair, and Uphold LITE demonstrated greater efficacy compared to native tissue repair when success was defined as "above the hymen" as opposed to "at or above the hymen."

Quality of life improvement was similar in the arms of each study at 12 months, and there is some data out to 36 months that we have reported now that shows sustained benefits for both Uphold LITE and Xenform compared to native tissue repair.

Overall, risks for serious adverse events and adverse events are comparable between the two mesh arms compared to native tissue repair, and there are low rates of mesh exposure that have not led to significant complications requiring complete excision of the mesh.

We looked at surgical intervention rates for all complications, and they are

comparable amongst all of the arms: 4.9% in the Uphold LITE arm, 5.3% for Xenform, and 6.6% for native tissue repair

In summary, subjects experienced equivalent results compared to native tissue repair at 12 months and without overall higher risk of complications.

I would now like to introduce Dr. Miles Murphy. He will talk about physician training, patient selection, and the impacts that they have on the assessment of benefit-risk for transvaginal mesh.

DR. MURPHY: Thank you, Dr. Morton.

My name is Miles Murphy, and I am a urogynecologist. I am serving here today as a consultant for Boston Scientific, and I'm being reimbursed for my time, but I hold no equity interest in the company, but I do appreciate the opportunity to present today.

Transvaginal mesh procedures have evolved over time and they've improved significantly since the 2011 FDA safety communication. We have moved towards more lightweight meshes with larger porosity and away from multi-incision trocar systems to single-incision procedures without blind passages. Of equal importance, we've gained experience in implantation. This experience with techniques such as full-thickness dissection has led to decreasing rates of mesh complications.

With the advent of board subspecialty certification in 2013, for the most part, the surgeons doing these procedures have greater training not only in TVM, but in all modes of prolapse repair and thus are more equipped to pick the right procedure for the right patient.

As a result, exposure rates such as those cited by the FDA of 11 to 18% are higher than what we have seen in the more recent literature, specifically with literature related to BSC devices such as Uphold LITE, where exposure rates are closer to 0 to 8% and where no visceral erosions have been reported. This decrease in mesh-specific adverse events in TVM

surgery in recent years is likely attributed to a number of things: improved material properties of the implants, improvements in delivery system design, and enhanced training.

Furthermore, in 2012, medical societies began publishing recommendations regarding the type of experience and training that surgeons should have if they are going to be doing these types of mesh procedures. This has helped guide hospital credentialing committees so that these complex reconstructive procedures are being performed by the appropriate surgeons.

Patients should always have a voice in choosing what type of treatment they receive and the existing options each present with various pros and cons, and not all prolapses are the same. Therefore, the therapy must be tailored to the patient's type and degree of prolapse as well as her comorbidities. Does she have comorbidities that may prolong general anesthesia, steep trend downward position, or intra-peritoneal entry less than optimal? And might these things put her at a higher-than-average risk for adverse outcomes, outcomes that could be avoided by a transvaginal mesh procedure that would still provide a long-lasting, durable repair?

Specific populations for whom a TVM procedure may be the best option include those seeking uterine preservation, as we've seen today, previously failed native tissue repair, injury to pelvic floor musculature or connective tissue disorders. Other things that can contribute to a higher-than-average risk of prolapse recurrence include things like a Stage III or Stage IV anterior compartment defect, women with chronic conditions like cough or constipation, and these factors become particularly important when patients have issues compromising abdominal access and thus making them poor candidates for sacrocolpopexy. While it certainly may not be the best option for every patient, the availability of transvaginal mesh is critical to optimizing the treatment of all patients.

We now have robust data in the literature that supports the safety and efficacy of

transvaginal mesh devices. As with the data prior to 2011, these studies showed clinically significant improvements in both anatomic and subjective outcomes, but there have also been many notable findings since 2011. This is both in the general literature and the 522 data specifically that we just presented. They show that transvaginal mesh repairs are superior to native tissue repairs in keeping the anterior vaginal wall above the hymen.

Furthermore, one of the biggest developments since 2011 is in regard to subjective outcomes. While in the past there was limited evidence showing that subjective outcomes in TVM patients were superior to those undergoing native tissue repair, we now have multiple independent systematic reviews showing superior subjective outcomes with anterior transvaginal mesh, such as less awareness of prolapse, less symptoms of bulge, and a better post-op POP distress inventory subscale score as compared to native tissue repairs, and notably, this is seen without higher risks of adverse subjective outcomes like de novo stress incontinence or dyspareunia.

Finally, the 2017 Cochrane Review of surgery specifically for anterior compartment prolapse found a twofold higher relative risk of repeat surgery for prolapse in women undergoing native tissue repair as opposed to transvaginal mesh.

So while we freely admit that the risk of mesh exposure is a unique risk of mesh repairs, both the overall TVM literature and the 522 data for BSC devices specifically show that the overall risks of the TVM procedure are comparable to native tissue and therefore they may be the most appropriate option for certain patient populations.

The 522 data that Dr. Morton just presented clearly establishes that these BSC devices result in both anatomic and subjective success after 1 year of follow-up. The secondary efficacy outcome, i.e., the rates of support above the hymen are superior to native tissue at 12 months, and the trend towards superiority in the longer 2- and 3-year follow-up of the primary efficacy outcome suggests that anatomic success will likely prove

superior over time in the long-term study of the transvaginal mesh.

The safety profile shows low rates of mesh-related complications and an overall complication rate that is comparable to native tissue repair. And the totality of the anterior TVM literature since 2011 shows consistent outcomes with low rates of anatomic recurrence, lower rates of bulge symptoms, and lower rates of reoperation for recurrent prolapse as compared to native tissue.

We conclude that Uphold LITE and Xenform provide the option of a minimally invasive, durable repair that does not demonstrate an overall increased risk as compared to native tissue repair, and they may be the most appropriate clinical option for some populations of women suffering from pelvic organ prolapse.

I'll now turn the podium over to Dr. Morton for the conclusion.

DR. MORTON: Thank you, Dr. Murphy. I do note that the light is blinking red, so I'll be very brief with my concluding remarks.

Our 522 data shows clinical benefit at 12 months, and the trend shows potential for durability of benefit compared to native tissue repair.

We note that superiority at 12 months for transvaginal mesh compared to native tissue repair was not anticipated when these studies were originally designed and should not be required for the assessment of benefit-risk.

There are comparable overall rates of complications for BSC's devices compared to native tissue repair. Mesh-related complications have been mild and easily managed in the office or with very brief surgical operations. And the overall risk for transvaginal mesh has not been greater than for the risk for native tissue repair.

BSC is committed to providing product labeling that will assist physicians in their discussions of shared risk with their patients, and providing physician training that is comprehensive and customizable to a physician's background and will be supplemental to

both residency and fellowship training.

In conclusion, both Uphold LITE and Xenform represent viable clinical alternatives for the treatment of pelvic organ prolapse.

Our 522 studies, in combination with the literature, show comparable clinical success for transvaginal mesh compared to native tissue repair, overall complication profiles that are comparable to native tissue repair, low rates of mesh-related adverse events that are generally mild and not requiring mesh excision and surgical intervention rates that are comparable to native tissue repair.

Moreover, as previously said by Dr. Murphy, there are populations of women for whom transvaginal may be the most appropriate clinical option.

And that will conclude our remarks, and we'll be happy to take any questions from the Panel.

DR. ISAACSON: Thank you very much. We're going to take questions from the Panel after we hear the next presentation from Coloplast, and I'd now like to invite Coloplast to approach the podium.

(Applause.)

DR. ISAACSON: And, again, we'll 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.

And are you -- you're ready?

MR. KLOUS: Yes, I'm ready.

DR. ISAACSON: If you'll just introduce yourself and go ahead.

MR. KLOUS: Mr. Chairman, members of the Panel, and FDA officers, my name is Dale Klous, and I'm the director of clinical science for Coloplast. We are honored by the opportunity to present information to the Panel as you deliberate important questions

posed by FDA. We appreciate the presentations by the public speakers and FDA medical officers. Thank you for the information that you provided.

Since our founding, Coloplast's mission has been to make life easier for people with intimate healthcare needs. We live our values and we have a passion to make a difference. We are here today as one of two remaining companies with a synthetic mesh device for the treatment of anterior prolapse. We are here because we believe in our products and we believe that patients and physicians need options. We firmly believe that Restorelle DirectFix is a safe and effective treatment when used appropriately.

I would like to introduce the team that is with me today. The Coloplast team includes Sharon Iverson, Head of Regulatory Affairs, and Diane Brinza, Senior Strategic Regulatory Affairs manager. Our physician team includes Professor Jan-Paul Roovers, who is co-lead investigator of the Restorelle 522 study, Dr. Janet Harris-Hicks and Dr. Karny Jacoby. Each of these physicians is an expert in pelvic reconstructive surgery and is an investigator in our 522 study.

For each of the five topics on this slide, FDA is asking the Panel's advice about the factors it should consider when evaluating the benefit-risk of mesh for anterior prolapse. The analysis of 12-month endpoint outcomes are under active PMA review by FDA and we look forward to continued interactions.

It is our understanding that the purpose of today's Panel is to provide recommendations to FDA on how to assess benefit-risk of pelvic mesh devices. Our presentation is going to cover mesh characteristics, MAUDE data, and published clinical literature that are directly relevant to the current generation of mesh devices. We also will provide observations about treatment selection in our 522 study. All of these topics are important considerations when assessing benefit-risk. We believe the information we will provide today will help the Panel in its deliberations.

This slide provides the context that is fundamental to our presentation. First and foremost, we believe that patients and surgeons need safe and effective treatments. Because each patient is unique in their condition and preferences, a range of options is needed. In addition, as described by previous FDA and industry speakers, a number of factors may impact outcomes, such as mesh characteristics, patient comorbidities, surgical skill or education and technique. Let's first turn to mesh characteristics and surgical technique.

When considering the impact of mesh characteristics on outcomes, it's important to understand the history of innovation in both mesh design and the surgical procedure. As illustrated here, over time advancements have occurred in both. Surgeons started using mesh for prolapse because native tissue repair was associated with high rates of failure. However, early mesh was heavier weight, stiff, and less porous. It was not designed for the pelvic space. Instead, these early mesh devices were originally designed to treat abdominal hernias. Recognizing the importance of mesh characteristics on clinical outcomes, eventually lighter-weight mesh was used. Today, only ultra-lightweight mesh is used to treat anterior prolapse.

The surgical procedure has also changed. In the past, surgical procedures were not standardized. Over time, physicians moved from surgeon configured hernia mesh using multiple surgical techniques, to the use of trocars and no fixation, to the contemporary surgical procedure which is used today and that is the single-incision approach with improved dissection and fixation.

The current surgical technique is important because it's less invasive while providing apical suspension and structural support that distributes load within the pelvic space. Mesh characteristics and the surgical technique likely affect outcomes. Therefore, it's important for the Panel and FDA to consider the outcomes of current-generation mesh and the single-

incision surgical technique that's used today.

A substantial body of literature describes the importance of mesh characteristics on the host tissue response. Current-generation mesh is ultra-lightweight and macroporous. These characteristics, weight and porosity, reduce the inflammatory response, potentially enhance mesh performance while promoting better integration into the host tissue. These important scientific observations were publicly recognized by FDA in 2011.

Restorelle DirectFix mesh represents the latest generation of synthetic mesh devices for treatment of anterior prolapse. Restorelle was purposefully designed for the pelvic space. From the beginning, Restorelle was designed to be ultra-lightweight; in fact, at 19 g/m^2 it's the lightest-weight mesh available. Restorelle is also macroporous, it's made of monofilament polypropylene, and it has a preconfigured shape. Restorelle DirectFix is implanted through a single-incision surgical technique that includes fixation to provide lateral and apical support.

DirectFix mesh has been marketed since 2009. There are 10 years of postmarket safety information which confirms that Restorelle's safety profile is consistent over time and well characterized. As noted, Restorelle DirectFix Anterior Mesh is under a PMA review. Typically, devices that are subject to a PMA review are investigational, and they do not have an established postmarket history, and their safety profile is informed exclusively through the clinical trial data submitted to support the application.

For this Panel meeting, Coloplast performed a search of the MAUDE database to identify all reports related to the use of Restorelle mesh to treat anterior prolapse. We used a date range from 2012 to 2018 in order to assess new data following FDA's prior MAUDE database review in 2011. Through this search, we find that the types of adverse events in MAUDE today are similar to those that were previously identified by FDA. In addition, these event types are consistent over time, indicating that new types of events are

likely to occur. Importantly, with the exception of mesh exposure, we note that all of the events in our MAUDE search also occurred during native tissue repair.

The published clinical literature including recent systematic meta-analyses are dominated by mesh devices and surgical techniques that are no longer used. To provide the Panel publicly available information concerning current-generation mesh and surgical technique, Coloplast performed a literature search. The search criteria and methodology are described in detail within our Executive Summary.

In brief, our search covered the period from January 2011 to November 2018. Selection criteria required that the mesh have characteristics similar to Restorelle mesh, including ultra-lightweight density and macroporous construction. We also required implantation by the single-incision transvaginal technique with fixation, and we required that the selected studies report follow-up of 12 months or more.

Our search identified 16 clinical studies reporting outcomes on 1842 patients with follow-up ranging from 12 to 60 months. Two prospective cohort studies compared ultra-lightweight mesh to native tissue repair and both studies report statistically significant improvement in objective outcomes when compared to native tissue repair. Fourteen of the studies were mesh-only cohort studies that compared outcomes to baseline. All 14 studies evaluated objective outcomes and all studies report improvement.

A majority of the studies also evaluated subjective improvement and when measured, substantial improvements from baseline were observed. Eight of these 14 studies collected data beyond 12 months and improvements from baseline were seen through the last reported follow-up.

Pelvic surgery with or without mesh carries with it the risk of pelvic pain, dyspareunia, and other events. The focus of this slide is mesh exposure or extrusion, a unique event which does not occur with native tissue repair. This figure shows the rate of

exposure for each of the 16 studies. All 16 studies from our literature review reported rates of mesh exposure or extrusion. You will note that the overall incidence is 2.3% with a range from 0 to 7.3% across the studies. These data reflect rates of exposure reported in clinical studies using current-generation mesh and the single-incision technique. This range is well below the range of 11 to 18% presented by FDA in its literature review, which again is not limited to current-generation mesh or the single-incision surgical procedure.

Next, I would like to share some observations on patient selection from the Restorelle 522 study. But, first, some background on study design. This ongoing postmarket study serves a dual purpose to meet FDA requirements. The first purpose is to provide real-world postmarket surveillance data through 36 months after repair using Restorelle mesh or native tissue repair. The second purpose of the study is to provide effectiveness and safety data at 12 months to support a PMA application.

Importantly, the Restorelle 522 study collects rates of all adverse events considered relevant, including rates of pelvic pain, infection, dyspareunia, mesh exposure, and others. The Restorelle 522 study also collects information concerning the treatment, duration, and resolution of adverse events. In addition, the study evaluates quality of life and patient satisfaction data. We believe that when assessing benefit-risk, the totality of the data need to be considered.

Moving into treatment selection, treatment selection in the 522, the Restorelle 522 study, did not occur through randomization. Beginning in 2008, multiple notices to physicians and patients had been issued by FDA, plus several medical societies issued guidance concerning the use of transvaginal mesh. In general, the statements recommended that transvaginal mesh should be used with caution and that surgeons should consider the use of mesh only in more complicated patients who are contraindicated for other procedures or those with risk factors for recurrence. Therefore, randomization

was not considered appropriate.

In the Restorelle 522 study, treatment assignment was based on a detailed and thoughtful pre-enrollment discussion between the patient and her surgeon taking into account the patient's needs and preferences as well as the potential benefits and risks of treatment options. In the Restorelle 522 study, patients and surgeons made real-world benefit-risk decisions about the choice of treatment prior to enrollment in the study.

So what was the result of this method of treatment assignment? A review of patients' baseline characteristics show that patients in the mesh group are more medically complicated patients and at a higher risk for recurrent prolapse. For example, nearly three times more patients in the mesh group had undergone prior prolapse surgery. Also, patients in the mesh group tended to be older, postmenopausal, and more likely to be receiving estrogen therapy and have vaginal atrophy. These patient selection observations from the Restorelle 522 study demonstrate alignment with medical society consensus statements and indicate that, today, surgeons and patients are actively making benefit-risk determinations.

We believe that the assessment of benefit-risk requires FDA to understand how patients are assigned to treatment groups as well as the consideration that patient characteristics between groups may vary.

The Panel is also asked to consider physician education and training. Coloplast offers comprehensive surgical skills workshops, one-on-one programs, didactic and hands-on courses using state-of-the-art simulation models, physician preceptorships and proctorships. In brief, Coloplast agrees that training and skill is essential and we are pleased to see the involvement of key professional societies at this meeting and we look forward to supporting their initiatives.

In summary, all mesh is not equal. Please keep in mind that FDA's literature search

is dominated by mesh devices and surgical techniques that are no longer used. Current-generation mesh is ultra-lightweight and macroporous.

In addition, we believe that patients and physicians need options. Each patient is unique, and through the Restorelle 522 study, we see patients and physicians making real-world benefit choices.

Thank you.

DR. ISAACSON: Thank you very much.

(Applause.)

DR. ISAACSON: I would like to thank Boston Scientific and Coloplast for their presentations and ask the Panel if anyone has any brief clarifying questions for either of the manufacturers.

Yes. Just state --

DR. LING: This question is directed -- oh, Frank Ling.

I'm directing the question to the Coloplast study. Just out of curiosity, what guidance, if any, did the physicians have in trying to reach a final decision with the patient about the approach he was going to take? Was there any structure to it? Was there any endpoint? Was there incentive to have the patient guided in one direction or the other? Some who are not?

MR. KLOUS: Yes, that's an excellent question for one of our medical experts, so I'd like to call up one to the stand. Thank you.

DR. LING: I asked question because obviously doctors and patients, when they're one on one in an exam room trying to discuss options, doctors have their preferences, patients have their preferences and, in this particular case, the doctors have a further agenda behind them. So I'm just wondering what, if any, direction they were given.

DR. ROOVERS: My name is Jan-Paul Roovers, and I'm a Professor of Urogynecology

in the Netherlands and a co-investigator of this 522 study.

As part of the decision process, we did not have a standardized decision grid, but we recommended that physicians consult the patients based on their experiences of mesh surgery in their own clinic and as you are aware, the results and outcomes of mesh surgery vary among studies, among countries, among settings, and it's extremely important that physicians have insight in their own performance and base that counseling on this performance. Then, of course, the patients' expectations are also very different, and in the end it's a joint decision process where the patient has the last voice.

DR. LING: So just as a follow-up because it, like you say, does simulate the real world, I guess a critic would say isn't that part of the problem, is that the patient is being given kind of an imbalanced view of the world.

DR. ROOVERS: So let's say you would at, first, such imbalance and you would perform a randomized controlled trial.

DR. LING: Right, that's the other option.

DR. ROOVERS: And randomized controlled trials are a great design if patients are in equipoise and physicians are in equipoise. That phase is far behind us, and if we would perform a randomized controlled trial nowadays, that means that only a very limited amount of the patients which would be meeting the eligibility criteria would participate in such a trial, and we most likely would make the mistake to then generalize the findings of such a trial to all future patients, whereas if we do a comparative study based on real clinical life, we have a kind of self-healing situation where those physicians will feel very comfortable with mesh and those patients will have good reasons to undergo a mesh procedure allocated to one and those patients and physicians will come to the decision to do a native tissue surgery or allocated to the other, which means that the results of such a study are generalizable to all other situations.

DR. ISAACSON: Yes.

DR. EREKSON: So I just had a --

DR. ISAACSON: Just --

DR. EREKSON: Oh, Liz Erekson.

My question is for Coloplast. I think when I read the Boston Scientific Executive Summary, they excluded patients with autoimmune disease and chronic pelvic pain. I didn't find that in your Executive Summary. Can you just clarify on that?

MR. KLOUS: We had a very similar exclusion criterion. In fact, the study design across all of the 522 studies is very similar.

DR. LOWDER: This is Jerry Lowder.

This question is for Boston Scientific. So in your 522 study, did you further characterize the surgeons that were implanting? I mean, you mentioned they were about 35% academic and 65% private practice, but were these primarily preexisting, high-volume surgeons?

DR. MORTON: So the surgeons had to have performed at least 10 procedures previously in order to be included in the study. We have the characteristics of those surgeons prior to being involved in a study. Some of the data are not complete because we don't have -- we only have data from their institution where they were at the time they began in the study. We don't have what they did before that. But there was no attempt made to ensure that there were only high-volume surgeons in the study, and in fact, some of the surgeons in the native tissue repair arm were some of the highest-volume native tissue repair surgeons in the country.

It's also important to note that the native tissue repair control arm in the study is not purely from the Boston Scientific arms of the study. So we used the AUGS registry to get patients who were part of our native tissue repair arm, and we had no control over the

background and the experience of those surgeons, as they came from our other industry partners.

DR. LOWDER: So a follow-up question, particularly with the SUPeR data but somewhat similar with the data that you've presented. Based on likely the skill set of the surgeons, particularly with the SUPeR trial, they kind of maximized outcomes for and success rates for both native tissue and for the Uphold and the complications are minimized, at least compared to prior studies. What do you expect kind of with the real-world experience when they're -- when these are being implanted by surgeons not of the skill set, and what would you find or anticipate to be acceptable results, as a company, both for mesh exposure rates and for the composite outcome definitions of success?

DR. MORTON: Well, first, I don't want to speak for the SUPeR study, and if the Panel would allow it, I would ask Dr. Nager to speak for that study because I think he's in a much better position to comment on that aspect than I am. But I would say that we did have a large number of our investigators come from private practices across the country, and we do believe that the physicians that participated in our study are representative of the physicians who treat pelvic organ prolapse today, and I don't believe that, given the improvements in mesh characteristics, improvements in physician and surgeon training, that the improvements we see in these studies won't be carried out throughout the remainder of the population, if you will, or the remainder of physicians treating pelvic organ prolapse.

DR. ISAACSON: I just have one brief question. Thank you. Keith Isaacson.

That's on the subjective results and within the study, does each center use the same QOL questionnaire or do different centers get to use different questionnaires?

DR. MORTON: No, the patient-reported outcome instruments were all validated instruments for a standardizing study, and each center used the exact same instruments.

DR. ISAACSON: The same. Thank you.

Dr. Morgan.

DR. MAZLOOMDOOST: Donna Mazloomdoost.

One other question. Were the follow-up exam POP-Qs done by the surgeon performing the surgery?

DR. MORTON: So the protocol was written such that there was to be an independent assessor for POP-Q. However, we did allow -- because a lot of our sites are in very remote areas of the country and we wanted to allow women the opportunity to come in, if they had an appointment and there was not an independent assessor there, that they could be assessed by the treating surgeon. That happened in approximately 40 -- I would have to get the exact number, and I could get that for you if you like, but approximately 40% of the time.

DR. ISAACSON: Yes, Dan.

DR. MORGAN: It sounds certainly that it was just the lighter-weight meshes that you have -- there's a lower rate of exposure and extrusions, so this could go to either you or Coloplast, but among those women that did have an exposure, do they have significant sexual dysfunction or other problems? I realize it didn't lead to a reoperation, but was there some kind of data you can tell us that if they do have this erosion, even though maybe it's not something that led to a reoperation, what kind of sexual dysfunction did they have and/or other problems?

DR. MORTON: So part of the issue is that most of the women who suffered exposure were postmenopausal and many of them were not sexually active. So that just is what it is. There were only 11 events in nine subjects and I believe seven of them of them were not sexually active. So I don't believe that the two remaining who were sexually active had issues with dyspareunia, and dyspareunia rates compared in the native tissue repair arm

compared to Uphold LITE and Xenform were comparable. That's a very good question. Unfortunately, these studies were not really designed to assess that question specifically.

DR. ISAACSON: That's great. Well, I appreciate both Boston Scientific and Coloplast for the terrific presentations.

