UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

March 23, 2021
9:00 a.m.

Via Zoom Videoconference

PANEL MEMBERS:

| | |
|---|---|
| FRANK R. LEWIS, JR., M.D. | Panel Chair |
| MARY H. McGRATH, M.D., M.P.H. | Voting Member |
| MICHAEL J. MILLER, M.D., FACS | Voting Member |
| KARLA V. BALLMAN, Ph.D. | Voting Member |
| MURAD ALAM, M.D., MSCI, M.B.A. | Temporary Non-Voting Member |
| JUAN M. GONZALEZ, Ph.D. | Temporary Non-Voting Member |
| JULIAN D. PERRY, M.D. | Temporary Non-Voting Member |
| KAREN E. BURKE, M.D., Ph.D. | Temporary Non-Voting Member |
| NEIL M. BRESSLER, M.D. | Temporary Non-Voting Member |
| ALAN N. MATARASSO, M.D., FACS | Temporary Non-Voting Member |
| JEREMIAH BROWN JR., M.S., M.D. | Temporary Non-Voting Member |
| P. LAMONT BRYANT, Ph.D. | Industry Representative |
| RACHEL S. BRUMMERT, M.S. | Consumer Representative |
| GEORGE A. BISHOPRIC, JR., M.D. | Patient Representative/Temporary Non-Voting Member |
| PATRICIO GARCIA, M.P.H., CDR, USPHS | Designated Federal Officer |

FDA REPRESENTATIVES:

CYNTHIA J. CHANG, Ph.D.
Director, Division of Health Technology 4 B (Infection Control and Plastic and Reconstructive Surgery)
Office of Surgical and Infection Control Devices
Office of Product Evaluation and Quality

BINITA ASHAR, M.D.
Director, Office of Health Technology 4 (OHT 4: Surgical and Infection Control Devices)
Office of Product Evaluation and Quality

AUDRA HARRISON
Press Contact

FDA PRESENTERS:

JULIAN KLOSOWIAK, M.D., Ph.D.
Office of Health Technology 4 (Surgical and Infection Control Devices)
Office of Product Evaluation and Quality

KIMBERLY M. FERLIN, Ph.D.
Office of Health Technology 4 (Surgical and Infection Control Devices)
Office of Product Evaluation and Quality

AMY ROGERS, BSN, RN
Office of Health Technology 4 (Surgical and Infection Control Devices)
Office of Product Evaluation and Quality

HENRY LEE, M.D.
Office of Health Technology 4 (Surgical and Infection Control Devices)
Office of Product Evaluation and Quality

CYNTHIA J. CHANG, Ph.D.
Director, Division of Health Technology 4 B (Infection Control and Plastic and Reconstructive Surgery Devices)
Office of Health Technology 4 (Surgical and Infection Control Devices)
Office of Product Evaluation and Quality

MICHELLE TARVER, M.D., Ph.D.
Deputy Director
Office of Strategic Partnerships and Technology Innovation

HILDA F. SCHAREN, M.Sc., CAPT, USPHS
Director, Medical Development Tools (MDDT)
Division of All Hazards Response, Science and Strategic Partnerships
Office of Strategic Partnerships and Technology Innovation

JACQUELINE FRANCIS, M.D.
Office of Health Technology 4 (Surgical and Infection Control Devices)
Office of Product Evaluation and Quality

ALEXANDER H. SUN, M.D., M.H.S.
Office of Health Technology 4 (Surgical and Infection Control Devices)
Office of Product Evaluation and Quality

INVITED SPEAKER:

JEAN CARRUTHERS, M.D., FRCSC, FRC (Ophth)
Department of Ophthalmology
University of British Columbia

INDUSTRY PRESENTERS

MICHAEL SILBERBERG, M.D., M.B.A.
Executive Medical Director, Facial Aesthetics
Allegan Aesthetics, an AbbVie Company

DEREK JONES, M.D.
Board Certified Dermatologist
Skin Care and Laser Physicians of Beverly Hills

SAMANTHA KERR, Ph.D.
Chief Scientific Officer
Merz Aesthetics

PATRICK TRÉVIDIC
Plastic Surgeon/Chief Scientific Officer
Teoxane

OPEN PUBLIC HEARING SPEAKERS:

GEORGE J. HRUZA, M.D., M.B.A., FAAD
Past President
American Academy of Dermatology Association (AADA)
Adjunct Professor of Dermatology
St. Louis University

MATTHEW AVRAM, M.D., J.D.
President
American Society for Dermatologic Surgery Association (ASDSA)

JOHN FEZZA, M.D.
American Society of Ophthalmic Plastic and Reconstructive Surgery
American Academy of Ophthalmology

PAUL J. CARNIOL, M.D., FACS
President
American Academy of Facial Plastic and Reconstructive Surgery
Clinical Professor
Rutgers New Jersey Medical School

STEVEN F. WEINER, M.D.
Facial Plastic Surgeon
The Aesthetic Clinique

WILL KIRBY, D.O.
Kirby Dermatology

CHRISTOPHER C. SUREK, D.O.
Plastic Surgeon
Plastic & Reconstructive Surgery
A Division of U.S. Dermatology Partners

BRIAN S. BIESMAN, M.D., FACS
Assistant Clinical Professor
Department of Ophthalmology
Divisions of Dermatology and Otolaryngology
Vanderbilt University Medical Center

INDEX

INDEX

INDEX

M E E T I N G

(9:02 a.m.)

DR. LEWIS: I would like to call the FDA's Center for Devices and Radiological Health General and Plastic Surgical Devices Panel of the Medical Devices Advisory Committee together on March 23rd, 2021, to order. It's now 9:00 a.m.

I'm Dr. Frank Lewis, the Chair of the Panel. I am the retired executive director of the American Board of Surgery, and have been associated primarily with trauma and critical care during my career.

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

For today's agenda, the Panel will discuss the risks and benefits of dermal fillers in two topic areas. The first topic will address the general issues regarding risks associated with intravascular injections of dermal fillers. The second and final topic will address general issues regarding patient preferences and informed decision making.

FDA is convening this meeting to seek expert opinion on the clinical evaluation and regulation of dermal filler products. In my opinion, this is one of the more difficult decisions that we have faced in many of these questions because the incidence of severe complications is quite low, but the consequences of those is catastrophic for the people involved. Typically, the people involved are younger or middle aged and the disabilities which occur from severe complications disable them for the rest of their life.

I want to lay down a few ground rules in this virtual environment. If a panelist wants to ask a question, please use the hand-raising function on your Zoom platform and I will get to your questions as we proceed through the program. We want to prevent multiple persons from speaking over each other as we proceed, as this entire meeting is being

transcribed for the official record.

Before we begin, I want to ask our distinguished Panel members and the FDA attending virtually to introduce themselves. I will call your name. When introduced, please state your area of expertise, your position, and affiliation.

We'll begin with Dr. Binita Ashar.

DR. ASHAR: Good morning, my name is Dr. Binita Ashar. I am a general surgeon and the director of the Office of Surgery and Infection Control Devices at FDA's Center for Devices and Radiological Health.

DR. LEWIS: Dr. Cynthia Chang.

DR. CHANG: Good morning, my name is Cynthia Chang and I am the director of the Division of Infection Control and Plastic Surgery Devices in FDA's Center for Devices and Radiological Health.

DR. LEWIS: P. LaMont Bryant.

DR. BRYANT: Good morning. LaMont Bryant, Worldwide Vice President, Regulatory Affairs, Johnson & Johnson/Ethicon, and I'm the Industry Representative.

DR. LEWIS: Dr. Mary McGrath.

DR. McGRATH: Good morning, my name is Mary McGrath. I'm in San Francisco at the University of California, San Francisco. I'm the Professor of Surgery, I'm a plastic surgeon and been in practice for many years and have used these products really since -- for the past 30, 40 years, to some extent.

DR. LEWIS: Ms. Rachel Brummert.

MS. BRUMMERT: Good morning, my name is Rachel Brummert. I'm the communications lead for the American Society of Pharmacovigilance and I will be the Consumer Representative today.

DR. LEWIS: George Bishopric.

DR. BISHOPRIC: Good morning, I'm George Bishopric. I am a pathologist, but I'm here as a patient representative. I had my face pretty much completely corrected with various products over the years and I'm speaking in that capacity.

DR. LEWIS: Dr. Michael Miller.

DR. MILLER: Hi, I'm Michael Miller. I'm a plastic surgeon. I am the chief of plastic surgery at Banner MD Anderson Cancer Center in Phoenix.

DR. LEWIS: Karla Ballman.

DR. BALLMAN: Hi, I'm Karla Ballman. I am the chief of the Division of Biostatistics at Weill Cornell Medicine in New York, and my expertise is biostatistics and epidemiology.

DR. LEWIS: Murad Alam.

DR. ALAM: Good morning. I am a dermatologist. I am the head of dermatologic surgery at Northwestern University where I am also a professor, and this topic is also an area of research interest.

DR. LEWIS: Juan Gonzalez.

DR. GONZALEZ: Hi, good morning. I'm Juan Marcos Gonzalez and I'm an assistant professor at Duke University School of Medicine. I'm also a preference researcher who specializes in the use of this information for benefit-risk analysis and in supportive shared decision making.

DR. LEWIS: Julian Perry.

DR. PERRY: Hi, I'm J.D. Perry and I'm an ophthalmologist and I'm an oculofacial plastic surgeon at the Cole Eye Institute, Cleveland Clinic.

DR. LEWIS: Karen Burke.

(No response.)

DR. LEWIS: Dr. Burke available?

DR. BURKE: Yes, my name went off. Hi, I'm Dr. Karen Burke. I'm a dermatologist

and a clinical professor at Mount Sinai School -- Ichan School of Medicine in New York, and I have done research on many of these implants.

DR. LEWIS: Alan Matarasso.

DR. MATARASSO: Hello, I'm Alan Matarasso. I'm a plastic surgeon and I practice in Manhattan. I'm a Professor of Surgery at Hofstra Medical School, past Professor of Plastic Surgery at the Albert Einstein College of Medicine, and I'm recent past president of the American Society of Plastic Surgeons.

DR. LEWIS: Neil Bressler.

DR. BRESSLER: Good morning, I'm Neil Bressler. I am former chief of the retina division at Johns Hopkins University School of Medicine. I'm currently the chair of the Ophthalmic Devices Panel, and editor-in-chief of *JAMA Ophthalmology*. Thank you.

DR. LEWIS: Jerome (sic) Brown.

DR. BROWN: Good morning, my name is Jeremiah Brown. I'm a retina specialist in San Antonio, Texas. I am adjunct associate professor at UT Health, and I practice at the Brown Retina Institute and do research there.

DR. LEWIS: Thank you, all.

Commander Garcia, the Designated Federal Officer for this meeting, will make some introductory remarks.

CDR GARCIA: The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery 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. 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. 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 the purpose of 18 U.S.C. 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 benefits and risk of dermal fillers concerning the topics of risk associated with intravascular injection of dermal fillers, and patient preference and informed consent.

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. 208.

Dr. P. LaMont Bryant is serving as the Industry Representative, acting on behalf of all related industry. Dr. Bryant is employed by Ethicon, Incorporated.

For the record, the Agency notes that Dr. Jean Carruthers, who is an invited guest speaker with us today, has acknowledged interests with affected firms in the forms of stock, research grants, speaking, consulting, advisory, research, and technical services.

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

A copy of this statement will be available for review and included as a part of the official transcript.

For the duration of the General and Plastic Surgery Devices Panel meeting on March 23rd, 2021, Dr. George Bishopric has been appointed to serve as Temporary Non-Voting Patient Representative. For the record, he is a consultant to the Endocrinologic and Metabolic Drugs Advisory Committee at the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflicts of interest review and has reviewed the material to be considered at this meeting.

The appointment was authorized by Russell Fortney, Director, Advisory Committee Oversight and Management Staff, on December 29th, 2020.

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

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

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

The press contact for today's meeting is Audra Harrison.

Thank you. And now I'll hand it off to Dr. Lewis.

DR. LEWIS: Dr. Cynthia Chang, Director of the Division of Infection Control and

Plastic Surgery Devices in the Office of Surgical and Infection Control Devices, Office of Product Evaluation and Quality in the FDA's Center for Devices and Radiological Health, now has some introductory remarks for the Panel.

DR. CHANG: Good morning and welcome to the U.S. Food and Drug Administration's Advisory Committee panel meeting. My name is Cynthia Chang and I am the director of the Division of Infection Control and Plastic Surgery Devices in FDA's Center for Devices and Radiological Health, or CDRH. Our division is responsible for the review and regulation of dermal fillers.

I would like to start by acknowledging and thanking the individuals on the FDA's dermal filler team who have devoted commendable efforts in preparing for this meeting.

The agenda for this meeting and the Executive Summary have been provided and they are also available online at FDA's website. Supplementing the Executive Summary, we have invited external speakers to provide their insights on specific topics. There are certain aspects of the agenda that I would like to highlight for you this morning.

Dermal fillers are aesthetic devices for which the decision to proceed with the injection procedure is elective. The benefits are dependent to a great extent on the value assigned to them by the patients themselves. Likewise, the risks need to be weighed against the benefits by each patient in consultation with their healthcare providers.

In recent years there has been an abundance of new dermal filler approvals, both in the form of new formulations and devices, and in the form of new indications and anatomical locations. While the risk of intravascular injection has always been present for dermal fillers, the increased popularity of fillers and their use in a broad range of indications has highlighted this risk, with adverse events such as vision disturbances and even blindness and stroke being increasingly reported in literature and medical device reporting.

The FDA will present our approach for assessing and monitoring intravascular

injections in clinical studies, and we will also highlight the important role that patient preference information plays in evaluating the benefit-risk profile. We will look to our esteemed panelists to discuss how to best manage these risks.

As a public health agency, the FDA also plays an important role in ensuring that patients interested in dermal fillers have accurate information regarding the benefits and risks of the devices to make informed decisions on whether dermal fillers are right for them.

We will be asking the Panel to discuss how FDA may ensure that patients are adequately equipped to evaluate the benefits and risks of fillers before making the decision to receive the devices.

Finally, FDA's evaluation of the effectiveness and benefits of dermal fillers has often been specific to the scales proposed by individual manufacturers, with a focus on clinician-reported outcome evaluations that may not fully incorporate patient perspectives.

While patient-reported outcomes are included in recent studies, the current approach may not allow patients to easily compare the multitude of products on the market, even across the same indication. It may not fully represent the perspective of patients, representative of the entire U.S. population, considering factors such as gender, race, and ethnicity.

We will be asking for the Panel's recommendations on how to fully incorporate patient preferences into our assessments.

We appreciate everyone's interest and work up to this point and look forward to informative discussions over the course of the day.

I would now like to introduce my colleague from FDA's Center for Devices and Radiological Health, Dr. Julian Klosowiak.

DR. KLOSOWIAK: Good morning, my name is Julian Klosowiak and I'm a medical officer in the Office of Surgical and Infection Control Devices. Today I'm going to be

providing an introductory clinical overview of dermal fillers. For my talk, we will be discussing some general background information about dermal fillers followed by an overview of various considerations when using dermal fillers, their indications for use, and some of their benefits and risks.

Dermal fillers, also known as injectable implants, soft tissue fillers, and wrinkle fillers, are used to create a smoother and/or fuller appearance in certain anatomic areas of the face as well as the back of the hands. They may be intended to correct age-related deficits of the face or hands or other body structures for aesthetic purposes such as augmentation of the cheek, chin, or lips.

Dermal fillers are one of the most commonly performed minimally invasive aesthetic procedures with over 2.7 million dermal filler treatments performed in 2019.

The modern landscape of dermal fillers has transformed considerably since the approval of the first dermal filler, Zyderm, in 1981. Indications now specifically target augmentation and changes in contour. Fillers are used increasingly by patients of diverse background and by younger adult patients.

Dermal fillers are composed of a variety of materials ranging from natural materials to synthetic materials. The material properties and sourcing can impact the absorbability and time to absorption of the product. In addition to the material components, some of the dermal filler products regulated in CDRH contain analgesics such as lidocaine in their formulation. These are drugs approved in the Center for Drug Evaluation and Research, or CDER, and therefore these dermal fillers are considered combination products.

As mentioned, there are a variety of different types of dermal fillers available. These include naturally derived fillers such as collagen, which is a molecule naturally found in the extracellular matrix. Collagen fillers are absorbable products produced from either a bovine source, such as Zyderm, or cultured human cells, such as Cosmoderm. Dermal fillers made

of collagen have an approximate duration of effect of 2 to 3 months. Please note that these collagen-based filler products are no longer marketed and are presented here for historical context.

Hyaluronic acid, also a molecule naturally found in the extracellular matrix, is an absorbable, naturally occurring polysaccharide. It is generally derived from bacterial fermentation. The first FDA-approved hyaluronic acid filler was Restylane in 2003, and many additional HA fillers have been approved since then.

The duration of effect of HA fillers varies depending on the material properties; for example, the molecular weight of HA and degree of cross-linking. HA is often cross-linked with BDDE to extend its duration. The duration of effect reported in approved PMAs ranges from 6 months for Belotero Balance to 24 months for Juvéderm Voluma.

Of note, the effects of HA may be reversed using enzymatic degradation by hyaluronidase, as advocated by some professional societies.

There are a variety of different synthetic dermal fillers available. These include poly-L-lactic acid, calcium hydroxylapatite, and polymethyl methacrylate.

Poly-L-lactic acid, marketed as Sculptra, is an absorbable filler. In a clinical study, treatment results lasted for up to 2 years after the first treatment session in most patients.

Calcium hydroxylapatite, marked as Radiesse, is also an absorbable filler. In a clinical study, treatment lasted for 1 year after the first treatment session in all patients.

Polymethyl methacrylate, marketed as Bellafill, is an absorbable filler composed of PMMA microspheres. Importantly, because it is a non-absorbable filler, treatment results are lasting and the PMMA microspheres can only be removed surgically.

Depending upon the anatomic area of injection and intended use, dermal fillers may be injected in a variety of locations or depths, including the mid to deep dermis, subcutaneous or supraperiosteal. Filler injections can be accomplished using either a

needle or a blunt-tipped cannula.

Shown here is a table that summarizes the 39 currently approved dermal filler PMAs by indication for use, and filler material and properties. Dermal fillers have been FDA approved for a variety of indications which fall into nine categories. These include:

- Augmentation of the chin
- Cheek augmentation to correct volume deficits or deficits in the mid-face
- Lip augmentation and correction of perioral lines
- Dorsal hand augmentation
- Correction of moderate to severe nasolabial folds
- Correction of acne scars and cutaneous scars
- Correction of facial lipoatrophy in people with HIV

The table is up to date as of January 29th, 2021, and a version is included in the Executive Summary document for reference.

As the various indications for use highlight, the benefits of dermal fillers include the correction of age-related deficits such as wrinkles, or augmentation of body structures of aesthetic purposes.

As with any device, there are risks associated with dermal filler use. These include local adverse events such as injection site reactions, some of which are commonly experienced by patients. Others are less common but potentially more serious, including adverse effects, adverse events involving inadvertent intravascular injection leading to blindness.

Common risks may include swelling, pain or tenderness, firmness or induration, bruising, redness, discoloration, or itching. Less common risks include granuloma, lumps or nodules, injection site infection, open or draining wounds, and allergic reaction. Note that a full list of risks and adverse events reported for each device is presented in the labeling.

Risks involving inadvertent intravascular injection, including skin necrosis, damage to facial structures, vision impairment or blindness, and stroke, will be the focus of detailed discussion during this meeting.

In May of 2015 the FDA released its safety communication in response to reports of unintentional intravascular injection received from Medical Device Reports or MDRs, publications in peer-reviewed journals, and clinician experts. Based on these reports, FDA requested that all manufacturers consider including additional warning and precaution statements.

Examples of recommended warning statements are shown here and include the risk of occlusion of blood vessels leading to ischemia or infarction resulting in skin necrosis, vision impairment, blindness, or stroke. Recommended labeling changes also include precautions that products should only be used by healthcare practitioners who have appropriate training, and that healthcare practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment.

Related to these efforts, FDA has also recently taken steps to bring awareness to and address the alarming trend of injectable silicone being used for the unapproved purposes of body contouring and enhancement. When injected into vascular areas such as the buttocks, silicone can embolize and result in permanent damage to local tissues and even lead to stroke or death.

Please note that there are no FDA-approved injectable silicone dermal filler products.

I would now like to introduce my colleague from FDA's Center for Devices and Radiological Health, Dr. Kimberly Ferlin, who will speak about the regulation of dermal fillers. Thank you.

DR. FERLIN: Good morning, my name is Kimberly Ferlin and I am a biomedical

engineer in the Office of Surgical and Infection Control Devices in CDRH. Today I will present background information on how dermal filler products are regulated at FDA.

Dermal fillers are considered Class III devices and are approved through the premarket approval or PMA process. Class III devices are devices that cannot be classified into Class I or II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness and in the case of dermal fillers, the product presents a potential unreasonable risk of illness or injury.

There are two product codes associated with dermal filler products, LMH and PKY. PKY is used for products that are intended for use in the back of the hand.

The final review to determine marketing of a dermal filler product is conducted through the premarket approval or PMA application process. The review focuses on the benefit and risks of the product, including information collected by FDA personnel on inspections of manufacturing and clinical study sites, as well as substantive review of preclinical and clinical data and the product labeling. Any information relevant to the safety and effectiveness of the device must also be provided and reviewed. For dermal fillers, both clinician and patient labeling are carefully reviewed by FDA.

The review of a new dermal filler includes the review of preclinical evidence such as materials' chemistry characterization; review of the drug constituent, if applicable; characterization of the injection instrument which includes the primary packaging of the syringe, sterility, biocompatibility, and manufacturing.

Dermal fillers are evaluated in clinical trials. If the study is conducted within the United States, the study is first approved by FDA prior to study initiation through the Investigational Device Exemption or IDE program. Study design can vary based on the objective of the study and the proposed indications for use, whether the dermal filler has

been previously approved for another indication and is on the market, as well as the material properties of the filler, which can influence the duration of effect.

Typically, dermal filler studies include the collection of injection site responses or common treatment responses through a safety diary filled out by subjects in the first 2 to 4 weeks after injection. Examples of injection site responses include bruising, redness, swelling, and pain.

In addition, adverse events are also collected throughout the study at all visits. The incidence of adverse events as well as the severity, duration, relatedness to the product or treatment and resolution are recorded and reported to the Agency.

Depending on the location of injection, additional safety data, including location specific functional assessments, are conducted. These include assessments such as the ability to smile broadly and sip through a straw.

Following the safety communication on vascular occlusion in 2015, the Agency continued to receive increasing reports of adverse events related to vision loss. In 2017, due to increasing reports, as well as reports in the literature of new injection areas such as the areas around the eyes, nose, and glabella, FDA incorporated additional measures into its regulatory strategy for dermal fillers.

The design of clinical trials was revised to actively and deliberately monitor for visual impairment and to have measures in place to quickly manage subjects enrolled in a study if an incident of vascular compromise occurs. These measures will be discussed later today by Dr. Henry Lee.

The collection of effectiveness data in clinical studies has continued to evolve with new emerging indications for use. Previous methods to evaluate the filling of a wrinkle may not be applicable to facial augmentation and contouring indications. Effectiveness data typically includes a combination of clinician and patient-reported outcomes.

As dermal fillers are aesthetic and elective procedures, the FDA considers the incorporation of the patient perspective critical to the study design. It is important that the effectiveness evaluations incorporate elements that are meaningful to the patient and that the results and expectations are clearly communicated. Emerging challenges with the evaluation of effectiveness will be discussed in greater detail in the afternoon session.

During the PMA approval process, if there are additional safety or effectiveness questions that were not answered by the clinical data provided in the submission, the Agency may require, as a condition of approval, that clinical evidence is collected through the use of a post-approval study.

For example, during the most recent Advisory Committee meeting on dermal fillers held in February 2015, the Panel discussed the proposed expansion of the indications for use for Radiesse to include hand augmentation to correct volume loss in the back of the hand. The Panel recommended that additional studies be conducted to evaluate the effect of filler on hand function and radiologic imaging, as well as the safety of a specific subgroup of subjects with more severe volume loss. Following the meeting, the PMA was approved and two post-approval studies have been conducted to evaluate the recommendations from the Panel.

Other post-approval actions include mandatory annual reporting. Annually, the sponsor of the PMA must submit a report which is reviewed by the Agency. PMA reports include information on changes made to the device and its manufacturing, published scientific literature, unpublished reports of data from clinical or nonclinical studies, information on devices sold and shipped, and device identifier information.

In addition, the Agency continues to conduct its own postmarket review through medical device reporting. All of these activities contribute to the presentation of postmarket information in the clinician and patient labeling for dermal fillers which is

frequently updated to communicate up-to-date adverse event information.

The Panel will be asked today to make recommendations on the regulation of dermal fillers at different stages of product development and approval. This includes discussion of clinical study considerations, appropriate labeling information as part of the informed decision-making process, and how to incorporate critical safety elements, as well as patient perspective, into the assessment of dermal filler products.

I would now like to introduce my colleague from FDA's Center for Devices and Radiological Health, Amy Rogers, who will speak about dermal filler medical device reporting. Thank you.

MS. ROGERS: Good morning. I'm Amy Rogers from the Plastic Surgery Skin and Wound Devices Team within CDRH. I'll be providing an overview of the MDR data associated with dermal fillers with a focus on vascular complications.

The FDA receives reports from manufacturers, healthcare providers, and patients. The medical device reporting system aids us in establishing a qualitative snapshot of adverse events for a specific medical device or device type. It's useful in detecting actual or potential device problems used in a real-world setting, including rare, serious or unexpected adverse events, use error, and off-label use.

The system has its limitations, including incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from the reporting system alone due to underreporting of events, inaccuracies in reports, lack of verification that the device caused the reported event, and lack of information about frequency of device use.

An all-time search of serious injury reports for dermal filler product codes LMH and PKY was conducted. The FDA defines serious injury as an injury or illness that is life threatening, results in permanent impairment of a body function or structure, or

necessitates medical or surgical intervention to preclude permanent impairment of a body function or structure. The results of the search showed that the number of reports has increased over time.

Next, a search was conducted from August 1st, 2015 until August 1st, 2020. In that 5-year time period, the FDA received 5,009 MDRs associated with dermal fillers that were labeled as serious injury. The top 10 most reported patient problems are seen here. Skin irritation and edema are the most commonly reported events.

There were 470 MDRs that reported vascular impairment. Those reports were filtered for duplicates and 411 reports remained. Vascular impairment includes vascular compression at the site of injection or in adjacent tissues and/or unintended intravascular injection of the filler substance, which has the potential for permanent injury.

Therefore, an in-depth analysis of all the reports related to vascular impairment was conducted. Of the remaining 411 reports, 374 detailed vascular events that occurred at or adjacent to the area of filler injection. Thirty-one reports detailed an event that occurred distant to the injected area and six of the reports did not contain enough information to be determined a local or distant event.

It's important to note that 49% of the reports the FDA received were originated outside of the United States. Unapproved uses should be considered, as well.

Additional data on the anatomic location of injection was collected from the analysis. The lips were associated with the highest number of vascular impairment reports. All of the associated reports following injection in the lips detailed localized vascular impairment. Of the injection areas that were reported, injection to the nose was associated with the highest number of reports detailing distant vascular impairment events including ophthalmic complications, complete blindness, and stroke.