DR. MORTON: Thank you.

(Applause.)

DR. ISAACSON: We are now moving on to the professional society presentations, and our first presentation will be from the American College of OB/GYN, and I'd like to invite Dr. Cheryl Iglesia to approach the podium. The same reminder to the public is that the attendees may not participate except at the specific request of the Panel Chair.

Thank you, Cheryl.

DR. IGLESIA: Thank you.

Good afternoon, my name is Dr. Cheryl Iglesia. I am director of the section of female pelvic medicine and reconstructive surgery at MedStar Washington Hospital Center, and I'm a Professor of Obstetrics and Gynecology and Neurology at Georgetown University School of Medicine. I'm also a fellow of the American College of Obstetricians and Gynecologists (ACOG), a national medical organization representing over 58,000 members who provide healthcare for women. I have no conflicts of interest to disclose.

So today I'm appearing on behalf of ACOG to provide an overview of the organization's guidance on the safety and effectiveness of transvaginal mesh placement for pelvic organ prolapse repair, and to present considerations for the review and interpretation of study data on this procedure in the anterior compartment. We have provided you with a more detailed written testimony as well. And ACOG wants to thank the FDA for holding this Advisory Committee meeting and for the opportunity to speak on this important issue.

So there are unique advantages and complications associated with synthetic mesh when used in pelvic organ prolapse surgery. Systematic review evidence shows that transvaginal mesh for anterior pelvic organ prolapse repair provides improved anatomic and some subjective outcomes such as decreased awareness to prolapse, decreased risk of repeat surgery for prolapse, and decreased risk of overall recurrence, compared with native tissue repair. However, there are unique complications associated with synthetic mesh when used in pelvic organ prolapse surgery, including mesh contracture and vaginal exposure as well as erosion to the urethra, bladder, and rectum. Multiple procedures often are required to manage mesh-related complications.

So given the potential complications, pelvic organ prolapse vaginal mesh repair should be limited to high-risk individuals in whom the benefit of mesh placement may justify the risk, such as individuals with recurrent prolapse, particularly of the anterior/apical compartments, or with medical comorbidities that preclude more invasive and lengthier open and endoscopic/laparoscopic/robotic procedures.

Before placement of synthetic mesh grafts in the anterior vaginal wall, patients should provide their informed consent after reviewing the benefits and risks of a procedure and discussing alternative repairs and treatments. The risk-benefit ratio is very individualized, underscoring the important role of patient counseling, education, and shared decision making for patients contemplating anterior pelvic organ prolapse repair with transvaginal mesh.

There is a critical need for data from high-quality studies on the use of the newer lighter-weight Type 1 transvaginal meshes in pelvic organ prolapse surgery. Much of the existing data on the use of transvaginal mesh in pelvic organ prolapse surgery comes from low- to moderate-quality, short-term studies of other multi-filament, smaller pore size synthetic mesh that is no longer in use in clinical practice. Many of these prior studies also

involved heavier-weight mesh with arms placed using transobturator trocars and these, too, are no longer available. So high-quality data are needed on the safety and effectiveness of the newer biologic grafts in pelvic organ prolapse surgery.

Systematic review findings show that the use of biologic grafts as well in transvaginal repair of anterior prolapse provides minimal benefit over native tissue. However, it is difficult to make an overall recommendation about the use of biologic grafts for vaginal prolapse repair because the available evidence is also of low quality and those of the biologic grafts that were used in studies, to date, are no longer available.

Information gleaned from the FDA's postmarket surveillance 522 studies, the large ongoing randomized trials such as the prolapse surgery pragmatic evaluation and randomized controlled trial from England, the PROSPECT study, and patient registries such as the Pelvic Floor Disorders Registry, will provide important efficacy and safety data on the newer Type 1, single-incision, smaller-profile and lighter-weight synthetic meshes and biologic grafts. So important considerations when viewing the newer data on the transvaginal lighter-weight prolapse repair meshes include the appropriateness of the objective and subjective outcomes, the validity of assessment tools, the adequacy of follow-up time, and potential confounding variables such as patient characteristics and surgeon experience.

In general, important subjective and objective outcomes for assessing the safety and effectiveness of transvaginal mesh for anterior prolapse repair include symptoms of a bulge, some objective quantification of prolapse, sexual function as well as bladder and bowel function, and the need for repeat surgery or intervention like a pessary for prolapse recurrence or intervention for complications. Validated questionnaires for bulge symptoms, bladder and bowel function and sexual function have been published and are included in the Pelvic Floor Disorders Registry and in NIH's NICHD Pelvic Floor Disorders Network

clinical trials. These include the Pelvic Floor Disorders Inventory (PFDI) as well as the Prolapse Incontinence Sexual Questionnaire Internationally Revised (PISQIR) among other validated assessment tools.

Assessment of surgical complications should include the severity of the condition and whether the condition needs further intervention. Surgical complications have been graded, including the Pelvic Floor Complications Scale as well as in general surgery complication scales such as Clavien-Dindo.

Patient blinding. So patient blinding is valuable to minimize assessor and patient bias. However, it is very difficult to maintain masking over the long term and there are feasibility as well as ethical considerations to blinding. Objective success and complications cannot be determined over the short term. In general, the longer the follow-up, the better. Two of the clinical trials in the NICHD Pelvic Floor Disorders Network with the longest follow-up after prolapse surgery reports, report data at 5 years and 7 years, respectively.

So with regard to certain patient characteristics, patient selection, certain patients' characteristics can influence pelvic organ prolapse repair outcomes and should be considered when reviewing study results. These include but are not limited to

- Is this a primary versus a secondary prolapse surgery;
- The baseline stage, higher stage versus lower stage;
- The age of the patient;
- The menopausal status and/or estrogen use;
- Obesity/BMI considerations;
- The presence of chronic pelvic pain;
- The presence of pelvic floor muscle damage;
- Hereditary collagen masker or other known risks, including cancer risks;
- Medical comorbidities including inflammatory bowel conditions, known bowel

adhesions, and other autoimmune conditions.

Surgeons who perform pelvic organ prolapse surgery with synthetic mesh grafts should have the training specifically for these procedures and should be able to counsel patients regarding the risk-benefit ratio for the use of mesh compared with native tissue repair.

In general, subjective and objective improvement in prolapse should be balanced against the tradeoffs made to the possible risk of added mesh or biologic graft for both anterior and apical prolapse repair, including symptomatic recurrent prolapse, de novo or new changes in sexual, bladder, and bowel function and mesh-related complications, particularly those requiring intervention.

The determination as to which intervention is better than -- which is better than one than another is a patient-specific judgment about the balance of risks and effectiveness. It is not indicated just by the degree of effectiveness. For example, for a patient with recurrent anterior prolapse, the greater chance of success using mesh versus native tissue may outweigh the higher risk of complications associated with mesh use.

In conclusion, ACOG supports the current efforts by the FDA, by patient registries and researchers, to investigate and improve the safety and effectiveness of surgical options for women with pelvic organ prolapse. On behalf of ACOG, thank you for holding this meeting and for the opportunity to provide input on the use of transvaginal mesh for the treatment of anterior pelvic organ prolapse.

(Applause.)

DR. ISAACSON: Thank you, Dr. Iglesia.

Next, we have the American Urogynecologic Society. Dr. Cundiff, please approach the podium.

DR. CUNDIFF: Thank you.

DR. ISAACSON: Thank you.

DR. CUNDIFF: My name is Geoff Cundiff. I'm a professor and head of OB/GYN at the University of British Columbia and a urogynecologist there. I'm also the president of AUGS, and that's how I'm here today. I have no relationships, financial or otherwise, with any pharmaceutical or surgical company and that is a requirement of all officers of AUGS. All of our board also have any potential conflicts listed publicly on our website.

At AUGS, we respect the vital role of the FDA in ensuring that our patients have access to medical devices that are efficacious, safe, and meet their healthcare needs. We also respect the FDA's leadership over the past decade in pursuing the mandate within urogynecology and we are honored to attend this Advisory Committee meeting.

This afternoon I will offer considerations of how to evaluate transvaginal mesh procedures for prolapse, including safety and efficacy. I will also lay out programs and policies that we propose to maximize the safety of their use, improve the availability of well-trained providers, and to more skillfully address the unintended outcomes associated with their use.

AUGS feels that women are better served when there are more treatment options. Consequently, AUGS supports the continued development and availability of transvaginal mesh devices for prolapse. We acknowledge the safety concerns, although we would like to take the opportunity to clarify that these are related to local anatomic issues regarding tissue incorporation, scar formation, and mesh exposure and claims of systemic complications have not been scientifically supported. Mesh does not cause cancer, and a Swedish healthcare registry examined over five million women and found no association. And, similarly, another study showed no link between mesh use and autoimmune disease.

All surgical interventions offer a benefit to the patient but must be balanced by the potential risk inherent to the intervention. The probability of benefit varies by procedure,

patient, and surgeon, as does the type and probability of a complication. In considering a potential treatment, patients should personally balance the probability of benefit with the potential risk of complications. Moreover, the evaluation of potential complications should not only consider the frequency of occurrences, but also the degree of associated morbidity and the degree of difficulty in treating them.

Providing adequate information to patients to prepare them for their decisions is a responsibility of the physician providing treatment, and physicians can help to frame the benefits and risks through shared decision making, but ultimately it is the patient that makes the decision. And because the balance in benefit and risk is a personal decision, women benefit from having a range of treatment options. This is especially true for treatment of pelvic floor disorders where the goal of intervention is to improve quality of life. Each individual experiences pelvic floor differently, and underlying the need for a spectrum of treatment options including nonsurgical options and alternative surgical interventions.

The FDA's safety announcement in 2011 demonstrated that transvaginal mesh procedures are associated with higher complications than native tissue repairs and abdominal mesh repairs with uncertain improvement in durability.

A systematic review of transvaginal mesh procedures for prolapse revealed different outcomes depending on the vaginal compartment where the mesh was used, and adding mesh to the posterior vaginal wall increased complications with no improvement in anatomical results or the relief of symptoms.

On the other hand, in the anterior vaginal wall, which is the area of greatest vulnerability for native tissue prolapse repairs, multiple RCTs show anatomic benefit with less evidence of subjective benefit. This highlights the need to focus on transvaginal prolapse procedures for the anterior compartment, although as recognized already, they're

often used for apical prolapse as well.

Some patients may decide that the mesh-based complications associated with transvaginal mesh procedures are outweighed by the added durability provided by these procedures. While AUGS does not feel that there's evidence to support the routine use of transvaginal mesh for prolapse, there are certain patient characteristics that increase the potential benefit of the transvaginal mesh approach and could create a favorable balance to the increased rate of surgical complications.

There are several glaring gaps in the evidence for procedures using transvaginal mesh. Firstly, many of the RCTs investigating mesh in the anterior compartment used devices or mesh materials that are no longer available and as material improvements, such as the lighter weight and open-pore architecture have taken place, mesh performance has improved. So older data should not be applied to newer materials and, as already noted, each device should be evaluated on its merits.

Moreover, there is a paucity of studies to compare the efficacy and safety in different populations of women. This compromises the ability to compare potential benefits to risk in a given patient. Additionally, best practices and algorithms for categorizing and treating mesh complications have not been well developed. Lastly, much of the available data comes from academic centers that may not reflect the real-world performance of these products.

AUGS supports the use of the FDA benefit-risk framework for evaluation of transvaginal mesh for prolapse. The basic structure includes five key decision factors: analysis of condition, current treatment options, benefit, risk, and risk management. The analysis of the condition and current treatment options provides the context that is essential to weighing the benefits and risk of the treatment under review. This can be effectively applied to the evaluation of transvaginal mesh procedures.

The analysis of conditions includes the prevalence and impact of prolapse and the recognition that prolapse refers to a broad group of support defects with a wide spectrum of symptoms and bother. Considering current treatments, the reported rate of reoperation for prolapse is 13% at 5 years raising to 17% at 10 years. But not all patients with recurrence seek additional surgery, so the actual recurrence rate is higher.

However, the reoperation rate is the highest for women who have previously failed a surgery for prolapse, and this population who has failed a surgery for prolapse are examples of patients who may be willing to assume a higher risk of complications for a more durable surgical repair.

Because prolapse procedures that use mesh offer better durability, offset by potentially higher risks of complications, any comparison to native tissue repairs must include assessment of both durability and safety. Key considerations of benefit include added durability or assessment -- added durability applied to the specific patient populations and whether the surgeon's experience impacts efficacy. Similarly, the considerations of risk include subpopulations of surgeons and their experience as well as the severity and reversibility of adverse events.

Because prolapse procedures that use mesh offer better durability -- I'm sorry. Risk management assesses the practicality of ensuring that the treatment is directed to those patients for whom the risk is considered acceptable, and the evidence is presently inadequate for this. And I think this underlies the need for evidence on best management of surgical complications related to mesh as well. Ultimately, this model provides a method to draw conclusions based on the standardized subjective assessment of the evidence and uncertainties in each category.

Looking more specifically at how to evaluate benefit, we should recognize that patients seek treatment of their prolapse to alleviate symptoms and this fact underlies the

primacy of patient-centered outcomes and ideally, patient-reported outcomes as the primary outcome measure. These are not really subjective outcomes. They're measured with objective clinimetric tools, and these instruments have already been described. They need to assess urinary as well as bowel function and prolapse symptoms, and sexual function is also important and should be assessed using validated tools that go beyond assessing frequency of sexual activity and dyspareunia to include desire, arousal, orgasm, and satisfaction. Not all patients with prolapse will be sexually active, either due to their prolapse or other reasons, but there must be sufficient numbers to assess sexual function before and after procedures.

Because surgery for prolapse seeks to impact symptoms by fixing anatomy, anatomical outcomes are frequently used as a proxy outcome. They also are favored in objective assessment that is valuable for longitudinal analysis. Nevertheless, anatomical outcomes should not be used in place of patient-centered outcomes.

Assessment of surgical complications should include general surgical complications and those specific to mesh procedures. The Clavien-Dindo Complication Scale is useful for the former and the Pelvic Floor Complication Score for the latter.

Reoperation or retreatment of prolapse is also a required outcome measure. This is a significant complication given the addition of a new set of perioperative and long-term risk, and this applies to reoperation for complications and recurrent prolapse.

There is ample evidence that mesh exposures are not time-limited but have cumulative risk, and this means that added durability must be continuously balanced against the cumulative risk of mesh exposure and underlies the importance of long-term studies of 5 to 10 years to assess both efficacy and safety.

Because patients will have different benefit-risk equations, defining patient subgroups is essential to personalizing the treatment of patients' wishes, and the most

important characteristics to consider are those that have been shown to increase the risk of recurrence or of mesh complications.

Blinding minimizes the opportunity for bias to confound results but also compromises external validity, and as noted, it's difficult when there's not equipoise. So given the importance of evaluating procedures in a broad range of surgeons and the feasibility constraints, we think surgical registries offer a real-world assessment that complements randomized trials.

AUGS initiated the AQUIRE registry for quality improvement, but the registry has evolved in focus and goals and now goes beyond providing quality feedback. It is designed to collect patient information based on condition and includes information on multiple treatments of that condition. And this allows comparison of different treatments using the framework. It includes physicians across a wide spectrum because it allows them to use a merit-based payment system, the quality payment program, and this encourages participation of practicing surgeons along a wide spectrum.

The AQUIRE registry offers a framework that will complement the evidence provided by the prospective trials. It meets the requirement of assessing both benefits and risk of treatments and allowing comparisons that include both. Through the inclusion of a broad range of physicians, it reflects a real-world performance of treatments and it maximizes the patient voice through patient-reported outcomes and allows an analysis of treatments in patient subpopulations that will facilitate the development of evidence to inform shared decision making. Ultimately, the AQUIRE registry will provide the data to expand physicians' understanding of benefit and risk of specific treatments, including mesh-based treatments within specific populations.

And so it also had educational value, and we see a number of educational needs, including for patients. The primary role of AUGS as a purveyor of surgical education is the

development and maintenance of competencies in diagnosis and management of pelvic floor disorders, and that includes nonsurgical and surgical treatments including those that use mesh and alternative procedures to support patient choice.

We believe that options should be available for all patients for any pelvic floor condition and this also extends to developing and promoting competencies in managing surgical complications. The literature describes a wide variation of complications associated with transvaginal mesh in prolapse repairs, and this suggests that there is a spectrum of competency. Moreover, there is ample evidence of a direct relationship between surgical volume and surgical quality outcomes, highlighting the importance of improving education and defining credentialing criteria for surgeons learning these techniques.

AUGS supports the role of professional organizations in developing and supporting surgical education for both learners and practicing physicians related to transvaginal mesh and prolapse. Our educational mission supports lifetime learning by defining the curriculum for learners and ensuring quality continuing education to support practicing physicians and we believe that surgeons offering transvaginal mesh repair should provide appropriate informed consent that includes discussion of alternative treatments and potential complications and should monitor their quality using a surgical registry.

And thank you for your attention and for the opportunity to speak.

DR. ISAACSON: Thank you, Dr. Cundiff.

(Applause.)

DR. ISAACSON: I would now like to invite the Society of Gynecologic Surgeons to speak, and on their behalf will be Dr. Megan Schimpf.

DR. SCHIMPF: Good afternoon. I'm honored to be here representing the Society of Gynecologic Surgeons. They did compensate me for the travel to come here, but that being

said, I have no personal financial relationships with industry.

The Society of Gynecologic Surgeons, more than 10 years ago, founded what they call the systematic review group. It's made up of 30 to 40 practicing gynecologic surgeons who use their everyday clinical expertise combined with that of research review experts in methodology to perform systematic reviews. The first review that this group did was in 2008, covering graft use in transvaginal pelvic organ prolapse repair. The major conclusion that grew out of this was that there was not enough data and more studies were needed. They also drafted some guidelines and we'll come back to those later.

Using that same research review, they published an adverse events paper in 2011. You see here I've highlighted the synthetic mesh results with regard to erosion, which was about 10%; granulation and tissue formation, which was about 7%; and then dyspareunia rates, which was about 9%. There was no significant difference in this review comparing synthetic graft material or synthetic versus biologic graft material.

As time went on, so did our reviews. So our most updated review was published in 2016 looking at the progress in research since then. In systematic review worlds we talk about the PICO, which it kind of looks at what are we looking at when we're doing a review. So the population that we looked at were women undergoing transvaginal repair of prolapse, so not sacrocolpopexies, not abdominal repairs, just transvaginal repairs. We compared the mesh and graft surgery to native tissue repair or, when possible, another mesh or graft surgery. We surveyed a number of outcomes that those various things reported.

And I need to clarify that any systematic review can only report on what the studies report on. We're not doing original research. So I have to explain that the erosion that we're talking about here might reflect a wide range of what we now have a variety of terms for. So it could be an exposure, it could be an erosion, it could be an extrusion. We're just

limited by what people report in their own studies, and when some of these studies were published, we definitely didn't have that richness of description.

So this is our literature flow diagram. You can see that we -- even in the roughly 7 years or so between the literature searches from Review Number 1 to the paper that we did, we found a wide range, virtually an explosion of literature in that time being, and also a big advance in the quality of that. So we had a much greater number of RCTs and higher-quality research in the second version of our review than we had available to us at the start. So we ended up having 66 studies that were reported in 70 articles.

And today we're just going to talk about the anterior vaginal compartment, and you see that we have 26 RCTs that we were able to summarize with the addition of 16 cohort studies. That, like I said, is a pretty substantial increase from the 11 studies that we had available to us in the 2008 paper. Length of follow-up, as we've talked about already today, was unfortunately quite short with the longest paper going out to 5 years but almost every other study being about 12 months.

So specifically focusing in even further on the synthetic non-absorbable mesh category versus native tissue repair, we had 20 studies to look at. We found that mesh use consistently resulted in improved anatomic outcomes, but as other people have mentioned today, subjective outcomes showed no difference between the native tissue arm and the synthetic mesh arm.

Looking at these studies, we did find that there was a low-weight, macroporous monofilament polypropylene mesh used in all but one study relevant to the time period that we had available to us. These were mostly a trocar-based prepackaged kit. I have them listed up there. None of those are still available. And the rest were self-tailored mesh products that the surgeon described in varying amounts of detail in their methods section for placement of the mesh. We found erosion rates ranging from 1.4 to 19% with return to

operating room for erosion about 3 to 8%.

Like I said, we are limited by the outcomes that are presented to us in the papers we're studying, so you can see the rich heterogeneity that we had here. That's both good and bad because it doesn't give us the opportunity to lump things together and provide big overarching statements, which is what everybody wants from a paper like this.

We were only able to do two meta-analyses on this data. This is for the question that asks about bulge symptoms. Not a validated measure, necessarily, but just did the patient have bulge symptoms afterward, and we did find that there was a trend towards favoring the use of mesh that was significant. We were also able to do a meta-analysis of a question on the POP-DI, which is a prolapse-related measure that was used pre- and post-op. There's one question that asks about bulge symptoms. And this as well was -- favored the use of mesh with regard to outcomes. We weren't able to do meta-analyses on any of the other outcomes, such as sexual activity or pain, just because of the variety in the ways at which those were reported.

We did have a very limited amount of information comparing different grafts, so we had 11 studies that looked at some form of mesh graft versus another form of mesh graft and the mesh arm in that consistently had better anatomic outcomes versus graft. Now, in the study, again, relevant to the time period we had, Pelvicol was the biologic graft of choice, also not available today, and very heterogeneous results here.

Other people have brought this up today about, throughout the process of doing this review, our group was struck by the fact that it's probably not fair to compare a traditional native tissue anterior colporrhaphy to a mesh surgery that involves some sort of fixation to perhaps the sacrospinous ligament, and we thought that was important enough to include in our discussion section.

That being said, we did do another review of multiple vaginal compartment surgery,

and we found 16 trials, 9 RCTs, that looked at that. These were often, again, various prepackaged kits and tended to favor the mesh arm of those surgeries, mostly driven by the anterior compartment results. So the posterior compartment, the apical support may not have been improved, but when you looked at the anterior outcome it's what drove the overall success of the mesh arm versus the other arm. There were only three studies in the cohort trials that looked at different mesh products versus each other and we found no difference in those trials.

For the multiple vaginal compartments, we found erosion rates going up to 36%, but still the reoperation rate was pretty low at about 8%, and we found that dyspareunia and urinary incontinence rates after surgery didn't differ between the arms. And we were able to conclude that high-quality evidence showed that anatomic outcomes were better with mesh in these trials versus native tissue repair, but the subjective outcomes were not different between groups. So our conclusion, not surprisingly, the best anatomic outcomes came with the use of mesh, but the subjective outcomes were not different between arms.

We were able to write some clinical practice guidelines and in our group, you have to have pretty good data for us to feel it's worthwhile to write a guideline. We know the implication that those can have. And so when we discussed this as a group and vetted it throughout the entire systematic review group, we concluded that native tissue repair was -- remained appropriate either compared to biologic or to use of synthetic mesh. If you were thinking about the use of synthetic mesh, specifically polypropylene, that's what we had in our research, for anatomic outcome of prolapse was reasonable. But there was not enough evidence to find a difference for some of the more subjective or secondary outcomes. And we could not provide any good recommendation on a specific product because of the paucity of data.

We've talked about the Cochrane Review several times already today, and generally

speaking, they found the same anatomic results that we did, with some variation in terms of the risks of repeat surgery depending on the different outcome. We tend to look at the similar trials to the Cochrane Group. They have sometimes a little bit more inclusion, where we are a little bit more focused, but our conclusions are not substantially different.

I wanted to give you a little bit of an update with regard to what that would look like today. It takes us a long time to do these reviews, which I didn't have the opportunity to do, but I did have our methods expert run our same search in December and tell me what would we find if we did that again today. And even in 3 years we found about the same -- we found 2400 new papers that we would have to search through to figure out if they met our inclusion criteria, but based on his experience he suspects that there would be 15 new RCTs and 11 new non-randomized trials that we could look at. And you can see the vast explosion in the amount of research in this area over the last few years.