Next, a query was performed for the reports with patient problem codes related to

vision. The codes listed in the box on the left were identified from the 5-year query of serious injury reports. Those problem codes were searched to identify any MDRs with adverse events related to vision. Following initial filtering for duplicates, 92 MDRs were identified and systematically reviewed. Fifty of the patients reporting adverse events related to vision were injected in various regions of the nose, to include the nasal dorsum, nasal root, nasal tip, and nasal apex. The number shown is greater than the number of MDRs due to the multiple injection areas reported in a singular device report.

Of the events reported, 58% of the patients had immediate onset of visual impairment symptoms. The most common symptoms were blurred vision, pain, partial or total blindness of the affected eye, headache, and dizziness. Of the events reported, 34 patients had unresolved or permanent injuries, 27 patients had partial resolution, and 14 patients had full resolution to baseline visual acuity. Of the 34 patients who reported permanent or unresolved changes in vision, 14 of them were injected in the nose.

Of the 92 vision-related MDRs, there were 17 reports of patients who also experienced neurological symptoms. The most commonly reported symptoms were drowsiness, non-reactive pupil, absent light reflex, facial drooping, and paralysis.

Now I would like to introduce my FDA colleague, oculoplastic surgeon Dr. Henry Lee. He will discuss assessing and monitoring for intravascular injections.

DR. LEE: Good morning, my name is Henry Lee and I am an oculoplastic surgeon and medical officer in the Office of Surgical and Infection Control Devices. Today I will discuss assessing and monitoring for intravascular injections.

Dermal filler injections have been associated with a number of serious adverse events including skin necrosis, eye-related complications including complete blindness, and stroke. While significant research continues in this field, the widely accepted cause of these adverse events is severe vascular compromise via vascular occlusion. The two commonly

proposed mechanisms of vascular occlusion are intravascular injection and external vascular compression, with intravascular injection the most likely cause of these serious adverse events.

Ophthalmic complications, including blindness, are believed to occur from intra-arterial injection of dermal filler resulting in retrograde flow to the ophthalmic artery. Occlusion of the ophthalmic artery or one of its branches may result in various ophthalmic complications such as blindness, drooping of the eyelid, and weakness or paralysis of the eye muscles.

Depending on the location of injection, there are numerous pathways to the ophthalmic artery which are readily accessible during dermal filler injection, as seen in this figure on the right. More specifically, the supraorbital, supratrochlear, dorsal nasal, angular, zygomaticofacial, zygomaticotemporal, and infraorbital arteries all provide a pathway to the ophthalmic artery via retrograde flow. Therefore, multiple areas of the face are at risk for intravascular injection leading to ophthalmic complications. In addition, nearly every filler type has been associated with vision impairment or blindness.

It is important to note that the incidence of vision loss secondary to dermal filler injection is unknown at this time. However, additional data has been evaluated to further characterize the risk of vision-related adverse events.

In a recent study by Dr. Beleznay and colleagues, for which our upcoming guest speaker, Dr. Jean Carruthers, was the co-author, a literature search resulted in a total of 48 published cases of partial or complete vision loss over a three-and-a-half year span. A medical device report analysis was performed by FDA, which was reviewed in detail in the prior presentation by Amy Rogers. As a reminder, with regards to vision-related reports, a total of 92 MDRs were noted over a 5-year period.

For context, the American Society of Plastic Surgeons estimated a total of over 2.7

million dermal filler injections in 2019 alone with 79% of injections performed with hyaluronic acid dermal fillers. In addition, during the years covered in Dr. Beleznay's study, as well as FDA's MDR analysis, there were between 2.4 and 2.6 million dermal filler injections each year. Thus, the reported incidence of vision-related adverse events secondary to intravascular injection appears to be low.

Vascular compromise may result in various clinical presentations depending on the location of the occlusion. Skin necrosis may present as blanching, violaceous mottling, delayed pain, and ulceration. This can then lead to scabbing and significant scarring.

There are also a variety of ophthalmic signs and symptoms which depend upon the degree and location of vascular occlusion in the ophthalmic circulation. Immediate pain is a common symptom and may be accompanied by ptosis or drooping of the eyelid, ophthalmoplegia or weakness or paralysis of the eye muscles, and either partial or complete vision loss. Bilateral vision loss has also been described following injection to the midline structures of the face, such as the nose or glabella.

If the vascular occlusion involves the central nervous system circulation, then a stroke with symptoms dependent on the location of the vascular occlusion may occur.

In clinical studies, assessing and monitoring for intravascular injection is essential to protect patient safety because early identification and treatment of vascular compromise may improve the chance for recovery. Therefore, appropriate methods for monitoring for these serious adverse events are important.

Given the severity of dermal filler related ophthalmic adverse events such as blindness, vision assessments have been identified by FDA as important and part of the Agency's efforts to actively and deliberately monitor for vision impairment to protect trial participants.

To date, the most common assessments utilized have been Snellen visual acuity,

which is a common method of testing one's vision, and results in a numerical score such as 20/20 or 20/40; confrontation visual fields, which is a test of one's peripheral vision; and extraocular motility, which tests of the movement of the eyes. These assessments typically occur prior to injection and are then repeated 30 minutes after injection regardless of symptomatology, as well as during follow-up visits. Some studies have also incorporated undilated retinal examinations and retinal photography where the photographs are taken locally and are then read at a central reading location. Finally, subjects who exhibit any signs or symptoms of vascular occlusion leading to ophthalmic complications must be immediately referred to a retina specialist for evaluation and management.

Additional situations should be considered. Multiple studies and medical device reports indicate that certain anatomic regions, such as the nose and glabella, have higher numbers of cases of severe ophthalmic adverse events. Though not routinely requested by FDA, additional safety measures such as dilated fundoscopic examinations, retinal photography, delayed contralateral treatment, and image-guided injections may be considered in order to mitigate and/or characterize risks associated with intravascular injection.

Furthermore, though there has been special focus on vision assessments thus far, additional assessments such as neurologic assessments may be considered. In the study by Dr. Beleznay in 2019, 18.8% of cases with blindness were found to have central nervous system complications, such as stroke. Therefore, it is reasonable to include neurological assessments and imaging for subjects with vision loss both in premarket studies as well as in device labeling.

As stated by Dr. Chang in the opening remarks, in recent years there has been an increasing number of new dermal fillers, including new formulations, indications, and anatomic locations. In addition, as seen in the American Society of Plastic Surgeons

surveys, the number of dermal filler injections have continued to increase over time. While the risk of intravascular injection has always been present for dermal fillers, the increased popularity of fillers has been associated with increasing reports of adverse events. As noted previously, FDA has taken steps to communicate these risks through public communications and updates to physician and patient labeling. In addition, FDA has ensured that focused monitoring is conducted in clinical studies. However, as new indications emerge which may pose additional concerns for vision-related and neurological impacts from vascular occlusion, FDA is interested in discussing the utility of implementation of additional approaches, through device labeling, for early detection of vascular occlusion in clinical practice.

Therefore, the Panel will be asked today to make recommendations for assessing and monitoring for intravascular injection in premarket clinical studies and in clinical practice. This includes discussion of the impact of the indication for use and/or anatomic location for injection on the recommended assessments.

It is important to note that in addition to the vision assessments mentioned earlier, premarket clinical studies typically utilize highly qualified physicians such as plastic surgeons or dermatologists with extensive experience with dermal filler injection. With these safety measures in place, since the initiation of vision assessments, vision loss secondary to intravascular injection has not been reported in studies supporting an approved PMA.

In contrast to premarket studies, in postmarket clinical use, the injector may not have adequate training to safely inject a device for a particular indication. Consensus recommendations in the literature note that well-trained and experienced providers may mitigate the risk of complications. However, it should be stated that there is insufficient evidence quantifying the effectiveness of training or the types of training that may mitigate

risk of adverse events.

Finally, premarket studies of dermal filler devices have typically enrolled 100 to 300 subjects. While this sample size is sufficient to evaluate the effectiveness of treatment and to characterize common site responses and local adverse events, the risk of less common events such as intravascular injection is unlikely to be adequately characterized in a clinical study of 100 to 300 subjects. Therefore, postmarket studies may help characterize the risks of serious adverse events such as vision loss and neurologic impairment.

The Panel will be asked today to make recommendations for additional safety measures to mitigate and/or characterize the risks associated with unintentional intravascular injection.

Thank you very much.

DR. LEWIS: I'd now like to introduce Dr. Jean Carruthers, a world-renowned oculoplastic surgeon from Vancouver, BC. She earned her medical degree from the University of British Columbia and completed her residency at the Institute of Ophthalmology and Moorfields Eye Hospital in London. She then completed her post-residency studies in ophthalmology at the University of British Columbia and the University of California, San Francisco.

As a pioneer in the cosmetic use of botulinum exotoxin A and an expert in the injection of dermal fillers, Dr. Carruthers has given presentations worldwide and has authored more than 300 peer-reviewed articles, 70 book chapters, and nine textbooks.

She is the recipient of numerous awards, including the Eugene Van Scott Award from the American Academy of Dermatology, the Henry Baylis Award from the American Society of Ophthalmic Plastic and Reconstructive Surgery, and the Samuel Stegman Award from the American Society of Dermatologic Surgery.

Dr. Carruthers, thank you for your participation in our advisory panel as our guest

speaker. We look forward to your presentation on the prevention of filler-induced vascular occlusion and blindness and stroke.

(Off microphone comment.)

DR. LEWIS: Dr. Carruthers, your sound is muted.

DR. CARRUTHERS: Can you hear me now, Dr. Lewis?

DR. LEWIS: Yes, yes.

DR. CARRUTHERS: Okay. Sorry for that. I wonder, could we have the next slide, please? These are my disclosures. And would it be possible, please, to have the slides a little bit larger? I just have them as a thumbnail. These are my disclosures. Next slide, please.

In January of 2020, a number of us at the American Society for Dermatologic Surgery got together in person in Chicago to have a discussion about the problems with filler-related vascular occlusion and we worked very, very hard. I commend our chair, Dr. Derek Jones, and the entire community.

Next slide, please.

And you will see here, this is the publication that we put together, it came out 1 year later in January of 2021, and you can see the dream team of authors here. I'm very, very grateful to have had the opportunity to work with all of these really excellent, excellent people.

Next slide, please.

This is what we're talking about, this kind of vascular occlusion where we have the disaster of someone who just wants to have a little bit of a higher bridge to their nose and they achieve blindness and a third nerve palsy as part of the healing process.

Next slide, please.

So this is something that started way long ago, a group of us, and you'll notice that

we're multi-specialists, oculoplastic surgeons, dermatologists, and plastic surgery, looking at what could we do about this and one of us, Dr. Steve Fagien, an oculoplastic surgeon from Boca Raton, Florida had the idea of perhaps we could inject retrobulbar or peribulbar hyaluronidase. So this was a really big thing for us to see if there is something therapeutic we could do about this disastrous problem.

Could I please have the slides a little larger? I have them as a thumbnail only. And I see that other people are saying they cannot see the slides. Would it be possible to put the slides up as large on the screen, please? I wonder if we could have the slides enlarged on the screen, please.

Well, next slide, please.

This is what we're talking about in terms of the vascular anatomy. I'm supposed to pin the image. How do I do that? I'm sorry.

UNIDENTIFIED SPEAKER: Just click on it.

DR. CARRUTHERS: There. Okay, thank you. That's much better. So this is what we're talking about. We know that the facial vasculature comes from both the internal and external carotid arteries and these are very communicative throughout the face. But when you get to the ophthalmic artery and the retinal artery, you have a different situation. This is an end artery system. So the only way to get rid of hypoxia is to move the embolus along.

Next slide, please.

So as mentioned by Dr. Lee, Dr. Katie Beleznay and Shannon Humphrey and Derek Jones and I looked at the world literature from 1906 to 2015, so in a hundred and nine years we found 98 cases of blindness. One in 1906 was actually from injecting liquid paraffin into the bridge of the nose, so this has been a common problem for many years.

Next slide, please.

So in our study, you can see, as was mentioned by Dr. Lee, most of the areas of

concern, injection concern, relate to the nose, the glabella, and essentially this upper central face.

Next slide, please.

Autologous fat, in 2015, was the commonest filler that was involved and hyaluronic acid at half that, but no filler was exempt.

Next slide, please.

So most reports that we found, though, were in the preceding 5 years. So it looks like not a common problem if you look at the number of filler injections, but when you have that problem, it's extremely serious.

Next slide, please.

The mechanism we've discussed, probably intravascular occlusion, embolic, but there is another method that is being pointed out, that in the glabella area there are venoarterial shunts and this may also account for some of the problems. So when the pressure on the plunger is released, the material that was injected intra-arterially moves along peripherally in that vascular area, be it the retina.

Next slide, please.

So we did an update in 2019, so looking from 2018 to 2019, we found a further increase in the cases. This is not a problem that has gone away. Next slide, please.

And you'll see, from the slides, that the pattern is exactly the same. On the left is our 2015 pattern, on the right our 2019 pattern. So the central area of upper face is our main area of concern.

Next slide, please.

Now the change of pattern of practice. Where you saw before in our previous study, most of the filler injection problems were with autologous fat, now it's with hyaluronic acid filler. Although again, other fillers are not exempt. And in our 2019 study, 39% of people

had complete visual loss, 60% had some loss, and we had two cases of CNS complication.

Next slide, please.

But again, most cases came from Asia. And so looking at that, it is really, really an important situation geographically, as well, for all of our patients. But you can see the nasal region, 56%; the glabella, 27%; the forehead at 18% and 20% CNS changes. There was visual recovery in 10 cases. Eight cases, partial.

Next slide, please.

So most of the cases from Asia, most result from injections into the upper face. Because of the easy arterial communication with the ophthalmic artery, most of the emboli are immediate and unilateral, and 50% of patients approximately get ophthalmoplegia, ptosis, pain, or skin changes, most of these which resolve.

Next, please.

So the 2020 ASDS filler task force were looking at inadvertent retinal vascular compromise themes, and so 50% of patients present with partial light perception, hand movements, finger counting, or Snellen visual acuity vision loss compared to 20% with fat; 20% had CNS symptoms as opposed to 40% with fat. Not all treated patients showed improvement, but all recovered cases had received some form of treatment and, from Dr. Sorensen's excellent paper, we see that it was immediate treatment that had the most success.

Next slide, please.

So prevention. We have to know our anatomy when we're doing this injection. Why inject into the trouble zone? So you can see in this profile of the forehead, if you inject above where the vascular -- where the supraorbital artery comes out of the bone, then you are missing it because it comes out and is superficial. It's detailed anatomy knowledge like this that makes things a lot safer. As before, we've said inject slowly with little pressure

with small increments, aspirate before injection, and keep moving your cannula or needle tip.

Next slide, please.

And the task force conditional recommendations include a very intelligent one of making a good relationship with your ophthalmology or retina colleagues, preexisting, so that if you did have such a disaster happen, it's not a big surprise to them, they know exactly what is needed and what to do. It's going to be much more helpful to the patient. What the injector can do is to inject hyaluronidase in and around the injected area along the path and in and around foramina and if they have the training, peri- or retrobulbar injection.

Conservative measures are also helpful: ocular massage to try and move the embolus along; breathing into a paper bag; medication such as Diamox to lower intraocular pressure, to facilitate the movement peripherally of the embolus; and specialist procedures such as anterior chamber paracentesis and intra-arterial therapy with hyaluronidase and other thrombolytics.

Next slide, please.

So include this risk in the informed consent. And currently, with our ASDS task force, we found no high-certainty, evidence-based standard for treatment. So these are conditional recommendations, but we must include this risk in the informed consent and we must have a preexisting IRVC protocol which our team members are all familiar with in terms of their role, to include the specialist contact information and needed supplies and the roles for each team member and to implement this at the first sign of visual compromise. I put document visual acuity prior to any treatment. This is something that is very natural in an ophthalmology practice, but this is something I think should be discussed by the group.

Next slide, please.

So treatment really relates to hyaluronidase. We need to make sure that every office that's injecting hyaluronic acid filler has an updated supply of hyaluronidase. It tends to peter out in terms of about 6 to 8 weeks to 3 months depending on the supplier, so we need to make sure everybody does have this. Obviously, IOP-reducing agents, IV or oral steroids, thrombolytics, anterior chamber paracentesis and anticoagulants, but hyaluronidase is our biggest help.

Next slide, please.

So the strong recommendations with moderate certainty evidence, have a thorough knowledge of facial anatomy and cutaneous landmarks of blood vessels because variability is the norm. Higher-risk locations, we know, are upper central face and superior nasolabial fold. And do not inject on periosteal planes where the arteries are rising. For example, the supratrochlear and supraorbital vessels coming out of the superior orbit at the medial canthus where the angular artery, the medial cheek, the infraorbital artery, and the antegonial notch of the jaw line for the facial artery. These are great places to avoid for trouble.

Next slide, please.

Strongly consider changing how you administer the filler. A larger blunt-gauge cannula such as 25 gauge, inject slowly with small volumes, keep the tip moving, and pretreatment and informed consent. And I think it's a good idea to do the reflux test as you come into the tissue because if you do get blood into the hub, you know you're going to pull out immediately and not use that particular location. It's not an absolute system, but if it's there, it's helpful.

Next slide, please.

So arterial wall penetration with a 27-gauge needle and 27-gauge cannula are

identical. So that's why we suggest you use a 25, because it's much harder to penetrate a blood vessel with a 25-gauge cannula.

Next slide, please.

So future considerations include studying facial vascular anatomy, not just once, but every year, because there's new information coming out from fantastic anatomical studies all the time. Expert knowledge of cutaneous landmarks of the facial vessels. Take a cadaver course. And there are many, many newer peer-reviewed papers and publications which are excellent resources to keep updating. It's exciting to see that there are new imaging modalities, such as ultrasound, which could be used to identify at-risk vessels both before injection and actually during the procedure.

Next slide, please.

I want to thank you very much, the FDA, for keeping your eye on this very important area. I hark back to the warning in May of 2015, do not inject soft tissue fillers if you do not have the appropriate training or experience. And I thank all my co-authors and our president, Dr. Matt Avram, for being at this very important FDA session. And I thank you, Dr. Lewis, for the very kind invitation to share our experience with you.

DR. LEWIS: Thank you, Dr. Carruthers.

Do any of the panelists have questions at this time either for Dr. Carruthers or any of the earlier speakers?

Dr. Carruthers, I have a question to start with, actually, while we're waiting for others to come forth. A question of using a slightly blunted needle tip is quite a simple thing. I don't know quite how much you could blunt it and still have it penetrate the skin easily for these injections, but it's relatively hard, I would think, if it's blunted, for the needle to penetrate into an artery which has a fairly thick wall. Has there been any really research done into optimizing both the needle diameter as well as the degree of blunting

that might help with that?

DR. CARRUTHERS: Yes. Thank you very much for pointing that out. A cannula would not easily go through the skin, and the patient would run screaming from the office. So what we have is an introducer, it's a small needle tip which penetrates the skin and then the cannula tip, which is blunt, as you point out, slips into the subcutaneous space very easily. So you're right that you need to have an introducer. And the research that's being done really shows that the smaller, more elegant and whippier cannulas are really dangerous, as dangerous as a needle.

I think with either a cannula or a needle, the other thing that you can do to minimize risk, instead of doing retrograde injection, is to do anterograde injection so that you slip the needle or a cannula into the subcutaneous space and start injecting the fluid, the hyaluronic acid filler that is coming out of the tip of your cannula is actually ballotting the tissues away instead of driving a metal pole into a vascular wall. Thank you for that question.

DR. LEWIS: Questions from the panelists?

Dr. Alam.

DR. ALAM: Thank you, Dr. Lewis, and thank you also, Dr. Carruthers, for that very helpful introduction. In listening to your suggestions for improvement, what it seemed that I was understanding was that you are not in support of some sort of blanket restriction, but rather very careful workup for cases where a significant serious event like visual loss has already occurred. Am I correct in understanding that you believe these procedures to be generally very safe without a need routinely for implementing a lot of these precautions but when something occurs, then great care should be taken in assessing what has occurred and managing it appropriately?

DR. CARRUTHERS: Yeah, I think that's a very fair statement because when we look at the numbers from 1906 to 2019, we're looking at 200 cases and we're looking, and the

current days, that's somewhere between three and five million filler injections done a year and I'm talking North America. It's much more when you consider the rest of the world. So it's an extremely safe procedure.

The question is what are the risk factors that would make you want to put a blanket restriction, and I don't think we see those here, but I see risk factors such as people who have had previous facial surgery, previous rhinoplasty, somebody who has had surgery of any kind on the lids, or a facelift, I think those are people with preexisting surgical conditions who we should really say there may have been some vascular changes in the healing process.

I think that we also have to realize, in terms of risk, that the perinasal area is somewhere that is a really, really difficult area, and I certainly injected lots of people in that area without any problems. I have learned from the great Dr. Woffles Woo that when you inject in that area, we're using a very tiny needle, a 31-gauge, 3 mm, 31-gauge needle and tenting the skin up from the -- from the underlying dorsal nasal artery and angular vessels.

So I think that a really great knowledge of anatomy and a great knowledge of techniques makes for safety. I think what worries me is that there's this filler world that's growing 15% a year and I know that a lot of people injecting haven't a clue where the blood vessels are and what to do if something happened. I think that it's largely a very safe procedure, but I'd like to make it much safer yet.

DR. LEWIS: I'll ask a follow-on question, Dr. Carruthers, to the issue of the blunt cannula. It's interesting, you described that technique of using the sharper needle to introduce through the skin and then a cannula. It's interesting that in the material provided to the Panel, I don't believe that was written up anywhere in the Executive Summary. Is that technique, as you described it, universally used or do you feel that people simply are using sharp needles because it's quicker and easier to do?

DR. CARRUTHERS: Yes, the cannula technique is well worked out and it's used by almost every aesthetic physician, including myself. I do use needles, as well. I use them in the temple because it's really hard to get through the layers with a cannula, but I use anterograde injection technique, I use -- when I'm doing intradermal injections. I use a tiny needle, a 31-gauge needle. But I think that a lot of people just haven't been taught how to use cannulas and I think that those are maybe people who are not part of the specialist world that I'm happy to live in. I think spas and places where individuals who may have less training, the needle is the first thing that they pick up. I think that's a very astute question.

DR. LEWIS: Are there further questions from the Panel?

DR. MATARASSO: Yes.

DR. LEWIS: Dr. Matarasso

DR. MATARASSO: Thank you very much. My name is Alan Matarasso, I'm a plastic surgeon in New York.

Jean, thank you for that wonderful presentation. It's good to see you. I have a question both for Amy Rogers and Jean Carruthers. I'd like to clarify, at least, the numerator on the visual problems.

Amy, can you go -- either go back to your slide or just verbalize what the numbers are? They sounded a little different than the cases that Jean compiled in these two studies. Can we get those numbers? And then I'd like to ask an extension of that.

MS. ROGERS: Which number is it that you're looking for?

DR. MATARASSO: The visual, the visual problems, the 92 MDRs you had.

MS. ROGERS: Yes.

DR. MATARASSO: Can you break that out? That was 48 cases from 2015 to '18?

MS. ROGERS: Oh, I don't have the breakdown of -- no, there were 92 MDRs from 2015 to 2020.

DR. MATARASSO: Okay.

MS. ROGERS: Ninety-two of them were associated with visual impairment.

DR. MATARASSO: Okay. And so just trying -- and Jean, please correct me here, I'm just trying to get a denominator here. If we presume that there's three to five million injections per year in the United States, so that's a 5-year period, so let's call that 20 million injections and 92 visual MDRs. Does that sound reasonable, Jean?

DR. CARRUTHERS: Yes, that sounds really reasonable.

DR. MATARASSO: Okay, so it's 92 out 20 million visual and fortunately, that's a very low number, but I think that's an important thing in addition to obviously all the safety issues.

The other thing I would go back to, that we haven't focused on, is a far more common problem and obviously, you can't compare visual loss to skin loss, but what we haven't discussed is the most common problem, which is skin ischemia necrosis which, for those Panel members or people that are not familiar with it, the term that you might use is gangrene, when the skin turns black. And our society actually has a video of someone who lost most of their face because of intra-arterial injection and skin loss.

Amy, do we have any numbers on skin ischemia and tissue necrosis?

MS. ROGERS: One thing you have to keep in mind is that the incidence or prevalence of an event cannot be determined from this reporting system alone.

DR. MATARASSO: Okay.

MS. ROGERS: There's a huge potential for under-reporting of events and lack of information about frequency of device use. So we don't draw conclusions about the frequency of events from this reporting system.

DR. MATARASSO: But do we have a comparable MDR for skin?

MS. ROGERS: As far as how many --

DR. MATARASSO: Skin losses.

MS. ROGERS: I believe when you ask for the skin losses, are you asking for skin losses that also had visual impairment?

DR. MATARASSO: No, no. There's basically three vascular events that were a concern to us: visual, skin, and neurologic, which is stroke. Those are the three primary things that we give these courses and think about it. So we have a rough handle, which I think is great, 92 out of 20 million, let's say, or so for visual. I know skin is far more common and I know we're going to focus on visual, but I'd like to get some handle around skin ischemia, skin necrosis or loss.

MS. ROGERS: So that number is 411.

DR. MATARASSO: Great. So that's over the same time period?

MS. ROGERS: Yes.

DR. MATARASSO: Okay. So we're assuming we're using Jean's number of three to five million filler injections in the United States per year and I just took the middle number, which is four, four million a year over 5 years is 20 million, so we're looking at 411 out of 20 million injections on skin ischemia.

MS. ROGERS: That were reported to us.

DR. MATARASSO: Right, right. I know, I know.

And my final question, and I don't know if this data is available, do we have any information -- I know that initially, Jean pointed out that these, a majority of these patients were fat and it shifted to HAs. Do we know -- and the HAs, I think, will become more prevalent. Do we know anything about the G prime of the HAs because, as many people know, there's a very, very different, big difference in the type of HA. Jean, do we know anything, is there a higher incidence with more dense G primes?

DR. CARRUTHERS: That's a great question. Often we don't know exactly what kind

of filler was injected because the doctors reporting the problem are the ones that didn't create it. They're the ones that are helping the patients afterwards. So we don't have great data on that. But just looking at the timing, Juvéderm Voluma and the other HA fillers really started in around 2003. So we've actually had such a modulation of all the fillers in all the filler families with fillers that are less viscous being produced for different indications. I would assume that it could be any HA filler and I -- that's a great question and I'll go back into our data and see if we can search out some data on G prime. Thank you.

DR. MATARASSO: Thank you both very much. That's very helpful information. Thank you.

DR. LEWIS: Dr. Perry, did you have a question?

DR. PERRY: Yeah, I did.

Thanks, Dr. Carruthers, for a great talk. I think there's two questions, one regarding cannula versus needle. Obviously, it seems to make a lot of sense and it's intuitive, but can you share with us the paucity of the data in clinical human trials or even just in case reports? Because they both can cause blindness, so I think it's important to point out the paucity of the data there. And also regarding the treatment, the paracentesis, the Diamox, retrobulbar hyaluronidase, those all seem really reasonable, but can you point out the paucity of the real clinical data regarding the possible success of those, which could have some real risks, too?

DR. CARRUTHERS: Oh, yes, I agree. The question of -- first of all, do no harm, and that's why our group said if you have the appropriate training. Let's start with your last question about retrobulbar hyaluronidase. It really works in the rabbit model. In Dr. Won Lee's studies, it's fantastic, but the human ophthalmic artery is encased in dura. The rabbit ophthalmic artery has quite a segment before it gets encased in dura. So that's why hyaluronidase works so great for the rabbit, but not so well for human beings. So we didn't

know that anatomic detail when we put our first paper out, the one showcasing Steve Fagien's idea about retrobulbar hyaluronidase.

I know that for anterior chamber paracentesis, if that was my patient -- and thank God, to-date I haven't had this happen -- it's something I would consider doing because I have had the training because of the vision loss. But I think you're absolutely right, it's not something that somebody who hasn't had the training should even dream about doing until they have had that training.

As far as the injection around the eye, I think it really makes a lot of sense to inject hyaluronidase around the foramina. The supratrochlear artery is only one and a half millimeters deep to the skin surface and you can feel, you know exactly, it's 18 to 22 mm from the midline, so you know you can flood that area and the deep branch of the supratrochlear is a direct entry into the ophthalmic artery and it only takes such a tiny amount of -- I think it's -- anyway, I'm blocking on how much it is. It was a very, very tiny amount, so if you could flood that area. And that was shown to be a great help with the two cases, one in Washington State and one in Australia, where they flooded these notches, supraorbital and supratrochlear, and they also did retrobulbar injections. But I think that that is a much safer thing for people to do.

And given that we know from Tobalem work, that really the retinal ganglion cells are brain and so they can only tolerate 12 to 15 minutes of hypoxia. It's not the rather generous 90 minutes that we learned from Dr. Sohan Hayreh from his studies in Iowa many years ago on monkeys. So I think that the 15-minute thing means that we have to think of treatment that we can do right now in our office because frankly, even if you get the patient to your retina surgeon, you've wasted a whole bunch of that time.

DR. LEWIS: Dr. Carruthers, could you clarify for me the mechanism by which a retrobulbar injection of hyaluronidase, which is obviously into the soft tissue but not into a

blood vessel, actually does something beneficial for the embolus which is within the lumen of the artery? I don't understand that.

DR. CARRUTHERS: Yeah, that's right, that's what we thought. We thought that there was -- because we know that hyaluronidase will go through vessel walls. Game seven, match, it's been shown many times, but it doesn't go through dura. That's been shown recently in three studies. So we know that it's not a helpful thing most likely to do the retrobulbar injection.

Now, if that patient, and you don't know this, happened to have a variant, an anatomical variant, so they had a little gap in the dura surrounding their ophthalmic artery, it would be helpful, but we don't know that. So I agree with you that perforating the globe with a 25-gauge needle is a very serious event and phthisis is an outcome that none of us want to see in any of our patients.

DR. LEWIS: Are there further questions from the Panel?

Dr. Alam.

(Off microphone response.)

DR. LEWIS: You're muted, Dr. Alam. Unmute your microphone.

DR. ALAM: I apologize. It's Murad Alam. Thank you, Dr. Lewis.

I just wanted to bring to the Panel's attention, there was a question raised about data pertaining to cannulas versus fillers, and there is a recent article in *JAMA Dermatology* that retrospectively looked at several hundred individual injectors 10-year experience with cannulas and with needles and compared the incidence of occlusive events, not necessarily visual events, but all occlusive events, and there was about per -- if I recall correctly, about for every 6,000 syringes they had one occlusion when they used needles, and for cannulas it was about 1 of 30,000. So there was a decreased incidence, so they had a numerator and a denominator and this is from *JAMA Dermatology*, I believe, earlier this year. It's not perfect

data, it's not prospective, but it's a reasonably large sample, so there's some evidence now.

DR. LEWIS: Thank you.

Dr. Brown.

(Off microphone response.)

DR. LEWIS: You're muted, Dr. Brown.

DR. BROWN: Yes. A question to Dr. Rogers and to Dr. Carruthers. In your study of these events, did you look at or did you have access to information about the level of training of the people for whom these events were occurring? And kind of as a correlate to that, did they tend to be clustered in certain practices, clinics, areas or were they kind of sporadic and everyone's had maybe one event but it's not really a clustering effect?

DR. CARRUTHERS: I think the question is difficult to answer -- it's a great question -- because the people reporting the problem are the people who have tried to fix the problem. So obviously, the cluster has been in Asia. If you look, three-quarters of the cases come from Asia and a lot of the cases, as we know, relate to the bridge of the nose. So there has been some, I'm going to call, internationalization of the -- of what makes somebody beautiful. A very flat nasal bridge is something that is easily fixed with some filler or not so easily fixed, depending.

So I don't know about the clusters. I think that we are seeing clusters of people in large quantizations in Asia, but we've also seen people who are really well trained who have sporadic issues such as there's one Canadian reported from -- a blindness reported from an injection of Sculptra in the temple. A hard question to answer because the people reporting, the people in the literature, are not the people who did the injecting that caused the problem.

DR. LEWIS: Thank you.

MS. ROGERS: And this is Amy Rogers.

And from an MDR perspective, one of the things we really struggle with is the omission of data, what's not in the report, and the qualifications of the injector are often not in the report. Something very generic like healthcare provider or healthcare member or sometimes nothing at all. And that's where MDR data limits us because we don't have that information. We can only report what we know from what is reported to us. I would agree that most severe cases I saw from MDR reports were from Asia, as well. So our data mirrors what's in the literature. It's pretty interesting, actually.

DR. LEWIS: Thank you.

We will now conclude this portion of the Panel and take a 10-minute break and we will resume promptly at 10:35. Thank you.

(Off the record from 10:24 a.m. to 10:35 a.m.)

DR. LEWIS: I would like to resume the deliberations of the Panel, so I call this session back to order.

I apologize to the people who may have had their hands up prior to the break. I have a limited number of people showing on my screen and I didn't see those. I would like to actually go back and ask Dr. Chang, who had a question for Dr. Carruthers, if she could repeat that now before we move on to the next part of the program.

Dr. Chang.

DR. CHANG: Yes, hello. This is Cynthia Chang from FDA. The FDA team had a question for Dr. Carruthers, requesting clarification on the timing of her recommendation.

Dr. Carruthers, in your presentation you recommended documentation of visual acuity before treatment and could you clarify if this means before dermal filler treatment or before treatment of a visual event or intravascular injection event? Thank you.

(No response.)

DR. LEWIS: Your microphone is muted, Dr. Carruthers.

(No response.)

DR. LEWIS: I'm sorry, Dr. Chang. Apparently, she did not hear your question, is not able to respond. We'll have to move on now.

Dr. Carruthers, are you -- did you hear the question?

(No response.)

DR. LEWIS: I guess not. Let's move ahead. We will now have the industry presentations. The first presentation will be from Allergan, Michael Silberberg and Derek Jones will make the presentation.

DR. SILBERBERG: Thank you.

Next slide, please.

Good morning, I'm Mike Silberberg, Executive Medical Director and Global Strategy Lead for the Facial Aesthetics Division at Allergan, which is now AbbVie company. I am also a board certified otolaryngologist and facial plastic surgeon. On behalf of Allergan, I'd like to thank the FDA and the members of the Panel for the opportunity to provide Allergan's perspective on the topics being discussed today.

Next slide, please.

Dermal fillers have been FDA approved since the 1980s, and their safety and effectiveness is well established. The use of fillers has grown significantly over the past several decades. Hyaluronic acid is the most common dermal filler material. In 2019 alone, it was estimated that nearly 2.2 million injection procedures using hyaluronic acid were performed in the United States, which speaks to the high demand for these minimally invasive aesthetic procedures.

Allergan's range of hyaluronic acid-based fillers is called Juvéderm. The first Juvéderm product was FDA approved in 2006. Currently, the Juvéderm fillers are indicated for the treatment of nasolabial folds; perioral lines; and for lips, cheek, and chin

augmentation.

Next slide, please.

Intravascular injection is an identified risk with the use of any dermal filler. While the likelihood of injecting into a blood vessel is low, the consequences can be significant. In the literature, rates can vary based on study methodology and sample size; therefore, precise incidence is unknown.

When an intravascular injection occurs, the resulting complications can be self-limited, such as reversible ischemia, or vascular occlusion can result in serious complications such as infarction, skin necrosis, embolism leading to visual impairment or loss, or stroke. The risk of intravascular injection can be reduced when injectors are familiar with the anatomy around the injection site.

Next slide, please.

Allergan's clinical development program has consisted of more than 20 clinical trials which includes over 4,000 participants, which is estimated to be over 24,000 injections. There have been no reports of intravascular injection in any of Allergan's clinical studies. In the United States, more than 40 million Juvéderm syringes have been sold since 2006. Our U.S. post-marketing reporting rate of intravascular injection has been low and remains stable with approximately one event per 100,000 syringes sold. We recognize that postmarket data is subject to under-reporting and may not accurately reflect the actual incidence of intravascular injection. Blanching and ischemia are the most frequently reported events. The reporting rate for severe outcomes of necrosis, blindness, and stroke is about one event per 2 million syringes sold. Where the outcome is known, the majority of AEs associated with intravascular injections were resolved or resolving at the time of report. Because prevention is the most effective management strategy for any serious complication, let's discuss what Allergan is doing to mitigate the risk of occurrence.

Next slide, please.

Labeling is an important component of risk minimization. Shown here are excerpts from physician and patient filler labeling. The risk of inadvertent intravascular injection is emphasized in both. Within the physician's directions for use, we include recommended injection techniques known to minimize the risk of intravascular injection. Furthermore, the precaution section reinforces the importance of proper training and education to healthcare providers prior to the use of filler products.

The patient labeling is written in easy-to-understand language to inform patients of the benefits and the risks when considering their treatment options. The patient labeling also includes instructions to seek immediate medical attention should any signs or symptoms present that could be related to an intravascular injection, such as changes in vision, signs of stroke, light appearance to the skin, or unusual pain during or shortly after treatment. As recommended in FDA guidance, patient labeling is easily accessible on the Juvéderm website.

Next slide.

To support healthcare provider education, we offer a variety of training opportunities through Allergan Medical Institute. AMI provides training through in-person hands-on programs, online modules, roundtable discussions, symposia of international, national, and regional medical conferences, and offers both print and downloadable educational resources. Despite the pandemic in 2020, AMI was able to train more than 65,000 United States healthcare providers. Training always includes injection anatomy with a focus on vasculature, tissue planes, and avoidance of high-risk areas, technique, the choice of needle versus cannula, injecting small aliquots with low pressure, aspiration prior to injections, and surveillance for signs and symptoms of an intravascular injection. Additionally, Allergan maintains an expert network and on request by treating providers,

facilitates peer-to-peer consultation to assist in prompt management and resolution of complications.

Next slide.

Patient safety is paramount and is Allergan's first priority. Allergan's postmarket surveillance and clinical trial data confirm that intravascular injections are rare, but serious and require prompt management. Labeling informs providers and patients of risk, and training and education can mitigate risk. Efforts don't end there. We are actively engaging with global experts to better understand the pathogenesis of injection related visual compromise to further inform prevention strategies and facilitate more targeted intervention.

Because much of the patient conversation regarding the risk-benefit profile of our products sits with the clinician, I would like to invite one of our HCP partners, Dr. Derek Jones, to provide his perspective on how he discusses risks in support of their informed decision making.

Next slide.

Dr. Jones.

DR. JONES: Thank you.

I'm Derek Jones, a board certified dermatologist in California. The topics discussed today are of the utmost importance to injectors such as myself and most importantly, our patients. Dermal fillers provide patients with well-characterized and effective options for facial correction and rejuvenation, but we need to satisfy this demand safely. Injectable fillers provide aesthetic improvements that have --

(Audio feedback.)

DR. JONES: -- must also be aware of potential risk. While we cannot eliminate risk, we can minimize it. Continued training and education and keeping ourselves informed of

new injection techniques should be a lifelong educational pursuit and the tools are available through academia, industry, and professional societies.

Next slide, please.

As you've heard, intravascular injections occur and can be serious. Fortunately, these adverse events are rare. More importantly, we know these events can be mitigated with proper training and managed with prompt handling, most often by utilizing high hyaluronidase to dissolve the HA filler. High hyaluronidase may have its limitations, especially with distal embolic events or non-hyaluronic acid fillers.

Regarding training, Allergan offers multiple opportunities for providing online, conference, and peer-to-peer training and education. Moreover, as injectors, and as part of our continuing medical education, we should take advantage of the available trainings that are offered through societies and through academies. For example, the American Society of Dermatologic Surgery offers robust courses and peer-reviewed papers covering safer injection topics and detailed anatomy for the injector, including cadaver courses. As an experienced injector, I highly recommend all treating providers to utilize these training opportunities before injecting their first patient with any filler product.

Communicating risk to patients is also an essential part of clinical practice. As physicians, we share the benefits and the risks with our patients as we discuss their preferences and consider treatment options.

(Audio feedback.)

DR. JONES: -- adverse events beyond what's currently approved and it's important that industry establish safety and effectiveness in clinical studies to support use in these areas.

Patients have unique perspectives about the value of their filler treatments and when developing that value determination, they should have a proper understanding of the

potential risks involved. To this end, I share the label with patients and communicate risks and ways I can mitigate such risks, and I strongly encourage my peers to do the same. This is an active discussion sometimes prompted by the patients themselves as they've seen an advertisement or have heard about the risks. Training and education matter, communicating risks to patients matters. Doing these things allows our patients to fully understand the risks and most safely achieve the balanced facial rejuvenation they seek.

Thank you. That concludes our presentation.

DR. LEWIS: Thank you.

We'll now move to the next presentation which will be from Merz. Samantha Kerr will be making this presentation.

DR. KERR: Thank you very much and thank you to the FDA for inviting us and having the opportunity to speak at today's public hearing.

Could we move to the Merz slides, please? Thank you.

Our VP of Global Product Safety and Vigilance was meant to present today, but unfortunately he's having some technical difficulties, so I am not John Reynolds, but I am Samantha Kerr, as introduced. I'm Chief Scientific Officer at Merz.

Next slide, please.

So today, we're just going to cover general observations, as my colleagues at Allergan had, and we're going to actually focus on our dermal fillers at Merz and potential risks of intravascular injection followed by benefits to patients, and then our outreach and ongoing education to healthcare providers.

Next slide, please.

As has been said often today already, fillers offer a noninvasive surgical alternative for facial enhancement and improvement, and they're associated with lower cost than surgery and limited to no recovery time, hence the increased attractiveness to the

consumer.

In 2019 some global estimates suggest over 15 million treatments with fillers globally were performed, and hyaluronic acid fillers are the second most common nonsurgical procedure performed by plastic surgeons in the U.S. That being said, within the U.S. it's clear that overall filler use since 2015 continues to use (sic), as you can see, with the below slide.

Next slide, please.

For the purposes of this talk, I will focus on three FDA approved dermal fillers that have been available in the U.S. market for a period of time. We have Belotero Balance, Radiesse, and then Radiesse (+), which is Radiesse plus lidocaine. The Belotero Balance with lidocaine was just recently launched, so we will not be speaking to that today.

Next slide, please.

So we've already heard today, and I'd just like to reiterate what has already been presented on the recent label history of our fillers. In May 2015, the FDA required updates to the warnings and precaution sections of the IFU for all soft tissue fillers to mitigate potential risk of rare but serious adverse events that are potentially associated with what we've been discussing at length already today with intravascular injection.

Next slide, please.

What we wanted to do today was to share with you how we've identified and looked at this in terms of our products, so we'd like to share our general observations of routine surveillance of these rare potential events interest pre and then post the 2015 label changes to each of our products that I listed on the previous slide.

The following consideration should be applied in using these data sources: Clinical trials offer insights from a controlled setting, and already Dr. Carruthers mentioned that, where clinical event details and outcomes can be verified and then, of course, we have our

spontaneous reports that offer insights from the usual care or real-world, as we tend to call it, setting. And such reports are made voluntarily, often lack medical details, which is very difficult then to understand what the background is, clinical diagnosis and outcomes. But nevertheless, they are a good pulse check as to what's happening in the real world.

Next slide, please.

So let's start with our first product, Belotero Balance. In our clinical trial setting, first of all, since 2011 there have been zero related SAEs of interest from company sponsored clinical trials. In terms of spontaneous reports pre-2015, so prior to the FDA label update, the absolute frequency of reports averaged about six per year from the years of 2012 to 2015. Post the FDA label update, the absolute frequency actually went down, averaging one per year, even using the most conservative assumptions, and there have been no serious spontaneous cases since 2015.

Next slide, please.

In terms of Radiesse, our calcium hydroxylapatite filler, we see similar trends. In clinical trials since 2015 there have been zero SAEs of interest. In spontaneous reports prior to the 2015 label update, we saw about 50 annually. Post-2015 this has decreased, effectively halving. So again, looking at the most conservative assumptions, we see a very positive trend after the previous FDA public hearing and decision of the label update.

Next slide, please.

With Radiesse plus lidocaine, again with clinical trials very similar, zero related SAEs. In terms of post-marketing reports, the reports are very rare, averaging approximately 10 per year, but it has just been approved in 2015 so we have no prior data to compare it with post the FDA label change.

Next slide, please.

In terms of ongoing surveillance of intravascular injection risk, what it suggests is in

clinical trials, evidence for all of our Merz products suggest these potential risks are consistently minimized with effective training and medical supervision and we go to a lot of extent of making sure that people, to Dr. Carruthers' point, know the anatomy, know where to inject on our clinical trials. In terms of spontaneous or usual care setting, Belotero and Radiesse were associated with a notable decrease in serious or non-serious potential events subsequent to the 2015 label revisions and then Radiesse (+), again, we see very rare events with this product.

Next slide, please.

So we've talked a bit about our products, and what we wanted to demonstrate here is that risk management and mitigation is a continual process. You can see here on the left our R&D clinical trials, everything that we do with those, that leads into how we monitor our products on safety, which of course leads into post-marketing education which feeds back all the way back to our R&D. So this is a continual process and we really monitor this very robustly, as I know the FDA does and I know our other peers do, and this is something that we cannot underestimate at all. This has to be done at every stage of development and, of course, in the real-world post-marketing environment.

Next slide, please.

So we've talked a lot about the risks, risk mitigation, and we did want to speak a little bit about the benefits of noninvasive fillers. We know that patients, that the way they see the fillers, the way they see their response to the treatment is great. At the most, fillers like Belotero, the rejuvenation has demonstrated immeasurable events in social, occupational, and even aesthetic success, and that's really important to the patient, and I don't think we can detract from how the patients feel. And as much as we talked about clinical outcomes in our clinical trials, we at Merz think the PROs are equally, if not more, important because this is what is really being assessed by the patient on how they feel post-

treatment. And with Radiesse in particular, we've seen 12 months sustained improvement, which has led to huge patient satisfaction, as you can see here, in terms of being attractive, confident, would recommend to others.

Next slide, please.

So we acknowledge that patient perspective is critical and we also acknowledge that the filler patient population has evolved. We have very much age-diverse patients and this is reflected in our clinical trials. Not everybody, for example, have décolleté unless they're a certain age. But some patients are coming to us younger, you hear from our HCPs, because they want to start getting a different type of effect on the face, for example. So we're seeing more age-diverse and more treatment-naive patients coming to our clinics, increasing gender mix and different ethnicities.

What we're trying to do here is make sure that our clinical programs are representative of that and it's really important we do that. And we do that by getting feedback from our HCPs, we have a very big global KOL network, we include relevant patients across our clinical trials. And of course, we develop and include clinically relevant patient outcomes, which are critical. We also ensure informed decision making for our clinical trial patients as part of our informed consent procedure.

Next slide, please.

In addition to how we speak to our patients is also HCP training, which we highly focus on safety. We ensure our HCPs are trained on how to use our products and I think this is absolutely critical, I really do. I think clinical trial injection training is at the first and foremost of everything we want to do at Merz. We provide injection guides and of course, we have the Merz Institute of Advanced Aesthetics where people can get training, read literature articles, and we do a lot of work and investment into that area. Our medical affairs clinicians reactively conduct hands-on training with HCPs, and our medical science

liaisons provide publications on AE management.

Next slide, please.

So in conclusion, we feel that Merz filler products continue to have a favorable benefit-risk. The absence of intravascular SAEs in our clinical trials suggest that education and training are effective in managing these rare risks. Spontaneous data trending from U.S. reports pre- and post-2015 correlates to at least a 50% reduction in intravascular events of interest, and that we recognize that risk minimization is a continuous process and we really welcome a close relationship and collaboration with you at the FDA, our regulators, our peers in the industry, and of course, our HCPs and our patients.

Thank you very much for your attention today.

DR. LEWIS: Thank you, Ms. Kerr.

The following industry presentation will be from Teoxane. Patrick Trévidic will be presenting.

DR. TRÉVIDIC: Thank you very much. My name is Patrick Trévidic, I'm a plastic surgeon based in Paris and I'm the Chief Scientific Officer for Teoxane, and I would like to thank FDA for inviting us during this meeting. What is important is that the philosophy for Teoxane and for the medical education of Teoxane in terms of vascular compromise is first prevent, then to recognize, and at the end, to treat.

Next.

If we are looking to the publication, the first publication regarding an adverse event with hyaluronic acid and vascular compromise was in 2002, so long time ago. But we have now a lot of publication about the vascular compromise and we know that some areas are very dangerous, like the glabella area, the nose, the upper lip, and the nasolabial fold. And we have also a good knowledge of the anatomy of these arteries that could lead to vascular compromise in this dangerous area.

Next slide.

A very interesting publication has been done in 2016 showing that it's underestimated always because if you are looking to this publication from Goodman with 52 respondents from 16 countries, you see that 62% of these experienced injectors report an intravascular injection. And the sign of the vascular compromise is sometimes not always there, so to prevent is very important before you recognize and treat. But what is optimistic in this publication is that 80% being resolved within 14 days.

Next slide.

What is important for us is to understand what is the mechanism and because if we can understand the mechanism, we can understand the prevention or we can have the sign of vascular compromise and also to treat the vascular compromise.

Next slide.

If we are looking to all the literature review, all the publications right now, the good publications show that the vascular compromise is really to a filler embolism and there is only one article published, it's a case report showing that perhaps there is a compression on ultrasound after vascular compromise.

So what is also very important -- next slide -- is that we can't reproduce in our lab any compression on animals. Even with huge quantity of fillers, it's impossible to reproduce the compression. People say perhaps it's because it's sometimes we can be inert (ph.) prior -- after an operation.

Next slide.

But even after an operation, you have -- you fix the artery and so sometimes it's easy to enter inside.

So next slide.

The mechanism for us, of the vascular compromise is, as you can see, a needle enter

in a threshold artery at the lower of the dissection of the drawing, then going up and because of the size of the particle, block an angiosome and so the anastomosis also were closed and you get the vascular compromise with the sign that is sometimes not at the place where you get your treatments.

Next slide.

So to summarize, as you can see here, the mechanism in this very good publication in rats you see that you get, with the blood flow and HA clots, but immediately after, you get a block clot inside. And this is important because sometimes even the hyaluronidase will have no action because we know that there is also just after the HA clot, the blood clot.

Next slide.

And always when you introduce a foreign body inside an artery, you get an inflammatory response that decrease the diameter of the vessels and could create, even with small particles, a blockage, another reason because of the inflammatory response.

So next slide.

It's better to prevent and this is the philosophy of Teoxane.

Next slide.

And we get two options to prevent. We get the knowledge of the anatomy because sometimes your medical school is far away and so you have to refresh your anatomical knowledge and this is for us the safety, the anatomy, is for us the first goal of our medical education and then when you use your needle or your cannula, the technique is very important.

Next slide.

And for that we give guidelines during our training and medical education, injection guideline, because we know that there is no safe zone in the face area, I'm an anatomist, so I know there is no safe zone.

But next slide.

There is safe layers, it's totally different. The 3-D anatomy needs to be the first goal for the safety to understand that if you're in a dangerous area, but if you're also in a dangerous layer, then it would be better to use a cannula than a needle.

Next slide.

It's for that we give a lot of method of education called ATP. A is the anatomy, it's the first thing we educate our consumers, and the anatomy brings the safety. Then the technique and last, but not least, the product that you need to choose to have the best outcome you could have for your patient.

Next slide.

So the way to inject, because we see first the anatomy, that is, for us, the main point of the prevention, the second point of the prevention is the way to inject. Inject slow, inject small volume. You can press on the vascular path, it means you know where are the vessels, so this is very important, and also you pay attention to the feedback of the patient during your injection and you keep your patient for 10 to 15 minutes to see if anything happens after this injection.

Next slide.

So the question is always, "Do I need a needle or a cannula?" We know that needle are responsible of 83%, it's an average depending on the article of the vascular compromise. But the cannula also could -- you could have a vascular compromise with cannula, it's 70%. It's an average, it's not always the same, but it's to understand that the cannula are safer than the needle, but not at 100%.

Next slide.

It’s for that, we try to get some injection guideline each time, but the injection guideline are done by areas of injection. So it's for that we do such a lot of cadaver

dissection where our healthcare practitioners can do their injection with -- on a fresh cadaver to understand where are the layers and how they can be safer and safer by using the right technique.

Next slide.

There is a controversy regarding the aspiration, always the same question, "Do I need to aspirate, do I need not to aspirate?" If you aspirate, go on, but we know right now that we have a lot of article studies showing that only between 50 and 60% of the aspiration is positive, so it means that if you think by aspiration you can get to 100% safety, it's totally untrue.

Next slide.

HA, hyaluronic acid, as one antidote that is hyaluronidase. So to understand and to recognize and to treat, it must be an emergency and to be an emergency, you need to understand the sign of the vascular compromise.

Next slide.

And we know that it is an emergency and in some countries, the hyaluronidase, to get some hyaluronidase in your fridge, it's mandatory by law when you do your injection because the treatment of hyaluronidase needs to be an emergency because we know if we are after 24 hours, the reverse effect of the hyaluronidase is not so good.

Next slide.

So for us, we encourage our healthcare practitioners to recognize the sign of the vascular compromise during the education and we recommend to get the hyaluronidase in the fridge because if you have any doubts, that's easy on the treatment of the vascular compromise with the hyaluronic acid because the hyaluronic acid has its own antidote.

Next slide.

So for Teoxane, the knowledge of the anatomy and the education of the anatomy

and the layers of the face is very important. This is the key for us. To decrease the risk of vascular complication is to understand where are the dangers, in which layers, then to educate our healthcare practitioners with a good injection technique. This is what we do with our guidelines of injection and to inject slowly and minimum product but always to get the best outcome for our patients. And if we are in a dangerous layer, because we need to do this injection for outcome reason, then to use a cannula more than a needle. If you aspirate, go on, and the hyaluronidase is the startup care for vascular compromise with the hyaluronic acid.

Next slide.

Thank you very much and I hope that it will be useful.

DR. LEWIS: Thank you, Dr. Trévidic.

We now have an opportunity for clarifying questions from the Panel and I therefore throw it open for those questions. The chat function doesn't work very well, so if you have a question, raise your hand in front of the camera and I should be able to see that for most of you. Unfortunately, I can only see 25 people here out of the 51 who are attending, so if I don't respond to your raised hand, speak up and let me know because I obviously missed a few people prior to the break.

Questions. Ms. Brummert.

MS. BRUMMERT: One question I have that's been brought up in quite a few presentations where the hyaluronidase helps with vascular occlusion. So as the Consumer Representative, I do talk to a lot of patients who have been harmed by this and they're saying that this hyaluronidase is causing more problems than it is fixing it. So I was wondering what industry is taking into consideration when it comes to that, because my understanding is that it's a medication and it will go to a different reporting system, so like how do you know that it's actually helping an occlusion as opposed to causing more

problems?

DR. LEWIS: Could any of the industry representatives respond?