We have a few points for thought. Over time, as we've talked about, there's been a substantial increase in the number of studies, the quality of studies has increased and improved and diversity of outcomes has been seen. So we're not just looking at anatomic outcomes anymore. There is subjective outcome data that we were able to look at. We definitely need studies of longer duration. That's true of almost everything we review in gynecologic surgery. And we need higher enrollment numbers to be able to see some of the more rare complications.

It's still unclear what synthetic material or placement technique is best. More data would help inform that and we hope the 522 studies can do that.

Complication rates in these high-quality study conditions don't seem to replicate general practice. Most of us, like I said, are practicing surgeons and we see mesh complications every day. So we know that this doesn't -- the trial doesn't seem to represent real life for all patients and we conclude that perhaps this is because skilled surgeons who

do research trials have lower complication rates.

Mesh itself is heterogeneous. There's little evidence that we have available to us today comparing different mesh options to give us what's the best mesh or what's the best graft.

Like I said before, this review excluded any form of abdominal surgery, so we don't have data on that. We don't have comparative data there. We've done other papers on apical support and slings, which are fascinating reading.

With regard to safety of mesh, this has been mentioned as well, but there are a number of trials that look at the risk of autoimmune disease or cancer, not finding any scientific basis for a connection of those conditions to mesh placement.

A moment on surgeon experience. So in the guidelines that we wrote coming out of our 2008 paper, I've put the exact quote here, but there is a need for practitioners to fully explain the relative merits of each alternative and carefully consider a patient's values and preferences to arrive at an appropriate decision, so shared supports or a shared decision model and discussing multiple options with patients prior to making a final decision as to how to move forward. AUGS has some guidelines on credentialing that's present in FDA materials already.

And looking at volume and complications, so again surgeon skill, there are multiple different studies. I've cited two here that look at the rate of surgeon volume and complication rate, confirming again and again that higher-volume surgeons have lower complication rates.

We haven't talked much today about mesh removal, so I wanted to spend one slide on that. Mesh removal is a complicated surgery, again, best done by expert surgeons. There's not much data on that, we haven't been able to do a review on that yet, but there is one trial that I'm aware of that does look at 90 women who underwent mesh removal by

expert surgeons. We were able to address their mesh exposure quite successfully in nearly a hundred percent of them, but pain only resolved in about half of the women who presented for surgery. There is a need to try to prevent these things because, as you've heard today, fixing them retrospectively is difficult.

So in conclusion and looking ahead, I wanted to point out that not all surgeons are the same, so fellowship training and extensive years in practice and, like we've talked about, volume, all predispose perhaps better outcomes for patients. We also think that the ability to offer a number of options to patients is beneficial for everyone involved.

Not all mesh is the same, so we can't extrapolate older products into newer products. We can't, perhaps, look at the biologic grafts and compare them to synthetic mesh without comparing them also to native tissue repair. The newer lighter-weight meshes that are being talked about for the 522 studies provide a whole new opportunity for research and data collection.

Not all patients are the same, and we've talked already today about the various different risk factors that put patients into different categories when we're thinking about what surgery they should have.

Native tissue is low risk and works for many patients and still should be considered a viable option in other groups of patients.

Thank you very much for this opportunity, and I look forward to any questions you might have.

(Applause.)

DR. ISAACSON: Thank you, Megan.

I would like to thank all three professional societies for their presentations and, of course, give the Panel a chance to ask some clarifying questions to any of these presenters and just again for the Panel, just state your name and direct -- who is the question directed

to.

DR. CONNOR: Dr. Cundiff.

DR. ISAACSON: Dr. Cundiff.

DR. CONNOR: This is Jason Connor.

In your presentation you mentioned populations for whom mesh may be most appropriate and one of the bullets you listed were patients with connective tissue disorder. So I'm not a doc, so someone correct me if I'm making the wrong connection here. But for instance, like rheumatoid arthritis, I think, is a connective tissue disorder, but it seemed like autoimmune diseases were excluded from both of the sponsors' studies, or both sponsors' studies, three studies total that we were looking at here today. So it seems like a disconnect that a group in whom they're recommending this may be most appropriate is a group who was excluded from the studies we're hearing about. Did I catch that right, to my surgical and colleagues on the Panel?

DR. CUNDIFF: Well, I don't think I actually listed connective tissue disorders, although that is considered a risk factor for recurrent prolapse. Although there's not a tremendous amount of data, there are specific connective tissue disorders like Ehlers-Danlos, for example. I think in terms of the autoimmune disease exemption, that's because there is, in the popular press, a popular idea that people get autoimmune disease from having mesh implanted and there really isn't evidence at this point to show that that is the case, but that's why there's been an active exclusion of those patients.

DR. CONNOR: Thanks.

DR. ISAACSON: Yes, Kay.

DR. HOSKEY: Kay Hoskey.

This question is for Dr. Cundiff. You mentioned evidence gaps in different patient populations. So currently, with regard to the most -- the highest-risk patient such as one

who has failed a prior native tissue repair, please share your thoughts about use of a vaginal mesh that has been proven non-inferior in a broader population study.

DR. CUNDIFF: Should we offer that? Yes, we should offer that to such a patient who has already had a failure. I think that has to be offered with the potential risk and benefits clearly stated, and my experience is the patients usually have their own -- they bring their own framework to that, and for some patients that's an appropriate decision and for others it's not. I think it's a personal decision.

DR. ISAACSON: Dan.

DR. MORGAN: I think, for just the Panel in general, I'd like to get your thoughts on -- a lot of people mentioned the importance of surgeon skill and training, and I'm wondering about -- I think we've all seen patients who have had very difficult outcomes and are all worried about the idea that this gets pushed out to all of practice in a way that maybe doesn't help keep track of that, and I'm just wondering about do you think that any kind of compulsory reporting, maybe, you know, I think like there's certainly an example in REI where you have to report what your pregnancy rates are and other things with IVF. Do you think that that type of approach would be helpful or indicated in this kind of --

DR. CUNDIFF: I think that surgeons doing these procedures should be entering their patients' data and the patients should also be entering their own feelings in a registry. I also want to highlight that there's not a paucity of surgeons who can put in mesh, there's a paucity of surgeons who can treat mesh complications, and we really need to improve the evidence on how to maximize outcomes for those patients.

DR. IGLESIA: As representing ACOG, which does not have any guidance regarding credentialing and privileging, Dr. Morgan, on this subject, I do believe, as a pelvic reconstructive surgeon, that it is important for us to know our own outcomes. Heretofore there hasn't been a great way of doing that, unless you're involved in research and have

access to residents and fellows and databases to look back at your data or be involved in research networks, like the Pelvic Floor Disorders Network, to prospectively evaluate that. And I think that is a shortcoming in the United States, and I think we could do a better job in terms of looking back and looking better at each individual outcome because it does matter for the women that we treat, and if there are opportunities for improvement as a surgeon, well, bring it. You know, we want to be -- we want to do the best for the people we have. So that's why something like the Pelvic Floor Disorders Registry or somehow, if we're implanting something that we could monitor because I know that other societies, like orthopedics and thoracic surgeons, have required registries. I think it's important.

DR. SCHIMPF: SGS stands by promoting the highest standards in gynecologic surgical care, which may not have always happened with mesh to date. And so it promotes research, promotes thorough excellent training of surgeons in these, so not maybe a quick, you know, oh, I can do this in a cadaver, so I can clearly start doing it tomorrow in a patient, and so it stands behind strong education, research, and ethical standards in care.

DR. ISAACSON: Yeah, Madeline.

DR. DICK-BIASCOECHEA: Hi. Given that you all three agree that we don't have enough data to make very stringent recommendations right now, do you think the 522 prospective studies that are being done now, once they're completed, would those give us the data that we need, given that they're not randomized controlled trials, they're not blinded and they're sponsored?

DR. IGLESIA: Dr. Dick, I think that's a great question, and I think that's the best data that we have currently available on outcomes that matter. I think the fact that they included objective and subjective, including bowel, bladder, and sexual function, and the development of pain is extremely important and they used that based on, you know, the nested trials within, you know, the Pelvic Floor Disorders Registry, which had shared control

arms. But I think that that was the best of what we had based on a lot of the outcomes that were actually predetermined by the Pelvic Floor Disorders Network. So, yeah, it's the best of what we've got.

DR. CUNDIFF: I think it's premature to say whether you can judge it on the 522 studies until we actually have the full data because, at that time, if we -- if there seems to be a potential late benefit to use of mesh in the anterior wall and if that is shown at 3 years, then that might be a basis to continue their use. But I think if it is shown, we still have to go longer than that and that's because we know that mesh complications continue, they don't stop at 3 years, and so that needs to be reassessed further down the road.

DR. SCHIMPF: In our discussions at SGS, we're looking forward to seeing the results of the 522 studies. As my colleagues have mentioned, it's the best that we've got for the products that are out on the market right now. And so a lot of the studies we have that are out in the published literature don't necessarily mean anything anymore with regard to what's available for a doctor who's operating tomorrow, so we're looking forward to what we have. In our systematic review group, we have, you know, grades for different kinds of literature and what's stronger than other things, but we regularly have to use less than pristine trials because that's what's available in GYN surgery.

DR. ISAACSON: Yes, Kay.

DR. HOSKEY: Kay Hoskey.

For the Panel, how soon is too soon to determine success versus failure?

DR. IGLESIA: Thank you, Dr. Hoskey.

In the ACOG testimony we say, you know, the longer we can get the better. Obviously, the largest, longest studies that we have in the networks are 5 and 7 years, and I think we have the CARE trial out to 9 years. But then you have a point of diminishing returns because of the lack of the follow-up and the denominator situation that occurs,

which is why if we have patient-reported outcomes, when you can follow patients and not necessarily, you know, rely on the clinical data input by surgeons, that might matter more. And I think we have that kind of technology to be able to assess that, you know, and query patients. So that way you can have much longer follow-up, and that's a practical matter.

DR. CUNDIFF: I think the E-CARE study really is an excellent example, and it's a different procedure, different types of mesh used, so -- but the point is that at 7 years the outcomes were very different and the actual anatomical and patient-based outcomes had fallen and the complications had increased. So I think that highlights the importance of following it longer.

DR. ISAACSON: Dr. Ling.

DR. LING: Frank Ling.

I appreciate the fact that each of you is speaking on behalf of a highly respected organization, so you're giving us kind of a 30,000-foot view of the subject. So just out of curiosity, at each of your individual institutions, which I again understand are academic institutions, what I'm getting at, obviously, is the whole implementation idea that everybody keeps referring to, that a doctor and a patient make a decision. So as of right now, at your respective individual institutions, not speaking as a representative of a national organization, if a provider at one of your hospitals says oh, I'm going to use one of these devices under discussion, what limitations, if any, does each of your hospitals currently have on their use?

DR. IGLESIA: Thank you, Dr. Ling.

This is in regards to credentialing and privileging at the local level and I work for a big institution which has nine hospitals, six of which do GYN surgery and we have stringent guidelines when bringing in new devices, new technologies, including getting the right training, cadaver training if appropriate, proctoring and preceptoring and bringing people

in. So they have to get permission to do new things.

That being said, we've also been involved in some of the clinical trials. Dr. Gutman is one of my partners, and we have a large study on uterine-sparing surgery, looking at vaginal mesh versus a laparoscopic uterine suspension using a mesh procedure in the world and, you know, we all had to go through special training and do special follow-up in order to be able to be -- to enroll in that trial. So it's hard because when you -- I don't think that going to a weekend course, as Madeline was saying, is going to equate if you don't have the basic experience, background, training, not just with the new device, but with the alternative options.

DR. LING: I don't disagree with a word that you said, but I guess I want to get to the exact answer. What limitations exist at your hospitals? If someone says I want to do one of these next week, are there any hoops that have to be jumped through before they can do it or they can just do it?

DR. IGLESIA: No, they cannot just do it. We have guidance that was actually created by the American Urogynecologic Society that said that you have to have experience where half of your procedures that you do involve prolapse surgery, you have to be able to have exact documented training, and in certain situations -- and I'll bring up vaginal mesh or it could be robotic surgery, you have to be proctored. It's a certain number of cases.

DR. LING: And that's the specificity I was actually asking for.

DR. IGLESIA: Sorry about that.

DR. LING: Yeah. Well, that's great.

DR. CUNDIFF: I practice in Canada, so it's a little bit different. We have a provincial credentialing system, and you have to have had training in FPMRS and had the patients to maintain the volume, but you couldn't do these procedures because they're actually -- they haven't been approved due to inadequate evidence of efficacy at this point. So we've only

done them as part of trials and I just want to -- pertinent to our discussion, one of those trials is a blinded trial, federally funded, and we're having great difficulty recruiting because of the equipoise issue that Dr. Roovers mentioned.

DR. LING: Great.

DR. SCHIMPF: At my institution, we have a specific set of FPMRS urogynecology procedures that go above and beyond the OB/GYN general procedures, and so you have to be privileged for that by the department, and currently we do extremely limited vaginal mesh and grafts. So it would take discussion and proctoring to start that.

DR. ISAACSON: So we're almost on track. Is there another question? I have one last question for Megan, if I may, from the SGS. I've read a lot of practice guidelines and I just need clarification on the SGS practice guidelines, if you'll help me on this. I'm reading and then it says for anterior wall only, when performing isolated anterior wall vaginal repair, we recommend that native tissue repair remains appropriate. You have the same language for synthetic absorbable mesh, and then you almost have the exact same language for the synthetic non-absorbable mesh. Can you just walk me through what the true recommendation is on that particular slide?

DR. SCHIMPF: It's actually a slightly nuanced difference, and it has slight nuances and it's like --

DR. ISAACSON: I've read it five times and I think I get it.

DR. SCHIMPF: -- a 45-minute discussion. If you notice for the biologic graft, it's actually that "we recommend." So that's a strong -- that's pretty much the best it gets. And then when you get down to the second bullet point where we're talking about synthetic absorbable mesh, the wording is "we suggest," and I get that that's a very nuanced difference, but in guideline writing that's a step down.

DR. ISAACSON: Okay.

DR. SCHIMPF: And so less stringent. And then you'll see that the third bullet point, where we start talking about synthetic mesh, is much longer and that speaks to the complexity of that. So we had to -- we felt that it was important to describe that, again, "we recommend," so that's a strong statement, but when we're -- that's for the anatomic cure. But then we had to qualify that and say but these are the concerns with regard to there's not adequate information on these other outcome points.

DR. ISAACSON: So you're recommending one and C -- or A and C but not -- and D is just -- it's okay. Or suggest.

DR. SCHIMPF: Recommend is stronger than the suggest, yeah.

DR. ISAACSON: That's what I was trying to clarify.

DR. SCHIMPF: And then the fourth bullet point says we don't know what to do with the other stuff.

DR. ISAACSON: I know. Thank you very much.

Yeah, Jerry, we'll take one last one if it's okay, Jerry, then we'll --

DR. LOWDER: This is Jerry Lowder.

DR. ISAACSON: -- take a break after that.

DR. LOWDER: To all three, do you think there's adequate, up-to-date, and easily digestible information for patients to assess the risk and benefits of using mesh and do you think the responsibility to produce that would be from the societies, from the FDA or the companies?

DR. IGLESIA: Well, ACOG has very current practice bulletins on pelvic organ prolapse treatments including nonsurgical and surgical, and we have practice bulletins on urinary incontinence. In addition to that, ACOG has a patient education board that makes pamphlets specific to surgery for prolapse and incontinence, which I think are on a reading level easy to read and easy to digest and to start to share the discussion. But at the end of

the day, it is a decision with the patient and a surgeon.

DR. CUNDIFF: And AUGS has a website called the Voices for Pelvic Floor Disorders, or Voices for PFD, that is an informational site for patients and has downloadable pamphlets as well. We're also in the process of developing some shared decision-making tools for different areas of FPMRS.

DR. ISAACSON: All right. Thank you all.

We're going to take a 10-minute break, almost 10 minutes. Let's come back right at 3:00, and we'll start back up. Thank you very much.

(Off the record at 2:52 p.m.)

(On the record at 3:04 p.m.)

DR. ISAACSON: Okay, we're about to reconvene. It's a little bit after 3:00, and our mission for the next 2 hours is to go through eight questions that are proposed by Dr. Fisher and the FDA. So did you want to speak first?

DR. FISHER: Actually, we're going to do a Panel deliberation and have an open discussion on a variety of issues for about an hour before we get into the questions. So I think we're actually scheduled for an hour discussion and then spend the last 2 hours going over the questions.

DR. ISAACSON: Perfect, you've got it right. So it is now time to begin the Panel deliberations. I'd like to call -- oh, Dr. Fisher has already made -- have you already made your brief statement or you're doing it now?

DR. FISHER: Not yet.

DR. ISAACSON: Oh.

(Laughter.)

DR. FISHER: But I promise, it will be that brief.

DR. ISAACSON: Go ahead, please.

DR. FISHER: Well, thank you very much. Before we begin the Panel deliberations, FDA would like to share a few additional comments and kind of reiterate to the Panel of the scope and the charge today.

We have had a lot of information presented today and if I could just take a second to briefly summarize. During the Open Public Hearing we had testimony from patients. We also had comments from patient advocacy groups, physicians, attorneys, and industry CEOs that were tossing out possible alternatives that we might be looking at in the future.

FDA then gave its presentation, and that included background regulatory history, MDR, and literature analysis, and challenges that are associated with determining benefit-risk. We had presentations from Boston Scientific and Coloplast with some discussions on the 522 studies. And then we finally finished up with presentations from the professional societies discussing the important components needed in assessing subjective and objective endpoints and how data might be reviewed. For everybody who presented today, I would like to thank on behalf of the FDA for your participation, and thank you very much.

So first a comment on data that was presented by the manufacturers. FDA does not intend to provide any specific comment on the data presented by the manufacturers on a currently marketed device, and I would like to say right now that all of the information that was presented today by FDA is publicly available.

However, FDA will note that we may not agree with how the data were presented and analyzed. Specifically, FDA notes that conclusions may have been drawn from endpoints that do not include pre-specified hypotheses or were controlled for multiplicity. In addition, data at later time points that we've discussed may be inconclusive due to limited follow-up. In addition, FDA notes that comments have been made today regarding specific devices having well-characterized safety and effectiveness, and FDA would like to point out that there is a distinction between a device having well-characterized safety and

effectiveness and a device meeting the regulatory standard of a reasonable assurance of safety and effectiveness.

And I also want to point out something that was discussed earlier today. It's important to note that while FDA reviewed the 522 protocols to determine if they would support a PMA, FDA does not approve 522 study designs. Therefore, our feedback to the manufacturers regarding this 522 study design, specific to whether they would support a PMA, are recommendations provided by FDA and are not requirements.

So FDA would like to remind the Panel of the scope of the meeting and the Panel charge for this afternoon. This is your portion of the Panel meeting. The scope of this Panel is limited to mesh placed in the anterior vaginal compartment to treat prolapse. Urogyn mesh for all other indications including mesh for posterior compartment repair of prolapse, abdominal repair of prolapse, and mesh for stress urinary incontinence are outside the scope of this Panel meeting. FDA is not asking the Panel to evaluate the safety and effectiveness of any specific mesh device, specific mesh material, specific mesh characterization or characteristic, or mesh placed in the anterior vaginal compartment as a device type. FDA is also not asking the Panel to determine whether these devices should remain on the market.

FDA is asking the Panel to provide insight on how FDA should evaluate safety and effectiveness data for these devices. In addition, the FDA would like the Panel to focus the discussion on the general patient population of women who are candidates for transvaginal surgical repair for prolapse.

FDA acknowledges that individual characteristics of mesh could affect the safety and effectiveness outcomes, such things as pore size, density, material, etc. But FDA would also like to remind the Panel that these individual characteristics are assessed as part of the premarket review process. As Class III devices, each mesh must demonstrate a reasonable

assurance of safety and effectiveness on its own.

FDA would also like to remind the Panel that their recommendations will not only apply to FDA's evaluation of the devices that are currently on the market but will also be used to evaluate future device types like these.

So with that, I would like to turn it back over to the Chair. Thank you very much.

DR. ISAACSON: Thank you, Dr. Fisher.

Now we'd like to give the manufacturers and the FDA the opportunity to respond to the Panel's questions posed this morning. I don't know if there are any outstanding questions that we have from this morning that the Panel didn't get answered.

I understand, I think, that Mr. Levit, you had an issue with a slide that you wanted to correct. If you could, this would be the time to do that.

MR. LEVIT: It's not a slide that I want to correct, but rather something that I think -- it's not related to our device but related to this discussion and this Panel, and I thought it would be worthwhile to throw this comment before the actual discussion begins. And it is related -- there were a lot of discussions here about the subjective results and the success criteria, and I think that the modified criteria that was adopted by the FDA following the recommendation of the Pelvic Floor Disorders Network, I think it's wrong, and I would want 1 minute to say why.

If you see the images on the screen, it's pretty obvious, okay, that that's the normal anatomy, that's the NIH previous success criteria, and this is the criteria which is right now acceptable by the FDA. Now, I'm not a woman and I don't feel my vagina, but I do see very clearly from this image that this vaginal canal is completely blocked and it's not the right criteria twice. Once is because it's blocked and this woman cannot have sexual intercourse without dyspareunia or most probably with pain, and the other thing which may be more important even is that we saw that there is the duration over time, in 3 years, 5 years, 10

years, always there is the duration in the anatomy and to accept a vaginal or a bulge, or not a bulge, but an anatomy that is in the level of the hymen, is to say to this woman next year you're going to be a failure and next year you're going to need another surgery.

The other thing is that -- just one more sentence. The other thing is that this criteria basically takes the subjective and objective criteria together. What I suggest, in order to have a real risk-benefit ratio determination, is to have a composite success criteria where the NIH criteria as an objective, subjective, as a subjective and a safety and only by combining these three and not combining it artificially by these criteria would bring all of us up to the same level and to make sure that the risk-benefit ratio is really assessed.

Thank you.

DR. ISAACSON: Thank you. I misunderstood. I thought there was a problem with one of the slides.

So before we proceed with the Panel deliberations, I'd like to ask our non-voting members, Mr. Wyatt Lison, our Consumer Representative; Ms. Sharon Timberlake, our Industry Representative; Ms. Barbara Berney, our Patient Representative, if they have any additional comments. And Barbara -- oh, whoever wants to start is fine.

Go ahead.

MR. LISON: Hi. Wyatt Lison, the Consumer Representative.

You know, coming into this, you know, from a consumer standpoint, it seems to me that these things were poorly introduced into the market, to say the least, and at this point in time the industry wants to say, well, don't look at what happened in the past, let's look at what we want to do in the future. But they're presenting data without actually going through the normal steps of preapproval to show that what they want to bring out in the future is going to be safe and effective.

And when we're talking about what's most important here, which is quality of life,

this isn't a life-threatening situation, it's a quality of life issue, I think that should be one of the most important things to consider which is, when you're looking at risk versus benefit, you know, is the quality of life equal to the risks of this potentially catastrophic failure? And if what we're being told is, is these new devices, you know, may or may not have those same type of catastrophic occurrences, we just don't know because they haven't been around long enough and we haven't had enough time to study these newer devices, I think these need to be very carefully scrutinized to make sure that they really are safe, when the subjective outcomes that everybody's talking about, the quality of life does not seem to be better than the alternatives that do not have those potentially catastrophic failures.

DR. ISAACSON: So before you move on, I think since this is a deliberation session -- go ahead.

DR. FISHER: Thank you very much. Ben Fisher, FDA.

I just have a point of clarification for -- I believe it was Dr. Levit who put up the slide and I just -- I was looking at that and I noticed that actually the slide says that it's NIH versus PFDN. It's being used in the 522 study, but I just wanted to make very clear that that's not part of FDA criteria per se. Okay, so just for clarification.

DR. ISAACSON: Go ahead.

MS. BERNEY: I'm Barbara Berney, I'm the Patient Representative.

My concerns with this entire proceeding revolve around the fact that we are asked to make determinations based on information that admittedly, from all parties, is old information. And I just don't feel like I agree with Mr. Lison that being asked to make all of these decisions based on what we heard today and how we should go about answering the questions, I personally am having a hard time trying to figure out how I'm going to take that information and make it all apply to today.

I also agree that subjective -- patient subjective outcomes need to be far more

prominent in the decisions that the patients and their doctors make because I can guarantee you that a large number of those patients, who's a subjective success or failure, don't really understand what they're being told when they're being given that information in the doctor's office. That's basically what I wanted to say.

MS. TIMBERLAKE: Sure. Sharon Timberlake, Industry Rep.

Obviously, a lot of discussion today about a lot of studies over the last 10, 15-plus years. Overall, since 2008, since the products have been on the market, FDA and the manufacturers have done a reasonable job evaluating the risks, reporting out to the physicians that use the products, working together with the last two remaining manufacturers on the market. And, you know, I can see the difficulty in, you know, looking at what data that we can look at retrospectively using various meta-analysis methods.

The product is on the market. FDA has reclassified the device into a Class III category, which is the highest-risk device, which is elevated extremely highly -- if you've never read through the PMA requirements, you know, free time, check it out on the FDA website. It takes millions and millions of dollars for the manufacturers to produce quality products in the market as well as work with the Agency to design studies.

With the 522 studies, comparing to what's available for alternative surgical methods on the market today, native repair surgery, the 522 studies are evaluating the most common adverse events that have been seen, including the ones with the older prior heavier mesh that was on the market, which is not on the market today. So please keep that in mind.

Also the point about training between the professional societies and their recommendations that they continuously share out in the market, working with the manufacturers developing the right labeling, the right messaging, including cautions and precautions so patients and doctors will have the most up-to-date information to share and

make the right decision and option that is best for their patient. I know I just said a lot, but those are things for us to think about as we go into deliberations.

Thank you.

DR. ISAACSON: So just to continue the deliberations, I just want to have the Panel just to refocus a little bit and understand, again, our objective this afternoon is really not to approve or disapprove or comment on old studies or new studies. It's really how do we help the FDA establish the criteria to assess safety and to assess the efficacy based on all of the information we heard today, and I think that's really what I want to kind of deliberate for the next 40 minutes or so is -- you know, it's interesting to me that the FDA did not design these 522 studies, so it's up to the individual manufacturers to design the studies and now the FDA has the responsibility of evaluating those studies when the data comes in, as to what's safe and what's effective.

So anybody have any comments on that? If not, I have to pick you out one by one.

Yes.

MS. TIMBERLAKE: Sharon Timberlake.

I just have a quick question about the 522 studies. I believe they probably weren't under an IDE. However, did the Agency give either of the manufacturers today any feedback about the design during discussions?

DR. FISHER: So, yes, I think I tried to comment on that. So following the Panel meeting in 2011, you know, the Panel made recommendations that there should be 522 studies and we've talked about one that's kind of a novel approach because, you know, we have a 522 study that is basically going to be -- the idea behind a 522 is to get additional information on either new adverse events or to get a better understanding of what the true adverse event profile is. It didn't need to be under an IDE because these were already approved devices. We did meet with the companies. Now, you can imagine our challenge

because when the order went out we were talking about 30 companies and sending out orders to over 100 -- for 130 studies, right? Now, some of those players dropped out, but FDA did go into conversations with the sponsors for suggestions on how to address the Panel recommendations which were, you know, they were looking at better defining the safety and effectiveness and looking at these studies, looking at longer outcomes, they recommended at least a year follow-up, the Panel did.

Now, under a 522 order, we can actually extend that out to 3 years, which we did. So we took the Panel recommendations and we acted on those and yes, we did provide feedback to the sponsors on their protocols. But like I just said, those are recommendations. We can't make those requirements because the manufacturers themselves are responsible for the protocols.

(Off microphone comment.)

DR. ISAACSON: Yes, Kay.

DR. HOSKEY: I wonder if, Dr. Fisher, you could clarify. In your introduction comments, did you mention that we should restrict our comments to general population?

DR. FISHER: So what I would like the Panel to deliberate on are a couple things. You know, when we're looking at the approval of this device type, I think we need to look at the general population of women that would be eligible or selected to go for transvaginal placement for POP repair. Now, one of the things that I will be asking -- so, you know, part of the question is yes.

Part of the questions that we'll be also looking at, though, are there specific patient populations in which the benefit -- where patients may benefit more so it would offset the risk. So general discussion on the general patient population, women that would go in for a procedure like this. But as we get into the questions, I'll be mining down a little bit deeper to find out if you think that there's a subpopulation where the risk-benefit might be

different.

DR. ISAACSON: No other questions. I think maybe we'll move on to the questions a little bit early, we might need the extra time. So I would ask Dr. Olson -- and the way this will work is, again, we have -- we're moving to the questions, we have eight questions with several parts to each question and Dr. Olson will read each question, and I would ask -- going to be asking each Panel member -- I think I have to stop again. Hold on one second, I went too fast. Go ahead.

DR. FISHER: Oh, thank you very much, I would ask of the Chair. So we talked about a lot of topics, and really, what I would like to have in this hour is a discussion with the Panel on a variety of topics before we actually get into the questions. Now I'm just looking at things that I jotted down. You know, we talked about things like validated tools for assessing subjective endpoints; patient blinding; patient characteristics; procedures, if it's primary, if it's secondary, what do we do in situations like that; how do we handle bias; balance a patient's characteristics; physician training; challenges of comparing anterior/apical with repair. I mean, one of the comments that we had earlier from one of the professional societies, you know, there's challenges when comparing anterior/apical repair with native tissue repair, how do we handle that? How do we handle patients that have failed primary treatment?

So I mean, there are a lot of things. Before we go to the questions, there's a lot of things that we had talked about today that I would appreciate a little bit more Panel deliberation on these topics if -- to talk about some of these things, please.

DR. CHAPPELL: I have such a comment --

DR. ISAACSON: Yes.

DR. CHAPPELL: -- although, if there's any -- Rick Chappell.

It seems to me that the scientific tragedy here is that we have excellent long-term

data on what the current manufacturers consider to be decremented products. That is not at all unique. It is almost ubiquitous in device trials. As you would hope and expect, there are devices that are continuously being improved. Nor surgery trials, our procedures are continuously being improved. And I believe those are both -- I hope both are true.

But I owe it to the patients who gave me such heart-rending testimony when I was at the 2011 version of this meeting, and the patients who gave similar testimony today, not to be here in another 8 years with the statement that, well, 2019's old-fashioned methods and devices were fine back then, but now we have much better ones. And so I've organized my thoughts, which I can present in about 3 or 4 minutes if that's all right, around several quotes which I've excised from today's testimony.

The first from Boston Scientific is to urge us to allow non-inferiority to suffice and, given the distinct possibility of strong toxicities of the erosion which cannot possibly occur in the absence of mesh, I think we need to ask for superiority.

They also quoted results at 2 years which showed superiority from Maher, but that was a selected outcome. Maher's main outcome of the composite outcome showed a very slightly increased rate of success for NTR. So I think that we should still require superiority and that can actually still be debated.

The SGS said that complication rates in high-quality study conditions do not seem to represent general practice. That makes sense to me. It can be shown in a variety of circumstances that patients in clinical trials, even in the control group, do better than similar patients not in clinical trials. These are not ordinary clinicians, typically, who participate in such trials. Therefore, even though I'm encouraged by the very low rates of some of the most severe toxicities in the most recent trials, I'm not completely convinced, and I think we need to follow them up more.

So I will argue, when the questions come for further trials, further recording of side

effects, especially mesh erosion, and over long periods of time because these are permanent implants and these women may well be middle-aged and live for a long period of time perhaps subject to those complications.

And, finally, I greatly appreciate AUGS, if that's how you pronounce the organization, urogynecologic surgery, they recommend the consideration of mesh in certain patients and I can easily see -- for example, the first patient they recommended is those who have failed native tissue repairs. I could imagine that would place women at an entirely different level. And so I hope not to discourage use of it, of the mesh procedure completely, but to encourage strong long-term further research on it and for us to issue guidelines, the FDA, with our advice, to issue guidelines saying be very careful in its current application and our current state of knowledge.

DR. FISHER: So, Dr. Chappell, kudos to you for speaking up. Thank you very much. So you put something out there on the table, you mentioned superiority and you thought that it should be superiority. One of the charges in the 522 was to look at both objective endpoints and subjective endpoints because we really thought that patient outcomes are important.

So one of the questions that we'll be talking about moving forward is -- I don't know how everybody feels around the table, I was hoping that I can get some more comments on how you feel about superior, superiority versus non-inferiority, and do you think that we have to win on both or is one more important? Is it, you know, only good enough to have objective outcomes that are superior? Do you have to have superiority in both? I'd like you guys to provide some feedback on that, if you would.

DR. ISAACSON: Go ahead, Kay.

DR. HOSKEY: Kay Hoskey.

I have a comment about that and that's we're bringing -- why I asked for clarification

of general population, because there are clinical cases where, for example, if someone has failed a prior native tissue repair but there are even clinical cases where someone's not a candidate for the most common native tissue repairs where the idea of non-inferiority seems more acceptable. For example, we heard a lot about vaginal hysterectomies with uterosacral suspension as the native tissue repair. There are some patients where that procedure carries additional risks due to their own past medical history, past surgical history, known adhesions. So it's a very individualized situation.

DR. ISAACSON: And I would agree to that -- it's Keith Isaacson -- and that is, you know, with everything we do we try to give the best evidence available to the patient for here's the potential benefits, here are the potential risks, and as was brought up earlier, you try to get the patient to make an informed decision. To my knowledge, I don't know of there being any benefit to the surgeon to do a mesh repair versus a native tissue repair. I'm not aware of any difference in reimbursements or any other reason. You look at the advantages and the disadvantages, and you help the patient with the shared decision-making process. And that comes to what you're saying is, you know, look at the whole situation, if they've had failed repairs, if they have -- what's their medical health and which is the most appropriate procedure for that patient.

DR. HOSKEY: If there are no other acceptable alternatives, proving non-inferiority may be enough.

DR. ISAACSON: I agree.

Yes, Daniel.

DR. GRUBER: Dan Gruber.

I just want to bring up something about pain, dyspareunia, those kind of things. So we've looked at lots of different studies, and when you look at whether it's transvaginal mesh or otherwise, I just wanted to point out that anything you do has complications and

risks. Doing nothing has complications and risks. Having a pessary in for a long time can be devastating in certain situations. So patients also have baseline pain and even just doing native tissue repair, they can have pain afterwards. Some of them have a new pain, sometimes their pain gets resolved, so it's a lot more complicated. You can't just say that the mesh causes this only, there's other things that cause it, too. So I just want to keep that in mind.

DR. ISAACSON: And I don't have the answer to this question, but does anybody know or can comment, when these studies are being performed, is there a baseline assessment for this quality of life before the surgical procedure is performed and then look at it at, you know, 6, 12, 24, 36 months out?

Go ahead.

DR. MAZLOOMDOOST: Donna Mazloomdoost.

Many of the studies do a baseline and do a follow-up and there are currently studies that are in the process of looking very more specifically at dyspareunia, but I'm not at liberty to give the details, though, but a lot of this is -- has been and is being studied.

DR. ISAACSON: Yes.

DR. EREKSON: I'd like to merge a couple comments, one from Mrs. Berney, our patient advocate, and kind of bring back the slide that we were just shown with the anatomic cure and arguing kind of how we should look at those cures. I think that goes back to exactly what you were saying, which is as we treat patients with pelvic organ prolapse, subjective symptoms are really what matters. And if I was ever going to say which matters more, anatomic versus subjective, I would say subjective. And so we really, really, really have to focus on the subjective outcomes. We have that in very structured randomized clinical trials where we already select out patients who have all of these comorbidities. So we've already selected out the patients with chronic pain, we've already

selected out the patients who may benefit from these procedures, and so that's where we're limited in the data that we have right now. But we do have the subjective outcomes for these highly structured trials.

When we go back -- when I go back to review who came into the 522 studies, they also selected out very similar to the criteria that we have in the randomized controlled trials from the PFDN, there aren't patients with chronic pain, there aren't patients with connective tissue disorders, there aren't patients with autoimmune disorders, and perhaps those are the patients that may benefit but we don't have that subjective data.

DR. ISAACSON: So I have one question for the Panel. The FDA presented their definition of high volume as more than three cases per year, and low volume was one case.

DR. FISHER: A point of --

DR. ISAACSON: I didn't finish my question.

(Laughter.)

DR. FISHER: -- clarification, please. This is Fisher, FDA.

DR. ISAACSON: Yeah.

DR. FISHER: We were actually reporting the results of a paper, so that is not our qualification. When we looked at that and we saw one case was low volume and two was intermediate and if you made it all the way up to three you were high volume, we could have a conversation about that, but that was not our criteria. We were just reporting out what was in that study.

DR. ISAACSON: I misspoke, but that was what was reported. Yeah, you're correct and I should have stated that. And I would say that I'm hoping my pilot, when I fly home, is a high-volume pilot.

(Laughter.)

DR. ISAACSON: Over three flights this year. But for the Panel, can anybody discuss

how you would define a low volume, a medium volume, and a high volume for this particular procedure?

DR. MORGAN: Dan Morgan.

So with respect to volume, that can really vary. I think that we can borrow from some studies done with respect to other gynecologic surgeries, whether it's hysterectomy or other major gynecologic interventions, and that is generally -- three would be a very low number, you know, even in those instances, but most of the time that has been thought of as like one major case per month, so 12 hysterectomies, 12 major benign gynecologic surgeries per year would be considered at least higher adequate volumes. So I think when you're applying a category, you know, one, two, three would be -- that's very low volume.

DR. EREKSON: And if I can follow up on that, I believe that the article that we were discussing was only Medicare data and so that doesn't capture an entire surgeon's surgical profile. So you know, if you extrapolate out, perhaps they have 20 or 30% of their patient load is Medicare and you're capturing if you're doing that out of insurance data. So there are limitations when we look at those volume data.

DR. ISAACSON: Yes, Frank.

DR. LING: Frank Ling.

There were references made throughout the day to high volume, low volume but also to fellowship trained and so on and I think -- again, I think we all know that volume doesn't define a good surgeon or good judgment or, for that matter, being fellowship trained doesn't define a good surgeon or someone with good judgment.

I did like the fact that, I think, all three society speakers did address the concept of something like an IVF registry where these patients are going to be followed, not just for 3 years but perhaps even longer than that. And I think what we've got to do is recognize that ultimately we're talking about patients, many of whom are, as someone said, out in the

hinterlands and don't have access to a high-quality or high-volume surgeon or whatever but again, people who have heart transplants don't have them in small hospitals; they go to big medical centers.

So I think, to some extent, whatever guidance we give the FDA I would like to see us make sure that the concept of long-term follow-up, better defined ability to put these devices in the hands of people who will use them wisely has got to be critically important.

DR. ISAACSON: Yes.

DR. MAZLOOMDOOST: I think that -- and I don't know how relevant this is to the FDA and the questions that they have to the Panel, but I do think that the matter of training and expertise is a very critical part of this. Female pelvic medicine and reconstructive surgery only became a formalized field very -- or recognized field very recently, and prior to that I have to wonder if we wouldn't be where we are today if the mesh kits weren't released out into a public that may just not have had the anatomical and the surgical knowledge to do them. So I think it's not a minor point, I think it's a very major point, in that something where you really should have some regulation as to who is going to, like, provide these procedures.

DR. ISAACSON: Dan.

DR. MORGAN: Dan Morgan.

And I would -- maybe following up on what Liz Erekson was saying, that in terms -- I would not put a number to any satisfactory volume. I really think, as Dr. Ling said, about the idea of surgical judgment, but I really like the idea of us being able to follow what's going on and being able to have an appreciation of where we are with respect to our peers and that if there was some mechanism that if things are not trending in the direction that they need to be, I think that's something that we want to know.

If we're talking about trying to limit this to certain patients who have a lot of risk

factors, the person who does very few may actually be doing this very appropriately and that's one of the reasons why I would really caution against saying put a number on this because we see all kinds of crazy things happen when you say you have to achieve a certain number. But I think, you know, at the end, it should really be your outcomes that's only going to be followed with a registry, I think.

DR. ISAACSON: So if I understand correctly, Dr. Fisher, you can correct me if I'm wrong here, there have been products in which the FDA has required a certain training module prior to getting approval to implant a particular device and I think it was in cardiology at some point. Is that something that is up for consideration with a product like this?

DR. FISHER: Okay, so FDA's view on training. We can require training as part of an approval. We cannot regulate training. So we rely on groups like yourself, the professional societies, to determine what type of training is required. Some of the institutions will have certification programs. And so we have had things in the past through the labeling where we have put some pretty strict requirements on physicians to make sure that they get information on benefit-risk to the patients, okay, so when it comes to training we can say that you need a training program, we can look and we can say if we don't think that that training program is sufficient, that it needs to be improved and work with the sponsors to improve that training, but we can't -- we don't actually have oversight over the training programs.

DR. ISAACSON: I remember a while ago they had -- someone had to go through a simulator and pass the simulator training before they could do a cardiac process, but I'll get back to you on that.

DR. FISHER: I'll see if can get some clarification on that.

DR. ISAACSON: Yes, Dan.

DR. MORGAN: Dan Morgan.

I would imagine that more so than even training, though, it's really following the outcomes long term that I would argue for, because I think it's one thing to say that you've done a course or you've done something, but if you're doing these appropriately and knowing that you're getting -- you're not having that patient who is suffering a devastating complication that I think we all are concerned about, I think that's the thing that will hopefully help steer us in the right direction.

DR. ISAACSON: Yeah, just a comment. I think that's been very effective, like you said, for the in vitro fertilization, the ART registry is called SART and you know, there's really no regulation other than you have to fill out this form and it is published by the CDC, so it's public, and that, in itself, was enough of a motivation factor to improve the outcomes.

DR. LOWDER: This is Jerry Lowder.

To follow up on Dan or Dr. Morgan's comment, I mean, I think registries would be ideal in some form. Unless the FDA mandates that, I can't imagine physicians in private practice sometimes or smaller communities always electing to participate, so I do think there needs to be a better safety net as far as following the complications.

And I guess my question now, and somebody from industry can correct me, I don't think that, you know, products, either a serial number or a lot number or whatever the case, is required to be reported or recorded of devices that are implanted. So maybe some mechanism where, you know, those are reported, not only just when they're sold, but serial number or whatever is reported has certain indentifying material, physician, hospital, date, those types of things.

And I guess I've always wondered why, you know, patients don't get some type of identification card as far as a permanently implantable device, I mean much like with an ID or other things that has the product, the serial number and date of implant and expiration

because a lot of the patients that I treat they, you know, come in with complications, have no idea, you know, what their mesh -- what mesh they had placed. And so if that was reportable and on that card, for example, there's a number for the FDA and the company to call, I think, you know, improving patient reporting of complications would be improved as well, so just a thought.

DR. ISAACSON: Yes, Barb.

MS. BERNEY: This is Barbara Berney.

I have a comment to make about that. I have lots of artificial pieces and implants. I have a card for every single one, cataracts, neurostimulator, hip joints, whatever. It makes a lot of sense for the patients because we may need that information, but I know lots of people who have had all kinds of procedures who do not have a clue what's inside. For me, it makes a big difference because I have lots of medical issues and they always ask me. But I really agree that we need to be better about that so that there is a way to require that patients be given that information or that the reporting requires that information, lot number, product, whatever. That would be a step in the right direction as far as being able to identify, when there are problems, which particular things have the problems.

DR. ISAACSON: Sharon.

MS. TIMBERLAKE: Sharon Timberlake.

Just a couple comments on traceability. Manufacturers are required, obviously, to have lot numbers, serial numbers, for every lot to which -- to what institution for recall purposes and other safety related issues. Generally, I believe the experts here, the surgeons, typically don't you record what lot you use and what type of mesh would go in the patient? So on that end, it is traceable. My only comment is, you know, it's something that a physician and a patient would discuss about the different types of mesh and that a patient would be able to ask those questions, maybe it's something you would just consider

adding to the patient information brochure that the manufacturers will share if they want to know that type of information.

DR. ISAACSON: Go ahead, Madeline.

DR. DICK-BIASCOECHEA: As one who has tried to figure out what mesh has -- you know, the patient has or anything, operative reports where you usually put the lot number and what you put in and everything are destroyed at 10 years, so it's useless. So I think giving a card to the patient is essential because the patients should have their own medical records.

DR. ISAACSON: So it seems to me that, listening to all the data, the majority of the complications occur in the first year, as far as erosion and what have you, and when we look at efficacy, that's important at 3 to 5 years. Do you have comments, or I'll ask the Panel to comment if you kind of agree with those numbers, or did you hear something different?

(Off microphone comment.)

DR. DICK-BIASCOECHEA: I think we don't have enough information.

DR. ISAACSON: We don't have?

DR. DICK-BIASCOECHEA: Enough information because most trials had 1 year, so -- and the ones that are up to 3 years, they don't say when the complications are happening, so if it was the first year or the second year or third year.

DR. ISAACSON: Did you guys hear the same thing?

Daniel?

DR. GRUBER: Just biologic. I mean, any of these things are going to have failure rates over time and the more time, the more failure rates. Gravity, life, everything else, people age. So we don't have -- I agree, we don't have the kind of information that we need on either side of it, whether it's native tissue or mesh or biologic or any of the above. So I do really think that more data and more time will really help differentiate.

DR. EREKSON: I think one of the things to consider when we think about complications and time is the provider that the patient's going to for that complication. So, then, I think that most patients who are going to see the providers who are high-volume surgeons or who are participating in the Pelvic Floor Disorders Network, know how to ask about these catastrophic complications or even less catastrophic complications, to know how to manage those complications.

But I think, maybe, balancing our patient voices and our patient advocates who are here today, is that there are a lot of patients who went to providers who then didn't know how to manage their complications and so then the complications persisted much longer than the year time frame that you're referring to. So I think if we're actively finding these complications and asking the right questions, I think you're proposing that a year is when we would usually see these adverse events is fairly reasonable. I think it's when the patients don't get listened to is where we lose it.

DR. ISAACSON: Dan.

DR. MORGAN: Dan Morgan.

With respect to seeing complications, I think when you look at the MAUDE database and you see that huge spike in 2012 and '13, I think that probably reflects how many mesh kits were being used and implanted at that time because there certainly is a very large number of patients who, I think, are seen in that first year with erosions, but then it changes a little bit over time. And I think we've all seen this where we did take care of a lot of erosions but now we tend to take care of patients who have chronic pain, chronic infection, and other problems so that I think the complication profile changes over time. In that first year you might see a lot of erosion, but as you go years later, I think the problems change a little bit, and they're not quite as obvious as a mesh erosion. And so I would argue for that time certainly being an important part of making sure that things really are as they

seem.

DR. FISHER: Ben Fisher, FDA.

I'm going to openly admit that the MDR reporting system is not a perfect one, it does have its limitations, and a lot of times when you see a change in the number of MDRs, it can be due to a variety of things. I think the comment, when we were presenting it, we made a comment that maybe the fall back down was due to the number of manufacturers that had decided not to market and distribute that device anymore. That could have been one factor playing into it.

What can cause a spike? A spike can be caused by a variety of things, FDA bringing attention to the public, okay, and people going, you know, I haven't reported this. But we get an MDR report, too. Manufacturers are required by FDA to report but patients themselves can voluntarily report into the system. So the other limitation is there's not necessarily a good correlation from when we see a report and when it was implanted and when the adverse event may have taken place.

So, you know, we use it, it's one of the tools that FDA uses to assess signals, but I have to say that, you know, that one spike was rather high. I think the other thing that can -- not necessarily in this case, but it could have, that when cases are brought forth with companies and things like that, they have to report, also. So take it with a grain a salt. We believe that there was an increase in reporting of those MDRs, we took it seriously, but the system does have its limitations, and I'll leave it at that.