DR. TRÉVIDIC: Yes. If you have a vascular occlusion, the consequence of the vascular occlusion could be ischemic or this scar -- face information and sort of balance between the benefits and the risks because hyaluronidase, the risk is urgent. So if you're in an emergency and you put in the balance the benefit and the risk of hyaluronidase, the balance is always to the benefit. It means you have no other option to treat your patient and so the only thing that you have -- that this rate, the rate of -- with hyaluronidase is very, very low. This product has been used worldwide for a long, long time. It's been used for other medical indication. And so when you have in the balance the risk of the necrosis and the risk of -- with hyaluronidase, you do your hyaluronidase each time you get a vascular compromise and this is a recommendation of Teoxane.

MS. BRUMMERT: Okay, but do you -- I mean, do you communicate those risks to patients or is it just the doctor that gets the information, because patients are reporting that they are not getting this information.

DR. TRÉVIDIC: Yes. Patients, normally, they get the consent form, so it means each time you do treatments to patients, the hyaluronic acid or the hyaluronidase, they have to sign because you give information to the patient. But personally, when you are in front of the vascular compromise, and I get five during my -- during my practice, you convince your patients that it is the only treatment and to reverse the effect of -- they understand that the hyaluronidase can have -- it's the best treatment and so they accept you do that if you treat your patient. I'm clear?

MS. BRUMMERT: I mean, you're clear, but it doesn't make sense. I'll try to make sense of it and ask questions later.

DR. LEWIS: Further questions from the Panel.

Dr. Chang.

DR. CHANG: Yes. I would like to see if Dr. Carruthers is on and able to answer a quick question about the recommendation to do visual acuity testing before treatment, as she mentioned in her presentation. We were wondering if that recommendation is to do visual acuity testing before the dermal filler treatment or whether that is before any treatment for an intravascular injection event.

Dr. Carruthers, if you are able to answer, that would be wonderful. Thank you.

DR. CARRUTHERS: Thank you, Dr. Chang. Can you hear me?

DR. LEWIS: Yes.

DR. CARRUTHERS: Okay, thank you. Yes, I actually put it in there because I wanted -- I wanted to have this discussed. Absolutely, one of the problems with the successful treatments being reported in the literature today about visual recovery with hyaluronidase is that in the heat of the moment, the injecting physicians did not test visual acuity, they did not record relative afferent pupil defects. So there's a question of did they really get a result other than you have to believe the patient who says that their vision is back.

But from an academic ophthalmologic point of view, it's not good enough, we need visual acuity. So absolutely, if you're in the heat of the moment, everybody has to have a visual acuity, a small visual acuity chart or a magazine and record at what distance the patient saw this print and stick it in -- photograph it and put it in the e-record so you can actually make a calculation of the visual acuity and also doing relative afferent pupil testing. But I actually wanted to know what people thought. It's a rare condition, this, but it's such a serious one and it would be such a simple thing to get your staff to test visual acuity on the patients before they have their filler injection for the simple reason that (a) it's simple and easy to do, and (b) 2% of the population have asymmetric vision because of amblyopia, lazy eyes, from childhood. So this is something that could confound things from a legal

perspective, as well. I just put it out there because this is a wonderful opportunity to have this discussed. Thank you very much, Dr. Chang, for picking up on it.

DR. LEWIS: Other questions. Dr. Alam.

(Off microphone response.)

DR. LEWIS: You're muted, Dr. Alam. Unmute your microphone.

DR. ALAM: Sorry. Thank you, Dr. Lewis.

Two quick questions. One, do any of the presenters have incidence data? I know we've been talking about that a lot because they know how many vials they're producing and they're getting adverse event reports. Do any of them have incidence data from the U.S. regarding the risk of serious visual events? That's question one.

And the other question I have pertains to training. I think a lot of the presenters have spoken about training, but there's two issues, one is teaching people who might not know anything about anatomy, who might not be physicians, even, to understand the problems that can occur. And then the other is to build upon training that people like dermatologists and plastic surgeons already have to make them aware of specific issues, but that's built on a base of training. So my question is, do the presenters feel there is a very significant difference in the safety of injection by people who have a lot -- I would anticipate that's the case, who have a lot of anatomic understanding prior to injecting as versus someone who gets a 1 or 2-hour rapid lesson on all the facial anatomy and how are they managing that risk?

DR. LEWIS: Anyone feel free to address that.

DR. SILBERBERG: This is Mike Silberberg from Allergan.

I'll answer your first, your second question first and then your first question. So regarding training, absolutely. There is a difference between training somebody who has a foundation where they got it through academia, through societies or private courses versus

just getting it through a weekend course. The training that we provide at Allergan Medical Institute is comprehensive, but it's meant to be supplemental and complementary to a foundational training that injectors should have established.

In terms of the incidence rates, as we highlighted earlier without the denominators, it's very hard to get a rate. I can highlight that in the United States we have recorded in our post-marketing surveillance six cases of visual compromise and three cases of stroke.

DR. ALAM: Thank you.

DR. SILBERBERG: Thank you.

DR. KERR: Hi, Samantha Kerr here.

Similar to, I think, the conversation that preceded these presentations is that the knowledge of anatomy, how you inject, the way you inject, is absolutely critical for anyone, so as Michael said, I think that having a 2-hour training session is not sufficient at all. So I think all of us would say that training in any walk of life, actually, is critical. So we at Merz take this extremely seriously and we spend a lot of investment in training injectors. At Merz Institute of Advanced Training we put all of that.

In terms of incidence rate, unfortunately, we don't have the details that you're requesting, Dr. Alam. A lot of the spontaneous reports are very difficult to sift through. We can speak very well to the clinical trial data, but the real-world evidence is only as good as the information you get reported, unfortunately.

DR. ALAM: Thank you.

DR. LEWIS: Further questions. Dr. Bressler.

DR. BRESSLER: Yeah, I was just wondering if any of the training includes being sure that you have access to an ophthalmologist who might be able to promptly, within an hour or two, see the patient in case there was a vascular event. I don't expect the -- necessarily that the person doing the injection to know how to manage it unless it's someone in

oculoplastics.

And also, do you have them trained to check the vision by covering one eye at a time so that it's not checking bilateral vision, is that clarified in their instructions?

DR. KERR: So the different settings, the clinical trials as per our collaboration with FDA --

DR. BRESSLER: Oh, I meant -- I'm sorry. I meant training -- not in the clinical trials, I meant training of people --

DR. KERR: In the real world. Okay, thank you.

DR. BRESSLER: In the clinical setting, right, right, right.

DR. KERR: Absolutely. So at Merz we offer and encourage anatomical and injection training for anyone that wants it, so we offer that to all HCPs and encourage as much as we can.

When it comes to visual acuity, it's difficult to mandate things in the real-world setting for injectors in their clinics. They know what we do in clinical trials, a lot of our KOLs are involved in our clinical trials. So as Dr. Carruthers said, I think it's what we should be encouraging them to do is to look at visual acuity, but we can't mandate that ourselves, this industry, but it's something I think that is a very good practice to do.

DR. BRESSLER: No, but I meant when you do instruct it, do you tell them specifically that you check one eye at a time, because they may not notice loss in one eye with both eyes open. I didn't know if that was part of any training, in addition to training, how to do the injection, to train to look for the side effects. Yeah.

DR. KERR: I haven't trained anyone myself, but I think that's part of the normal ophthalmological assessment. The other thing we do is that we do recommend very strongly that our HCPs and injectors have access and a good partnership with a retinal expert or an ophthalmologist, it's really critical. Again, hopefully they do, but we can't

mandate that.

DR. BRESSLER: Thank you so much.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: Thank you very much, it's Alan Matarasso from New York.

I'd like to just drill down on some data that I think probably will be increased with the MDR that we don't have now. It was very clear by the industry presentations that I think they're doing an excellent job in mitigating risk. I know professional societies, I personally am part of ASPS, they have in-depth informed consents, dermal filler safety, CME modules, patient-facing websites, patient brochures, they recommend a crash -- in the office. So I think there's a lot of information out there.

What I'd like to drill down on is if the industry has any data for us because again, the MDR reporting doesn't have some of this, which may be helpful, if we can look at specifically where we're having issues. We use this term HCP. Is there one type of provider that we're seeing a greater incidence in, is there a setting that we're seeing a greater incidence in, you know, and that might be important, particularly with the ophthalmologic issues. You know, it's one thing for me, I'm in an eye hospital where I have eye doctors with me. If this is a clinic in someplace rural, they may not have access and as Jean pointed out, you have a very limited time frame to get to a specialist. So I'm wondering if industry which, again, I want to emphasize, has done an excellent job with their education and risk management, do they have any data on which HCPs are having issues or where it's being done?

DR. SILBERBERG: So I'll chime in here. Mike Silberberg from Allergan.

So as you heard earlier today from Dr. Carruthers, oftentimes the individuals who are the treaters are not necessarily the ones who have caused the complication. So we don't have that data based on the specific healthcare professional. But it's very important

to note that when these complications do occur, especially the serious ones, there is the opportunity to mitigate risk through training, but we have seen with -- in the very skilled hands, individuals who have the most serious complications. So it's not necessarily tied to a skill level. Training mitigates risk, but this is a rare occurrence but it can occur in the most skilled hands.

DR. MATARASSO: Mike, just to take it a step further on, do you know what percentage of the people that purchase the product actually take the training?

DR. SILBERBERG: I do not have that data available to me today. I can work on trying -- later.

DR. MATARASSO: I'm just trying to drill down on, you know, if we can get some more statistics on where -- what are high-risk situations or individuals or so on. Thank you.

Any of the other industry people have any comment? Samantha.

DR. KERR: Similar to --

DR. MATARASSO: Dr. Trévidic.

DR. KERR: Yeah, similar to what Michael said, we don't have that information about HCP or whatever the specialization is. We do know that there are certain -- and I think Dr. Carruthers covered this, certain areas that are more likely to have adverse events and problems, but again we don't really get -- the consumer reports, the spontaneous reports don't necessarily tell us who treated, it's more about who is actually, unfortunately, sort of like treating the patient.

DR. LEWIS: Dr. Trévidic, I have a question for you and the other industry representatives, but you spoke a bit about cannula use. Generally, when one has a safety problem and you consider addressing it either by modifying environmental factors or modifying human behavior, it always works much better to modify environmental factors. If you want to prevent traffic accidents, it's better to have a wide straight highway than to

tell people to drive safely.

Therefore, it occurs to me that an unexplored area here that would be extraordinarily productive is more investigation of the use of cannulas versus needles for the injection, because we've heard that many times needles are still used but a cannula, which is square-cut, made of plastic rather than a steel needle made of -- with a sharp bevel, is going to have a dramatically different likelihood of penetrating an artery and the variables that are needed in that are multiple: the diameter, the consistency, the type of material, etc., etc. And it doesn't sound as if there has really been intensive investigation into those possibilities. Have you all considered that? Because if that modification could dramatically reduce the issue of arterial penetration, it would be a remarkably direct way to deal with it.

DR. TRÉVIDIC: We know from the clinical studies that the cannula is safer than a needle. But sometimes when you do injection, how many injectors, I do that every week, you need to have a needle for some areas, some layers. For example, you can't put the cannula in the dermis, it's impossible. You have to use a needle for that. So for some indication, needles are still useful for the technique you will use. Cannula is safer, but it's not 100% safe. We thought at the beginning, cannula start in Europe, so we thought that the cannula was the future of all the injectors, all the injectors, but now we discover that the company who sell the cannula sell less and less 27 and 30-gauge cannula and more and more 25 and 22-gauge cannula because it's much safer to get cannula with a big diameter than with a small one that would enter in a vessel. So what we do during our education on fresh cadaver -- is to understand that with a large diameter cannula, you are safer but moreover, is to use this cannula where -- in a place where you need to do that for your technique and where there is a vessel and so it's much safer in this area to use a cannula, this is the indication. To put the cannula in 100% would not be possible because we know

that in some location or for some indication, needles are still the best tool to use for injection.

DR. LEWIS: Thank you.

Dr. Silberberg.

DR. SILBERBERG: Just to add something to what you just heard. Just to clarify, the cannula that we're using in aesthetics is a metal device, it's not a plastic device. It's blunt tipped, but it is a metal device. And as you heard, these do follow natural tissue planes, so there are certain areas where a needle would be essential, as demonstrated, putting it into the dermis because the cannula will follow a natural tissue plane. And it's important that, from a physician or a provider's perspective, that we preserve their ability to use the tools that they are more tactile at using and their choice.

It's important to note also that in our studies we have included the use of cannula and in the most recent studies with Voluma in the cheek and the chin, and so that does appear in our label with safety and effectiveness data in the study. Thank you.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: Just to expand on your important question, I think there's just -- for the understanding of those people that are not doing these injections, this is labeled as a dermal filler panel. These products are being used intra-dermally, which is just below the skin, which is where Michael just pointed out that a needle is absolutely necessary and they're also being used as volumizers and structural, to build up the jaw line, to build up the neck, where they're much deeper, where -- as Jean pointed out, the cannulas are important because that's where the vessels are.

So I just want to point that out, that I keep drilling down on where are we having the problems, is it with the G-prime, is it with who the injectors are? And the third point I want to make is the site. So we know this area is very dangerous, but being superficial here is

much different than being deep as Jean said, building up the Asian nose here because you're in a deeper plane. So knowing the site of the injection is going to be very important. Being intra-dermal in my fine lines here is not going to be problematic with a needle. Thank you.

DR. LEWIS: Does anyone have further comment on that point?

Dr. Jones.

DR. JONES: Let me add a couple of nuances to some of the answers, which have been very excellent. It is very difficult to get prospective data on the safeties of cannulas versus needles in the randomized controlled clinical trials that industry does because the end is way too small. These are very rare events, so it is near impossible to get prospective data on this, so the best tool that we have at this point is to do retrospective analysis using surveys and questionnaires.

We've heard of two good studies today, one done by Goodman et al. and the one that Dr. Alam mentioned, as well. And in my own clinical practice, I can tell you, having been injecting now for 25 years, that cannulas are indeed a much safer way to go.

One other thing that I would like to offer on a different note to Rachel's earlier question about things getting worse with high hyaluronidase, we have a number of patients, because we do use high hyaluronidase more often to take away unwanted filler, something where there's too much or for an aesthetic reason we want to reduce the amount. Dr. Alam has a nice paper in the literature --

(Audio feedback.)

DR. JONES: -- using small amounts. There seems to be a misperception out there among a lot of patients that the high hyaluronidase is somehow harming their skin in some way, that it is taking away their own collagen, pre-atrophy of their skin, doing something like that, whereas we really have no evidence to date that that is actually happening, we

certainly don't see it clinically. I think it's a good area for a future study.

DR. LEWIS: Thank you.

DR. MILLER: Dr. Lewis, Mike Miller here. I'm not sure you can see my hand, I just have a question, though, for the industry representatives.

Is there any way to -- or do you try to confirm training on the part of people you send material to, and recent training, because especially with something unusual like this, if you were trained 5 years ago and you've been doing this consistently, you may not see an event or be prepared to think about handling it if you haven't been recently trained, that's one concern I have.

The other concern is that it's been my observation that there are so many people doing these things, dentists and independent nurses, and I just wonder if there's any monitoring of who the product gets sent to and the quality of their training experience from the industry point of view.

DR. LEWIS: Anyone like to address that?

DR. SILBERBERG: Yeah, Mike Silberberg from Allergan.

So at Allergan we only provide products to licensed providers and that's guided by state licensing regulations, so in some states that will be a physician or it will be another provider guided by state law. Those are the only -- who have access and they do need to, when they establish an account with us, demonstrate that licensing, so it is verified before any product is sold. As part of the sale of our products, there is some online training which is more around indication and important safety information around a product which the individual must complete before they can open that account and get product, but it's not robust training around anatomy and it's included in terms of the indication but it should not be seen as a foundational training. That is where the societies, academia, and these other training courses play the most important role. Thank you.

DR. LEWIS: Thank you.

Are there further questions?

DR. BRYANT: Yes. Quick question for industry. LaMont Bryant.

How often do you evaluate your training and is there coordination between the various societies and the industry representatives -- your training models?

DR. LEWIS: Any of the industry representatives respond to that?

DR. TRÉVIDIC: Yes, we -- each time we do a medical indication, whatever the medical indication, meetings, training anatomy, training on the platform, we evaluate and we have the feedback, we -- evaluation each time. But the issue with that, we have the people in front of us or in front of computer, but we have also a lot of people that are never doing training and they do injection.

In some countries, for example in Europe, it's not allowed by law unless if you are a doctor to do injection and in other place in Europe, nurse or dentist can do injection, so it's more a question of -- after you can educate. But for example, for nurse, the training in anatomy, it's sometimes a little bit low so we have to educate them because we didn't decide, as manufacturer, who is allowed to do the injection. It's a question of regulation to authorize somebody to do an injection. It's not the provider who can do that. We can educate, but we can't go and we are -- we sell to the people who are authorized to provide the HA or the fillers, that's all.

DR. KERR: Similarly from Merz's perspective, we offer training for all new accounts, but we can't mandate it. And the other thing that we do is that we use our medical information department to continuously track medical inquiries to establish where the gaps could be because that's again real world. So then we can structure our training around that kind of evidence-based collection of data. So we do try to adapt our training based on what we hear from the HCPs and the real world.

DR. LEWIS: Thank you.

Dr. Brown.

(Off microphone response.)

DR. LEWIS: You're muted, Dr. Brown.

DR. BROWN: There we go.

Dr. Trévidic, you spoke a bit about the mechanism of action of the thrombosis and I wondered, you know, we've been presented information that says maybe up to 10% of the cases may have a delayed onset in terms of their visual events, maybe even 24 hours later. Is there any evidence that there can be slow, progressive thrombosis retrograde that could cause something like this, or is it perhaps that maybe the patients didn't have their vision checked after the procedure, didn't really realize that they have lost vision and then reported 24 hours or later? I just wondered what the thinking is on that issue.

DR. TRÉVIDIC: It's really a good question because in this case you don't know if you missed the first sign. For example, for vascular compromise, the first time is pain and it's the skin that is whitening, but because you have your light bulb and you do your injection, you don't see always, you know, the whitening of the skin so you let your patient go away and you have to leave it open.

Perhaps that's the same for the visual acuity and that's -- in all the review we did about blindness, the case of delayed blindness was very rare and it's more in the next hours, in the next minutes of the injection that you get the sign. But to answer to your question, we don't have any data regarding how much delay and how much immediate, you know, we have and it could be 24 hours after. But in my point of view, we have the sign at the beginning, but we -- the patient is going away and it's up to -- needs the day after or 12 or 16 hours after because they saw the skin is changing, the color is changing or the vision is changing, so they call the doctors and sometimes it's late and sometimes they can't reach

the doctors on the day after, so for that we have a delay regarding the sign and the treatment, so that the prevention is very important for us.

DR. BROWN: Thank you.

DR. LEWIS: Further questions.

DR. SILBERBERG: It's Mike.

DR. LEWIS: Yes, Mike. Go ahead.

DR. SILBERBERG: I was just going to add to what was just stated is that the signs and symptoms of visual compromise are not subtle. When they happen, they're quite acute, quite dramatic. Usually accompanied, as you heard earlier today, by headache, dizziness, nausea, vomiting, pain, a number of different symptoms.

So in terms of a necrosis or an impending necrosis from ischemia, yes, you might miss it in clinic. If there's a delay in terms of a visual compromise, the presumed pathophysiology issue you heard earlier today from Dr. Carruthers is that the gel or the -- needs to embolize and in order to create a cause, it has to go into end artery circulation, so it's potentially possible that some gel has not fully embolized and over that period of time it would then get into the end artery circulation, but then it would be an acute onset at that point.

DR. LEWIS: Thank you.

Dr. Miller, do you have a question?

DR. MILLER: No. Maybe I didn't put my hand down.

DR. LEWIS: Okay. Dr. Alam.

DR. ALAM: Yeah, I just wanted to address a question to Dr. Jones. I know that Dr. Jones has been involved with guidelines with the ASDS for treatment of and prevention of visual impairment, so I wanted to ask him a very directed question. Is there anything that we haven't discussed today as a potential prevention or treatment for vision loss that

his guidelines group would recommend that we consider?

DR. JONES: Thank you for the question, Dr. Alam. I think we've done a very thorough job today covering most of the elements that work and are evidence-based guidelines that were produced by the ASDS multidisciplinary task force. The biggest issue, as far as I'm concerned, is that of training and anatomical knowledge. I think that there is a certain lack of anatomical knowledge, particularly the plane in which an artery may reside in a high-risk location. I think that perhaps we could do a better job at teaching all injectors on anatomy and as we said before, there is plenty of literature out there and industry is doing a very good job at presenting this information, but I think that is the biggest issue, is good training.

DR. ALAM: Thank you.

DR. LEWIS: I guess, Dr. Jones, as we've already heard, the difficulty of that is that there's no enforcement mechanism for that at the level of application in terms of who has been trained, so it would have to be voluntary on the part of the person doing the injection.

Further questions. If anyone has a question that I'm not calling on it's because I can't see you on my screen, so speak up if that's the case.

Dr. Burke.

DR. BURKE: Thank you. This has been a really interesting session. Dr. Karen Burke from Mt. Sinai Medical Center in New York.

One, I have fortunately never had an ischemic event and I just usually use very small volumes superficially, but I have participated as a consultant for several litigations and in these particular litigations, the difficulty was usually using very large volumes, I would say inappropriate volumes in certain sites, so one variable that's kind of never really reported is the volume per site. I mean, we have to be especially very careful, we learned early with the Zyderm experience, of using small volumes especially in the glabellar area, and I think

the nasal occlusions have risen just because of the use, particularly in Asians, for that aesthetic correction. So if there were some way to monitor this in the future, it would be very interesting and I only today kind of realize the full difficulty because the people reporting the adverse reactions are not the people that -- are not the physicians who did the treatment, usually. So that's the first thing.

And the second thing I might suggest, I mean, we saw the data that when the patient brochure was updated that there were far fewer kinds of complications and I just wonder if just like we all take our infectious disease tests and our painkiller tests and our HIPAA tests every year. And I wonder if the companies might consider having a kind of certification that people should watch a short video, it doesn't have to be 4 hours, it could be less than a half hour, but that everyone has to watch a video and answer 10 questions about the video and receive a certificate every, let's say, 3 years in order to keep purchasing the material.

And of course, this doesn't fully regulate the fact that the physician purchasing the material might not be the person injecting the material but, I mean, the companies could, perhaps, say that everyone injecting the material within the physician's office should watch the video and answer a limited number of questions.

DR. LEWIS: Do any of the industry representatives want to comment?

DR. SILBERBERG: Yeah, Mike Silberberg from Allergan.

I would like to comment on the first part, which is around volume, and I think it's important that we separate out extravascular compression versus intravascular injection. So absolutely, ischemia through extravascular compression can occur by having larger volumes, especially in a contained skin envelope like the nose. You do need to use very judicious volumes if you're going to be injecting the nose, especially in the tip. As far as intravascular volume, injecting intravascularly, the smallest volume can cause the most serious risks that we're talking about today. So it's not necessarily correlated to a larger

volume, it correlates to the fact that the implement is in the vessel and if you're using -- typically, also when you're using a needle where there sometimes is an advantage to a needle is if you're constantly moving the needle, even if you're in the vessel, you will move through the vessel or skewer it and get outside of the vessel, whereas if you enter with a cannula, you will stay in the vessel, so the volume is not necessarily related.

In terms of the second part of the question, which is around having some sort of training certification, we do, as I stated earlier, are guided by regulation and obviously, if the Panel today makes some determination that this is a path they want to go, of course we would work with the FDA in implementing anything along that, that regard. Thank you.

DR. BURKE: Thank you.

DR. LEWIS: Thank you.

DR. KERR: It's Samantha here.

I think that -- yes, I think we've discussed training is utmost paramount, but I think the issue we have is, to your point, and having the training video and the set of questions, I think the point is if people could get it anyway and it's not mandatory, it's not so much industry, I feel the issue we have here is how do we control that and how do we monitor effectiveness. That, I think, is the issue that we need to discuss, as an industry and a regulator, is how do you actually monitor for that. If they got six out of 10 questions right, do we then -- you know, it's what are the thresholds and if they can get hold of the product anyway, what does that bring to the table. So I think it's a really good point but it's how we enforce that or how we monitor that would be my question.

DR. LEWIS: Thank you.

Seeing no further questions, I will declare this session at an end and we will adjourn for lunch. We will reconvene at 12:40 sharp for the remaining sessions and we'll begin at that time with the Open Public Hearing. Thank you.

(Whereupon, at 11:56 a.m. 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. LEWIS: Okay, this is Frank Lewis chairing this session and I call us back into session. We'll now begin 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.

Commander Garcia will now read the Open Public Hearing Disclosure Process Statement.

Patricio.

CDR GARCIA: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency during this 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. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Thank you.

DR. LEWIS: Today we have eight public hearing speakers and we will begin with Dr. George Hruza, who is representing the American Academy of Dermatology.

Dr. Hruza.

DR. HRUZA: Thank you very much. Good afternoon, I'm George Hruza, the immediate past president of the American Academy of Dermatology Association, or AADA, and an adjunct professor of dermatology at St. Louis University. I have no conflicts of interest to disclose.

Thank you for the opportunity to speak before this distinguished committee. I speak on behalf of the AADA and represent nearly 16,500 dermatologists in the U.S. Dermatology is the leading specialty for the provision of minimally invasive cosmetic procedures including fillers.

All fillers are associated with a risk of both short and long-term complications. Most significant is vascular occlusion, which can develop up to 72 hours after injection and is a potential condition that causes ulcerations, scarring, and most seriously, visual disturbance and permanent blindness. Another serious complication is the development of nodules weeks to months after filler injection that may last for many months and are often highly distressing to the patient.

When administered in a professional setting, adverse events are rare. Patients receiving filler injections should be educated about common and especially serious adverse events such as nodules, vascular occlusion, and the remote possibility of blindness. Patients must be instructed to seek immediate medical attention if they develop symptoms of impending vascular occlusion, such as tissue blanching, severe pain, and visual disturbance, as intervention to reverse or mitigate these complications must be done in a matter of hours for vascular occlusion and within less than an hour in the case of visual disturbance.

The severe complication rates can be mitigated by detailed knowledge of facial vascular anatomy, correct patient selection, and proper technique. In addition, the physician should have in place detailed protocols to deal with a vascular occlusion emergency with all needed supplies and medications available on a moment's notice.

In view of the potential risks of filler injections, the AADA strongly believes that filler injection should be performed only by appropriately trained physicians or non-physician personnel under the direct on-site supervision of a physician. Only a physician has the training and experience to minimize the risk of severe complications, identify impending complications, and manage them effectively. For the safety of the public, do-it-yourself administration of fillers by laypersons or by non-physician providers without direct physician supervision should not be permitted.

Thank you very much.

DR. LEWIS: Thank you, Dr. Hruza.

We will now hear from Dr. Matt Avram, who represents the American Society for Dermatologic Surgery.

DR. AVRAM: Thank you for having me. I do serve as a consultant to Allergan.

Next slide, please.

So the slides are going to be cut back a little bit because a lot of this has been presented previously. We have 7,000 current members. In the last year, 1.6 million dermal filler procedures were performed by our membership, which is an increase of 78% over the past 8 years.

Next slide, please. Next slide, please.

So one of the keys is the knowledge of vascular anatomy in terms of knowing where we can have complications because it can happen anywhere on the face and the key to know this is to know which locations are those which are at the highest risk.

Next slide, please.

With that in mind, the ASDS has a task force that has looked at adverse events and guidelines with regard to dermal filler procedures and that has been presented several times this morning. In addition to that, we have developed the Cutaneous Procedures

Adverse Events Reporting registry in association with Northwestern University Department of Dermatology. The idea is that we think that these events are underreported and we will be reporting dermatologic surgery complications, including those with dermal fillers.

Next slide.

Now, we know that those can -- next slide, please. Next slide.

These are just the -- some of the guidelines that we've presented that have been previously shown.

Next slide. Next slide.

So one of the things we've done more recently is with respect to the Moderna FDA trial. There were instances of facial and lip swelling in conjunction with the Moderna vaccine and that's something we've developed guidelines for that have been written and published and we've made a major purpose of communicating that to our membership as well as the public, as well, to have that information available.

Next slide.

We also alerted the FDA as to an alarming trend having to do with children doing social media presentations of Hyaluron Pens, injecting themselves with these Hyaluron Pens as for filler treatments, in addition to the fact that there were adults doing this with actual syringes.

Next slide, please.

So the ASDS pledges its help to the FDA making sure fillers are safely given to patients and stay in the hands of physicians who, on site, can properly supervise other medical personnel.

And then respectfully, we would ask that the Panel may be named General, Plastic and Dermatologic Surgery Advisory Committee to reflect board certified dermatologists' contributions and expertise in these areas.

Next slide.

Thank you.

DR. LEWIS: Thank you, Dr. Avram.

We'll next hear from Dr. John Fezza, who represents the American Society of Ophthalmic Plastic and Reconstructive Surgery and the American Academy of Ophthalmology.

DR. FEZZA: This is Dr. John Fezza and I'd like to thank the FDA for the opportunity to present today on behalf of ASOPRS and the AAO. Foremost, we'd like to acknowledge that dermal filler injections are generally safe and effective for facial enhancement with a high patient satisfaction.

Patients have a variety of filler options based on brand, cost, filler properties, loyalty programs, and indications, and there's a continually increasing choice of dermal fillers available with specific FDA label approvals.

Practitioners use their judgment in product placement, as FDA indications may not be applicable to all patient scenarios. For example, fillers are often used off label in many adjacent facial areas based on desired outcomes, treatment goals, convenience, and cost control without compromising safety or efficacy. Many of these off-label areas are awaiting FDA approval, such as the tear trough treatment for infraorbital hollows.

Adverse events are rare, but side effects and complications are possible. Most side effects of dermal filler agents are transient and minor. Hyaluronic acid fillers can be reversed with the enzyme hyaluronidase. More serious and uncommon adverse events of dermal filler injections include delayed nodules and intravascular injection. Inadvertent vascular injection can cause vessel occlusion and ischemia. This can result in very rare events such as tissue necrosis, blindness, or even stroke.

Certain facial areas pose a higher risk for vascular events. The risk of ischemic

events is highest in the forehead, temple, glabella, nasal dorsum, tear trough, and lip. Regions with large vessels may pose additional risk. A keen knowledge of facial anatomy and attention to proper injection technique is paramount when injecting these areas. An informed consent outlining possible adverse events is critical. It is important that patients be advised of the serious and the less serious complications prior to deciding to proceed with filler injections so they can make a proper decision.

Filler can be injected with either needle or cannula at the discretion of the injector, and skilled injectors can achieve safe results with either device. In order to mitigate intravascular events, recommendations such as aspiration, slow injection speed, use of a larger blunt cannula, attention to tissue response, and closely monitoring patient signs for excessive pain may be helpful to clinicians.

Lastly, ASOPRS's members and many ophthalmologists are familiar with complications in the periocular area and are available to consult with colleagues when issues after dermal filler injections occur. Potential benefits for the treatment of intravascular adverse events in the periorbital region have been supported by both experimental studies and anecdotal evidence. Ophthalmologists have unique specialty training and equipment that may be useful in treating such rare events as tissue necrosis and potentially restoring compromised vision.

References are provided. And thank you.

Frank, I'd like to also acknowledge that I'm a speaker and consultant for Allergan and also for Revance Therapeutics. Thank you.

(Pause.)

DR. LEWIS: Sorry, I wasn't paying attention to the mute. We will now hear from Dr. Paul Carniol, who represents the American Academy of Facial Plastic and Reconstructive Surgery.

DR. CARNIOL: Good afternoon. I'm Dr. Paul Carniol, I'm president of the American Academy of Facial Plastic and Reconstructive Surgery, and I'm asking -- thank everybody for their attention today. I've listened to prior presentations and so some of this will be redundant, but the slides and presentation were prepared a week ago, so we will go through this.

The American Academy of Facial Plastic and Reconstructive Surgery is 2200 members. Our members have all completed a 5-year residency and super specialize in facial plastic surgery. Many of them also have additional facial plastic surgery fellowships.

Soft tissue fillers, as we've heard already, are certainly on the increase, there's been huge growth in the amount of fillers done, and there are more people doing injections and very high patient satisfaction.

Okay, when we talk about fillers, we talk about what are the adverse events related to fillers and we discussed those already. Vascular occlusion has been reported to occur as often as 1 in 5000 cases, but most of the time not with significant sequelae.

Dr. Murad Alam and his associates did a 10-year retrospective review published in 2020. They reviewed 1.7 million syringes of filler that had been injected, and there were 370 dermatologists who reported in this review and they're the ones who found 1 in 5000 injections had a related vascular occlusion. Importantly, 85% of these vascular occlusion episodes resolved without any sequelae.

Vascular occlusion with associated vision loss is the biggest concern that we have, and 48 cases reported worldwide in a study that included Dr. Beleznay and Dr. Carruthers, and out of 48 cases over a 3-year period, only six of these cases were in the United States. Interestingly, you have to look at the anatomy of where these occurred. So 56% of these occurred in the nose, 27% in the glabella, 18% in the forehead, and 14% in the nasolabial folds, and although not reported, I would speculate that it was in the superior portion of

nasal folds, nasolabial folds, up-righting (ph.) angular vessels.

To minimize the incidence of adverse events, it is really important that anybody doing injections have a detailed knowledge of facial anatomy, vasculature, have detailed training and education -- experience has proven to be a big help -- and that people who have injected over a 5-year period have a 70% less chance of having a significant adverse event. They should use techniques to minimize vascular occlusion, some of which are (1) avoid high-pressure injection; (2) minimal pressure; (3) avoid arterial vasculature, which is sort of self-evident; and finally, you get into the controversy of whether aspiration before injection helps, the issue being that you can put a needle in a vessel, aspirate, not get a return of blood and still be in the vessel. Limited-volume injection is also important because we speculate, although we don't have hard evidence, that besides intravascular injection you get occlusion of vessels by external pressure. Very important as it is for other injections is to move the needle or cannula, if you choose to use one, during the injection.

It's been recommended by Dr. Beleznay and Dr. Carruthers and others to avoid the subcutaneous vasculature when you're injecting, to either go superficial where you're in the dermal vessels or deep, close to the underlying osseous structures. People discuss and debate over whether or not to use a cannula. If you do, it should be 25 gauge or larger because of the lower incidence of arterial cannulation with smaller cannulas, and there are many physicians who use only needles, who have not had problems with adverse events.

Possible ocular vascular occlusion is a major complication and one we're all concerned about. It demands urgent treatment, so for that reason we recommend only having these procedures performed by people who are ready and prepared to deal with this event, were it to occur.

Retrobulbar injection is controversial. There are papers in front of it -- in favor of it and papers against it. We do recommend recombinant human hyaluronidase injection, and

it's been found that injection into the supraorbital and supratrochlear notch region where those arteries are is effective and seems to be helpful. Other methods are listed, and I don't have to detail them, but they're all important. Other possible treatments are also listed and there is still some controversy about these.

In summary, and I thank you again for listening, most of the adverse events with filler injection are minor or to major adverse events, vascular occlusion. Most episodes resolve uneventfully, but vision loss is the most concerning. There's a variable response to treatment and risk of permanent visual loss. For that reason, we recommend it be done by people who are prepared to treat this and have recombinant human hyaluronidase on hand, know how to inject it, and are ready to treat with it. And it's important for fillers only to be used by well-trained, well-knowledgeable healthcare providers.

I'm available for questions, and I thank you for listening to this presentation.

DR. LEWIS: Thank you.

We'll next hear from Dr. Steven Weiner.

DR. WEINER: This is Dr. Steven Weiner, a facial plastic surgeon from Florida.

Next slide.

Dermal fillers have both early and late onset complications. The most important of these are vascular occlusion, necrosis, and blindness.

Next slide.

Vascular occlusion occurs when filler is injected within a vessel and then it spreads throughout the face via embolic phenomena. One in every 6,000 syringes injected leads to a vascular occlusion. If an injector has greater than 5 years of experience, he or she is 70% less likely to cause vascular occlusion. If the injection is done with cannula, there's a 77% less likely occurrence of vascular occlusion when compared to needle injections of filler. Eye injuries occur one in every 500,000 injections.

Next slide.

Filler-associated blindness is unfortunately increasing. This is because we are injecting in higher-risk areas, there are more injections, and there are less knowledgeable and less experienced injectors. Twenty percent of these completely recover and 16% partially recover. Reversibility is difficult and controversial.

The current protocols for treating vascular occlusion due to HA filler are large doses of hyaluronidase injected into the areas of suspected vascular occlusion. This requires multiple injections over several hours. Unfortunately, the endpoint is very difficult to assess.

Next slide.

High-frequency ultrasound is able to identify the areas of vascular occlusion very well, and identify the pocket of the offending hyaluronic acid. Under ultrasound guidance, the hyaluronic acid pocket can be targeted using the hyaluronidase, and reestablishment of flow can be rapidly identified using the ultrasound.

Next slide.

Hyaluronidase is unfortunately not approved for dissolving HA filler. Consequently, none of the filler companies can discuss treating complications with hyaluronidase. If hyaluronidase was approved for this treatment, there could be training and education in filler complications. Ultimately, there will be better outcomes for our patients.

My proposed improvements are improved training including cadaver lab dissection; improve the standards, there are currently no national standards for injectors. There are only a few cannula indications for fillers and I would consider broadening the approvals for all fillers using cannulas. I would recommend injectors incorporate high-frequency duplex ultrasound for patient assessment and treating complications.

Thank you.

DR. LEWIS: Thank you, Dr. Weiner.

Next, we'll hear from Dr. Will Kirby.

DR. KIRBY: My name is Dr. Will Kirby and I am a board certified dermatologist. I'm also an associate clinical professor of dermatology and my areas of expertise are aesthetic injectables, like fillers, and aesthetic energy based devices. I'm coming to you today from ground zero of aesthetics, Los Angeles, California. Just a little levity for you there, but the truth is, we are the epicenter of aesthetics.

Now, today some of my dermatology colleagues may be speaking to you under the auspices of advocacy. I think we need to raise an eyebrow every time we hear the word advocacy today because I can't help but note that dermatology advocacy has traditionally represented the suppression of RNs, NPs, and PAs, registered nurses, nurse practitioners, and physician assistants. More so is that advocacy often results in financial gains for dermatologists. On top of all of that, much of the data in the publications indicating that physicians have a safer track record than non-physicians when it comes to filler injections isn't objective or scientifically sound, and those publications are funded by the dermatological societies. The simple truth is that the vast, vast majority of filler injections in the United States are administered safely and effectively by non-physicians. I simply want to make sure that all clinicians are fairly represented in this forum and have a voice. With nearly 15 years of experience working extremely closely with RNs, NPs, PAs, as well as dermatologists, it's my contention that I'm uniquely qualified to be part of this discussion.

Now, we can all agree that transparency, integrity, and rectitude have a seat at the table. That's why I wanted to make sure I was available to you. I'm purposely keeping my comments brief because it's my belief that the best way I can assist this Panel is by addressing any questions or concerns that you have. Again, if you hear the word advocacy today, please raise an eyebrow and be a little more discerning with your questions to that

individual. But I conclude my statement and I simply want to ask you all one last thing: How can I best serve you? Again, my name is Dr. Will Kirby, I am a board certified dermatologist and I am at your service.

DR. LEWIS: Thank you, Dr. Kirby.

We'll next hear from Dr. Christopher Surek, who represents the Aesthetic Society.

DR. SUREK: Hello, my name is Dr. Chris Surek, board certified plastic surgeon and member of the Aesthetic Society. Our objective in this short presentation today is to discuss the importance of anatomy and education to help improve safety and efficacy of dermal filler use in the U.S.

These are my credentials. I speak, teach, consult, and publish on facial injections.

Based on our society's statistics, over 3.4 million dermal filler injections were performed in the United States alone last year. Now, who's performing these injections? Forty-five percent were the plastic surgeon themselves and the other 55% were physician extenders, whether that be a nurse practitioner, doctor/nursing practice, RN or PA. It's important to recognize this is a big component of a lot of practices, is having physician extenders; however, these extenders are under the guidance and supervision of the plastic surgeon and our society.

Now, what is being injected? And this is a key thing to understand. Based on our statistics, over 94% of the products are hyaluronic acid based, meaning they can be reversed with hyaluronidase. Additionally, in that final 6%, half of that, which is Radiesse, 3.18%, is also 70% gel carrier. We believe the utilization of reversible products does help increase the safety and efficacy profile for this high-volume procedure performed in the United States. Most importantly though, we have to be properly educated on the three-dimensional architecture and anatomy of the face. This allows the injector to navigate to their target while avoiding unwanted interactions with vessels and lymphatics.

This is an example of an anatomy slide that I utilize to teach anatomy to our colleagues and fellow injectors. It's important to recognize the face has layers that include fat compartments, potential spaces, ligneous anatomy, a fascia that wraps around the muscles called the SMAS, as well as all of these structures enhance surface topography and alter as we age. Understanding this is critical for education.

Additionally, in our society we put a lot of emphasis on peer-reviewed research and education. In our key journals from the society, we have had 44 peer-reviewed publications just in the last 2 years alone. Additionally, the society, over the past 22 years, has had over 30 events committed to injection training, 285 hours of dedicated injection content training, as well as an injectable safety handbook on our online resource. All of this is important for education.

Here is a bibliography of some of those articles, including ones looking at outcomes as well as injection technique, as well as product science, patient assessment, and anatomy and all of the important components of injection safety education.

So in summary, this procedure can be performed safely and is performed in high volumes in the United States. The use of reversal product does increase the safety profile but, most importantly, anatomy and education are critical, just like any other procedure; consistent recurring education, a strong understanding of the products used, proper supervision, implementation of safety protocols, dedicated peer-reviewed research, and most importantly, proper informed consent for our patients.

Thank you.

DR. LEWIS: Thank you.

We'll now hear from Dr. Brian Biesman.

DR. BIESMAN: Good afternoon, everyone. If we could please advance the slide.

I am an oculoplastic surgeon here in Nashville, Tennessee. I have been performing

filler trials for many years and wanted to talk to you a little bit today about visual safety assessments. Visual assessments are part of all the trials. I'm not going to recapitulate everything you heard already today. One important note that I'd like to make is that if a visual event is to occur, it is sudden; and visual loss is dramatic, it's to the level of no light perception, maybe bare light perception, which means you can see the light but that's all you can see, maybe you can see someone's hand move, but that's it. So it's not a one or two-line movement on an eye chart, it's dramatic and it's sudden.

Next slide, please.

There are a number of other signs that occur during an event. When an event occurs, we assess for these different signs and again, these have been talked of earlier, and the current protocols do account for looking for these other changes.

Let's go to the next slide, please.

Now, as I've commented, I've performed a number of trials over the years and I commend FDA on having visual safety requirements for these trials, recognizing that safety of patients and the public is of paramount importance, but there is a wide degree of variability amongst the requirements and this is specifically what I would like to address.

Next slide, please.

So the protocol that I feel really is optimal is one which assesses visual acuity, extraocular movements, and confrontation visual fields. If you assess for those three items, you'll be able to detect whether or not IRVC has occurred. In the trials in which I've participated, additional requirements have included waiting 30 minutes between sides of the face, waiting 30 minutes between sides of the face and adding fundoscopic examination, and even taking fundoscopic photographs with a special camera, sending the photos off to a reading center and waiting to get results back.

Next slide, please.

I'd like to recommend that we have standardized visual safety assessments across all soft tissue facial filler trials, which include visual acuity testing, confrontation visual field testing, and extraocular movement testing. These are simple, straightforward tests to perform and this is very important because we have a window of about 30 minutes to reverse visual changes, if they're going to occur, to try to save vision. If we spend some of that time doing additional procedures such as fundoscopic examinations and taking photographs and so forth, that really aren't needed to make the diagnosis, that can come at the expense of patient safety.

Next slide, please.

In addition, I would like to recommend that we continue to require these visual safety assessments for all facial soft tissue filler trials, not just HA fillers, but all fillers, but that there not be a requirement for visual safety assessments for injectable studies performed in the neck or below the neck because there's just no data or anatomic work to support this.

And finally, I'd like to thank the FDA for the opportunity to engage, and encourage FDA to continue to engage with us experts so we can come up with protocols that make good sense and help us protect not only our subjects in the trials, but the public as a whole.

Thank you again for the opportunity to address the Committee today.

DR. LEWIS: Thank you, Dr. Biesman.

That completes the presentations, and I thank the speakers for their presentations. We will now open the session to questions from the Panel for the previous speakers. Anyone who has a question, please raise your hand and we ask everyone to -- most of you have your videos turned off, so I can't see your hand, so please turn your videos on so we know who is interested in asking questions.

Dr. Bressler.

DR. BRESSLER: Thank you. And thank you to the speakers.

I'd like to address this to Dr. Biesman, if possible, just a clarification. I think towards the end, the recommendation was to consider in the trials checking visual acuity, but I think you also alluded to that these are massive events on vision, that is, to the point of count fingers or hand motion. So did you really mean visual acuity like on a chart or you just meant to check the person's vision? And I would also want to confirm, I assume that's in one eye at a time.

DR. BIESMAN: Yeah. So thank you for the question and I appreciate the opportunity to clarify. Again, I'm trained in ophthalmology. In ophthalmology, when we refer to taking visual acuity, that means assessing someone's vision. It must be done in a unilateral manner; we occlude the other eye and the patient visual acuity could range from no light perception where they can't see anything to 20/20. So we start by saying can you -- usually after I inject someone in a trial, can you see my fingers, that's the first thing. If they can see the fingers, then great. Can you read the eye chart? And we go from there. If they can't see your fingers, then you go to your hand motions and your light perception, but that's all considered part of visual acuity.

DR. BRESSLER: Thank you.

DR. LEWIS: Dr. Alam.

DR. ALAM: Thank you, Dr. Lewis. I have two questions, one for Dr. Biesman again.

Sir, there was an issue that came up earlier with Dr. Carruthers, I think FDA directed a question to her pertaining to whether we should do visual testing in all comers, anyone getting a filler, or whether we should restrict this primarily for people who had an adverse event and then test them right when the event is being detected and after treatment has occurred to see if treatment is therapeutic. So the question for you is do you feel this should be done in every filler patient or should it be really localized just to people who have

had a problem?

DR. BIESMAN: And I'm sorry, Dr. Alam, to understand the question, is the question should all patients enrolled in facial soft tissue filler trials have visual acuity assessment?

DR. ALAM: It's an even broader question, sir, it's should all patients who are getting a filler injected, even in a clinical setting outside of a trial, be looked at in terms of what their vision is at baseline before they get the filler or should we either do it just in trials or should we do it just in an instance where there's been a problem either in a clinical setting or in a trial?

DR. BIESMAN: It is my practice. In my clinical practice -- well, we do check everyone's vision prior to injection because there's a lot of people walking around out there who, for various reasons, have poor vision in one eye and a lot of them don't necessarily know it. There's lots of reasons to have poor vision in one eye. In my practice, we do check vision in everyone who's going to have soft tissue fillers.

DR. ALAM: And as a follow-up question, do you feel this would be practical? Obviously, you have special training in the eye, as does Dr. Carruthers, but there are other trained professionals who use fillers who are not ophthalmologists or oculoplastic surgeons. Do you feel that you would want everyone to be checking some kind of vision, performing some kind of visual acuity testing? And if so, what would you recommend for the general group of physicians?

DR. BIESMAN: You're asking me a challenging policy question, Dr. Alam. I think that it is a good idea to do baseline assessments, there's a variety of ways you can do that from near cards, which are very inexpensive, to just looking at a magazine or a newspaper. It doesn't have to be as formal as having a 20-foot lane and an eye chart, which no one's going to have, but to get some type of baseline documentation, I think, helps protect providers, from a liability standpoint. They're also identifying issues that patients may not know they

have.

DR. ALAM: Thank you very much.

And if I could also ask a question to Dr. Avram. I think at the end of your talk, Dr. Avram, and this might be off topic, you recommended making a change to this Panel and adding dermatologists to it. Do you want to expand on that a little bit? What was that, your suggestion?

DR. AVRAM: Yeah, I just -- you know, so we have a great group of different specialties here and dermatologic surgeons have contributed a lot to developing these procedures and looking at the safety of these procedures, and we've all worked very collaboratively. And in fact, the guidelines that have been referred to repeatedly at this session actually are not -- they are from the ASDS, but it represents multiple specialties. So just respectfully request that if dermatology could be reflected or dermatologic surgery could be reflected in that, as well.

DR. ALAM: Thank you.

DR. LEWIS: Further questions for the speakers?

(No response.)

DR. LEWIS: I have a question for Dr. Kirby. In your presentation you made a case for having other practitioners and physicians and plastic surgeons able to do the injections. You didn't speak to educational requirements beyond the basic training for nursing or whatever their specialty is, and you didn't speak to the issue of immediate supervision. Could you address those and give us your point of view on that?

DR. KIRBY: Yes, absolutely. Thank you for the question.

I, of course, am a huge advocate of education. As I noted, I'm an associate clinical professor of dermatology and I believe in quality amongst educational pathways. So again, it's M.D., D.O., RN, PA and NP, and everyone with the proper training, education, and

supervision can perform filler safely. Again, if you look at the statistics, it is verified in the data. So how that education should be quantified, well, I mean, that's not necessarily the topic for today's discussion, but I'm happy to get into that in detail at any other time and any other forum. It really just depends on how much time you have.

Would you like me to go into depth, Mr. (sic) Lewis?

DR. LEWIS: No, I think that's not necessary here. Thank you.

DR. KIRBY: Okay.

DR. LEWIS: Dr. Avram.

DR. AVRAM: Yes, I just wanted to speak briefly on that point. I was an attorney before I was a physician and we've done studies looking at legal databases with regard to not fillers, but with energy based device procedures. These have been published in *JAMA Dermatology*, our leading journal, and another one is coming up for publication.

There is a clear trend towards more injury in aesthetic procedures; this is energy based devices, not fillers, as they are performed by non-physicians, particularly in settings where there is not direct supervision. So that's something that there's clear data on, it was published in 2014 and it's being published again now and listening today, I think it's very important to know that we do have data on that. And I know that that's not really the topic of today's discussion, it's more about dermal filler safety, but I think it's important for the record to reflect the actual data.

DR. KIRBY: May I retort, Mr. Lewis?

DR. LEWIS: Yes, please.

DR. KIRBY: I just want to emphasize that's not apples to apples. That's not apples to oranges. That's apples to a 1974 carburetor on a VW Bug. And also in terms of data, I have data I'm publishing soon, too, with the highest amount of nurse practitioners, PAs, and RNs in the entire nation. So we need to stick on topic and talk about fillers and safety and

education. I would defer to Dr. Surek on it, I mean, he's probably the single most knowledgeable person on this panel today and that's coming from someone who has more experience, supervision, delegation, than anyone in the nation. So Dr. Surek, do you have a comment on education and in terms of allied healthcare professionals, other clinicians performing filler safely?

DR. SUREK: Well, thanks so much. I think the overarching goal, right, is to figure out how can we continue to perform this procedure and do it safely. You know, delegating that to who does it, I think, is a longer discussion, but I do know for a fact -- and I do work closely with a lot of non-physicians who seek appropriate training because there isn't really any foundational training. Remember, this is kind of the wild, wild west. There's not standardization in technique education.

I think what you've learned today from this morning and now, is that this procedure can be done, high volume and safely, by and large, most of the time. The matter is making sure there's a foundational understanding of anatomy, the science behind the product utilized, and the techniques employed, as well as complication management.

So I think it's -- regardless, necessarily, of exactly the provider doing it, once we lay those ground rules, I think it's important to have the proper training or emphasize the proper training so we can get some standardization here. You know, I mean all of us go through this training. I'm a board certified plastic surgeon. I agree, I think plastic surgeons have a presence on whatever future panels there are, absent these other specialties. But the reality is, the precedent is we need to emphasize the importance of anatomy and safety. And I've trained several non-physicians who do have a great skill set on that, but they had to seek that out because they wanted to make sure they were at top of mind and performed the most safe and efficacious approach for their patients. So it's a broad topic, but the bottom line is we need really strong anatomy training and technique education to

improve safety. That's my feeling about it.

DR. AVRAM: And again --

DR. LEWIS: Thank you , Dr. Surek.

(Cross-talk.)

DR. AVRAM: -- data on this. We published it and I haven't seen the data on the fillers, and let's also recall that we're not talking about immediate blindness and stroke with energy based devices. But I know this is a state legal issue and I'm not going to comment on it further, but I didn't want the opportunity to address that to go by without speaking on the actual data that exists.

DR. LEWIS: Further questions for the speakers. I don't -- Dr. Alam.

(Off microphone response.)

DR. LEWIS: Dr. Alam, you're muted.

DR. ALAM: Sorry. Sorry again, Dr. Lewis.

I'm glad we had this discussion among the members of the public who are speaking about the training issue. I do think that's something that hopefully later on they'll get a chance to speak more about, but I don't think we've completely clarified exactly what training is necessary, but I suspect it's more training than an average non-physician has at the get-go. So they need to be taken up to a certain level and we have to figure out -- because we can't change state licensing requirements, we have to figure out what is that appropriate training so that even if we can't reduce the risk of bad complications to nothing, we can make it as low as possible.

DR. LEWIS: Thank you.

DR. ALAM: Thank you, sir.

DR. LEWIS: I don't see any other hands. Does anyone -- Dr. Surek.

DR. SUREK: Yeah, it's an excellent point and the reality is many of us already do a lot

of this training, okay, and there's a lot of additional platforms existing because we recognize that there is a void, so there is an infrastructure already existing and that can be built upon appropriately with the right circumstances and right individuals. Pending approval, that can be done. But that's happening as we speak, because a lot of us recognize this void and so there's training on multiple platforms and so I encourage you guys to explore what those are and how that may improve, because we recognize the voids and a lot of us are doing it already, whether it's with industry or through separate educational platforms. Just something I want to add and it does exist, just so the Panel knows that these do exist partially already but can certainly be expanded.

DR. LEWIS: Thank you.

Dr. Perry, did you have a question?

DR. PERRY: Yeah, I did, thanks. I'd like to ask John Fezza and Brian Biesman about visual acuity testing and then about the treatments for vision loss.

So Brian brought up a great point that usually the visual acuity is going to be terribly diminished to count fingers or light perception. If we have practitioners who aren't used to checking vision, check vision, find a two or three-line decrease, what do you think about some of these procedures like paracentesis, retrobulbar, hyaluronidase, Diamox, anticoagulants, intra-arterial injections? Some of those are going to have some risk. It might be helpful to the Panel for you guys to give your thoughts on sort of the balance between the benefits of checking vision and possible risks with some of these mainly unproven treatments.

DR. FEZZA: Thanks, J.D.

I'll take an initial stab at that, Brian, if that's okay.