DR. ISAACSON: I want to bring up a question about indications for surgical repair, and is it necessary that the patients undergo nonsurgical treatments first before the surgical repair is offered? We're certainly seeing that with other types of procedures, even if it's insurance requiring it, but I didn't know -- do you think that's a good idea? Is it necessary? Yes.

DR. GRUBER: I mean, I think it comes back to patient autonomy. I think it's important that they get the options listed. And every now and again I'll see a patient who had a procedure and then came to me for some other reason and they don't even -- never even heard of what a pessary is, and it really makes me upset, and then you show that -- I physically show it to them. And it's up to them, but if they don't want to deal with it or hassle with it or for whatever their reasons, that's not to me to judge, and they prefer surgery, that's fine. But I kind of just go with whatever they choose, really.

DR. ISAACSON: Any other -- yes.

DR. MAZLOOMDOOST: As a quality measure, the conservative options have to be offered, but I would agree, I don't think you can -- I don't think there's ever a way you can absolutely say this person has to have surgery and it should never be forced for them to try conservative management if they would prefer surgical management. It has to be patient directed.

DR. ISAACSON: I can say, for a hysterectomy for abnormal bleeding, they are forced to try a progesterone treatment before the insurance will cover a surgical therapy. So I'm not saying that's right or wrong, I just didn't know if that applied in this field.

Dr. Fisher, what else did you have on your list?

DR. FISHER: Dr. Erekson, thank you very much. She was willing to go out on a limb and say that she thought -- excuse me, that subjective endpoints were very, very important, maybe even more important than objective endpoints. I'd like to kind of hear what the rest of the Panel members think about that.

The other thing that was brought up with AUGS in their presentation, they said that in assessing subjective endpoints, validated questionnaires, you know, that was a good idea to go with that, a good way to capture that. They also suggested collecting information on prolapse symptoms, urinary symptoms, bowel function, and sexual function. Do you guys

feel that all of that is required? Do you feel that additional things might -- should be added?

DR. MORGAN: Dan Morgan.

I think certainly we have to include subjective outcomes in any discussion of the success. I think the thing that we would all most want to avoid is somebody who's an anatomic success but subjectively, for whatever reason, bowel, bladder, sexual function, feels that they have not had a good outcome. So I would, you know, echo certainly what Dr. Erekson said, that subjective outcomes have to be a part of that assessment.

DR. ISAACSON: Is the opposite true? If they have subjective success, do you need objective success?

DR. MORGAN: And I think that really is a good question. I think that we all see some patients who have a small prolapse afterwards, but given the size of their prolapse before surgery, they're incredibly happy and that speaks to that -- there was a question, I think, about trying to adjust for severity of prolapse and trying to stratify that and I think that's an important thing to keep in mind because, yeah, you can have somebody who has an anatomic failure but subjective success, and I'd still consider them satisfied and happy if they say they're satisfied and happy.

DR. LOWDER: Jerry Lowder.

And that provides good counseling information to the patient, both to be able to provide the subjective and objective outcomes, and we saw that with the TVT in the past. And I think, kind of going back to some questions about -- a discussion about pain that I think ideally, going forward -- because Dan mentioned, Dan Gruber mentioned about, you know, with any surgery we do, even native tissue repairs, patients can have pain afterwards and I think ideally both assessing, for example, the pelvic floor muscles, you know, preoperatively and then postoperatively, especially since some of these meshes are

inserted or attached to the pelvic floor muscles, would be important, but also -- and I haven't seen these in the studies where the surgical sites both for native tissue repairs and for mesh insertion sites are actually palpated and, you know, the patient is asked, you know, is this spot painful or tender? There might not be existing measures for that, but I think that would be important to follow.

DR. ISAACSON: So my comment on the validated questionnaire, I think that's a huge part of this and very important, and not only because there are lots of different validated questionnaires out there. So I think what we would like to do is to try to find one with the recommendation of the various gynecologic societies that's standardized for this particular procedure and all use the same one because there's QSF-20 and 40 and 60 and then some specific for this. So I think we should just agree on what's the best validated questionnaire so that we can compare apples and apples.

DR. MORGAN: I think the one thing is there actually has been a great amount of work in our field and FPRMS about establishing some validated questionnaires and there are good instruments available. I think it's just what aspect do you want to get to; if it's urinary symptoms, the UDI, and CRADI for colorectal symptoms; PISQ for sexual function; if you want to get to more general health function, short form 12 or 36, as you're saying. So I think there are the instruments out there, and I don't think anybody would argue that that should be the standard for our studies, that the instruments are there and we can use them. I think most people do in these studies.

DR. CONNOR: Yeah, Jason Connor.

No, I think Dr. Erekson is totally right and that really the subjective measures are probably the most important here, especially when dealing with, you know, a non-life threatening condition that women are having largely, in my understanding, an elective surgery for. I mean, in terms of capturing these, you know, catastrophic, devastating, life-

changing events it seems to me that that's what we need to quantify. I mean, the efficacy seems a bit better with these and it's faster surgeries and I understand why, you know, surgeons want to use them. But it seems like what we need to do in order to have the fair and appropriate conversation with patients is to really quantify the likelihood of these devastating, catastrophic, life-changing events and measuring rare things is really hard and, as a statistician, estimating the prevalence of super-rare events that even present in many different ways is even harder.

So I think trying to estimate that almost has to be subjective. I mean, I heard one of the women today say that this was the worst day of her life, and my guess is, you know, many of the women we heard from would say that and I think it's fair for a surgeon to be able to say, you know, here are all the benefits, but 1 in 5,000 women said they, you know, regret ever having this done and it led to -- you know, it was the worst day of their life. I mean that's a very subjective question, but that encompasses the wide range of things.

When I worked at Cleveland Clinic as a junior statistician, in colorectal surgery there they mail a survey to everyone who had -- at least 20 years ago mailed a survey to everyone every year who'd had a colorectal surgery and said would you have this procedure again? And so, you know, longitudinally, we looked at this data all the time and that was actually very valuable information, totally subjective and broad because, you know, it had built-in efficacy/safety tradeoffs. I understand that's really hard to do given, you know, this is happening in private practice, there's little incentive for the company or even physicians to track this information.

I sat on a panel for cosmetic breast implants, silicone breast implants. When they were reapproved for cosmetic uses, FDA tasked the makers with following 40,000 people for 10 years, and one of the makers lost 90% of patients within the first year because if you don't track people you'll never find AEs and that was probably to their benefit. And it's

hard to keep track of people. So I understand it's very difficult, but I think the subjective measures are probably the most important because all of these validated questionnaires aren't even really made to get at these extremely rare catastrophic events.

DR. GRUBER: Since you're talking about questionnaires, I mean, they're extremely important to do and we have a lot of really good validated ones, but I just would caution, over-survey, survey fatigue, is a very real thing and I know I've seen patients -- I've done it myself as a patient, where you fill out stuff on the first page and then the second page and the third page, yeah, just kind of start pencil whipping. And there's actually industry data that actually shows that more than about -- I think it was 8 or 9 minutes to have them do math problems and then the answers were completely wrong after about 8 or 9 minutes and these were people who were paid to do it. So questionnaires are very important, but it's also very important to get the exact right ones for the questions that you're looking at rather than just throwing out a hundred questions to these random patients; it's a big problem.

DR. ISAACSON: I have one more. Yes.

DR. MAZLOOMDOOST: Donna Mazloomdoost.

This is a clarification for Dr. Fisher. Were you asking whether one of the recommendations should be to look at, like, bowel function and urinary function as a -- like an adverse event or baseline?

DR. FISHER: No, my comment was going back to subjective outcomes that AUGS presented, that in assessing benefit they would recommend four validated questionnaires to assess prolapse symptoms, urinary symptoms, bowel function, and sexual function. And so my question was did you agree, should more be collected, and things like that. So, you know, I hear there's a lot of great talk about, you know, the subjective endpoints, I think it's great. There's also something called the placebo effect, which we always have to be careful

of. So we're not going to totally dismiss objective outcomes, either, but it's good to hear this discussion.

I had people leaning into the table, so I want to thank you that -- I don't know if I jarred the table and woke everybody up, but it's been a good conversation and I appreciate this deliberation. We do have questions and I do want to set time aside for those questions because we have eight questions, and I think we have about 15 minutes for each one. I'd ask the Chair to go around and make sure that he has an opportunity to question each of you to get your point of view. So with time in mind, I would like to go ahead and if we could move to the questions.

DR. ISAACSON: Very good. So at this time let's focus our discussion on the FDA questions. Panel members, the copies of the questions are in your folders. I would ask that each Panel member identify himself or herself each time he or she speaks to facilitate the transcription. I will tell you, at the end of each question, which I hopefully can do each one in 15 minutes, we would like to give Dr. Fisher kind of what the Panel generally believes in and what we have some concerns about and then we'll ask Dr. Fisher if that's adequate or if more discussion is needed. So without further ado, Dr. Olson, if you'll read the first question.

DR. OLSON: Sure. The first question relates to effectiveness. Question 1. In light of its increased risks compared to native tissue repair, to demonstrate reasonable assurance of effectiveness, FDA believes that surgical mesh used in the anterior or anterior/apical vaginal compartment for transvaginal prolapse repair should be superior to native tissue repair. Does the Panel agree?

a. If yes, at what time point should superiority be demonstrated, for example, 12, 24, 36 months, or longer?

b. If no, how should the effectiveness of mesh compare to native tissue repair and

at what time point should the effectiveness be assessed?

c. Does the Panel have additional comments related to the mesh material, for example, polypropylene or non-cross-linked biologic or other mesh characteristics?

DR. ISAACSON: Thank you.

And so I want everyone's help on this, so if you don't mind, I'll just start with Kay Hoskey and you get to volunteer as the first one, since we're in Washington. And can you give us your opinion on this first question?

DR. HOSKEY: I do believe that generally, yes, mesh when used in the anterior compartment should be proven superior to native tissue repair. As I said before, it's a hard question to answer, but we are being general. Superiority should be demonstrated at each of those time frames and longer.

DR. ISAACSON: Any other comments? Anybody feel differently?

Yes, Rick.

DR. CHAPPELL: I would --

DR. ISAACSON: State your name.

DR. CHAPPELL: Oh, Rick Chappell.

I would agree with what Dr. Hoskey just said and backtracking a little bit of my earlier severity, I would suggest that superiority be demonstrated on at least one of those time points and equivalence on the others. So, for example, superiority only occurs at 36, preliminary data seems to indicate equivalence early, perhaps superiority later, that would also be satisfactory.

DR. ISAACSON: Yes.

DR. CONNOR: Yeah, I'm glad that you said that because I agree. I mean, it seems that frequently the point estimates are even higher at 12 and benefits actually increase

over time, I mean, efficacy is not the concern, and why we're having this meeting. So it seems like if they can prove efficacy at 12, the longer-term time points don't concern me because it seems like the degradation is higher with native tissue repair.

DR. ISAACSON: Daniel.

DR. MORGAN: I would agree that we should, at some point, show superiority. I would not go so far as to say that we have to show it at every point. I think, as you get that -- native tissue repair, possibly, has more degradation, it would -- I think we should expect to see it at some point in those time points, 12, 24, 36 months. I do like the idea of making sure that when we're talking about superiority that we're comparing like groups of patients. I think if we're looking at a group of patients who have very few options, you know, we really -- we don't -- we want to be able to make sure that we're comparing, say, primary prolapse to primary prolapse and making sure that we're not comparing patients who are different.

DR. ISAACSON: And that was going to be my concern with this, what everyone is -- it seems to me that if a patient is not a good candidate for whatever reason a physician and a patient believe for a native tissue repair, should not the mesh be equivalent to native tissue repair as opposed to superior?

Rick. Oh, please.

DR. HOSKEY: But to clarify, it should be superior for that type of patient in that subgroup.

DR. ISAACSON: Does that mean that they have to test both in that subgroup? If you've already determined -- how are you going to determine it's superior if you don't test the native in that subgroup? You've only offered one. So it should be -- I still think in that subgroup it should be equal.

Yes.

DR. CONNOR: I mean, in the situation you propose, which I totally understand, it seems difficult even to test non-inferiority because it sounds like in that circumstance there isn't a control group even on which to test, I guess, non-inferiority. You're saying if it's not appropriate, for instance, for native tissue repair?

DR. ISAACSON: That's right, but you still, since these are not randomized, these are cohort studies, you know what the expectation of the efficacy should be for native tissue repair at, you know, 12, 24, 36 months. It's different if they were randomized.

DR. CHAPPELL: I'm worried that too many times in the past we have said, well, that's obvious, this patient clearly is or isn't suitable for such an intervention and then maybe decades later we find out we were wrong. In this case, going back to the quote from SGS -- sorry, AUGS, failed native tissue repairs, that seems to indicate that a native tissue repair is inappropriate if it didn't work. So there are some pretty clear indications, but I'd want to be very careful with that, other than allowing the surgeon to say, well, no, you're not a good candidate, you get mesh.

DR. ISAACSON: Yeah. Dan, does failed mean that only failed once or could it be multiple failures?

DR. MORGAN: I think it could be -- yeah, it could be failed once or multiple times.

DR. ISAACSON: Right.

Yes.

DR. MAZLOOMDOOST: Just to clarify, so I do think that it does need to have superiority because there are very specific complications associated with mesh, so I don't know what the purpose would be of finding an equivalently bad process that might also have higher levels of complications. But I'd also disagree that I think 12 months is not sufficient because the whole purpose of using the mesh is durability and to me, 12 months is not durability. So if there's the potential of having increased risks over time, then you

also need to show that it still remains more effective over time, and we don't have enough data to show that maybe those two lines might cross and perhaps at some point the rate of deterioration, you know, may plateau in one and increase in another, but we just don't have that sort of data. So one problem we do run into, though, with long-term, obviously, as you get patient dropouts and the numbers get fuzzy, so in the ideal, perfect world, you know, we really would want to study that longer. I just don't know how feasible that is in real life.

DR. ISAACSON: So I just want to remind the Panel that we're really talking about efficacy on this particular question and not the safety, so it's, you know, should it be equally as effective or does it have to be more effective.

Yes, Frank.

DR. LING: Frank Ling.

I think because the mesh has inherent additional risks over the native tissue repair that, in fact, showing equivalence is actually good because then it shows equivalence despite the additional risk it carries with it. So my support would be equivalence all the way through and carrying it up to 5 years, albeit difficult, I mean, I'll be a fan of, you know, ongoing monitoring of these patients as a registry, not just stopping at 5 years because I've certainly seen patients in my practice with problems long after 5 years, with problems through this.

DR. ISAACSON: Jason.

DR. CONNOR: Yeah, I mean, I think Dr. Ling, the -- to me, as a statistician, the concern is that we test efficacy and safety separately sometimes, so if we acknowledge that inherent safety risks exist, then we should need to show something is superior on efficacy. So I agree with you that somehow we can show everything is the same for safety and efficacy, but it has benefits in surgical time and ease, I totally agree. But if we're acknowledging that there are safety risks or at least the possibility of such, showing

superiority for efficacy in particular is key to me.

DR. ISAACSON: Elisabeth.

DR. EREKSON: I think, when I read this question, I looked at effectiveness and I think -- I immediately started thinking about the anatomic or objective cures that we were shown and you -- I don't think we're thinking as much about the subjective cures because we weren't shown as much of that data. I think it's really important that we do show superiority of effectiveness for the subjective cures and I agree with the fact that these things may overlap as we follow it out over time in terms of the effectiveness because we don't know where these might -- these lines might start to cross. So I think we should ask for as much follow-up as we possibly can get and really go into the next question, I'm jumping ahead, which is we really have to concentrate on the subjective outcomes.

DR. FISHER: A point of clarification.

DR. ISAACSON: A point? Yes, sir.

DR. FISHER: Fisher, FDA.

You know, we've talked about time points where we need to see effectiveness and safety demonstrated with -- Dr. Iglesia, I believe that when she was presenting for ACOG today, she said the longer the better, and I agree that long-term data is going to be fantastic. As a regulatory agency, though, we have to make a decision at a certain time and we can't necessarily carry every study out 10 years before we make a regulatory decision. So when we start taking these time points into consideration, think about it from our regulatory perspective, you know, for effectiveness, when do you think that you would feel comfortable, okay, maybe that might change how you're looking at this a little bit. When would you feel -- when would you feel comfortable with safety, when would you feel comfortable with effectiveness?

DR. MAZLOOMDOOST: I'd like to actually comment on that from the perspective of

a patient, not the provider, because I think, as a patient, if your procedure is going to fail at some point, you know, and you know that it's going to fail, why take additional risks of the other procedures? So I think, from a regulatory perspective, a minimum of 36 months is necessary because if you know, at 24 months, 12 months, highly superior but I'm going to need another surgery at 24 months anyway, well, why did I do the mesh to begin with, is sort of my thought process on all that, so minimum of 36 months, but really, as long as you can get it out to get good quality data, which is a difficult balance because you lose the patients.

DR. FISHER: So Fisher, FDA.

I wasn't trying to sway your opinion in any one way, I was just trying to put it in a different perspective. Thank you.

DR. ISAACSON: You know, again, I'm a little bit confused here because does effectiveness equal failure? Okay, so you have symptoms, you have to have symptoms by which a patient has indicated to have the procedure. Those symptoms are relieved at 12 months and at 24 months. Now the symptoms come back at 36 months. So it was effective for the first 36 months, but then it failed after that. Does the mesh, according to this question, does it have to be superior to native tissue repair as far as how long it's going to stay up and last or does it have to be equivalent?

DR. MAZLOOMDOOST: No, I think this is where, for me, it's really hard to separate out the two because if you could provide a durable, a more superior product and there is a little bit of an increased risk, you know, that makes sense but I think you have to take into consideration the long-term outcomes. I mean, unless you're doing this procedure on somebody who has a life expectancy of 2 years, we have to consider the safety, I think, along with the efficacy, and I think anything that we have, if you're introducing a new possible treatment with additional different risk factors, it needs to be superior in order to

make sense for it to -- for you to accept those additional risks. I understand like, you know, the dilemma here, but I don't know how you can separate out the two.

DR. ISAACSON: Sharon.

MS. TIMBERLAKE: Hi. I just want to point out what about women -- considering the patient population when you're evaluating for superiority versus inferiority where you may have women that present that really want to keep their uterus intact, where native tissue repair can't offer that option. So when we're considering the efficacy endpoint, there's different patient populations that would -- we would want to consider as part of that study design.

DR. ISAACSON: I think you can keep your uterus with native tissue repair, can't you?

UNIDENTIFIED SPEAKER 1: Yes.

UNIDENTIFIED SPEAKER 2: Yes.

DR. ISAACSON: Yes.

UNIDENTIFIED SPEAKER 2: Absolutely.

DR. ISAACSON: Yeah. Jason.

DR. CONNOR: Yeah, Jason Connor.

And I think, dealing with some of these about, you know, either impossible-to-repair situations and things like this, I mean, the question we're asking here is a more general regulatory what is the comparison to show efficacy to get on the market, we're not talking about really difficult cases because those are cases that would be excluded from an RCT or such analyses anyway, right? Like once it's on the market, a surgeon can choose to use something in a case where native tissue repair isn't necessary. These are more typical comparisons to show that when you have a choice, this has benefits over native tissue repair. So I don't think we're really asking about those really difficult-to-treat cases in terms of showing efficacy, right?

DR. FISHER: So Fisher, FDA.

This kind of goes back to Dr. Hoskey's point, you know, here we're talking about general population, right, and we're looking at a broader scope. We have a whole question that is just dedicated to patient characteristics and surgeon training.

DR. ISAACSON: So to finish up on this. Does the Panel have any additional comments related to the mesh material? Oh, you had one more comment? Go ahead.

DR. DICK-BIASCOECHEA: I agree that the -- it should be proven superior to the native tissue repair, but I think we have to be careful as to what native tissue repair they're comparing it to. Both meshes that we saw today do the anterior compartment but also they provide apical support. So if we're going to compare it to native tissue repair, it can't be just do an anterior colporrhaphy; it has to be as well to something that would correct the apical compartment.

DR. ISAACSON: Yes, Daniel.

DR. MORGAN: Dan Morgan.

You know, in thinking about the non-inferiority and especially some of the trials when they weren't randomized, these patients were actually -- so the treatment group with mesh was maybe a little sicker or they had more prior prolapse surgery, so in that way they may be a more difficult group to treat. So maybe a word for non-inferiority, I guess, is what I would like to say is that if we're looking at a group that already maybe has fewer options, or because they've had more prolapse surgery or they've had other medical problems, you know, as we've been discussing, I've been thinking that maybe the non-inferiority actually is a reasonable standard because you're already treating a patient population that has fewer options and at least they're doing as well or if not, a little bit better.

DR. ISAACSON: So your vote is --

DR. MORGAN: As I think about it, I would probably go -- I would think strongly about

non-inferiority being adequate given what we know about the studies, I think. And as I think about it in general, if I was thinking, like, two primary prolapse populations, I would say I'd want to see superiority, but when we're looking and realize that this patient population may actually already be sicker, may have more problems, fewer options, it's -- I think it's a reasonable standard to apply.

DR. CHAPPELL: So then do we want to discuss the population for which non-inferiority would be adequate?

DR. MORGAN: I think that's a good one, yeah.

DR. CHAPPELL: I mean, unless we say one or the other, we had better or else we'll have failed.

DR. ISAACSON: Right, right.

So, Dr. Fisher, with regard to Question 1, if I'm reading the signs here, I would say that the Panel agrees, for the general population, not for specific groups, that the mesh should be superior to native tissue repair for efficacy and from what I heard, that should be at 12, 24, and 36 months. We all want more data, but 36 months would be -- we'd be happy with that. And then I'm also hearing that for specific patient populations, for those in whom native tissue repair is not deemed to be appropriate, and that's going to be up to the physician and the patient, that just equivalence to native tissue repair would be sufficient, also at those same time points at 12, 24, and 36 months. Any comments, disagreements?

DR. DICK-BIASCOECHEA: This is Madeline Dick.

Section (c) asks for any comments between the polypropylene and the biologic, there have been no studies that show the biologic being superior in effectiveness to a native tissue repair. None of the historical or none of the ones that were, you know, glanced at on the 522. I don't know what anybody else thinks, but I'm not sure where the

place is for a specific -- for the anterior compartment, biologic mesh graft.

DR. ISAACSON: Daniel.

DR. GRUBER: Dan Gruber.

I think, again, the old studies were done in such a different way and they talked about different materials, but I think more importantly than just different materials or doing biologic materials, is that the way it's done previously versus the way, maybe, we're doing it more now is so different that I don't think we just have enough time on efficacy. Fortunately, the biologic, it seems like the risks are a little bit less, overall. So I would say, you know, that we definitely need more time. Again, I think time is the key, with the biologics especially, but I just think it's just you can't compare. You're bringing up the older stuff, but I think it's so different, you know, with the different anchorings to the sacrospinous whereas in the past they were just kind of thrown in there.

DR. ISAACSON: Yes, Barbara.

MS. BERNEY: Well, I just wanted to comment on your most recent comment. I agree that in the general population it should demonstrate superiority, but I also, as a patient, know that I'm the anomaly, always. I want to know that there is something out there that would help me, so even if it's not superior, as long as it isn't going to, you know, be inferior, I would like to reserve the opportunity to have that if I need it. So you can't make a blanket statement, but I think there has to be some provision for the exception to the rule for those subgroups that cannot have natural tissue repair.

DR. ISAACSON: Yeah, I think we agree and hopefully that came out with this summary.

Are you satisfied, Dr. Fisher, with that?

DR. FISHER: Yes. I'd like to thank everybody for the comments. Yeah, we can move on to Number 2.

DR. ISAACSON: Congratulations, Kathy, you got your question answered.

All right, it gets harder. Dr. Olson, Question 2.

DR. OLSON: Question 2 also relates to effectiveness. The FDA literature review identified that while anatomic/objective outcomes generally favor mesh, subjective outcomes demonstrate similar effectiveness for mesh and native tissue repair. FDA believes that both anatomic/objective and subjective outcomes should be used to assess the effectiveness of transvaginal anterior or anterior/apical mesh repair compared to native tissue repair.

a. Does the Panel agree that both objective and subjective outcomes should be used to assess the effectiveness of mesh compared to native tissue repair?
b. If the Panel agrees that both anatomic/objective and subjective outcomes should be used to assess effectiveness, should improvement in both outcomes be required to consider a patient to be a success? Why or why not?
c. Should the assessment of anatomic/objective outcomes be completed by a blinded evaluator?
d. FDA believes improvement or resolution of patient symptoms are an important component in demonstrating effectiveness of a mesh versus native tissue repair. Please address the following:
    i. How should symptoms be measured, for example, a validated questionnaire?
    ii. How should we assess if a patient has a meaningful/significant improvement, for example, what if a patient has symptoms but is not bothered by the symptoms?
    iii. How is a patient's assessment of her symptoms affected by sexual activity (or other patient factors), for example, would a patient who is not

sexually active find her prolapse less bothersome compared to a sexually active patient?

iv. When patients are not blinded to their treatment (mesh or native tissue repair), how might that affect their assessment of symptoms?

e. Does the Panel have additional comments related to the mesh material or other mesh characteristics?

DR. ISAACSON: Does anybody have a burning desire to start? If not -- oh, Dr. Fisher.

DR. FISHER: Fisher, FDA.

So for (e), we kind of got to that, like, a little bit later in the last one. It's just kind of like a real high-level question, you know, we're not talking about mining down, I'm talking about pore size, you know, it's just -- you know, if we were talking biologic versus polypropylene, would that kind of change your thinking, that's all.

DR. ISAACSON: Elisabeth, do you mind tackling this, starting this one?

DR. EREKSON: Well, I think I've already been fairly adamant in my thought process on this one. I would go back and say if a patient doesn't have symptoms, I shouldn't be doing surgery on her, even if she has anatomic prolapse. And so I really think that focusing on the symptoms and the symptom improvement with these surgeries should be the primary outcome and I would also agree that validated questionnaires need to be used. And I guess that's -- I'll leave it to other people now.

DR. ISAACSON: Oh, you're done. Oh, okay. You forgot (c) and (d), but that's okay.

DR. GRUBER: Can I flip back on the slide?

DR. ISAACSON: Yes, Dan.

DR. GRUBER: Back to one. Thanks.

DR. ISAACSON: Any other comments?

DR. MORGAN: I thought that most of the -- this is Dan Morgan.

I thought most of the studies had used a composite outcome looking at both subjective and objective outcomes as well as retreatment for prolapse, which, I mean, I think in many ways is much better than picking just one by itself. I think we can probably rank order some of those within that composite outcome as being, you know, more important. But I think I would lobby for some kind of composite outcome, as the studies have done.

DR. ISAACSON: Kay.

DR. HOSKEY: I also would agree that both need to be evaluated, preferably by a blinded evaluator.

DR. ISAACSON: By a blinded, okay.

Daniel.

DR. GRUBER: I would say, yeah, a composite's good, but I'd really heavily weight it to the subjective. I mean, if I had to throw out a number, then I'd say at least 75%, if not more. I think it should be based on the subjective.

DR. ISAACSON: So if someone was subjectively greatly improved but you could not demonstrate it objectively, would you not -- what would you think of the product?

DR. GRUBER: Well, I mean, if it's on a composite basis and subjectively if they're improved, then that should be reflected in the outcome.

DR. ISAACSON: So then the question is yeah, what's the role of the objective measurement?

DR. MAZLOOMDOOST: I think that's what I was going to say. I mean, I definitely think the subjective should be the only -- not should be the only, but is the more important criteria. However, you know, we've all encountered the patient who swears they have symptoms but then on exam they don't have prolapse. So I think in the one exception where anatomically things may be supported and their symptoms are coming from

elsewhere might be the benefit of having the objective as well.

DR. ISAACSON: Yes, Rick.

DR. CHAPPELL: After advocating strongly for superiority, I don't want to be too stringent and demand superiority on one, two, three, four, many outcomes, that's a very hard bar to jump over and therefore I will phrase my comments in two parts, that a composite outcome might be useful here and the composite outcome should definitely include blinded objective and subjective outcomes. My earlier question is what do you mean by objective? It seems to me that an objective outcome here is an opinion by a doctor and the subjective outcome is an opinion by a patient. I don't see that there's a fundamental difference between the two in terms of scientific reliability.

I've known situations where patient outcomes seem to predict future subjective -- sorry, objective outcomes, for example, dictated by X-rays, better than the doctor looking at the same earlier X-rays. So I don't think we can ignore patients' subjective outcomes, but perhaps a composite endpoint is a way of keeping the burden from being too onerous.

DR. FISHER: So if I could -- Fisher, FDA.

If I could follow up on that comment. I think part (c) says if you're going to go with an objective outcome, an anatomical outcome, could you get around that by using a blinded evaluator?

DR. CHAPPELL: Sorry, by what?

DR. ISAACSON: A blinded evaluator.

DR. CHAPPELL: Oh, blinded. Yeah.

DR. ISAACSON: So I kind of see both sides here because if I go back to my experience when the FDA was evaluating fibroid therapies there was one study that was approved based on subjective measurements, there was another study after that that required objective measurements even if it didn't correlate with the subjective. So I don't know if

the same applies here. Can we say that there's a fairly high correlation -- and you guys are seeing the patients -- between the objective and the subjective? Are you comfortable with that generalized statement? Anybody. Dan? Or Kay?

DR. HOSKEY: I would say at the extremes it correlates but it does not always correlate in milder cases.

DR. MORGAN: I always have a hard time -- I mean, I think we see so many patients who, as Dr. Mazloomdoost was saying, think that they have prolapse and they do have some other -- say other urinary symptoms or some other symptoms that understandably lead them to think that whatever the operation they had was not a success and I think that I would -- it would be difficult, I think we would be misled if we said that, you know, that one means the other.

DR. ISAACSON: Is there any surgery effect on these patients' subjective symptoms, meaning you know the first usually 4 to 6 months after surgery you're going to notice some improvement, but whether it lasts more than 4 to 6 months really is dependent on the objective measurements. So, for example, if someone's having pain and they'll say okay, my pain is better for the first 3 to 6 months, and we see this with a lot of other surgeries. But then, after 6 months, if it's really not due to the objective measurements, the pain comes back. Do you see anything like that in patients who have this pelvic organ prolapse? Is there effective surgery that's not necessarily due to the anatomic result?

DR. DICK-BIASCOECHEA: You're talking like a placebo effect?

DR. ISAACSON: It is and it isn't. I mean, it's a true benefit, but it doesn't last very long.

DR. DICK-BIASCOECHEA: Well, in my experience, when you're -- right after pelvic floor surgery you have more heaviness and more pain and then that gets better over time, but I haven't seen it.

DR. ISAACSON: So you feel it's necessary to measure objectively? That's what this has boiled down to?

DR. DICK-BIASCOECHEA: Yes, yes. And to counterbalance, I've seen patients that have a significant prolapse that have no symptoms, so it's -- you know, it can be one way or the other, it's not --

DR. ISAACSON: So this gets to the question of, you know, if the patient's not blinded to their treatment, does that affect the assessment of their symptoms? It's all on the same line. It's a question that's asked by the FDA.

Yes, Daniel.

DR. GRUBER: I think ideally you would have blinded observers, but I wouldn't be so strict as to say -- because somebody earlier mentioned that if you're having a site that's doing a study and they're in an outlying area and they don't have ancillary personnel, you could be -- in the real world, it could be extremely restrictive. So, ideally, you're blinded, but as long as they report that it was and it wasn't, then you can at least ferret that out later on in the data analysis.

DR. ISAACSON: Other comments?

Barbara.

MS. BERNEY: I live in a state that has a very large rural population and that's the southern part of Illinois and I can tell you that there are many, many clinics set up where there is one -- one person qualified to do that. And if you are requiring ancillary personnel, you're not going to get it, which would disqualify them, those sites, leaving a significant population without any involvement. So I really -- you know, I think as long as there's somebody qualified and you get both the objective and the subjective information, that should be all right.

DR. ISAACSON: So, Dr. Fisher, with regard to Question 2, if I have this correctly, the

Panel generally believes that both objective and subjective outcomes should be used to assess the effectiveness of mesh compared to native tissue repair, but with the caveat that it be weighted. It seems like we feel, and I'm just taking a stab at this, that if you had a score of 100 that 75% of that score should be subjective and 25% objective, so it came up. So they should be looked at together but not weighted the same, that if the Panel agrees that they should be used to assess if they showed improvement and both outcomes be required and again, if it's weighted, it's not necessarily that they're both required. If someone feels a hundred percent better but very little objectiveness, then maybe that's sufficient. I think that's what we're saying, but it should be weighted.

Yes, it should be -- the assessment should be completed by a blinded evaluator, I think, when possible. If it's not a rural area, that's ideal. A validated questionnaire is essential. My view on it, just personally, is that it should be the same validated questionnaire as opposed to multiple ones that are out there, but I think a validated questionnaire is yes. And let's see. We didn't really talk about should the patient's assessment of her symptoms be affected by sexual activity, and does anybody want to speak to that?

Yes, Kay.

DR. HOSKEY: It can be affected in many ways or none at all. And to answer the question of would a patient who's not sexually active find her prolapse less bothersome, not necessarily. It's highly patient dependent.

DR. ISAACSON: And does the Panel have any additional comments related to mesh material or other mesh characteristics? I don't think it came up in this question.

So, Dr. Fisher, is this adequate or is there more you'd like to expand on?

DR. FISHER: Just a real quick follow-up to Dr. Hoskey's question. So you said it could be all or none for sexual activity, possibility of doing a validated questionnaire before and

after so that you have a baseline?

DR. HOSKEY: I do believe that the validated questionnaire related to sexual function should be completed before and after, but the severity of prolapse does not always correlate with those questionnaire answers.

DR. FISHER: Thank you.

DR. COLDEN: I just have a question, a clarifying question. Certainly whether or not --

DR. FISHER: You need to come up to the microphone.

DR. COLDEN: Okay.

DR. FISHER: With the Chair's permission, could I have Dr. Colden come up to the microphone?

DR. ISAACSON: Absolutely.

DR. FISHER: Thank you. I don't know that I can stop her.

(Laughter.)

DR. COLDEN: I guess it really becomes when patients aren't sexually active yet and still they may have adverse events that if they were sexually active may be an event, adverse event, that would be meaningful, so how that translates into a clinical practice setting where patients are not sexually active at one time point, sexually active at another time point, in terms of counseling. And so it may not be just sheer numbers of we didn't see a lot of complaints of painful intercourse despite erosions, but it may be more that we did not have the patient population to adequately assess that and how to counsel patients related to that in their decision-making process to proceed with one surgeon or another.

DR. HOSKEY: Yes, if a patient is sexually active, I would say, generally, if comparing an erosion of the same size in the vagina, it is much more detrimental to the patient who is sexually active and the patient who is not may find that same situation completely

asymptomatic. Does that answer what you're getting at?

DR. COLDEN: Well, certainly it answers the question but it makes it more difficult in terms of counseling patients to look at the big picture, if that makes sense.

DR. HOSKEY: Ideally, the studies should include patients who are sexually active and those who are not and ideally, counseling should include how this may affect your future sexual function if these complications do occur. Similarly, we have patients who have very small erosions who may be symptomatic when they're not sexually active or may be very bothersome even if they're not sexually active, so it just tends to be a subject that is highly specific to the patient and very difficult to generalize because sexual activity for one lady is not the same as another, and that's just part of the variety of patients we deal with.

DR. COLDEN: Thank you.

DR. EREKSON: So we already talked about how there was a difference between repeat surgery and primary surgery. I think one of the things that I would advocate for is perhaps we need some information on, you know, there are patient populations who are not sexually active before surgery and that's one category, but we definitely need that subcategory of these are the patients who are sexually active before surgery and this is what happens after surgery. And you are right, I agree, we need that data.

DR. ISAACSON: Anything else for Question 2 that you wanted?

DR. FISHER: No, I think we're good, and the good news is the questions get shorter as we move forward.

(Laughter.)

DR. ISAACSON: I know. Thank you.

So for Question 3, Dr. Olson.

DR. OLSON: Question 3 relates to safety. The following adverse events have been associated with mesh and/or native tissue repair and are being collected in the 522 studies:

a. Pelvic pain

b. Erosion/exposure

c. Dyspareunia

d. De novo voiding dysfunction, for example, incontinence

e. Infection

f. Vaginal shortening

g. Atypical vaginal discharge

h. Neuromuscular problems

i. Vaginal scarring

j. De novo vaginal bleeding

k. Fistula formation

Please discuss these adverse events and consider their importance, potential to be debilitating, how they should be assessed, when they should be assessed, and key considerations related to the mesh material or other mesh characteristics. Please also comment on any important adverse events that may be missing.

DR. ISAACSON: And I thought this was a perfect question for Dr. Ling to start off with, if you don't mind. Start the discussion.

DR. LING: Well, I think, more than anything else, any evaluation of these side effects or adverse events have to have a very thorough pre-surgical assessment and what I'm struck by, when you look at the literature, is that there is not a good description of how these problems are kind of eliminated before the person has the mesh intervention. And I think what you really need to do is make sure that any way that you assess them before surgery does include these likely adverse events. At the same time, a lot of these adverse events obviously occur with native tissue repair, some not, but a lot of these things.

In fact, the patients that I see who have problems after mesh repair -- because we

have two urogynecologists in our practice and I end up dealing with all their pain stuff, both before and after. There's a whole lot of pain stuff, as all of you know, that has nothing to do with prolapse either before or after surgery. And so I think there's a lot of noise around these other symptoms surrounding mesh and surgery, and I just -- I can't emphasize enough the importance of being able to tease out that just because something occurs after surgery it doesn't mean it had anything to do with the surgery.

DR. ISAACSON: Comments? Yes, Donna.

DR. MAZLOOMDOOST: Donna Mazloomdoost.

One thing I would probably recommend to the FDA is to be cautious in what we would consider being debilitating because there's more data coming out that shows a discrepancy between patient-reported adverse effects and provider-reported. So that is one thing to consider.

And then the other thing is to look at the relatability, you know, the common reason why patients are dissatisfied after prolapse surgery is, like, a rapid bladder or urinary frequency/urgency, which is not related to the surgery. So I think it's, you know, probably being a little bit more specific on some of these and looking at, okay, stress incontinence versus an actual urgency urinary incontinence.

DR. FISHER: Fisher, FDA.

A quick follow up. Do you feel that anything is missing from the list?

DR. MAZLOOMDOOST: This is pretty comprehensive, so I would say not -- like, immediate. Not more commonly, yeah.

DR. ISAACSON: Kay.

DR. HOSKEY: Perhaps the comment of general health or well-being may be useful.

DR. ISAACSON: Yes, Jason.

DR. CONNOR: Yeah, that's what I was going to add, I mean, something -- it's not

exactly an AE, but this idea of, you know, would you have this done again, because I think that's something that gets to the totality of risk-benefit and I think that's very important.

One thing, and I'm sure it will be ignored and I probably would, too, if I were you, Dr. Fisher, but I think something very valuable that has been produced by FDA is when FDA elicited the study from RTI regarding weight loss device benefit and risk, that FDA was trying to understand, you know, what risks patients would take for some of these weight loss devices and FDA commissioned a study and it was published in a surgical journal by Martin Ho and Telba Irony from FDA and others. But it was really informative in terms of -- because I think none of us even on FDA panels, and I've served on weight loss panels, could understand benefit-risk from the patient perspective, and so FDA commissioned that study and I think it was very illuminating.

DR. ISAACSON: Yes, Liz.

DR. EREKSON: So we don't have repeat operation on this list and there is certainly repeat operation that goes with a failure of a native tissue repair or a mesh-based repair for prolapse, but then there is a repeat operation that has to do with complications from these devices. And I think that we're trying to balance that, but it just strikes me that it's not on the list.

DR. ISAACSON: Daniel.

DR. MORGAN: I would say that -- Dan Morgan -- that on the list, too, de novo voiding dysfunction, I think a lot of us think about obstructive voiding and maybe recurrent UTIs and there's kind of -- you know, it's not really sorted out in there, whereas de novo stress incontinence would be something separate from voiding dysfunction, so maybe just separating those out would be worthwhile.

DR. ISAACSON: Yes, Dan.

DR. GRUBER: And to add to that, I mean, getting a baseline for overactive bladder

symptoms because we were kind of talking about, like a lot of people have that before but then afterwards -- and then that's really what bothers them a lot, afterwards you've fixed other stuff and then now they have this left over which, when you get back into it, they actually kind of had it before.

DR. ISAACSON: So if you take out dyspareunia, what other pain assessment are we really looking at here? So say chronic pelvic pain now that is not -- is stimulated by anything other than just being alive or can you address that?

DR. GRUBER: Yeah, I mean, it can be chronic pelvic pain, it could be with just sitting there doing nothing, it can also be with movement, like musculoskeletal type of thing, too.

DR. ISAACSON: Can that be teased out a little better here?

DR. GRUBER: I don't know, I mean, it's just pelvic pain so, in my mind, I put them all in a category, but I don't know if they want to separate it all out. It is all important, though.

DR. ISAACSON: Because it's number one on this list, so it needs -- go ahead, Jerry.

DR. LOWDER: This is Jerry Lowder.

Again, kind of what we were talking about earlier. I think, kind of alluding to what Dr. Ling was saying, I think having pelvic pain and assessing it with both subjective and objective measures when possible and particularly, you know, getting a baseline pelvic floor myofascial exam, again, as many of these meshes are either attached to or implanted in the pelvic floor muscles, you know, and some work we've done from a baseline extremely high rate of pelvic floor myofascial pain on examination and a large percentage of those women, they actually don't complain of pain but they have pelvic floor pressure and heaviness symptoms. And we see that when we stratify it by POP-Q stage and, just like Dr. Mazloomdoost mentioned earlier, I think a lot of times when the patients have pressure and heaviness, but the prolapse, it often is the pelvic floor myofascial pain. So I think having a baseline because, again, sometimes even the native tissue repairs can kind of

trigger the pain afterwards that might have been existing but not recognized by the patient or surgeon if they get an exam of those muscles.

DR. ISAACSON: Frank.

DR. LING: Yeah, Frank Ling.

DR. ISAACSON: You're off.

DR. LING: Oh. Frank Ling.

Yeah, the specific issues that, in addition to pelvic floor tension and fibromyalgia and the things that patients don't even think about telling the doctor because once they tell the doctor yes, I have pain and the doctor sees the prolapse, then everything kind of fits, but unless a good thorough examination or evaluation can rule out fibromyalgia or at least reasonably rule out neuropathies and things of that nature, your data is totally skewed.

The one condition that just pops up all the time in some of these patients is vestibulodynia which, you know, unfortunately gets lost in the shuffle, but it presents as dyspareunia and oftentimes a woman has pain for multiple reasons, let's say the prolapse and vestibulodynia and other neuropathic issues. Then once you remove one thing, then they say oh, now my pain is over here, well, that's because they removed just one source of pain and the other one still exists.

So I think it's really important that, just like voiding dysfunction being an awfully general term, you need to have specific voiding dysfunction questions or assessments, you need to have pelvic pain assessments that are broken down to several categories depending on what it is that the FDA ultimately wants to tease out.

DR. ISAACSON: Yes.

DR. DICK-BIASCOECHEA: They don't have, like, intraoperative adverse events like organ injury, hemorrhage or --

DR. ISAACSON: That's a good point.

Yes.

MS. TIMBERLAKE: I was just going to comment based on this list, these are pretty much known adverse events that we've seen through the literature, that in the study designed for the 522s, they're also, I'm assuming, capturing all other events that are related to the procedure, potentially to the product as well as the pelvic floor, at each follow-up visit for both groups of patients. So the data will be there and it will be analyzed and the manufacturers are presented -- as well as show them raw data with the Agency so the statisticians can look at it in various ways as well.

DR. FISHER: Right. Fisher, FDA.

So yes, I think the comment was made earlier that we want to capture all adverse events. We agree that some can be adjudicated, we like to look at those adverse events through an adjudication by our self, we have quite a competent crew of OB/GYNs who can look at these, also, and there's other things that may not just be device related or procedure related that we may want to take a look at, so thank you for that comment. One thing that we have not touched on is when these adverse events should be assessed. Prior to, immediately following, time points after? Thoughts?

DR. ISAACSON: I think prior to it's not an adverse event but it's a baseline, so -- but no, I think one of the general recommendations that we all agree is that we need to be very -- a little more diligent in our baseline measurements of pain, stress incontinence and what have you, and it should be done universally for any symptom that we're going to be asking the patient about as the study progresses. So if you're going to ask them about pain at 6 months, you should ask them at zero months and the same with stress incontinence and what have you.

Daniel, do you have a comment since you're --

DR. MORGAN: I was going to say, with respect to sexual function, I think there's

some good evidence that you really need to wait a certain period of time before assessing it afterwards, at least 6 months. I realize that we're all talking about data later, but I think if we were to assess it before then, I think you'd really be getting a not accurate picture just because surgical recovery takes a lot longer for -- especially for sexual function.

DR. ISAACSON: So I think 6 months for any of these is kind of at the earliest, correct? Right.

All right, so Dr. Fisher, with regard to Question 3, the Panel generally believes that the list that you have here that's included of these 10 events is a comprehensive list, we didn't really add anything. I think one we should add, that was brought up by Madeline, was intraoperative complications. I don't see that on the list. I think the Panel agrees that we need to be very careful with our preoperative assessment for any of these symptoms that we're going to be asking about as the study progresses. I think if we are able to add a question in the study at some point, maybe at 36 months, maybe Jason can comment on this about would you do this procedure again, it can be incredibly invaluable as a tool to assess quality of life.

Jason, at what point would you ask that question?

DR. CONNOR: Yeah, I mean, I think if you're following people at 1 year for sure, and if they're still tracking at three, I'd add that question at three.

DR. ISAACSON: Dan.

DR. MORGAN: Dan Morgan.

I know one of the -- use the patient global impression of improvement, which I think a lot of us think is a valuable thing and it just asks, on a seven-point scale, how much better or worse off do you feel at this point and, you know, that's been something that's been a valuable thing that I think is one item getting to that respondent burden, it's just one item, and that kind of gives you the general thing to consider.

DR. CONNOR: I agree.

DR. ISAACSON: Great.

Dr. Fisher, is this adequate?

DR. FISHER: Fisher, FDA.

Right, I'm not quite done with this one yet and I just want to dig a little deeper. Real quick survey around the table. Which of these do you feel are the most important and which ones do you feel are potentially the most debilitating? So importance or what would you consider, you know, the key ones, the most important, and which ones really have the potential to be debilitating to a patient?

DR. MORGAN: This is Dan Morgan.

I think (a) fistula formation would probably be the most devastating because that's going to be a difficult problem to fix, it's probably going to be the rarest of all the --

DR. ISAACSON: Which one?

DR. MORGAN: Fistula formation.

DR. ISAACSON: Fistula, okay.

DR. MORGAN: Would be the most severe. And then, you know, you could probably order them from there, I mean, but I would say that that's going to be the least common but the most devastating, and then I think the more common things, pain and infection and erosion would be the ones that's I'd order next.

DR. ISAACSON: Anybody disagree?

(No response)

DR. ISAACSON: So I think, as a general consensus, pelvic pain -- yes. Oh, I'm sorry.

DR CHAPPELL: Well, I was just about to agree with you. So pain is always important. Ask any patient. And based on the data, for present purposes, (b) erosion and exposure must be important.

DR. ISAACSON: Yes, Donna.

DR. MAZLOOMDOOST: And a little bit -- Donna Mazloomdoost.

A little bit of it would be persistence, like one urinary tract infection may not be that debilitating, but recurrent would be. So a little bit of it is, you know -- or does the exposure resolve with estrogen? So I think some of this is based on more of the presence and long-term follow-up rather than a one-time event.