DR. BIESMAN: Yeah.

DR. FEZZA: So there are certain things that an ophthalmologist can do, like myself

and J.D. and Brian, and certain things we would not expect a practitioner in another field to be comfortable with. But I do believe there's a baseline that we could all obtain. The first thing is assessment, so every practitioner should be trained to do assessment. That means after an injection, if there's any concern, monocular vision checking, as Dr. Bressler said, should be done. That could be done on a near card and don't forget, our cell phones have almost everything on them, so you have an app with a vision chart on the cell phone.

Two, if your vision is checked monocularly, the next step you should do is check pupils. You need a bright pen light or a muscle light but again, your cell phone does everything today, so you have a bright light with your cell phone to look for a relative afferent pupillary defect. People should be able to do a swinging flashlight test with their cell phone and assess if that pupil dilates, indicating optic nerve damage. Then we should be able to look for ocular motility and ptosis, looking at a marginal reflex distance of a lid, meaning a droopy lid. Those are basic things that every practitioner should be able to do.

Once the assessment is made and if there's a determination of visual loss, then an emergency kit should be sort of enacted where that person, if they don't feel comfortable, calls up an ophthalmologist or retinal specialist, but they certainly can start increasing blood flow to the retinal circulation with an aspirin. If they have things like Cialis or Viagra, which are arterial dilators, they can have that in the practice. Things that will also enhance circulation, breathing into a paper bag has been discussed, to increase hypercarbia. These are cheap and effective.

And then pressure-lowering drops. Pressure-lowering drops such Timoptic, a beta blocker, acetazolamide or even Latisse, bimatoprost, are usually available in many aesthetic practices. So I'd encourage, just like we have hyaluronidase, carry Combigan, which is a beta blocker, and a carbonic anhydrase inhibitor combination or Alphagan, a combination in your practice, it's cheap to do.

Then the things they could also do as a normal practitioner is digital massage, press on a closed lid, pulsatile, and that decreases and releases pressure on the eye in a pulsatile fashion. Those are things a practitioner should be able to do.

Then the next level is hyaluronidase or Hylenex injection, which is a name brand. Flood the area that's been compromised, all the time looking for vision and then calling up an ophthalmologist. The next step, such as anterior chamber paracentesis, which is a rapid decompression of pressure in the eye, or retrobulbar hyaluronidase should be done, I think, by an ophthalmologist, that's the safest way to do it, but certainly the initial crash cart and the initial assessment can be done by a practitioner and I think preparation is key.

DR. LEWIS: Dr. Fezza, it occurs to me that if someone had an injection and immediately developed an ocular complication, the ability to put your hands on ophthalmologists or to get the patient to an ophthalmologist or retinal specialist within an hour would be fairly small. Ergo, how valuable are these recommendations? I mean, they're theoretical, but do they really have any practical value?

I think you have to ask yourself if, in fact, the likelihood of this is close to zero. I'm not sure that it has practical value. The statistics indicate, for the most part, that when optical complications occur, they may evolve slightly over time in about 20% of patients, but in others they're permanent. And so I just don't know how we're going to consider implementing recommendations like this, which physically would be very hard to implement.

DR. FEZZA: Well, Dr. Lewis, your point is well taken and certainly, if it's a disastrous outcome such as blindness, you want to do everything possible, even if the chances are low. And it's the same discussion we've been having for years with a central retinal artery occlusion. If someone throws an embolic phenomenon from their carotid artery to their eye and has a blockage, we do everything we can to restore vision. And I think, although

the chance is small, you have to take that option because there is a small percentage of people that do have vision reversed and if you're that person or those few people, you're really glad that's done. So I would recommend preparation is key, developing lines of communication. You're absolutely right, it was said by Dr. Carruthers earlier that the Hayreh studies looking at 90-minute retinal circulation being restored is really not reasonable. The retina probably starts dying within minutes because it's really brain tissue. So you have to start acting in your practice and if you have that connection and you have a hotline to an ophthalmologist close by, I think it's reasonable. I would not send someone to an emergency room and have them wait for hours, so your point is well taken.

DR. LEWIS: Are there other questions?

Dr. Carniol.

DR. CARNIOL: Yes, I want to make two points. First of all, in terms of education of allied medical people, I would recommend that we establish standards for education and minimum standards so that it becomes very uniform across the country, so if someone has something done by an allied medical person, they know that they've met certain standards. And it's the lack of standards that make it -- and I think Dr. Surek said it -- more of a wild west, and I think that's an issue. So I think we do need to establish a standard for allied medical people.

The second thing is related to the eye and the vision loss and blindness, I think it's a very important issue and the ophthalmologists on the Panel have made some excellent, excellent points. I just want to say that there's some controversy over the value of retrobulbar injection. It is not found to be totally successful, even in the hands of ophthalmologists. But any physician can inject hyaluronidase into the supraorbital and supratrochlear area and possibly even cannulate the vessels and get some retrograde flow with it which may restore vision, and that is something that any physician can do but they

must have the human recombinant hyaluronidase available in their office and ready to go so they can immediately do that. Thank you.

DR. LEWIS: Further questions from the Panel?

(No response.)

DR. LEWIS: Seeing none, I pronounce this Open Public Hearing to be officially closed.

We'll proceed with the agenda and now take questions from the FDA. Dr. Jacqueline Francis will be presenting these questions on behalf of the FDA, and we'll therefore open the floor to the experts sitting around the table here -- or virtually around the table -- to begin deliberating on the topic, considering everything that you've read, preliminary information, as well as what you've heard from the various presenters today.

Dr. Francis.

DR. FRANCIS: Currently, clinical studies include vision assessments to actively and deliberately monitor for intravascular injection in all patients receiving dermal fillers regardless of the indication for use or risks associated with the injection area. Is this strategy appropriate, or do you recommend the approach be revised such that active and deliberate monitoring is conducted in clinical studies for:

- all patients receiving dermal filler in anatomic areas with more reports of vascular occlusion-related events, or
- only patients who exhibit symptoms of vascular occlusion or vision-related complications after injection?

Are there other circumstances or factors, such as injection volume, that would modify the approach?

DR. LEWIS: So the question has been put to the members of the Panel and the first question is, should the FDA mandate visual assessments, and presumably this would be the brief screening assessment which would consist of some sort of a visual acuity exam that

could be briefly administered, covering each eye alternately, followed by a field of vision, confrontational field of vision, followed by an examination of the ocular movements. All of those three could be completed in less than 5 minutes easily.

And so is that a worthwhile recommendation to make for all patients or only those very few who develop symptoms in the immediate aftermath of the injection? Could we have the Panel express opinions on that?

Dr. Alam.

DR. ALAM: I have listened carefully to, and I've questioned some of the presenters about this topic and from what I've heard, the only people who seem to feel that we should do this in everyone are the ophthalmologists among us and I suspect, in part, that's because it is extremely easy for them and they're very well trained in doing this.

My concern is that for us to make this simple enough for the average, well-trained specialty physician who does this procedure, who's not an ophthalmologist, to do this -- for us to do that, we'd have to make it so streamlined and also to make it feasible to do before every filler injection. You'd have to make it so streamlined that I'm not sure there would be much value left in it. It would be kind of just a thing that you did almost like reflexively without that much care.

I would rather see it focused on cases where it was really necessary because there had been some problem or some concern about some problem, rather than having people do this on a rote basis in a minimal way, document it but not really pay much attention to it, create another bar, but one that really isn't helping patients.

DR. LEWIS: Dr. McGrath, did you raise your hand?

(Off microphone response.)

DR. LEWIS: You're still muted.

DR. McGRATH: Thank you.

I think this question was just asking about clinical studies, not all treatments, and so I think there's two different issues. I think --

DR. LEWIS: Actually, you're entirely correct. The next question is about clinical reviews.

DR. McGRATH: Right. So I think we need to --

DR. LEWIS: So thank you for correcting me.

DR. McGRATH: I think we need to clarify that as we discuss it because in a clinical study, obviously you're going to want to have much more robust evaluations where indeed, doing a very well-described assessment that would be fairly standardized would probably be a very good thing. I'm still not clear on whether that would be necessary even in a clinical study, pre-treatment, because I think my understanding from the discussion is that pre-treatment evaluations mainly are of assistance with liability issues should there later be a complication.

But I guess my only question on this would be, to the group, is there any value in even the clinical trials of doing VC evaluations before treatment, except to help with the gathering of the best data? In other words, is there any clinical implication of an abnormal VA treatment before the injection?

DR. LEWIS: Dr. Alam.

DR. ALAM: First, I stand corrected. You're quite right, I misspoke a little bit, a little jumping the gun. I think it is a different issue whether it's in a clinical trial or in standard clinical practice. I definitely don't think it should be in standard clinical practice. Clinical trials, I would -- I'm a little more ambivalent about. I think in clinical trials we often like to collect a lot of data because we have the resources to do so and sometimes we find things that we didn't expect. So I think a greater degree of thoroughness in clinical trials is not inappropriate.

DR. LEWIS: Thank you.

Dr. Bressler.

DR. BRESSLER: So for clinical trials, it's clear that these are very rare events, but we don't know, as you're testing new indications or new products, whether it might be a little easier or a little harder for these rare events to occur. So I would recommend that the vision be tested beforehand, first of all. It is a catastrophic event, typically, so really you only need to test one eye at a time for just can they see your hand moving or counting your fingers before and after.

And I do believe that that should be done beforehand because the person, as was pointed out, may not realize that they already don't have good vision in one eye and you want to know that ahead of time before you do that, because that person who doesn't have good vision in one eye, they may need a special examination, a rare possibility they need a special examination after the fact where somebody looks in to make sure there wasn't something that occurred to that poor-seeing eye that they may not notice.

But taking the typical person in a clinical trial, they're going to have good vision in both eyes. I do think you want to test it beforehand and test it afterwards. I think it doesn't have to be an ophthalmologist and that most of the people who are doing this in the clinical trials who are not ophthalmologists would be able to test one eye at a time, just can you count my fingers or see my hand moving.

I think they also should check the pupils, as well. I think most or all of them should be able to detect an afferent pupillary defect with a bright light. Maybe it's only on their phone, a light. But that also will tell you if there was some, perhaps, optic nerve damage that was not detected before the injection was done. So I think those are relatively simple for these rare events that in clinical trials should be looked at. I would not recommend any confrontation fields, I think those are very poor from a sensitivity standpoint. There are lots

of false negatives because people can't test them too well and again, it's a catastrophic event, they're either going to be able to see your hand moving or count fingers or not.

So those are my opinions. I don't know enough about the anatomy, I have to turn to my plastic surgeon specialists. There was a comment made that if it's below the jaw, nothing -- there's no way it could go retrograde to cause a problem, but that may be a limitation where you only have to do it when it's above the jaw. But as to that, I turn to my surgery colleagues.

DR. LEWIS: Are there further comments on this question now, as to should screening ophthalmological tests be mandated in the course of clinical studies that are being done? We know that from the reports that were given, the data supplied to us, that in all of the studies done to date by the FDA in approving these devices, that they never detected any ophthalmologic complications, so it would be a very uncommon event.

Ms. Brummert, did you have a comment?

(Off microphone response.)

DR. LEWIS: You're still muted. Ms. Brummert, you're muted.

MS. BRUMMERT: Yeah. I mean, I definitely think that as much testing as can be possible during the clinical trials would be a good thing. You know, I find when I sit on these hearings that -- you know, the commenter said well, we didn't know until later. So I kind of feel like if there's a way to do testing for everybody, I think we can catch information that we may not be able to catch until it's too late. So I kind of echo what everybody's saying about all patients, like having this kind of testing in clinical trials.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: Yeah, I think capturing as much data as you can earlier on. You can always not use it, but you can't get it back. But I would say, just moving on from a trial and practically speaking, I apologize for not having the right name of the ophthalmologist,

but I think his points were well taken.

I think if we were not talking about clinical trials but talking about the clinical setting, we may recommend a tiered approach where we do a very rudimentary eye test, because I think somebody said 2% of the population has issues that they are unaware of. So some rudimentary test for vision and then -- and this could be a card for the practitioners and the four eye tests you would do if, after treatment, they have a problem and then if you're thinking they have a problem, what you can do in your office, you know, the pressure or the aspirin, the vasodilators and so on, and then the retina specialist because if we give them a tiered approach, it may allow them to do something while they're reaching out to a retina specialist.

So my suggestion is, is this four-tiered approach, and print it so they have it and it becomes part of what we're using now as our filler crash cart because if you look at the filler crash cart data that we have, it doesn't have anything about how to do, really, this tiered approach to eye problems.

DR. LEWIS: Dr. Matarasso, are you addressing the use of these clinically as opposed to in clinical studies?

DR. MATARASSO: Yes. Yes, I was saying in clinical studies. I agreed with the speaker before me, Rachel Brummert, that we capture as much data as we can because you can decide not to do it and you may get data that -- you may get information that you never even thought about. You can't go back after the trial is done. What I was referring to at the end, yes, Dr. Lewis, was in clinical practice.

DR. LEWIS: Thank you.

Dr. Miller, did you have a comment?

(Off microphone response.)

DR. LEWIS: You're still muted.

DR. MILLER: I'm sorry. Yeah, I think my comment had more do with clinical practice and so I'm jumping ahead to the second question, but I think that there's value in pausing people who are doing these and checking the patient's eyes because if nothing else, it highlights this is a potential problem. I mean, with rare events like this it's so easy to get so complacent about it and then when something happens, you're completely shocked and unprepared because you've never seen it or you haven't seen it in a very long time. So I think if every time you inject somebody you at least do ocular motion and just see how many fingers you have, just at least psychologically stopping the practitioner and telling them look, this could be a disaster, be mindful about how you do this.

DR. LEWIS: Dr. Ballman, did you have a comment?

DR. BALLMAN: Yeah, I think for clinical trials it should be done because we know that this happens, I understand it's rare, but if there's a new indication that's being brought forward, I think it really should be tested. And also, the other question is, are there circumstances or factors, such as injection volume, that would modify the approach? There's just not enough data to make a recommendation on that, so I think it should be all patients in a clinical trial.

DR. LEWIS: Thank you.

Dr. McGrath.

DR. McGRATH: One other. In reading about this in preparation, it appears that about 19% of patients who develop severe ophthalmologic problems also have CNS involvement, and I wonder if in clinical trials it should not also be part of it to have some sort of a basic neurologic examination as part of the protocol.

DR. LEWIS: It would appear that there is slight consensus on the Panel about asking for ophthalmologic screening exams in clinical studies, although it's not unanimous from the comments that have been made so far.

Dr. Francis, is that adequate for your purposes?

DR. FRANCIS: Yes.

DR. LEWIS: Shall we move on to Question 2?

DR. FRANCIS: Yes. Question 2: For PMA-approved devices, do you recommend that vision assessments be required to actively and deliberately monitor for intravascular injection, before and after injection in all patients receiving dermal fillers, or are there circumstances where monitoring for visual impairment is not needed?

DR. LEWIS: So it's the same question now applying to clinical practice.

Dr. Alam.

(Off microphone response.)

DR. LEWIS: You're muted, Dr. Alam.

DR. ALAM: Thank you.

Here, I think we should not require it and I've heard the very eloquent statements by Dr. Miller and Dr. Matarasso that there is some utility and I agree, there is some utility. It maybe reminds you to be extra careful, and that's true. But if we look at, as Dr. Matarasso previously tried to discuss, the incidence -- and I know we don't have the exact incidence data, but it's about one in a half a million or some very large number, if you look at how rare serious visual complications are, to do such a large workup preemptively, I think, is unreasonable.

If we did this for every procedure we do, we'd have to do 20 different exams before we did everything because there's a one-in-a-million or one-in-10-million chance something might happen. I just don't think it makes reasonable sense. I think we could have other methods, perhaps, of reminding the practitioner about the need for being very vigilant. In terms of injecting to avoid ocular complications, we could have a standard for training, something similar to that, but I'm just not sure this would be fruitful.

DR. LEWIS: Dr. Matarasso.

(Off microphone response.)

DR. LEWIS: You're muted, Dr. Matarasso.

DR. MATARASSO: Thank you. Yeah, thank you very much.

I don't disagree with you, Murad, I think it would be onerous for that incidence, but what I would suggest is sort of a middle ground here before we do a blepharoplasty, and we often test for tear production and visual acuity, and blindness in a blepharoplasty is one in a hundred thousand. So what I'm suggesting is, as Michael Miller suggested, is at least bring awareness to it. I have a filler crash cart that our societies have published and the closest we get to anything about the eye is having hyaluronidase around.

So what I'm suggesting is, as our ophthalmology colleagues suggested, is that you can decide you want to do a very rudimentary visual acuity exam, hand them the cell phone, hand them a magazine to read, cover one eye, it takes one second, or we may decide if you said that may be onerous for what this incidence is. But I do think that every practice should have available to them the four eye tests that were suggested. If post-treatment you're having a problem, then -- and tier this, what the practitioner can do in the office immediately: the pressure, the massage, the aspirin and so on and what -- and then the next level, what the ophthalmologist might do. So (a) it does -- Michael Miller said it brings awareness that this could be a problem, and (b) there are things that you can do while perhaps an office person is trying to get the retina specialist.

So I think a little card, something that could be available to everybody, of what the four eye tests they can do post-treatment if somebody's experiencing a problem, what they can do in their office and what the ophthalmologist does. And I think that is not burdensome at all, it's just helpful.

DR. LEWIS: Dr. Ballman, did you have a comment?

(Off microphone response.)

DR. LEWIS: Okay, thank you.

Dr. Bressler.

DR. BRESSLER: This is a very hard question because the incidence we have, of course, is rare, but are we able to capture everything? The way it's worded, is it -- should it be required, I think, is too strong. I don't think it should be required, but I do think there needs to be some sort of assessment in clinical practice setting and it could be as brief as -- I'm sure people are asked, after their procedure, you know, "everything feel okay?" It could be everything feel okay and it could be strongly recommended, not required, to also say" is your vision okay?" Again, this would be perhaps a habit as you're finishing the injection.

It's sort of like our intravitreal injections that we do into the eye tens of thousands of times for some ophthalmologists each year. They don't check the eye afterwards, there is a risk that something catastrophic could happen, but they might quickly say is everything okay and again, it just puts in the person's mind the fact that you might have this sudden event. But of course, what are you going to do about it, because most of these are not reversible. The treatments that are suggested, by and large, have not been proven except perhaps a paracentesis or some massage in the hands of an ophthalmologist. So I guess it would just bring to the attention of the person doing the procedure that a catastrophic event has occurred.

But I do think it's worth at least trying to consider checking for it with perhaps a simple question in clinical practice and try to consider having people aware of an ophthalmologist that they could call immediately to try to get them there within the hour. An emergency room will not work, as has been pointed out, but it may be that if they have that sort of telephone number, those sort of ideas might help, if nothing else, to explain to the patient about this catastrophic event, that it might not be reversible, but in the hands of

someone who's dealt with artery occlusions perhaps before.

DR. LEWIS: Dr. Perry.

DR. PERRY: Thanks. I agree with Neil's comments, but I would recommend a rudimentary vision check prior and the reason is -- and I say only rudimentary and it could be just a recommendation. If we get too specific a visual acuity, let's say the patient has the little betadine or chlorhexidine or something in their eye and they have a few-line decrease, well, then the clinician may go down the rabbit hole of some of these treatments and, given the rarity of the actual event, there's going to be a lot more of these pseudo-events that could then produce complications or adverse events from the treatment, whereas with a very rudimentary vision check prior, at least the clinician has a baseline to know whether there's a significant decrease afterwards.

DR. LEWIS: From what we have heard, it's my impression, and I certainly stand to be corrected by the ophthalmologists here, that in the vast majority of cases where there's embolic damage to the eye, the effects are relatively dramatic. The likelihood that you would have significant embolism and have very minor symptoms related to that, like blurry vision, perhaps, or floaters in the eye, essentially is almost nonexistent. As such, it would seem like the occurrence of such an event would not be subtle and would not require radial testing to detect. Testing would potentially be of value only prior to treatment to document that there was nothing before. Is that an incorrect statement, from the ophthalmologists here?

DR. BRESSLER: Frank, I think you're totally correct. In most cases, if not all cases, it should be readily apparent. However, you know how some patients can be so nervous that even if they saw that it sort of darkened one eye, they might not say a word, and that's why I do agree with you, it should be obvious, it should be something very simple, but maybe not zero, maybe not required but recommended or encouraged to just not only ask how

you feel in general after you finished with the fillers but, you know, "is your vision okay?"

DR. PERRY: And I agree, it's typically a catastrophic sudden vision loss. And the other important thing to remember is that none of these treatments have ever been proven to work. So I think that's the other part of the equation here, is even if it's documented, these treatments, while I agree with Dr. Fezza, yes, they should be tried, they haven't been documented to work. So that's the other part that I think we should keep in mind.

DR. LEWIS: Dr. Alam.

DR. ALAM: To your point, Dr. Lewis, and to just point to several others who suggested some rudimentary test, if the test is done prior to treatment -- and this is someone else's idea. I just want to give credit, it might have been I'm not sure who -- but if the test is done before treatment, the test could entail just asking the patient how their vision is and that obviates the need for the treating physician to document the complex test, to go down the rabbit hole and have a false positive and then have to investigate with additional tests because some betadine got into the eye.

But just asking the patient ahead of treatment "is your vision okay" does a couple of things. First of all, it gets you an answer so if there's something seriously wrong, you know that that's not related to your injection because it hasn't happened yet. And secondly, it is a reminder, as some other people have said, to both you and the patient that this is something that is something that can occur, albeit very rarely with this treatment. So it's almost part of a consent process, to some extent.

DR. LEWIS: Dr. Chang.

DR. CHANG: Yes, this is Cynthia Chang.

Just to try and guide the conversation a little bit, we're particularly interested at the FDA about not just the general recommendations but also if there are specific recommendations for certain anatomical areas. For example, we've seen from the

literature and the MDRs that certain areas may have a higher frequency or higher number of reports of these types of events, for example, periocular or areas around the nose. So we're interested in knowing if your recommendations might change if applied to specific areas of concern or if there are other factors in addition to anatomical location that might modify your recommendations, which are for the general applications. And I guess that would be both for clinical trials as well as in clinical practice. Thank you.

DR. LEWIS: Dr. Brown.

DR. BROWN: So in clinical practice, unfortunately, patients can be very grossly unaware of problems with their vision on a daily basis and I think I come down on the side of some sort of rudimentary test such as counting fingers in the setting of an injection in an area that is more likely to cause a problem, and I do think it should be done before and after and I think that that would add only seconds to the evaluation and it think it is very helpful.

DR. LEWIS: Further comments.

Dr. Bressler.

DR. BRESSLER: For Dr. Chang, since these are rare events, except for this business about the anatomy from the jaw and below, for everything above I would be careful both in clinical trials and practice about differentiating "gee, we see a lot of these from the nose but rarely from the forehead" or something, I'd be careful because there could be compounding factors. Maybe it was just that the population from the continent of Asia were more likely to report these, there was a different medical/legal concern or whatever and maybe they were just doing more procedures to the nose and so you get more events in that way. So unless the anatomy dictates that it's nearly impossible, I'd be careful so far, given the rarity of the events, about trying to break out one versus the other because I'm worried that the compounding factors may have led you to have more in one place versus

another.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: Yeah, I was just going to say exactly the same thing, Dr. Chang, we just don't have data to parse it out, that's accurate enough to give us any guidance on it. So no, I can't say that we can pick out one area.

DR. ALAM: And I would agree with that strongly.

DR. PERRY: Agreed, as well.

DR. LEWIS: So there seems to be a majority opinion that in clinical practice a very brief ophthalmological assessment before and after treatment is desirable, something that in reality would take less than 30 seconds. So those specifics could be defined. As was stated by someone earlier, the confrontational visual field test is probably not very accurate, but simple things like reading from a card or testing extraocular movements is quick and quite easy to do and requires minimal training, so it adds very little to anything.

Dr. Burke.

DR. BURKE: Yes. Well, I think actually just in the common sense of a clinical circumstance, I think the most important thing after this whole discussion is to perhaps have the patient stay in the office for 10 or 15 minutes after the injection and then ask them if they don't -- I mean, certainly, we ask them as we finish treating if there are any problems and if they feel okay, but I mean, sometimes something could be 10 or 15 minutes later in these vascular occlusion situations, although usually it's immediate.

And then the thing to stress is if it's immediate, the thing you do is all the emergency training or all the emergency -- the emergency practices rather than testing their eyes. I mean, if the person says they can't see, then you get out your crash cart and do all of the things that we've mentioned immediately and call the ophthalmologist. So I think in a practical commonsense situation, we use the crash cart if there's an occlusion, but I must

say that I always ask the patient if they're okay, but I don't necessarily have them stay in the office for an extra 15 minutes at the end and I think after these conversations, that might be one change that I make.

DR. LEWIS: The FDA has not explicitly asked any questions about the things we've heard in regard to emergency measures that you're referring to with the crash cart, start a routine, the things that a non-ophthalmologist could do and have available versus the things that only an ophthalmologist would feel comfortable doing. We've also heard, as we heard just a few minutes ago, that all of those things are suggested on a theoretical basis, but there's no data demonstrating effectiveness. Does the Panel feel that any of that should be codified and perhaps mandated by the FDA?

Dr. Alam.

DR. ALAM: I know there is not a lot of data on hyaluronidase reversing blindness, but there is data on hyaluronidase helping with vascular occlusions when used properly. So I think that's a reasonable thing for people who are injecting to have available. Obviously, that applies primarily to hyaluronic acid fillers, but that's the majority of fillers used in the country.

DR. LEWIS: Any other comments by anyone?

DR. ALAM: I'm sorry, one other thing. And also having an ophthalmologist that you have some relationship with. I think that's not something you have in your office, but that's a relationship that I think has to be established ahead of time because even if you have a small chance of resolving the issue, that requires usually very rapid referral, which would be difficult to do without a preexisting relationship. Thank you.

DR. LEWIS: Dr. Perry.

DR. PERRY: I agree with Dr. Alam, especially about the cutaneous effects of the vascular occlusions, but vision loss, I would not recommend hyaluronidase. Retrobulbar, I

think we just need more data, the animal models are 50/50 on that and we don't have any clinical evidence, so I think that would be a little premature without more data.

DR. BRESSLER: I agree, there is a paucity of data that shows the effectiveness of any of these treatments. Even the massage, you want to be -- if you're pressing on the eye because of some embolic material there, if it's down one branch arterially and you press and it goes retrograde and it goes up the other branch arterially, you could cause more damage. So all of these treatments must be, you know, very cautious in anybody's recommendation and should be done just on the individual basis, I think, and not with -- in my opinion, with any broad guidelines coming from any regulatory group. But urgent connection to having a telephone number of someone to call would be wise.

DR. LEWIS: Thank you.

Are there any further comments around Question 2?

Dr. Miller.

DR. MILLER: Just one more. I think it's clear that the most important thing is awareness and prevention and how your technique is used. So I think anything we can do to help raise the awareness amongst people doing this and especially people who are not ophthalmologists or they may be plastic surgeons, and with nurses and dentists who are doing this stuff, to make them -- to have some requirement that they're prepared to handle these things. Even though the treatments are not effective or whatever, I mean, if you require a dentist in his office who's doing fillers to have something in his office to try and reverse blindness, he may never use it in his entire life, but every time he injects somebody he's going to think about it, you know.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: Thank you very much.