DR. ISAACSON: Yes, Frank.

DR. LING: Yeah, and the fact is so many of these things really are overlapping, anyway. You're talking about -- some of these things have no symptoms, vaginal scarring, she doesn't know if she has vaginal scarring. Vaginal shortening, she doesn't know. Unless she has sex. Then she has dyspareunia, also called pelvic pain. It's just a question of how she describes it or how you extract it from her, taking her history, because pelvic pain can be generalized, it can be localized, dyspareunia, it can be entrance dyspareunia, deep dyspareunia, so a lot of it depends on how you try to biopsy her problem.

DR. FISHER: Thank you for the follow-up.

DR. ISAACSON: Sure. So is this adequate, Dr. Fisher? If so, we're ready for the next question.

Question 4, Dr. Olson.

DR. OLSON: Question 4 also relates to safety. To demonstrate reasonable assurance of safety, FDA believes the adverse event profile for mesh placed in the anterior or anterior/apical vaginal compartment should be comparable to native tissue repair, or any increase in risk should be offset by a corresponding improvement in effectiveness. FDA also believes that all adverse events (not just those adjudicated as device- or procedure-related adverse events or serious adverse events) along with their severity/seriousness, timing, resolution, and relatedness to the device and/or procedure should be used to evaluate the

safety of mesh compared to native tissue repair.

a. Does the Panel agree with this approach?

b. What are the effectiveness scenarios where an increased safety risk may be acceptable, for example, patient with recurrent prolapse?

c. At what time point should comparable safety (or increase in risk offset by a corresponding improvement in effectiveness) be demonstrated, for example, 12, 24, 36 months, or longer?

d. Does the Panel have additional comments related to the mesh material or other mesh characteristics?

DR. ISAACSON: Jerry, are you burning to answer this one, please?

DR. LOWDER: So Jerry Lowder.

So I think that, ideally, they should be comparable to native tissue repair. You know, the thing that we'll never get around is that we're not going to have a mesh exposure with a native tissue repair, but you will with the mesh. And I mean, just something I've been kind of toying with is that, I mean, to compare more apples to apples is whether or not we should kind of judge the rate of mesh exposure comparable to sacrocolpopexy, since this -- a mesh prolapse repair as is the transvaginal mesh repair. So I think, except for the risk of mesh exposure, I think they should be comparable to native tissue repair but it may be something to consider as far as the rates of mesh exposure when we're kind of judging transvaginal mesh.

DR. ISAACSON: Donna, any comments?

DR. MAZLOOMDOOST: Donna Mazloomdoost.

I mean, I think this goes back to the same thing as Question 1 in order, I agree that if the benefits and the success offset the adverse events, then it would make sense. And, you know, the time points, Number 3, I mean (c), I think really the longer, the better. To me, 12

months is just inadequate, it's not long enough.

DR. FISHER: So Fisher, FDA.

Just to follow up, there are specific effectiveness scenarios. I mean, we put a patient with recurrent prolapse and there are other things that you can think of.

DR. MAZLOOMDOOST: Donna Mazloomdoost.

I do think that the recurrent prolapse population is definitely different or somebody who, you know, has already failed a prior native tissue repair, then I do think that in that capacity it does offset a little bit of the risk, so in that special population, sure, but in the general population, you know, it's different.

DR. ISAACSON: Comment, Liz?

DR. EREKSON: I just want to strongly support that I think all adverse events should be reviewed and so I would agree with that, that approach, and I want to put that on the record.

DR. ISAACSON: And if someone could comment, what are the effectiveness scenarios in which increased safety risks may be acceptable? You mentioned recurrent prolapse, is there anything else?

DR. MORGAN: There's certainly, I think, certain situations where you may be considering multiple different surgical approaches to it, to the condition, and I can imagine certain situations where you -- a native tissue repair might end up resulting in -- you'd be concerned about it causing more scarring and stenosis and that a mesh-augmented colporrhaphy in the fashion that we're considering, I think might be a very good option. It could help you avoid going through an abdominal incision when somebody has a very complicated surgical history, let's say they had a kidney transplant or they've had a diversion or they've had some other kind of neuromuscular congenital neural tube defect and you just really would like to do something else other than go abdominally. So I think

that, you know, that would be more specific but that would certainly be a situation I'd be thinking about, wanting to think of this.

DR. ISAACSON: Kay, you look like you're burning.

DR. HOSKEY: I would just say that the question says increased safety risk, they may have increased safety risk for the other adverse events we talked about but, like you mentioned, decreased safety risks for abdominal surgery or whatever alternative surgery is being considered.

DR. ISAACSON: Anyone else?

DR. DICK-BIASCOECHEA: We had mentioned, also before, connective tissue disorders like congenital connective tissue disorder and patients who have had uterine preservation.

DR. ISAACSON: Uterine what?

DR. DICK-BIASCOECHEA: Preservation. They want to keep their uterus.

DR. ISAACSON: So, Dr. Fisher, the Panel, with regards to Question 4, generally believes that all adverse events should be considered along with the severity and seriousness, timing, resolution, and relatedness to the device. We also believe that there are scenarios in which there should be -- increased safety risk may be acceptable, which included what you've mentioned here, recurrent prolapse and surgical risk as well as some medical conditions that would predispose the patient to be at higher risk for one approach, such as native tissue repair, over another. And is this satisfactory?

DR. FISHER: Yes. I think I also heard uterine sparing would be a condition, also.

DR. ISAACSON: What's that?

DR. FISHER: I said I thought I also heard uterine sparing might be --

DR. ISAACSON: Well, there was a debate on uterine sparing because it's -- this side of the table felt uterine sparing could be done both with native tissue repair as well as with

mesh, where this side of the table may not have thought that.

DR. FISHER: Equivocal findings. So we'll take them all into consideration, thank you.

DR. ISAACSON: Yes. Am I right on that? I don't want to misspeak for you.

(Off microphone response.)

DR. ISAACSON: You can do uterine sparing even with native tissue. So I'm not sure that that's a factor. All right.

Dr. Olson, we're going to Question 5.

DR. OLSON: Question 5 relates to the patient population. The FDA literature review identified concomitant procedures (hysterectomy and sling placement) and surgical/medical history (age, obesity, current level of sexual activity, parity, premenopausal estrogen therapy, diabetes, and smoking) that may affect the safety or effectiveness outcomes of an anterior or anterior/apical mesh or native tissue repair.

a. Does the Panel agree that the identified concomitant procedures and surgical/medical history may affect the safety or effectiveness of a mesh or native tissue repair?
b. Which additional concomitant procedures or surgical/medical history could affect the safety or effectiveness outcomes of mesh or native tissue repair in the target compartment?
c. How should FDA factor concomitant procedures and surgical/medical history in its interpretation or evaluation of study results, for example, balance of these characteristics between study arms or assessment of adverse events associated with concomitant procedure versus primary procedure?

DR. ISAACSON: Madeline, would you take on -- start the discussion, please?

DR. DICK-BIASCOECHEA: This is Madeline Dick.

I agree that there are certain concomitant procedures and history that may affect

the safety and effectiveness of the mesh or native tissue repair that are included here. I'm not sure what the -- yes.

DR. ISAACSON: You would agree. Can you comment on which procedures would affect the safety and efficacy of the mesh?

DR. DICK-BIASCOECHEA: Well, I said before apical support procedure and the concomitant incontinence procedure in some studies with the sling.

DR. ISAACSON: Can anyone comment, other than me, on why premenopausal estrogen would increase the risk of a failure in this procedure?

DR. DICK-BIASCOECHEA: I think they meant postmenopausal because --

DR. ISAACSON: Well, they said --

DR. DICK-BIASCOECHEA: -- it goes to vaginal atrophy, but I don't know.

DR. ISAACSON: They said it several times, that it said premenopausal estrogen therapy. Does anybody --

DR. HOSKEY: The question sounds confusing because generally, in a premenopausal woman, we wouldn't call it estrogen therapy, it would be considered oral contraceptive pills or something else like that. We usually don't use the term replacement therapy in that context.

DR. ISAACSON: So you think that's what the studies are referring to, is OCPs?

DR. HOSKEY: I would think that vaginal estrogen therapy is given so rarely in a premenopausal woman that the study did talk about oral estrogen of any type.

DR. ISAACSON: Okay. So we would agree that that's probably not a risk factor, is that what you're saying? I mean, true premenopausal hormone replacement therapy or estrogen replacement therapy, can't think of an indication to do that, but that's what the studies said and that's what it says here. Okay.

So any other comments about uterine sparing, non-uterine sparing that would affect

the outcomes?

Liz.

DR. EREKSON: So I think when we talk about concomitant procedures, we have to balance that with the need to do those procedures. And so, you know, when you look at postoperative complications after any surgery, the more surgeries you do at one time, the more complication rates you're going to have, the longer -- you know, the longer time the surgery's going to take and all these things happen, but we weigh that with having to have multiple repeat surgeries, and so in a patient who has prolapse and stress incontinence, they absolutely need a sling placed. And so I think that identifying that these procedures are often performed at the same time as prolapse repair is a good thing and I don't think we should discourage any surgeon from doing multiple procedures at one time, needing more repeat surgeries on patients that they don't need it.

So I absolutely agree with the approach that we need to either stratify how we report these outcomes when we're evaluating these different mesh products or adjust for that in some way rather than try to get surgeons just to do a transvaginal mesh repair and not include all of the other procedures.

The other comment I would have is that we haven't talked about the uterine-sparing procedures and the need for really appropriate preoperative evaluation of these patients such that you don't perform a uterine-sparing procedure and then need to do a hysterectomy a year later for a different indication.

DR. ISAACSON: Yes, Donna.

DR. MAZLOOMDOOST: Donna Mazloomdoost.

So an additional medical history would be chronic Valsalva type things like chronic constipation or somebody who has like COPD or bad asthma, so those medical conditions might impact somebody's recurrence risk.

DR. ISAACSON: Yes, Dr. Fisher.

DR. MORGAN: Dan Morgan.

I just had a question about other surgical therapies that didn't get mentioned, just a posterior repair at the same time. I don't know if that's a matter if we're talking about it has to be prolapse in the same operated compartment but, you know, I think there's often the potential for correcting prolapse in one compartment, having prolapse develop in another and, you know, it would be worthwhile to, I think, make sure that we're keeping track of that, in addition to hysterectomy and midurethral slings.

DR. ISAACSON: So if I'm interpreting the question, Dr. Fisher, correct me if I'm wrong, this is not whether concomitant procedures should be done or should not be done, the question is what are the procedures that will impact the efficacy or the safety of the anterior repair.

DR. FISHER: That is correct. Fisher, FDA.

In the FDA presentation this morning, we presented in the literature search review that there was a paper, Chughtai 2017, and it talked about concomitant procedures with midurethral slings and it talked about erosions that with a concomitant sling, that you saw 2.7% erosions where without the concomitant sling it dropped down to 1.9. If you talked about reoperations with the sling, it was 5.6. Without the sling, it dropped down to 4.3. Now, those numbers aren't hugely different, but there does appear to be a different -- a difference between the concomitant procedures here.

I guess another question is should there be -- should there be like a -- should we have another comparator group that we compare this to instead of just looking -- since we know concomitant procedures may have an impact do we have to change the comparator that we're looking at? How do we adjust for this?

DR. DICK-BIASCOECHEA: I think if the control group has the same qualities, I don't

know why we'd separate them out.

DR. HOSKEY: For example, if the vaginal mesh group that has a sling is compared to the vaginal/hysterectomy/uterosacral group that has a sling, that would eliminate some of the take-backs and complications, voiding dysfunction that the sling may have created, and perhaps the increased mesh exposure rate that the sling may have created, albeit small.

DR. FISHER: Great, I'm not -- oh, I'm sorry. Fisher, FDA.

I'm not even sure they're really delineated in these papers, if you saw an erosion or a reoperation, which of the meshes it was due to. So I don't know if, moving forward, we need to have additional documentation for these so we have a better understanding of what's going on, also.

DR. ISAACSON: Well, I think, as you heard and I think Liz said it first, if we stratify these patients, it's those that do have a concomitant/those that do not, and then which concomitant procedure. This should absolutely be part of the evaluation of the 522 study. Doesn't mean it shouldn't be done, but they do need to be looked at as a separate group.

DR. FISHER: Right.

DR. MORGAN: As you said when we were just talking, that paper that you were just referencing -- this is Dan Morgan, sorry -- about erosions and reoperations. And I think that makes a lot of sense when you're talking about midurethral sling and hysterectomy because your incisions are so close to where the anterior repair is, I mean, but if we're talking about the effectiveness and whether or not they have prolapse recur, you know, to the patient whether if a prolapse recurs in the posterior compartment and they have to have surgery, that's equally -- to them, you know, it's like okay, I have to go back for another prolapse operation. So, you know, I think maybe keeping those separate, like, for the safety part and then the effectiveness part for concomitant procedures.

DR. ISAACSON: Any other comments?

(No response.)

DR. ISAACSON: Dr. Fisher, is that sufficient? You want a generalized opinion, I forgot to give you that.

(Off microphone comment.)

DR. ISAACSON: Yes. The Panel feels that the concomitant procedures should be a part of the study and that they should be identified and that there are certain procedures that could affect the effectiveness and safety of mesh or native tissue repair. Some of those procedures included doing hysterectomy, posterior repair, apical repair, so I think any surgery in that area could affect the safety and efficacy of the anterior repair and we also feel that those patients should be stratified when looking at their data as far as the safety and efficacy, certainly up to 36 months.

DR. FISHER: So we did a great job at talking -- excuse me, on touching on concomitant procedures. Any comments on surgical and medical history, which include age, obesity, current level of sexual activity, parity, postmenopausal estrogen, etc.?

DR. ISAACSON: So you're asking -- I didn't hear you very well, was it comment --

DR. FISHER: I said we did a great job at talking on concomitant procedures. I'm just wondering if there were any comments on how surgical and medical history may have an impact.

DR. ISAACSON: Well, I think the Panel did comment on, not surgical history per se, but certainly medical history as far as conditions that could increase the risk of complications or, I will say, affect the safety and efficacy of the anterior repair. Those included connective tissue diseases, you know, chronic lung disease, coughs, obesity. I think we didn't name them all, but we named several medical conditions, preexisting medical conditions, that could affect --

DR. FISHER: So we do have a comment that I think that we will do our best to try to

balance these characteristics between study arms.

DR. ISAACSON: Absolutely.

DR. FISHER: In a perfect world.

DR. ISAACSON: Absolutely.

DR. FISHER: Thank you.

DR. ISAACSON: All right, Dr. Olson, Question 6.

DR. OLSON: Question 6 also relates to the patient population. In non-randomized studies, selection bias can influence safety and effectiveness outcomes. FDA believes the following factors may determine whether a patient undergoes a mesh versus native tissue repair.

- Patient, for example, recurrent prolapse, severity of prolapse, age, obesity, sexual activity, parity, other surgical/medical history
- Procedure, for example, need for a concomitant procedure
- Clinical Site, for example, whether site offers only mesh versus native tissue repair, whether the site is a specialty center for one type of repair
- Surgeon, for example, experience with mesh versus native tissue repair, surgeon preference based on individual patient characteristics

Please discuss how these factors or any additional factors may bias the safety and effectiveness outcomes of a native tissue or mesh repair.

DR. ISAACSON: And I want to thank Rick for volunteering to start on this question.

DR. CHAPPELL: I've been volunteered in the transitive sense that I volunteer my graduate students. Well, to quote another Dr. Fisher, the founder of modern statistics, "There is no science without randomization." So the only proper answer to this is a randomized clinical trial and that has already been mentioned as being very difficult in the present circumstances and I note that the FDA has not asked us our opinions on a

randomized clinical trial. So in its absence, there are only stopgap measures and what was used in -- what was it? Coloplast? I may remember wrong. They use propensity scores, right, in their analysis. That involves certain assumptions which can't be verified without a randomized clinical trial, but those are the best we can do.

DR. ISAACSON: Comments? Comments from the Panel?

(No response.)

DR. ISAACSON: So I think one thing I'd like to try to answer for Dr. Fisher and the FDA is we have -- we know that we're not getting randomized controlled trials, but what are the factors, maybe other than the ones listed here, that could affect bias that we should look into? So is there anything other than, you know, patient -- variations within the patients, procedure, the clinical site or the surgeon or if you have comments on any one of these four.

Yes, Dan.

DR. GRUBER: I mean, I think that there are a lot of these factors that do go into it in the real world. I think that patients ideally should be offered or that there are lots of different ways of doing these kind of procedures and given the gamut of them, and if a specific surgeon isn't comfortable or not capable of doing one or the other, the patient should be aware of that so they can go elsewhere if they choose to.

As far as, like, characteristics, I'm assuming age and sexual activity, I think, would be very important, that can sway one way or the other because, for example, if you have somebody who's very elderly and they have a large prolapse and they're not sexually active anymore, then you do a colpectomy or colpocleisis and so, you know, which isn't on this list, necessarily, but so yeah, so a lot of these things should absolutely be involved in the decision making.

DR. ISAACSON: Liz.

DR. EREKSON: So I think when we're evaluating -- I think the question is asking when the FDA evaluates studies that are brought to them about these products, what things do they need to be presented with to evaluate these products, and I would say that as these studies come forward, wouldn't it be nice to have a very transparent table that shows who -- like, this is the site exactly that does this type of repair versus that type of repair and these are the volumes at that site. I think other ways we can account for that are the propensity matching and regression modeling where we account for surgeon volumes in sites, but even pulling that data more to the forefront where we see that very transparently would be helpful.

DR. ISAACSON: Yes, Frank.

DR. LING: The reality -- Frank Ling.

The reality is when -- on the fourth bullet point when it says "surgeon," you've got all of these words, but the reality is it's the surgeon's preference. It doesn't really matter what the patient's characteristics are, and it doesn't really matter what place, what the clinical site is or anything about the patient or the procedure, the surgeon's going to do what the surgeon feels he or she wants to do. And I say that only because to some extent, that's where some of the unfortunate events, I think, have occurred in this field in years gone by which have led to some of the unfortunate outcomes we've heard about today and that we read about and we see end up in court, etc., etc. Because you can't legislate the doctor's individual thought process in the room with the patient.

DR. FISHER: Right. So Fisher, FDA.

So I agree 100%. I know that we're going to be faced, when we go through the data, we're going to be going through and we're going to find sites that specialize in one procedure over another, so we may find that, you know, that site, the majority or all is going to be one treatment. We know that there's going to be patients that, for one reason

or another, opinions vary, we had talked about, you know, that may go to one procedure over another and then, you know, we know that surgeons may be better at one than another and we know that patients just, for themselves, may prefer one over another. So, you know, we know that we're going to see this. Dr. Erekson said that transparency, put it all right out there and you know -- and see if the two arms balance out, but I'd be interested in any other comments around the table. This is a hard one. I mean, we know we're going to see this.

DR. ISAACSON: Yes, Donna.

DR. MAZLOOMDOOST: Donna Mazloomdoost.

If the FDA's question is how do these factors contribute to the bias, I think any of those factors that put the patient at higher risk for a recurrence is going to more likely have, you know, selection into a mesh category most likely if you're not in a randomized setting. So ultimately, maybe that person might be at a higher risk in theory of recurrence but also maybe just more complicated in general and maybe more prone to some of the adverse effects.

DR. ISAACSON: So when it comes to surgeon experience, it's important to gather data as to how many of one procedure a surgeon has done compared to the other procedure and I mean, in the -- you don't have to say in their lifetime, but certainly in the last 12 to 24 months, and I think when it comes to transparency, that would be interesting to have that data out there as well.

Yes, Dan.

DR. GRUBER: I mean, for the -- I don't know if you have to necessarily -- it would be nice to get all that nuanced data, but just -- even just if we got how many of the prolapse surgeries that they've done in the last couple years, just in general, versus "I've done one here and there" kind of thing. I think that would be just as valuable.

DR. ISAACSON: Yeah, the question is, is that going to bias you in one direction or another?

DR. GRUBER: I'm sure.

DR. ISAACSON: Yes, Kay.

DR. HOSKEY: I agree that the number of prolapse surgeries as a whole is pertinent, also the severity or the acuity of the patients that that surgeon sees, because one potential challenge would be the hope of seeing the healthiest, mildest prolapses because everyone is so critical of the data that is on display.

DR. ISAACSON: Okay. Dr. Fisher, did you have anything else before I summarize?

DR. FISHER: No, thank you very much. The survey bar is now 75% of the way over and we have two more questions, so please hang in there.

DR. ISAACSON: I know. So to summarize Question 6, I would say that the Panel does believe that certainly randomization would certainly be the best data that we could achieve, but that it's very difficult to do. We have spoken that concomitant procedures could bias the data as well as the surgeon and the surgeon experience. We did not comment on the clinical site and I don't know if anyone has strong feelings as to whether or not the clinical site would influence or bias. My personal opinion is that I think that would be at the bottom of the list. It's not really the site. It's the surgeon and the patient more than anything else. So if that's adequate, Dr. Fisher, are we ready for Question Number 7?

DR. FISHER: Yes, thank you very much.

DR. ISAACSON: Thank you.

DR. OLSON: Question 7 relates to training. The FDA literature review indicated that surgeon experience may affect safety and effectiveness outcomes of a mesh or native tissue repair.

a. Please comment on how a physician's level of training and experience affects

safety and effectiveness outcomes for mesh versus native tissue repair.

b. How should FDA incorporate the level of training and experience of investigators in a clinical study in its interpretation/evaluation of study results, for example, need for comparable experience between study arms, clinical study results may not reflect real world results?

DR. ISAACSON: Donna, do you mind starting a new conversation on this one, please?

DR. MAZLOOMDOOST: Donna Mazloomdoost.

I was kind of hoping I wouldn't have to, but I think absolutely, I'm very biased, I think the training is very critical and I think the FDA should take -- I don't know if the level of training is the right word, but appropriate training, having the anatomical and the surgical expertise. And then, again, that wouldn't necessarily translate into who might be performing these procedures in real life because they may not have an adequate training background. So I don't know what that minimum should be or what that training should be, but I do think that is an important factor, but I think it's a little bit maybe more important in the future of who can use the products than, you know, even just evaluating the current study.

DR. ISAACSON: So I have maybe a point of clarification, if you guys on the Panel remember, but am I right in that the randomized controlled trial that's ongoing now, every clinician or surgeon in that trial is fellowship trained?

DR. MAZLOOMDOOST: Which trial are you talking about?

DR. ISAACSON: Oh, it was presented -- there's only one.

DR. MAZLOOMDOOST: SUPeR, for example, yes.

DR. ISAACSON: What's that?

DR. MAZLOOMDOOST: In SUPeR that Dr. Nager --

DR. ISAACSON: SUPeR.

DR. MAZLOOMDOOST: -- presented, yes. And everybody had to have a minimum number that they had performed.

DR. ISAACSON: So how do we extrapolate that data to the general population?

DR. MAZLOOMDOOST: That's where it becomes tricky because you're going to end up in rural areas where there's not a fellowship-trained urogynecologist and that person is going to have to probably seek that treatment -- I mean training or proctoring from somebody else. So I think you run into -- I don't know the answer to that.

DR. ISAACSON: Madeline, you're shaking your head.

DR. DICK-BIASCOECHEA: Then I don't think in that case the procedure should be performed. I think the person has to be -- I mean, I'm a gynecologist, I'm not going to perform cardiac surgery any time in Alaska, you know, or anywhere else.

DR. ISAACSON: So then, let's start at the highest bar. The highest bar is a fellowship-trained urogynecologist and we all agree okay, they're trained, they -- everyone who completes that fellowship --

DR. LING: I'm going to interrupt. But when you say fellowship-trained urogynecologist, one, you still got a cadre of folks who were not fellowship trained but who got grandfathered in when they took the exam. Then you also have fellowship-trained urogynecologists who truly did get fellowship trained but did not do anything with this particular technique or didn't do much just because for the reason they went through earlier on and it wasn't the thing to do at the time. So you got kind of layers of urogynecologists that may or may not be who you want doing this.

But then also to address the question of, you know, where they are, you may very well have a smaller community out in rural America where, let's say, somebody who was fellowship trained and very qualified decided I'm going to go take care of my mother-in-law, I'm going to go practice in such-and-such an area. So there are some subtleties in the

fellowship training part of this that I think you have to be careful not to just sort of include everybody with one fell swoop because I think the diversity of your urogynecologists is fairly significant.

DR. ISAACSON: Yeah. I was going to get to that.

(Laughter.)

DR. ISAACSON: But I was interrupted, but that's okay.

DR. LING: This is Frank and I take it all back. Delete that.

DR. ISAACSON: What he said. If you'll put that under my name.

Kay.

DR. HOSKEY: I would agree with that. Many of the teachers of current urogynecologists may not have been fellowship trained, but certainly have the experience, training, as a new urogynecologic fellowship grad.

DR. ISAACSON: Dan.

DR. GRUBER: We talked about this a little bit before, I mean, in the ideal world you'd have some sort of registry and then we'd track our numbers and outcomes and all that kind of stuff, which is -- which would be great and hopefully we can do that, but it will take time for that to happen.

As far as, like, training and experience, those are surrogates for outcomes, it doesn't -- you're right, it doesn't guarantee it for sure, but would it sway in that direction? Most likely. I think as time goes by that's going to be more and more true, though, because yes, our subspecialty is relatively new, but over the next, you know, 20, 30 years we're basically where GI and oncology was, you know, 25 years ago and so we'll catch up to them and I think, more and more over time, it will become like that. So as far as, like, regulatory environment today, you have to kind of account for these different things, but in the future, I think it will be a little bit more straightforward.

DR. ISAACSON: So I'm going to ask a hard question and then I'm going to get to you, Barbara. And Liz, you look like you're ready for a hard question, but what is the -- what is the learning curve for this procedure for the mesh that's currently -- the ones here, at what point can you expect someone to do a certain number and then have plateau in their, say, complication rate?

DR. EREKSON: So I'm going to hit on the learning curve, and then I really want to talk about rural care delivery and a little bit on these surrogate measures. So my understanding of learning curve is that we don't have a perfect learning curve for transvaginal mesh procedures. We certainly have different learning curves for where people start, right, so if you can do a sacrospinous ligament fixation you're a lot better off than somebody who can't start that procedure knowing how to do that procedure. And so I think the best surrogate we have is doing 10 of these procedures. Going with the AUGS guidelines for proctoring how a new surgeon starts, that were published in 2012, are some of our surrogates for that, for the learning curve. I don't know that we have perfect data on the rest of it.

I did want to highlight, in terms of rural care delivery, I work at an academic, a rural academic medical center and so there are significant issues with rural care delivery. But I would say that for an elective surgical procedure, in general, my patients are willing to drive for their surgical procedure; it's their pre- and postoperative care that they need care in their communities and that's where telemedicine and outreach clinics are very helpful and very effective to outreach to those communities rather than saying that a low-volume, untrained surgeon would be an adequate surrogate. So I just would say that we should make sure that we keep that bar high knowing that these are elective surgeries.

The final thing I wanted to talk about is there's lots of things that we look at in terms of surgeon characteristics. We look at volume, we look at whether or not they're fellowship trained, now you can look at if they're board certified, you can look at if they work at an

academic institution, you can look at if they train fellows, do they train residents, is their institution high volume, and all of those are surrogates for better outcomes but it doesn't mean that if somebody doesn't have one of those things that they don't have good outcomes. And in studies, not in gynecology, but in studies that look at gastric bypass surgery, your peer-review scored, so when you have peers look at how you do as a surgeon is more effective in predicting those outcomes than any of the things that I just mentioned.

And so we just have to make sure that we include all of these levels of training and experience and there should be a bar, but we don't want to completely nix the person who maybe just does five of these procedures a year but has excellent outcomes because there are high outliers and low outliers when we look at that.

I think the final issue in this debate, and we are talking about gynecologic oncologists, they don't have a registry, either. People who have registries are the Society of Thoracic Surgery, they do heart surgery and every -- there's a thousand hospitals in this country that pay a lot of money to have nurses extract data and I don't -- I would love that for women's health, I don't see that coming for women, I don't see an advocacy movement behind that for women's health, and I would love to see it.

DR. ISAACSON: Barbara.

MS. BERNEY: Elisabeth already covered it for me.

DR. ISAACSON: What's that?

MS. BERNEY: Elisabeth already covered it for me. I was going to mention telemedicine because I know -- I work with the RMED program at the College of Medicine in Rockford in Illinois. It's the University of Illinois. And those students promised that they will go back to their very rural communities, some of which are populations of 200. They aren't going to do those surgeries but they have to know how to follow up and that's where -- you know, you can go someplace else to have surgery. I went to Madison to have hip

surgery, but I had follow-up in Rockford. And if I hadn't, I wouldn't have been able to do it. So I think that the advent of telemedicine is very important, especially for the after care. But I think Elisabeth is right, if you have to have surgery that's elective, you'll go someplace where there is somebody who can do it.

DR. ISAACSON: Okay. So, again, I don't know that we really answered the question of how we compare the experience in the study arms where in one study it's done by highly-trained, highly -- high-volume surgeons versus those that are not high-volume surgeons.

Yes, Frank.

DR. LING: So just out of curiosity, is that current randomized trial, the SUPeR trial, I know it's done by highly -- the senior guys, in reality, and this is just among us girls, are there fellows doing it?

DR. ISAACSON: Are there fellows doing it?

DR. LING: No.

DR. ISAACSON: I assume at a fellowship institution they are, but --

DR. LING: Because I don't consider a fellowship -- a fellow doing it, the top guy. The top guy's in the room.

DR. ISAACSON: If they're supervised by the other, shouldn't it be the same?

DR. LING: I don't think so. I don’t think the consumer would think so.

DR. ISAACSON: Liz.

DR. EREKSON: So to play the devil's advocate, if only five people in the country can do the procedure, should we be doing the procedure?

DR. ISAACSON: Say it again.

DR. EREKSON: So if only five people in the country can do the procedure, if it's that complex or that -- you had to be that higher volume, should we be doing the procedure? I

mean, I'm just looking at its complete conclusion, which is the procedure has to be generalizable to a certain segment of the population who is trained to do that procedure.

DR. LING: And in a sense, I'm being a little bit of a devil's advocate, also, because the vast majority of data that comes out of surgical studies and so on are done by fellows or they're supervised by the PIs and so it's probably comparable but, at the same time, I don't think we should necessarily fool ourselves and say, oh, here are the data done by the senior surgeons. It's just not the case.

DR. MORGAN: I was just going to say, I mean, I don't think that many of us could -- I couldn't live with that, if I was -- if I was saying that I let fellows operate, am I only getting the same results? I mean, I think that surgery is much more about the setup and the approach and the planning than it is about who places a stitch or who, you know, sets a clamp and it's -- you know, so I mean, I just want to say that, I mean, I am really worried about the potential. I think that we've seen results from the very best people and like how that's going to disseminate, I really have questions, and I really like the idea of a registry, but I hope that when -- at the sites that people are well supervised and, you know, that the setup is so good that it doesn't really make any difference at that point who passes the Capio or who, you know, does that. I mean, I hope that -- I think that they would field that. I hope so.

DR. ISAACSON: Dr. Fisher.

DR. FISHER: Fisher, FDA.

I was going to say that I appreciate the interest in the SUPeR trial, but FDA is going to have to stay focused on the 522s, which are non-randomized and we are going to have a variety of surgeon experience in there. So we took (a) and we knocked it out of the park, (b) we've kind of skidded on a little bit, Dr. Morgan just touched on it a little bit. I'd like to know, since there may be variation in clinical expertise, how do we need to factor that in?

DR. MAZLOOMDOOST: Donna Mazloomdoost.

I mean, in that same line, then, I think a 522 that is non-randomized in the hands of anybody is a lot more generalizable. In other words, I wouldn't recommend interpreting the data and saying oh well, the safety is probably better than this because that is probably more representative of what would be in the general population.

DR. ISAACSON: But I do think, in looking at the 522s, what you can do is you can ask the surgeons in a particular site what is their volume, number one, per surgeon, and what is their level of training. Is it just general or is it fellowship or what have you, so -- and then take it with a grain of salt. But I think those two pieces of information are important to gather even within the 522s.

Yes, Kay.

DR. HOSKEY: Also, perhaps adding focus of clinical duties. If someone spends most of their time doing pelvic organ prolapse, it's a very different, perhaps, clinical scenario than someone who does a little bit of it here and there.

DR. ISAACSON: I'm hoping that will show in the volume, in volume numbers.

So, in summary, we do -- I think the Panel agrees that surgical experience may affect safety and the effectiveness outcomes of mesh or native tissue repair. We feel that clearly, a higher volume surgery -- surgeon is less likely to have -- experience adverse outcomes and that the FDA should have some way to measure the volume of the surgeon or to capture the volume. And then, like you said, I think we knocked (b) out of the park already, so are you satisfied?

DR. FISHER: Yes. Thank you very much.

DR. ISAACSON: Good. All right, we're going to benefit-risk, Dr. Olson.

DR. OLSON: Question 8: Surgical mesh for transvaginal repair of pelvic organ prolapse in the anterior or anterior/apical compartment is an implant, and its benefit/risk

profile may change over time.

a. What is the appropriate expectation for the durability of a mesh repair and native tissue repair, for example, remainder of the patient's lifetime?
b. How quickly should the data demonstrate the benefit of a mesh repair versus a native tissue repair?
c. In broad terms, a device subject to PMA is approved for marketing when the benefit/risk profile is favorable for its proposed indications for use, with a reasonable assurance of safety and effectiveness. In light of this regulatory framework, what is the most appropriate time point to assess benefit/risk to support a marketing application, for example, 12, 24, 36 months or longer?
d. What is the appropriate duration of follow-up needed to support marketing approval versus the follow-up needed postmarket? What data should be collected postmarket? Please consider rare adverse events, long-term durability, and use of real-world evidence to collect safety and effectiveness outcomes.
e. Does the Panel have additional comments related to the mesh material or other mesh characteristics?

DR. ISAACSON: Okay, Jason, what do you think?

DR. CONNOR: So I think that, honestly, I'm pretty frustrated by the Panel and all the questions -- not my colleagues, but the discussion here. I mean, I think we aren't here because dyspareunia rates a little bit higher in mesh, and we're not going to fix that by getting the right doctors to do surgery, we're not here because re-op rates are too high and we're going to fix that by understanding the appropriate cases, and I think much of what we've discussed in these questions is really fundamentally about subgroup analyses and rare events, that these events are rare and we're talking about all of these subgroups and can we fix any of these problems by understanding where events are a little bit higher or a

little bit lower in subgroups. So I think (a) it's impossible to do that, (b) it's certainly impossible to do that in the confines of, like, 200-patient trials that we saw from our sponsors.

You know, all medical devices have benefits and risks, and I still feel like maybe I'm missing it because I'm not a clinician and I'm not a woman who will ever be at risk of this, but the fundamental question is there are, you know, women who had devastating, life-altering events due to mesh implant and those are extremely rare and if these want to stay on the market, how do we quantify that? And quantifying that has nothing to do with, you know, subgroups, probably little to do with surgeons, but it feels like, to me, this whole conversation should've been, you know, what is the right way to identify what is, thankfully, a very rare event but an enormously devastating event? So I don't know if any of this, to me, gets at the heart of the issue and the heart of, quite frankly, why there have been multiple panels on adverse events related to this product.

DR. ISAACSON: Dr. Fisher is not going to be happy with you on that one, so --

(Laughter.)

DR. ISAACSON: I want to go back to the specifics. What is the appropriate expectation for the durability of a mesh repair and a native repair? So if we can just tackle these one at a time. We'll just come up with a number that we generally agree with. Should it be the remainder of the patient's lifetime, should it be 5 years?

Dan.

DR. GRUBER: Dan Gruber.

I mean, this is just -- this is all opinion at this point, but I personally think, like, any of our repairs, actually I'll throw out a number, it would be 10 years. I don't think lifetime is necessarily realistic. You got, you know, a 35- or 40-year-old, they're going to have a long lifetime. When you go to the orthopedic surgeon, they don't promise you that your hip or

your knee is going to last you your entire life. I think we put unrealistic expectations on ourselves, and I don't know why because you go to other parts of medicine and they don't impose this on themselves. So I would just say -- and if you get over 10 years, I'm a big fan of under-promising and over-delivering, so I'll just throw that out there as opinion.

DR. ISAACSON: Any comments on 10 years?

(No response.)

DR. ISAACSON: Good. So how quickly should the data demonstrate the benefit of a mesh repair versus a native tissue repair? Should it be at 6 months or 12 months? Anybody?

DR. MORGAN: Dan Morgan.

I would imagine that we'd want to wait at least that amount of time, as I mentioned, for sexual function, but maybe even other things because certainly there can be some symptoms that I think are related to post-op recovery.

About the first one, just a quick comment. Whether it's mesh or native tissue, I think we often don't know the primary reason that they develop prolapse. There's a lack of understanding about the -- I mean, is it a levator avulsion? Is it a connective tissue disorder or is it some kind of rupture in the apical supports? We don't really have that answer so, you know, I think we're doing the best we can with compensating with whatever surgery we do, but to expect that it will last a lifetime, I think, is probably unrealistic, so I don't know what number to give to that, but it just -- it feels like that's too much, you know, to expect.

DR. ISAACSON: Dr. Fisher.

DR. FISHER: Fisher, FDA.

Just a point of clarification. First, off the top. Jason, I always appreciate your opinion and your comments, so thank you very much. We had two companies in today that were talking about future devices that might be on the horizon, all right? So I said when I --

before the deliberation, your comments and your opinions are not only going to be used for the 522s that we're looking at, but also for future devices that might be in this arena. So that's kind of what this question is, is kind of, you know, we're not barking back at the 522 but kind of looking forward, okay? You know, from a regulatory perspective, like I said, you know, we can't expect to do a 10-year study, so what do we feel comfortable with if we're looking for durability if something else were to come our way? Thank you.

DR. ISAACSON: Well, for me, it gets to Question (d), then, what is the appropriate duration of follow-up needed to support marketing approval versus the follow-up needed for postmarket? It's not really patient expectations, then, it's what's realistic and practical for the FDA. And I would say that you really should have -- in order to get approval, I would think that you need 24-month data, and then I'd like to see, personally, postmarket data out to 5 years. And I'll just throw that out there for people to yea or nay.

Yes.

MS. TIMBERLAKE: Why not 12 months? What would you expect to see between 12 months and 24 months when it comes to safety?

DR. ISAACSON: Yeah, so the question is why not 12 months?

MS. TIMBERLAKE: Yeah.

DR. ISAACSON: Because I think there's -- you got to almost eliminate the first 6 months, which is healing and from the surgery and getting a patient back to normal activities, so then I'm really looking at is it 6-month data or 18-month data and if I had to pick one of the two, I'd -- I mean, I don't mind compromising and say let's do -- look at 18 months as opposed to 24, but it seems to me that either 18 months or 24 months post-procedure is -- should be more reflective than that 12 month.

Yes.

DR. GRUBER: I think this kind of goes back to our discussion earlier about superiority

versus non-inferiority trials and I think I've kind of been swayed a little bit more to the -- I think it's okay to have the non-inferiority/equivalency, you know, at 1 year or 2 years but, I mean, at 2 to 3 it would be nice to see superiority trials, but even if you get non-inferiority/equivalency, then -- that at least it gives you some information and it lets patients have extra choices, too. It doesn't necessarily have to be, you know, in big trials because every patient is their own study, their own individual, and then we balance it out across the spectrum.

DR. ISAACSON: So, Sharon, I want to get back to your comment, which is -- I don't want this to be too onerous, you know, I want it to be good data but I don't want it, you know, to go from we had 34 companies down to three and then because of -- down to two, I'm sorry, three products, and then go from two to zero because it's 24 months. Is there something along that line, as the Industry Rep, that you're thinking?

MS. TIMBERLAKE: Yeah, honestly, I would think -- I'm obviously not a surgeon, but 12 months would be a good time point to establish safety and healing and for initial assessment, and then long-term effects would be handled through the postmarket surveillance requirements as well as, keep in mind, a lot of the long-term unknowns from the study can be presented in the patient labeling and as well as the physician labeling and training, and then as the data comes in, those would be updated and reported out as well as, you know, there will be a lot of other studies ongoing as we go through the process, just with the societies and the registries.

So 2 years, just thinking about all the other Class III-like devices, UFE, for example, which is permanent. I know it's a different indication, but there were no studies. It was based on minimal data and that's a permanent implantable. So it's kind of how do we get something on the market -- well, it is on the market, but how does FDA and the team and the manufacturers just review it, you know, every 6 months, every year, and get that

information out to the public, but I think 12 months would establish the safety piece of it and then erosion, and I think earlier there were comments about some erosion you see quickly within 6 months, correct me if I'm wrong, or a year with longer-term results, it can be seen yearly or later on based on how the patient presents.

DR. ISAACSON: So for those of you who are doing this, is 12 months fairly predictive on efficacy versus 18 and 24 months? So if they're doing well at 12 would you expect them -- you'd predict they're going to do well at 24 or is that not necessarily the case? As far as efficacy, not safety.

DR. LOWDER: This is Jerry Lowder.

You know, I don't think necessarily that 1 year predicts. I mean, if you see later erosions at 3 and 5 years, obviously the 1-year follow-up is not going to predict that. I think that's a little -- I think that's too soon. I mean, based on the data from Boston Scientific today, I mean, they don't -- I mean, at 2 years being non-inferior, I don't have -- as a surgeon, I mean, nothing drives me to do a mesh procedure over, you know, a native tissue repair. So I mean, I personally deal with it and appropriately counseling patients that there is benefit to doing the mesh over native tissue repair. I think that long-term -- longer-term follow-up is imperative.

DR. ISAACSON: So it's kind of getting -- when you sum all this up, we need to answer Question (c), which looks at both the risk-benefit. So what time point is the best time point to assess risk-benefit? Is it 12, 24, 36, or longer?

Kay.

DR. HOSKEY: I feel like I don't have good data to show that if a problem is going to arise that they are all going to arise before this certain day, so in many ways I feel like the question is hard to answer because it's a guess.

DR. ISAACSON: I know, but they have to answer it. So we have to give them

guidance. Anybody else?

DR. MAZLOOMDOOST: Can I ask a clarification? So is reasonable assurance 51%, 85%, or 99%?

DR. FISHER: We have backup slides where I can give you the regulatory definitions of what they mean.

DR. ISAACSON: We can't hear you.

DR. FISHER: I said we actually have some backup slides where I could show the regulatory definitions of what they mean. So I think that when we look at a reasonable assurance of safety and effectiveness, we're not looking for 100%. I think we have to make a benefit-risk decision on there's always going to be some uncertainty, also. Safety is always going to be paramount, effectiveness is going to be important, and we're looking for a reasonable assurance with, in mind, that there may be some uncertainty and some risks involved.

So in certain situations, depending on the risk profile of the device and what we find in the study, we may find reasonable safety and effectiveness sufficient for a regulatory decision and feel comfortable with collecting additional data postmarket, as a follow-up. We may find that the risk profile is so high that we want to see much more data and feel much securer on the front end before we're willing to collect any additional information on the postmarket end. So it really -- I hate to say it, it really depends.

DR. EREKSON: So I guess when I'm thinking about the answer to that question, then, it's hard not to go back to bad experiences in the past where we asked for postmarket data and the postmarket data lagged very long periods of time. And so I would propose that 36 months is where we need to be because when we don't get that postmarket data or we get that postmarket data 10 years later, it's very difficult.

DR. FISHER: You know, in addition to that, when we were presenting the literature

search this morning, we noticed some AEs don't show up until after a year, we know that AEs continue to be reported 1, 2, 3 years, and sometimes the literature that we reviewed doesn't provide long-term information; it only looks at 12 months. So that's why we're probing.

DR. DICK-BIASCOECHEA: If we are asking for superiority of the mesh versus the native repair and our assumption is that the mesh is -- would be superior in duration, I would think the longer the study the more likely it is that the mesh would be proved superior and would be, you know, approved. So I think I agree with Liz, that 36 months is good, is an appropriate time.

DR. ISAACSON: Time frame for that, okay.

Yes, Rick.

DR. CHAPPELL: I support this for the reason that Madeline just mentioned but also, from the other perspective of safety. So you wait a long time for efficacy which, I hope, and judging from their earlier -- from the preliminary results, 3 years would be better for mesh than 1 year, but also I think we owe it to the patients to look at safety for -- I don't know why we picked 3 years, but it seems a lot better than 1.

DR. ISAACSON: So, Dr. Fisher, if I may summarize, I think the Panel's feeling on Question 8, what is the appropriate expectation for the durability of a mesh repair, from the patient's perspective we said 10 years to expect a repair to last. We didn't really go over (b). Question (c), what's the most appropriate time point to assess benefit-risk ratio to support marketing application, it seemed that 36 months was agreed upon by most people, if that's correct. And I think as far as follow-up support, again, marketing approval, we felt that the duration of follow-up needed to support marketing approval is somewhere between 18 and 24 months, if we can say that, with the postmarket analysis up to 5 years. And, again, even though it was asked on four or five other questions, I don't think we had

any more comments related to the mesh material, I'm sorry. I don't think that came out, I think we failed you on that one. Does this suffice or is there more?

DR. FISHER: So (e) just said, did you have additional comments? So if you don't, that's fine.

DR. ISAACSON: Okay.

DR. FISHER: Going back to (b) it says, "How quickly should the data demonstrate the benefit," and I think there's kind of two elements to this question and I think, you know, what I hear is, you know, 1 year is -- for a clinical trial we should be looking at endpoints at 1 year and then we still have the question of durability, so we would want to follow it out, of course.

DR. ISAACSON: Yeah. I agree with that, I think that was the consensus.

Yes.

DR. MAZLOOMDOOST: Donna Mazloomdoost.

If I could just make one comment. Thirty-six months isn't completely arbitrary. It has been shown feasible with reasonable patient follow-up, I mean, albeit with incredible resources, but -- and then that works. So I think it's a reasonable longer-term follow-up.

DR. ISAACSON: Okay.

DR. FISHER: Thank you.

DR. ISAACSON: We're not quite -- that's it for the questions. I'm sure I have some more. Let's see. So I want to thank, particularly, the Panel, the FDA, the manufacturers, the professional societies, and all the patients who came out today and sat through this meeting and contributed. And I think it's been, hopefully, a very productive day for the FDA.

Dr. Fisher, do you have any final remarks?

DR. FISHER: Yes, thank you.

I'd first like to thank the patients who came out and provided your testimony this morning, it was extremely moving, and I think it's very important to capture the voice of those patients. So I'd like to thank them. And for the others in the Open Public Hearing, thank you very much, once again. You took your time, a lot of you paid your own way. We'd like to thank you again for coming out. For the professional societies and for the companies for taking the time and coming in, once again, thank you. To the Panel, I'd like to thank our Industry, Patient, and Consumer Reps, and all the other members of the Panel who came out today to make this possible. It is a topic that is, you know, sensitive. Moving forward, the Agency will be making some decisions on these 522s. Your input is extremely important, so I'd like to thank you all.

So just for tomorrow, when we reconvene -- okay, I just wanted to see your faces, see if you're still paying attention.

(Laughter.)

DR. FISHER: And I'd like to also thank Dr. Isaacson for keeping us on task and keeping us almost on time, so thank you very much.

DR. ISAACSON: We're early. We're not supposed -- so we have until 6:35. If anybody has other --

(Applause.)

DR. ISAACSON: But I also want to thank Evella. She was special, she poked me, kept me going. Thank you.

DR. CHAPPELL: And the FDA employees for working under dubious circumstances.

(Whereupon, at 6:18 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 DEVICES PANEL

February 12, 2019

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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Official Reporter