I think I said this earlier, I think my ultimate conclusion here is that -- and this is for

clinical practice -- a rudimentary eye exam just to make sure they're seeing, just like we do for eye patients for blepharoplasty. And then post-treatment, if it's a catastrophic event, we know where that needs to go. If there's any question, just some guidelines, not mandates but guidelines, on what the four eye exams are, what's the treatments you can do while your staff -- or you're calling a retina specialist, I think, as Michael said, it raises awareness. It's very similar to what we do with malignant hyperthermia on a cart in the operating room. So I'm not sure if I'd mandate it, but I do think I would create these guidelines because right now these guidelines don't exist. I put up in the air before what guidelines are available to us and I think it does a lot of things, it buys you some time if you need to and, at the very minimum, it creates an awareness.

DR. LEWIS: Thank you.

Further comments?

(No response.)

DR. LEWIS: Seeing no hands, I would conclude this question, on Question 2, if you have adequate material, Dr. Francis.

DR. FRANCIS: I believe that we do, yes.

DR. LEWIS: Let's proceed to Question 3.

DR. FRANCIS: Postmarket evaluation of vision and neurological abnormalities in a larger subject population, such as through post-approval studies, may help to characterize the risk associated with intravascular injection into a blood vessel. In what specific indications or situations would you recommend such post-approval studies be required?

DR. LEWIS: All right, Dr. Alam.

DR. ALAM: I think this is a very, very important issue because one of the problems we're struggling with today, and the companies are admitting this, is they don't have data, they don't know exactly what happened in whom and they're not getting this data. So I

think we have to highly motivate them to having something like registry data where every time an adverse event occurs -- of a serious nature, at least -- there's a lot of information pertaining to that, that they're required to go and dig up and put into some kind of database where it can then be saved in perpetuity. Now, that's still tricky because some people might not report an adverse event and if they don't report it, then how will the manufacturer that's trying to do a postmarket study know that? But I think we do want to put some onus on them to collect this data and I think we should help define the very wide range of fields that we want, like how much was injected, where was it injected, what tools were used to inject it, what caliber were they, because we have a lot of questions, we have a lot of hypotheses today. Certain kinds of cannulas might be better. Low-volume injections might be better. But we don't have any data. So we need to collect that information when something goes wrong so over time we get a sense of what preexisting or technique features were associated with a bad outcome. Thank you, sir.

DR. LEWIS: Dr. Alam, I think you've identified an extraordinarily important point, a key point. The problem I have, and I don't readily see a solution, so I solicit those from the group, is that any sort of a post-approval study that was done in terms of defining a certain population or whatever is going to be limited to, at most, a few hundred patients, if that. And as we've already seen, the likelihood of seeing a complication within those studies is close to zero, if the incidence is even 1 in 50,000.

And the MDRs, which is currently the main method by which the FDA hears about this, is a very spotty situation, it's entirely voluntary, it has inadequate information, there's no format to it, etc., etc. Whereas what you're suggesting, even if it's not extensive, would involve some basic information about how the process occurred and what the damage was.

So I guess the question is, is there any way in which a practical solution could be devised so that the extremely rare events, which probably occur at most, we have reported

about a hundred times a year from vascular events, it may be double that since we certainly don't have a good reporting system, but is there a system that could be implemented whereby only those cases when something adverse occurs gets reliably reported, including specific data elements?

DR. ALAM: Yeah, I would agree with you, it's very challenging. I don't know how to do it. One thought that I had was, in addition to having the really catastrophic events supported, like those with visual impairment, we even have the minor occlusions that just cause a local redness or a little bit of a scale or something like that, because even though there's no necessary causal connection, I think it makes reasonable prima facie sense that if you're getting an occlusion, even if it's not an eye occlusion, it could have been if things went slightly wrong. So if we also capture that sub-serious level of bad events, and that would be a bigger group, that might give us a slightly larger *n* to investigate what sorts of techniques cause some kind of vascular occlusion because, like you said, if we just focus on the catastrophic ones, well, that's a handful and that will take forever to gather.

DR. LEWIS: Is there any method by which the professional societies that are all involved in this area could devise a registry of some sort for these adverse reactions?

DR. ALAM: Well, ASDS, one of the -- the American Society of Derm Surgery just last month initiated such a registry and they're reaching out to their members to encourage them to report these cases. So I think it's still voluntary but hopefully, like if we can get enough awareness out there, we'll get a higher proportion.

DR. LEWIS: Thank you.

Other comments?

Dr. Miller.

DR. MILLER: Thank you.

Yeah, I think a post-approval study, it's a very formal thing the FDA requires, they're

very expensive, they're very cumbersome, and for an event like these that are so rare, I think it would just be an enormous, impractical thing to try and do. But I think something through the societies, a voluntary perhaps registry like we run in the plastic surgery world with breast implants, that seems like a practical thing. But I think there's enough understanding of the mechanism of what goes on here that if we ran a post-approval study we would discover that yes, indeed, this patient had this event because of a well-understood mechanism and we really learned nothing except to have a lot of cumbersomeness added to the system. So I would resist something as formal as a post-approval study.

DR. LEWIS: Dr. Perry, did you have a question?

DR. PERRY: Yeah, I agree with resisting the post-approval study because of the numbers. I think the registries for societies is a great idea, but it's going to miss so many providers who are not in the four or whatever major societies. It seems that the companies already vet the practitioners that they sell the medication to. Is there any way that they could re-vet them every year with the practitioner filling out basically a registry card of any vascular events that occurred?

DR. LEWIS: Further comments?

DR. BRESSLER: I had a comment on your question, Dr. Lewis. So I don't think it's feasible to do a post-marketing evaluation per se, nor is it easy to evaluate those people because they've already had a catastrophic event and it's likely at this time there's no treatment for that. I do think there is value, as will come up with Question Number 4, to work on some uniform guidelines for societies to do and for research people to do. This has happened in Asia where they've looked at large databases of their insurance to look for, let's say, retinal artery occlusion matching in somebody who's undergone some dermal filler procedure to at least understand those incidences, but I think otherwise, it's just not

feasible.

One thing that could come out of any of these recommendations, as well, is to point out whenever the papers or the industry says that there's been recovery, I think people should not claim that unless they have checked both visual acuity and formal peripheral visual fields. Very often someone can lose vision in an eye, they lose it centrally and peripherally, the central recovers but they still are left with a visual field defect but they may just report to a non-ophthalmologist that their vision's come back when in fact they have no peripheral field inferiorly, for example. So at least that should be clarified as these registries or research is encouraged in this area.

DR. LEWIS: Ms. Brummert, did you have a comment?

MS. BRUMMERT: Yeah, I mean, I say this at most of the hearings that we do, but I do think that there should be some sort of registry and that there has to be a lot of awareness around it because patients don't know that they can report their adverse events. Sometimes they don't even know it is an adverse event until later on. So I think that there should be a way that we should be able to track patients and see their progression or whether they're getting worse and just sort of follow them for a while to collect data. I think we're doing a disservice to patients if we don't do that.

DR. LEWIS: Are there any other comments regarding Question 3?

(No response.)

DR. LEWIS: If not, Dr. Francis, can we move to 4?

DR. FRANCIS: Yes, we can.

What steps can manufacturers and professional societies take to educate providers on risk factors for intravascular injection and the strategies that can be employed to mitigate risk?

DR. LEWIS: I think this is an extraordinarily important question for us to think about

because the reality is, in the form that these disastrous complications occur, no matter what's done, the outcome is probably going to be bad. And so improving the situation here is almost totally dependent on trying to prevent it from happening and currently, as has been pointed out, we have virtually no data regarding those issues.

So the real question is what can we possibly learn about ways to significantly improve injection technique, educational requirements, etc.? What education? We've heard that a slight majority of the people who are injecting are non-physicians. What educational requirements beyond their basic licensure should potentially be required? And what can we do to potentially ask the relevant societies and/or industry to develop the appropriate curriculum, standards, requirements, regarding that sort of issue, even if it's all voluntary?

Dr. Alam.

DR. ALAM: I have a question maybe for FDA. Dr. Lewis, I think what you said was very eloquent and that's exactly the core issue. I guess the question I have for FDA is to what extent can we mandate or can FDA mandate specific training or will this always just be a suggestion? Because what I'm hearing is the companies, the societies, have a variety of training modules and some are more complex, and some practitioners, physicians or otherwise, avail themselves of a lot of that and get a lot of information and others don't. So if we recommend something, is there some way to require practitioners to do that or will that be a state-by-state determination since they practice medicine and they regulate medicine?

DR. LEWIS: Dr. Chang, can you address that?

DR. CHANG: Yes. This is Cynthia Chang.

So regarding what FDA may mandate or not, you know, I think that is more of an implementation question. We do have some regulatory authority that we could perhaps

implement. However, I think what we're really interested in is the Panel's recommendations on what you think would be appropriate training or education to mitigate the risks and, you know, we will take that information under advisement in terms of what may be done to further the safety of these products.

DR. LEWIS: Dr. Miller.

DR. MILLER: Thank you.

I think we've heard in our discussion today a lot of good information about the things one must understand to safely do this and the things that one needs to do to safely do it, and I think those things packaged into a -- you know, every year I have to go through computer-based learning modules or they shut my computer off at my hospital. So I mean, I think that before anyone is shipped a product they need to be able to demonstrate that they have gone through some required training that at least reminds them of how this should be done properly and the risks involved so that the complacency doesn't creep in because of the rarity of this. So I think it would be nice to see the manufacturers have an online sort of training module that no one can receive product unless they can -- unless they've clicked through that training module.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: I would agree with that. I think this will be a multifaceted approach, I think, that the manufacturers may want to consider certification by who buys it and who uses it because it may be two different people. I know ASPS, the American Society of Plastic Surgery, would be very interested, I believe, in starting a registry for our members and perhaps wider. So I think it's going to come from both industry, the medical groups and societies, as well as the FDA, if the FDA can gather some of the data that I spoke about this morning because, as Dr. Surek said, 55% of the injectors aren't doctors. So you know, we might find out that we found that with 5 years of experience your complications went

down. Well, are we seeing that 90% of the problems are with physicians or 90% of the problems were outside? So I think we've also got to collect data so that we know who to target because we can target the dermatologists and the plastic surgeons and the ENTs and the ophthalmologists, but we're probably missing a vast segment of the people that are doing it. So I think it has to be multifaceted. The manufacturers have to require certification of those who buy it and use it. We can have a registry in addition to all of the other educational things we're doing as a society. And I think if the FDA can get some more data for us as to who's getting the complications, with what product, at what site, and at what depth and also perhaps even volume, as much data as they can get, and then we can reduce complications by the earlier things and then know who to target by these FDA things. Thank you.

DR. LEWIS: Dr. Burke.

DR. BURKE: Thank you. I'm Karen Burke in New York at Mount Sinai.

I just absolutely agree, I think that the companies should have -- I mean, they already have the videos and the teaching modules, but I just think that they should require every person -- I mean, they should, or induce every physician purchasing this to, number one, watch the video at least every 2 or 3 years and have a test and, as an inducement, they could offer a lesser price to one purchase or something and that they should have a yearly survey.

We all fill out so many surveys and it would not be so difficult to have a survey to just see how many patients did you treat. And, I mean, we know how much we purchase and just list the whole list of side effects from the initial ones, was there considerable edema or erythema or was there swelling, I mean was there immediate, sort of intermediate or long-term sequelae and were there any of these very severe adverse reactions. And I think that just having the yearly survey, because physicians remember

within a year the difficulties and having the training certificate and in that certificate, I mean, everyone should say if they're a physician or if they're a dentist or if they're a nurse, so that we accumulate or the company accumulates data about their own products and has this information which then could be compiled into at least a publication or data available to that society, that eventually would be in medical journals that we would be aware of. And there could be this kind of financial enticement to do it, that if you do this you get a certain percentage discount on your next purchase or you get X number of complimentary syringes.

DR. LEWIS: Other comments?

Dr. Perry.

DR. PERRY: I agree with maintenance training modules by the company, I think that's pretty straightforward, and if an exhaustive survey of multiple adverse events is too onerous, we're really only concerned with the vascular events, there could even be the very last question is -- you know, you check a box off saying that I registered any vascular events with the registry.

DR. LEWIS: As we heard, all of the companies are currently providing their own proprietary educational information, but the uniformity of that across the different companies is not clear and I assume it's somewhat different. It would seem that some sort of a little more uniform standard, perhaps arrived at between the companies and the professional societies to achieve a minimum desirable knowledge at least of the anatomy around the face and injection techniques to be used and an awareness of potential volume of injectate as a role, some basic things that might affect prevention would be a desirable thing to do, at least to have some uniformity about this with or without a certification process for the company.

Okay, I see no other hands and no other comments. So Dr. Francis, is that

satisfactory?

DR. FRANCIS: It is, thank you.

DR. LEWIS: We're running a little ahead of schedule, but there's nothing wrong with that, so we'll now take a 10-minute break and return at 2:40 to begin the afternoon session. Thank you.

(Off the record at 2:28 p.m.)

(On the record at 2:40 p.m.)

DR. LEWIS: We will now resume discussion in the General and Plastic Surgery Devices Panel, and we'll address the afternoon session focused on patient preferences and informed decision making. This session will be led off by Dr. Cynthia Chang, the FDA, who will make her presentation and then introduce Dr. Michelle Tarver.

Dr. Chang, would you begin?

DR. CHANG: Good afternoon and welcome to our final session of the day, which will cover how considerations regarding patient preference and informed decision making process may be incorporated into FDA's review of dermal fillers.

We will begin with a high-level overview of FDA's approach to patient-reported outcomes and patient preference information by Dr. Michelle Tarver, followed by a description of FDA's medical device development tools program by Captain Hilda Scharen. FDA speakers will then move into specific discussions on how these concepts are relevant to dermal filler assessments. Dr. Jacqueline Francis will present on how effectiveness is evaluated in clinical studies and how this may be improved, and Dr. Alexander Sun will provide an overview of patient decision making and labeling and how they may be enhanced as part of the informed decision-making process. These presentations will set the stage for the questions to the Panel.

With that, I am pleased to turn the discussion over to Dr. Michelle Tarver from the

FDA.

DR. TARVER: Welcome. I'm Michelle Tarver, the Deputy Director of the Office of Strategic Partnerships and Technology Innovation at the Center for Devices and Radiological Health. I'm also the prior Assistant Director of the Patient Science and Engagement Program. Today I will be speaking with you about the incorporation of patient perspectives in medical device regulatory decisions.

CDRH is galvanized in its mission to protect and promote the health of patients. Patients are truly the inspiration for all the work we do. This is reflected in our vision statement that patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world. "Patients" is the first word because they are the most important customer and the group most impacted by our decisions.

The benefits of receiving patient input can be realized across the total product life cycle of medical devices. Patients can share their unmet needs to help inform the discovery and ideation phase for a given medical device. Once the prototype is designed, patients can provide input that can improve the usability of the device. Patients' input can inform how a clinical study is designed, making it more patient friendly and including outcomes that are important to patients. The insights gleaned from patients may help in setting a meaningful effect size. It may also inform the benefit-risk decision that regulators make, as well as how one might communicate the benefits and risks to patients and providers. Once devices are on the U.S. market, patients can be part of the boots-on-the-ground intelligence system for real-world effectiveness and postmarket safety information.

Before we begin, let me share some definitions to clarify the different types of patient input. In draft guidance, we have defined patient engagement as intentional, meaningful interactions with patients that provide opportunities for mutual learning and effective collaborations. Fundamental to this definition is partnership. While patient

engagement does not constitute scientific evidence, it is foundational to the generation of scientific evidence.

The science of patient input represents structured, well-defined, systematic collections of how patients feel and function, as in the case of a patient-reported outcome, or an assessment of the tradeoffs that patients are willing to make among different benefits and risks associated with their condition and its diagnosis or management, which is patient preference information.

Different types of patient input are used for different purposes in a regulatory context. Clinical outcome assessment is the umbrella term that includes patient-reported outcomes. They are commonly used to measure outcomes in medical device clinical studies. They may be used to inform the eligibility criteria or the endpoints in premarket or postmarket clinical studies. They are increasingly being integrated into clinical care, recorded in electronic health records, and play a role in some payer decisions. As such, this real-world data may potentially impact FDA's regulatory decisions. The ubiquitous integration of these outcome assessments underscores the importance of measuring outcomes that are important to patients.

In contrast, patient preference information is not the outcome of a clinical study. Instead, patient preference information can help elucidate the value that patients place on the outcomes. It may help prioritize which outcomes to measure if there are many of interest identified by the clinical study developer. Patient preference information may capture what effect size is important to patients, helping to inform performance goals in clinical studies. It may also give us insight into the uncertainty that patients are willing to accept for a given benefit. This information could potentially inform the alpha error which may be used to determine the sample size of the study.

Lastly, patient preference information can inform the benefit-risk assessment and

can shed light on the preferences of patient subgroups. To date, patient preference information has been used to expand labeled indications for a medical device, as well as set performance goals for a clinical study.

We have issued guidance documents with recommendations for how to collect quality patient preference information, as well as how to develop well-defined patient-reported outcome instruments. In August 2020, we issued a draft guidance outlining principles for selecting, developing, modifying, and adapting patient-reported outcome instruments. This draft guidance further clarifies least burdensome approaches to bridging, also known as modifying, existing instruments and for developing new instruments in an efficient way. Not only have we provided recommendations about how to develop well-defined measures of the patient perspective, we clearly describe in our benefit-risk guidance documents how patient perspectives can impact our premarket and postmarket regulatory work. We continue to see the impact of clear regulatory policy on medical device submissions with 24 industry sponsored patient preference studies and over 50% of premarket approval applications, Humanitarian Device Exemption applications, and de novo submissions containing patient-reported outcomes.

Let's take each type of scientific patient perspective information individually, starting with patient preferences. Well-designed and conducted patient preference studies can provide valid scientific evidence on patients' risk tolerance and perspective on benefit. This information could be used to inform FDA's evaluation of a device's benefit-risk profile during the review process. Features of high-quality studies can be grouped into three overarching themes: being all about the patients, reflecting good study design, and being conducted and analyzed in a robust manner.

Let's first focus on patients. Because patients are completing the patient preference survey, the attributes being measured should be something that patients can assess. For

example, we would not ask patients to weigh in on changes in the ejection fraction of their heart, which is a reflection of how well their heart can pump. Instead, we might ask them to reflect on the shortness of breath they experience while performing everyday tasks. The attributes that we are assessing should be phrased in a manner that is understandable to patients.

The guidance document also recommends assessing how well patients understand the harms, risks, uncertainty, and benefits by using knowledge checks. This step precedes patients performing the preference exercise where they are choosing amongst those characteristics or attributes. Inclusion of the step has the potential to improve the quality of the study results.

A well-conducted preference study includes patients that are representative of the patient population of interest. This means that the patients in the preference study reflect the sex, racial, and ethnic composition of the patient population intending to use the medical device along the breadth and severity of the disease. In some cases there may be features of the patient population that could impact their risk tolerance. By having a large enough sample size and including characteristics of patients that could impact their risk tolerance such as age, socio-cultural factors, disease severity, study developers may have more confidence that the preference spectrum is represented in their particular preference study.

It is important to note that diversity in the appearance of a study sample does not necessarily mean that the preferences will be heterogeneous.

The study design of the preference study should maximize patients' ability to provide insights accounting for multiple ways in which information is accessible to people. For example, the risk of an outcome could be presented with words, numbers, and images. The survey used in the preference study should undergo evaluation by patients prior to being

widely disseminated. This is called pretesting. It allows for the wording and other features to be improved, as well as to determine whether the structure of the survey or items in the survey could lead to cognitive biases.

Lastly, the questions addressed by the study, as well as the attributes included in the survey, should be relevant to the regulatory question, as well as relevant to the patient. In particular, the attributes in the preference survey should align with the outcomes of a clinical trial if the study is intending to be considered in the benefit-risk decision.

Like any research study, it is important the study staff adhere to the study protocol. The guidance document recommends that there are checks built into the survey assessing for conformity of patients' responses with logic and consistency. This built-in feature will detect patients who select the same option throughout the exercise without attending to the choice task. Lastly, multiple analytical approaches should be performed to reflect the robustness of the results.

Now let's switch gears and talk about clinical outcome assessments. Unlike patient preference studies, which are standalone studies conducted to inform a clinical trial or contextualize the findings of a trial, clinical outcome assessments are the outcomes measured as part of the clinical investigation. These measures describe or reflect how a patient feels, functions, or survives. All clinical outcome measures have some degree of subjectivity since they are impacted by human choices, judgment, and motivation.

There are four types of clinical outcome assessments which we will briefly discuss. A clinician-reported outcome is a measure that comes from a trained healthcare professional. For example, a structured assessment of skin folds could be a clinician-reported outcome.

An observer-reported outcome is one in which a parent, teacher, caregiver or other non-healthcare professional reports on the observed behaviors of a patient using a structured tool. These types of measures are commonly used with pediatric patients or

people living with cognitive challenges. For example, a questionnaire could be completed by a teacher reflecting how a child is performing and socializing at school.

A performance outcome assessment is a measurement where the patient is asked to perform a specific standardized task that is administered and evaluated by a trained individual. This could be a task such as how far a patient can walk within a certain time frame.

Lastly, a patient-reported outcome is the only measure where the patient actually reports on how he or she is feeling or functioning without interpretation by anyone else. A given clinical study may use one or more of these types of assessments in addition to other clinical measures.

When FDA evaluates the measurement properties of a clinical outcome assessment, we are examining whether the instrument is well defined and measures what it claims to measure. It is important to provide evidence about the reliability of the instrument. This information can reveal whether noise can be distinguished from true change in the measure, as well as whether the score or summary measure from the COA instrument changes in a clinically meaningful way when something about the patient or consumer changes. We evaluate the evidence that is submitted looking specifically for whether that information supports the use of the instrument. In other words, is it fit for purpose?

It matters how the clinical outcome assessment instrument is incorporated in the clinical study, including how frequently it is administered, how it is administered, and when during the study visit the patient completes it. Lastly, the analyses should be able to demonstrate with in-person change in the instrument score or the summary measure, as well as between group differences.

In summary, patient-reported outcomes, which are reflected in clinical outcome assessments, measure how patients feel, function, and survive. One instrument may not

measure all things for all patients and may not capture what is most important to patients, so it's important to talk to them to get a sense of what they value.

In addition, well-defined instruments with structured data collection can really yield valid scientific evidence that can inform the benefit-risk decision.

Patient preference information can also be useful to help identify outcomes of importance to patients, as well as set performance goals for those outcomes. FDA may consider submitted patient preference information along with other evidence from clinical and nonclinical testing when making benefit-risk determinations.

Our guidance documents do not change any review standards for safety or effectiveness. Instead, they provide recommendations relating to the voluntary collection of patient preference information and patient-reported outcomes that may be submitted for consideration as valid scientific evidence as part of our benefit-risk assessment.

Thank you very much for your attention.

DR. LEWIS: We'll now hear from FDA's Captain Hilda Scharen. She will be presenting on the Medical Device Development Tools program.

Captain Scharen, please proceed.

CAPT SCHAREN: Good afternoon. My name is Hilda Scharen and I am Director of the Medical Device Development Tools (MDDT) program for CDRH.

The MDDT program is a voluntary program launched three and a half years ago and is a way for FDA to qualify tools that medical device sponsors can use in the development and evaluation of medical devices. The intent of the MDDT program is to expedite medical device innovation, development, and regulatory approval or clearance through qualifying and making MDDTs publicly available.

Tool submitters may include traditional device industry developers or it may include research organizations, academia, clinicians, or other members of the medical device

development community including groups with common goals and interests.

There are many benefits to the qualification program listed here. Particularly beneficial, the program provides medical device manufacturers with a mechanism for discussing early concepts about a tool, fostering collaboration on tool development, and potentially increasing adoption and use of the qualified tools in emerging medical technology in device areas.

An MDDT is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. It is scientifically validated and qualified for a specific context of use (COU). COU is analogous to indication for use and describes the way the MDDT should be used, its purpose in device evaluation or regulatory submission and specific output or measure from the tool.

Qualification is an FDA conclusion that within the context of use, an MDDT can be relied upon to have a specific interpretation and application in medical device development and regulatory review.

CDRH reviewers should accept the validation of the MDDT methodology if used within the qualified context of use without the need to reconfirm the suitability and utility of the MDDT when used in a regulatory submission.

CDRH recognizes three types of MDDTs which can be distinguished primarily by how the tool measures the relevant parameters; of particular interest to this group, clinical outcome assessments such as patient selection for clinical studies or clinical study outcomes. Other types include biomarker test to assess risk or measure safety or predict outcomes, and nonclinical assessment models which can be computational or animal models.

Before the creation of the MDDT program, tools used by developers were evaluated on a case-by-case basis for each medical device submission. Now, with the creation of the

voluntary and optional MDDT program, we are creating both efficiency and transparency in the review process for submitters and reviewers.

Qualifying tools for a specific use, FDA facilitates application for multiple medical device submissions and manufacturers. A qualified tool's methodology does not need to be re-reviewed as long as it's being used within the qualified COU. Only the output from the qualified MDDT is assessed as part of the regulatory review. In terms of transparency, submitters have assurance that a qualified tool will be accepted by FDA without the need to reconfirm the suitability and utility of the tool.

FDA has qualified eight MDDTs with wide-ranging applications for cardiovascular, neurology, plastic surgery such as BreastQ reconstruction module, automated insulin dosing and imaging devices, as well as cross-cutting tools for implanted medical devices and cybersecurity.

The MDDT process has two phases: proposal and qualification. The goal of the proposal phase is to determine if the MDDT is suitable for qualification through the MDDT program. During this initial phase we are asking submitters to provide up front their data collection plan or qualification plan to help the submitter provide the key elements they need to include for FDA to determine its suitability. The proposal review time is approximately 60 days.

Once an MDDT is accepted into the program, it advances to the qualification phase during which we ask submitters to provide the data collected according to the qualification plan. So FDA reviews all the evidence to support qualification and make a regulatory decision. The goal of the qualification phase is to determine whether, for a specific context of use, the tool can be qualified based on the evidence and justification provided.

Included here are resources on how to submit a proposal, as well as links to the guidance, MDDT web page, and e-mail to contact the MDDT program.

To conclude, MDDT qualified tools have the potential to streamline medical device development and regulatory review. Through programs such as the MDDT program, we are modernizing the regulatory evaluation process and reducing the time and resources needed to develop and assess new medical products.

Thank you for your time and interest in the MDDT program.

DR. LEWIS: Thanks very much, Captain Scharen.

We will now hear from the FDA's Dr. Jacqueline Francis regarding assessment of effectiveness in clinical trials. Dr. Francis will introduce Dr. Alexander Sun at the conclusion of her presentation.

Dr. Francis, please proceed.

DR. FRANCIS: Good afternoon. My name is Jacqueline Francis and I'm a medical officer in the Office of Surgical and Infection Control Devices in CDRH. Today I will be discussing the assessment of effectiveness in clinical trials.

Demonstrating the clinical effect of a dermal filler in an unbiased manner is critical in the process of evaluating medical device performance. Developing a primary effectiveness endpoint is useful in this regard. Typically, the process includes the use of a validated sponsor-specific scale that assesses wrinkle and/or defect severity from a clinician's perspective for the proposed indication for use. This is a clinician-reported outcome.

The effectiveness scales are typically 4 or 5-grade photo-numeric scales that are validated to demonstrate good inter- and intra-rater agreement, as well as have the ability to demonstrate a point change on a scale to represent a clinically meaningful change. The scale may be validated using photographs or through live validation.

We have identified challenges to this type of effectiveness evaluation. While the use of clinician-reported outcomes to evaluate primary effectiveness endpoints offers a validated and objective means to assess clinical meaningfulness of the study treatment,

there are challenges to this approach, as a scale is often proprietary as it is developed and validated by the sponsor of the clinical study.

For example, for review of effectiveness, scales used to evaluate nasolabial folds showed that out of 13 different PMAs, seven different effectiveness scales were used based on both live and photo evaluation with primary effectiveness endpoint evaluations performed at various time points ranging from 12 weeks to 13 months after treatment.

Therefore, because the scales are proprietary, not publicly available for other interested study sponsors seeking similar indications and vary between manufacturers, we are finding that it becomes challenging to compare results of clinical studies.

Additionally, we have identified challenges associated with the effectiveness evaluation through patient-reported outcomes. A patient-reported outcome is any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else. Dr. Michelle Tarver discussed this earlier. Dermal filler studies typically include input from the patient as a secondary or ancillary effectiveness endpoint. These assessments include validated patient-reported outcomes assessed by subjects throughout the study.

Patient-reported outcomes measures face similar challenges to clinician-reported outcomes. While there are some widely used patient-reported outcomes, study sponsors often include their own proprietary measures of subject satisfaction which may not be adequately validated or widely available for use. As new indications for use emerge, including augmentation and face contouring, the definition of a clinically meaningful outcome increasingly depends on patient preference and expectations.

Dr. Tarver earlier discussed patient preference, so I won't define it again, but it is important to point out that the endpoints of the study should be clinically meaningful and that this efficacy may ultimately depend on the patient. Therefore, PPI is useful in

evaluating a device's benefit-risk profile when patient decisions are preference sensitive.

For example, for a facial contouring indication, each patient has specific aesthetic goals and a certain tolerance level for risk. The level of risk that is acceptable may differ by the patient demographic such as age, ethnicity, or gender identity. Additionally, the definition of clinical success may vary depending on patient demographics and the perspectives of different patient populations.

FDA proposes that study sponsors use publicly available validated clinician-reported outcomes and patient-reported outcomes to approve clinician-reported and patient-reported effectiveness outcomes across dermal filler studies which can be accomplished by study sponsors publishing clinician-reported outcomes and patient-reported outcomes used in their clinical study, and study sponsors submitting their clinician-reported outcomes and patient-reported outcomes to the MDDT program, which was discussed before by Hilda Scharen.

The Panel will be asked for recommendations on the development of publicly available outcome measures for dermal filler studies and how to facilitate comparisons of effectiveness outcomes across dermal fillers.

While patient-reported outcome measures provide a snapshot of a patient's own assessment of an outcome at a given time point, they do not convey how much the patient values one specified outcome when compared with other potential outcomes. Due to the elective nature of cosmetic procedures, clinician-reported outcomes which measure improvement may not adequately represent patient perspective on the benefit or tolerance of risk. The definition of clinical success may vary depending on the patient demographics and the perspectives of different patient populations.

I spoke before about an example of facial contouring indication in which we noted that each patient has specific aesthetic goals and certain tolerance levels for risk. What is

considered acceptable risk may differ by patient demographics such as age, ethnicity, or gender identity.

As another example, a patient seeking correction of age-related changes in the lips may have a different idea of clinical success compared to the patient seeking lip augmentation. Current effectiveness measures may not adequately incorporate these diverse perspectives.

Because we believe that current effectiveness measures may not adequately incorporate these diverse perspectives, FDA proposes that the design and validation of clinician-reported outcomes and patient-reported outcomes should represent diverse patient populations based on gender, including transgender and non-binary patients, age and ethnicity, as well as diversity of aesthetic treatment goals for each patient group.

Since safety and effectiveness outcomes of a clinical study may vary based on patient demographics, FDA believes that dermal filler studies must clearly define the intended study population, gender distribution, and Fitzpatrick skin types. Fitzpatrick skin type is a numerical classification schema for human skin color. The Agency has encouraged sponsors to design studies that include enrollment goals by Fitzpatrick skin type with at least 20% of the subjects of Fitzpatrick skin types IV through VI and 10% from Fitzpatrick skin types V through VI.

We recognize that these enrollment goals may not be reflective of the distribution of Fitzpatrick skin types in the United States population and that enrollment goals that better align with the demographics of a broader population of patients may be appropriate for key subgroups such as age, gender, or ethnicity.

We anticipate that there will also be indications where the demographics of patient populations who are seeking specific treatments differ from those of the general U.S. population, as well as indications where patient demographics can evolve over time, for

example, increasing representation of men.

FDA has identified the importance of the following measures to overcome the challenges associated with emerging indications for use to encourage the incorporation of patient satisfaction and perspective into the study of dermal fillers and informed decision-making process:

- Incorporation of patient perspective and diverse subject populations in the development of validated clinician-reported and patient-reported outcomes
- Early identification of enrollment goals to ensure that the study population is appropriate for the indication

The Panel will be asked to discuss factors to be considered in determining the appropriate patient populations and development of clinician-reported/patient-reported outcomes in clinical studies.

Prior dermal filler approvals may have been based on clinician-reported outcomes and patient-reported outcomes that did not incorporate patient perspectives and the diversity of subject populations, or may have been based on studies that enrolled only small numbers of important demographic groups such as men or those with higher Fitzpatrick skin types.

The Panel will be asked to discuss incorporating patient perspectives in device labeling.

FDA proposes the proactive incorporation of patient preference information into the design of clinical studies in the approval process. This may include the incorporation of study endpoints to query subjects regarding the level of risk that is acceptable to achieve various levels of perceived benefit.

The Panel will be asked to comment on the utility of PPI in informing the benefit-risk assessment of dermal fillers.

I will now introduce Dr. Alexander Sun, who will discuss informed decision making and labeling. Thank you for your time.

DR. SUN: Good afternoon. My name is Alexander Sun and I am a medical officer in the Office of Surgical and Infection Control Devices. Today I will be discussing informed decision making and labeling.

As discussed previously, FDA recognizes that the patient perspective plays a key role in several aspects of the regulatory process for dermal fillers. As dermal fillers are aesthetic devices, choosing treatment lies with the patient's perspective on benefit versus their tolerance for risk. Given the growing use of dermal fillers and reports of adverse events such as intravascular injection, the informed decision-making process is crucial. The goal of labeling and informed decision making is to provide the patient with information about the benefits and risks of a device in a manner that is meaningful to the user and should aid the user in deciding whether to undergo the procedure.

In the practice of medicine, labeling information is often not directly seen by patients but is instead communicated by the provider. Discussion includes, but is not limited to, addressing patient goals, preferences and concerns, and discussing anticipated benefits and possible risks to ensure that expectations are clear. The goal of informed decision making is to inform, not influence.

Informed decision making should include information from labeling. Dermal fillers are accompanied by provider labeling and patient labeling which give an overview of key information regarding the device. The labeling includes a device description, indications for use, precautions and contraindications for where the device will not be appropriate; benefits and risks, including periprocedural information such as common treatment responses and precautions for serious findings such as visual or neurologic symptoms or the possibility that adverse events may need further medical or surgical management. The

labeling discusses alternative therapeutic choices including surgical or nonsurgical options or not pursuing treatment. Finally, the labeling includes details about the clinical study and other findings during postmarket surveillance or any other information that can help the patient make an informed decision.

Labeling is updated as further information becomes available. As dermal fillers continue to be used and approved for new intended uses in anatomical areas, labeling needs to be updated to convey risks. As discussed earlier, more and more indications are focused on augmentation and contour deficiencies instead of traditional wrinkle filling. Surgeon practices or anatomical locations including unapproved uses may be associated with a different risk profile and current practices may not adequately communicate these risks to patients.

To ensure that patients are aware of the risks of these procedures, FDA has proposed additional strategies to consider for communicating labeling information to patients. An example of a strategy may include developing more consistent patient labeling among device sponsors. The benefits of consistent patient labeling would include the structure and labeling content as discussed previously, but with consistent presentation and formatting of the information. Labeling can include additional information regarding the risks for anatomical areas or intended uses with different risk profiles.

In addition to consistency in patient labeling, FDA is proposing other examples of possible strategies such as a box warning or a patient and provider decision checklist. A box warning appears on the device labeling and not just the box itself and is designed to call attention to serious or life-threatening risks of a device. A box warning can more clearly delineate the serious adverse events of vision impairment and stroke from intravascular injection.

A patient and provider decision checklist can be another example of a strategy. The

checklist can include information and risks of dermal filler injections with specific mention of the risks of intravascular injection including soft tissue necrosis, blindness, and stroke.

If approved through the PMA process, areas with more reports of vascular occlusion related events can require an additional informed decision making checklist acknowledging the acceptance of increased risk. Finally, a checklist allows for patients and providers to mutually acknowledge that each item was read and discussed.

In addition to informed decision making, there are areas for improvement in communicating information to patients after injection. Currently, patients often may not know which filler they had, the amount injected, or the specific injection location, especially in patients who have multiple areas injected or have had dermal fillers more than once. This may prove consequential if the patient develops an adverse event, if they transition care to another provider, or are seen by another medical specialty for another issue. As the presence of dermal filler may affect their diagnosis or management of other conditions, injection information should be readily available to the patient.

FDA would like to discuss with Panel members whether there are any methods by which this information can be conveyed to patients.

FDA would like to propose an example such as the concept of a physical or digital patient device card. This card would contain specific information about the dermal filler including the following information:

- Patient information;
- Device location and amount injected;
- Provider information;
- Date of injection;
- Adverse event information and precautions;
- Device and manufacturer information; and

- Contact information for adverse event reporting.

This may also include post-procedure instructions such as for managing common treatment responses.

This type of post-procedure information has several benefits. First, it provides a record of the product that was used for injection along with the unique device identifier.

Secondly, this can provide information about common responses and adverse events. In the setting of transition care between providers such as to another injecting provider or in the event of an emergency department visit, the patient can have documentation of prior filler use and locations. Information about the device that was used can also allow patients to stay updated with any new information as new safety data is uncovered.

Finally, the card may offer instructions on reporting events to the manufacturer, the provider, and the FDA MedWatch System. As Amy Rogers mentioned in her MDR presentation, the data we receive through our device reporting system is often incomplete or inaccurate. Providing information to patients on the card may help to increase the capture of adverse events and facilitate communication of information about the specific device that was used. This may additionally allow FDA to understand whether certain adverse events are correlated with any injection attributes such as injection volume, if the patient reports the adverse event.

FDA would like Panel input on questions regarding informed decision making and labeling. The Panel will be asked whether the current strategies are adequate or if additional strategies are needed to appropriately convey risks to patients. The Panel will be asked to comment on the example strategies.

Next, the Panel will be asked for their recommendations on a patient device card as a part of patient labeling. The Panel will be asked to comment on the proposed mockup

card example. Thank you.

DR. LEWIS: Thank you, Dr. Francis and Dr. Sun.

The floor is now opened for the expert Panel to question the four previous presenters about any of their information. So we will -- if I can get this off of my screen here. We'll begin with Dr. Alam.

DR. ALAM: Thank you for all of those very helpful presentations that show how much work FDA is doing to clarify the whole issue of measurement and communicating well with patients. Before we get into the nitty-gritty of the questions, I guess a question that I have for you is I was reading through the questions that you have based on your presentations and I'm a little concerned that this could become such a complicated process that it might help -- instead of helping patients understand the risk-benefit, where their preferences fit in, how certain processes might be safe or dangerous, we might actually confuse them more. So I guess my question to you is, are you wanting a relatively simple solution or are you wanting a definitive solution that would be optimal but somewhat cumbersome to implement?

DR. LEWIS: Dr. Chang.

DR. CHANG: This is Cynthia Chang. So maybe I can start and if my colleagues have anything to add, they may do so.

But you know, in general, we recognize that we have been trying very hard to incorporate patient-reported outcomes and patient perspectives in our review, assessment, and regulation of dermal fillers because of the special considerations with aesthetic devices. In general, we do recognize that there is a lot more that we could be doing to try and keep up with the diversity of new indications, the trends that we see in different demographic groups. And so in terms of how complex or how simple of a solution we're looking for, I don't know that we have anything specific there. I think we recognize that we can always

do better and that's what we're looking to the Panel to advise us on. It may be, of course, that there's no one-size-fits-all specific recommendation due to the diversity of indications, patient populations, and issues here. It may be that there are some general principles that we should consider as we evaluate each specific situation. Hopefully, that helped to address the question and to frame the discussion.

DR. ALAM: Thank you.

DR. CHANG: Thank you.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: I also had a question for the FDA and Dr. Chang. As I was preparing for this, I was puzzled about why there were questions so much about the patients' evaluations of whether these are clinically meaningful because I would think that de facto, the fact that 92% of people are repeat users and that they pay for this out of pocket, a substantial amount, certainly even on the surface of it suggests that there is already a patient valuation process in place and happening in real life, and I just wondered why there needs to be more done to try to somehow calculate whether there are valuation standards for patients.

DR. LEWIS: Other questions or comments.

Ms. Brummert.

MS. BRUMMERT: I like the idea of a card. I mean, I keep saying this, but patients are just not informed of the risks. So what I like about the patient card is that there could be like the adverse reactions that are mild, but then the ones that also are considered -- get more of a major event and that way they can track the information because they have information about what they were injected with or what the device was or what medications were in there and then if they go to a different doctor they can share information. This is something that patients have wanted forever. I think this is perfect.

DR. LEWIS: I guess -- Dr. Chang.

DR. CHANG: Yes. So to address Dr. McGrath's comment or question about why we're putting such focus on patient-reported outcomes and patient preference, I would actually like to allow my colleague, Dr. Michelle Tarver, to make a few comments.

So Dr. Tarver, would you like to speak?

DR. TARVER: Thank you for the opportunity to present to you all today. Can you hear me okay? Excellent.

So what I'd like to clarify, a couple of things, we often measure the patient's outcome because they're the only ones who can tell us how they're experiencing the condition, whether there's true improvement from their perspective, and we do that in clinical trials in a standardized way because we want to be able to combine it and analyze it, so that's why patient-reported outcomes are important. To your point about clinical meaningfulness, I think there's a difference between what's meaningful to patients and what's meaningful to clinicians.

And as a clinician myself, we know that in a lot of procedures, particularly in LASIK, I'm an ophthalmologist, we know that there's a different experience than what we, as clinicians, measure versus what patients sometimes tell us and so that is only able to be measured if we have a standardized tool in our trials, so that's why that's an important element in clinical trials.

The second point that I want to emphasize is that it doesn't have to be complicated, though. We have some very simple ways of assessing patient-reported outcomes, so it depends on what the intent is and making it fit for purpose, which is what I alluded to in my talk. And the last point that I did want to clarify, I think, to a prior comment, which is not all patient-reported outcome measures are intended for every use. In other words, there may be tools that are used in clinical trials that are not appropriate for clinical care and vice

versa. So I think our statements are largely about the clinical trial or postmarket surveillance process. I hope that answers your question.

DR. LEWIS: Dr. McGrath, any further comments?

DR. McGRATH: No, it was not -- I'm sorry. It wasn't clear to me that that was for clinical trials. I thought this -- it just seemed so obvious that this is so different from something like an implant, a body implant, or LASIK where it's a one-time procedure. This is something where the patient can make their sense of approval known by returning in 6 months, which they do, over and over in over 90-some-odd percent of the patients. So thank you, that helps.

DR. LEWIS: Dr. Chang, in regard to having standardized evaluations, I'm not really familiar with the plastic surgery standards and literature on this. Are such things not available now through the societies and is FDA proposing to develop them uniquely or exactly what are the specifics of the proposal?

DR. CHANG: Yes. So this is Cynthia Chang.

Regarding the effectiveness scales, there are a variety of scales out there, so they are usually specific to the specific indication, and Dr. Francis gave an example in her talk about, I think, wrinkle assessments where there were seven different scales used by 13 manufacturers, for example, for wrinkle assessment. And so if you're a patient, it's very difficult to potentially compare different products for the same indication.

So one possible solution that we're discussing is for the specific scales for a specific indication to be made public, either through a publication in the literature so that multiple manufacturers may use them, and also that they could be evaluated through our FDA MDDT program. So hopefully that helps to address the question.

DR. LEWIS: Thank you.

Are there further questions from the Panel for the speakers?

Dr. Gonzalez.

DR. GONZALEZ: Yes, thank you. So yeah, I was actually going to sort of echo an earlier comment about the important distinction between the use of this information, both PROs and PPI, for a clinical trial, such as clinical practice. I guess it makes it more obvious, of course, once the product is available and we can observe a behavior from the patients in a fairly free way, right? That we can make some conclusions, reach some conclusions based on that behavior.

That said, I think I do need to point out that obviously, that decision is not taken in the void, it is taken in conjunction with the physician. So it is true that sometimes, of course, the judgments of physicians play a role into how they can make decisions themselves. This is a very particular problem and I don't mean to imply that this particular case is an issue, but I think we do need to be very careful, even in situations where it seems like patients are making these decisions on their own, to be careful to pay attention to whether there are signals that suggest that the information that they're getting might be incomplete or somehow they're making decisions in a way that may be leaving out some important considerations. And while nothing happens, everything is okay, but once things start happening, then regret starts setting in and then they want to understand why they were not informed in a particular way and of course, there's consent and other ways of achieving that. So it doesn't have to be through patient preference information entirely.

But in the clinical context, I think based on what I've heard, it does make a lot of sense to consider the use of patient preference information for a variety of reasons. Number one, the differences in the way that efficacy is being measured through these different instruments, the patient preference information could potentially provide a way to uniform those measures by comparing apples against oranges using a banana, right, so saying this PRO measured -- gives this particular change, this PRO measured this -- gives you

this particular change.

But I can tell through patient preference information, what is the exchange rate between these two different measures and a common bad effect, right, a common adverse event, and that can give me a bit of an exchange rate between the two, so it's something to consider as well as, of course, determining the minimum meaningful change that might be at play when making decisions for specific interventions.

DR. LEWIS: Thank you.

Are there further questions?

DR. ALAM: I just have a quick comment, if I can make it with your permission, sir.

DR. LEWIS: Yes, go ahead.

DR. ALAM: I just want FDA -- I'm sure they're aware of this. Aesthetic outcomes after filler injections of minimally invasive aesthetic treatments do not often have clear outcomes to measure. So I just want to -- I'm sure you're aware of the fact this is for all. So for instance, if a specific filler is approved for filling periocular lines, for instance, in a study that might be once done, but in clinical practice it's quite different and someone might get an off-label indication with that filler and another filler and get a neurotoxin and get a laser and then what they're looking at is the cumulative improvement in their sense of how their spouse thinks they look.

So it's not quite the same as if somebody gets a procedure for weight loss and we just subtract their weight, it's not quite that clear cut, it's a very muddy outcome. The outcomes are very emotional, they're not quantitative, they're like how you feel about stuff, how other people feel about how you feel about stuff, it's better/worse compared to some baseline that is not uniform and that is not even easy to define because what really is the contour, like do you care really about the wrinkle or do you just care about the shape of your face. I don't want to go on and on, but I just want you to be aware, which I'm sure you

are, that this is a situation where you're looking at things in clinical trials with relatively directed instruments in a very controlled setting, but how that instrument performs or how the change in that instrument is after use of that product in a controlled clinical setting doesn't clearly abstract to how that device will be used clinically or its impact in an aesthetic sense in typical clinical use.

DR. LEWIS: Thank you.

Dr. Brown.

DR. BROWN: Yeah. And I was just going to add to that, and I think that is why patient-reported outcomes are so helpful, because a patient could keep going back for treatment thinking that there's no other option, this is the only thing I have, I might as well just keep doing it, even though they're only lukewarm satisfied with that treatment. So that's why I think these patient-reported outcomes are so helpful.

DR. LEWIS: Thank you.

Further questions.

DR. ASHAR: This is Binita Ashar. Can you hear me, Dr. Lewis?

DR. LEWIS: Yes, I can. Thank you.

DR. ASHAR: Yes. So I just wanted to thank the Panel for their comments and just to emphasize the fact that either these wrinkle fillers, there is growing use among various populations, so there's more patients that are exposed, that will be exposed in the future, there are more applications and there's more devices, and with each device, if every sponsor creates their own proprietary scale, there is less of an opportunity to compare devices across similar indications.

And so I guess the question for the Panel really is, are we doing all the right things? It's a little bit muddy in that right now. I mean, we've been trying to be very systematic in our reviews and evenhanded, and we are committed to being least burdensome, but it

could get muddier as more patient exposure occurs, as more devices and more uses emerge for facial contouring and wrinkle filling. And so really, that's the question, that's the big question, how do we systematically set things up so that we're prepared for that, whether it be informing the patients or making sure that our metrics are helpful both in the clinical trial arena and out in clinical practice.

DR. LEWIS: Dr. Alam.

DR. ALAM: Dr. Ashar, I think it's a very admirable goal that you have, which is to use uniform nonproprietary measures to compare all of these products because that's obviously much better than comparing using different measures that potentially are a little fungible and particularly, given the financial and other incentives, could be more favorable to one device than another, so I think that's great. I think there are some barriers, which is that I'm not sure the proprietary -- the companies that have proprietary devices are terribly interested necessarily in lowering the bar for their competitors and when it comes to -- like, for instance, my group is trying to work on something, an outcome measure in this arena, full disclosure, because we're in a university and we like to do things for fun, but it's difficult because there's not a tremendous amount of resources and money for doing such things, except for with the companies.

And so if you want to be fully detached from the companies, it can be quite a complex endeavor, as you know, to draw the face validity and then all of the various methods you need to do to standardize an instrument. So I suspect you'll make progress, but if you're a little frustrated by the lack of availability of these, I think some of the barriers are just pragmatic barriers.

DR. LEWIS: Further comments or questions.

(No response.)

DR. LEWIS: If not, we will close this portion of the session and open the floor now to

the FDA questions for the remainder of the afternoon. I would ask the members of the Panel to please turn on your videos, if you haven't already, until you're ready and remain on mute until you're ready to speak. We'll go specifically to the FDA Question Number 5. Dr. Francis will again be presenting the questions on behalf of the FDA and this is a deliberation period among the Panel members only. Our task is to try and answer the questions for the FDA and based on the presentations we've heard.

So Dr. Francis, would you proceed?

(Off microphone response.)

DR. LEWIS: Dr. Francis, we can't hear you. Or at least, I can't. No, I don't hear you. We need a little audiovisual help, I think, because Dr. Francis indicates that she's not muted but we're not hearing her. Is anyone else hearing -- is there anything wrong with my sound? Okay, thank you. I don't think anyone hears you.

(Pause.)

DR. CHANG: Hi, this is Cynthia Chang. We're having IT issues with Dr. Francis. I could read the question.

DR. LEWIS: Yes, why don't you go ahead.

DR. CHANG: Okay, sure. So Question 5 is: Development of publicly available validated effectiveness measures, and use of these measures in premarket dermal filler studies, would facilitate standardized evaluations with uniform endpoints and success measures, permitting comparison of effectiveness outcomes across dermal fillers.

a. Do you have recommendations on how to encourage both the development of publicly available measures and the use of these measures in dermal filler studies?

b. Are there additional measures, resources, or tools that would allow patients as well as clinicians to compare products for a similar indication and to address

patient's expectations?

DR. LEWIS: Thank you.

All right, could we have some responses? So the question is not about the virtue of having such measures, it's about how to develop such measures presumably in the face of the proprietary interests of the manufacturers and the numerous ones that already exist. So do we have recommendations on how to encourage the development of publicly available measures?

Dr. Ballman.

DR. BALLMAN: I keep moving around. Yeah, I mean, so I work primarily in cancer and we do have sort of standardized things, and people just don't get approval unless they use the standardized measurements and I think that -- you know, so RECIST criteria came into being and so forth, and I think that was partially funded by companies because they wanted their products approved. And so if approval gets withheld unless they use these standardized or come up with standardized measures, I think that's one way of sort of going about it.

DR. LEWIS: Dr. Bressler.

DR. BRESSLER: I'll mention two things from ophthalmology and I don't know if it will work in this arena. The FDA, in ophthalmology, has partnered with some research society groups in ophthalmology to try to develop either questionnaires, perhaps after LASIK or other patient preference questions that are then available to the public, both industry and university-based centers, so I would encourage you to look into that. I know the FDA knows of this. Dr. Tarver has done some of these with ophthalmology herself.

As far as encouraging people to use them, I can only tell you that in ophthalmology, not in the United States, but for reimbursement of elective procedures elsewhere in the world, the patient-reported outcomes became critical. They helped explain to payers, often

government payers, how to translate visual acuity, which meant nothing to them, to perhaps -- it didn't mean nothing to them, but it was harder to understand than life, for example, in oncology -- so that these patient-reported outcomes gave value to clinical trials to allow them to assess where they wanted to pay. So if those avenues are looked at, that might be ways of encouraging this, and we benefited by having that additional information in ophthalmology.

DR. LEWIS: Dr. Alam, did you have a comment?

DR. ALAM: Yes, sir.

First, looking at (b), in terms of additional measures, resources and tools, there do exist some for global aesthetic improvement and I would suggest kind of like RECIST criteria, using something like that would be a good idea because otherwise you run the danger, even if you have specific tools for fillers that you use for off-filler studies, then you have different tools for the laser studies and different tools for the neurotoxin studies and again, you'll get in trouble because you're really trying to look at aesthetic improvement. So that would be one thought.

And then with regard to how to encourage development, I think a bunch of people have said this already, but I don't know what your leverage over the companies is, but you might want to use some of your leverage to have them submit their tools to the MDDT program or failing that, to have them give some money to some group that then could give grants to other academics to help develop some of these tools. Thank you.

DR. LEWIS: Dr. Chang.

DR. CHANG: Yes. I would like to ask Dr. Tarver to address a few points that have just come up.

Dr. Tarver.

DR. TARVER: Sure. So I'd like to first talk about the issue of collaboration in the

precompetitive space. We have a number of efforts under way to develop patient-reported outcomes where industry is sitting at the table with professional societies and funding the development of a tool that everyone can use. So it is being developed in the precompetitive space and it's to measure a concept that transcends one particular device. So it may be looking -- in ophthalmology, there are many different lenses that do many different things and one questionnaire, though, can measure visual symptoms.

So I think to Dr. Alam's comment, the fact that there may be a concept of aesthetic improvement, that technology, it's agnostic to that technology, right? Aesthetic improvement is a concept and that same tool potentially could be used in many different device studies. So we are doing that in ophthalmology and we are doing it in other disease spaces. So I think that the idea that each one has to do one, which I think Dr. Ashar alluded to, makes it challenging for that patient-provider conversation because the scales are different, the scores are different, and it's hard to know what they need when they're done in each individual trial. So that's part of, I think, the impetus behind the questions. Thank you.

DR. LEWIS: Thank you.

Are there further comments?

Dr. Perry.

DR. PERRY: Hi, thanks.

Yeah, I think that with almost 40 approved fillers that this is critical, and I really like the idea of asking or mandating the proprietary measures to become public and then using those as the basis to create a more standardized system, I think that's a great idea.

DR. LEWIS: Yes, Dr. Gonzalez.

DR. GONZALEZ: I have a question. The existing instruments to measure that are being used, are they being validated against specific broader measures or how are they -- I

mean, how are they developed? And I'm only asking that because the instrument, I guess, which -- that would be validated could actually be also required as part of the trial and it could also help add another layer of comparability across trials, as well.

DR. LEWIS: I assume they're developed by the individual companies, but -- Dr. Chang, is that correct?

DR. CHANG: Yes, when we evaluate a particular new filler or indication, whether in a clinical trial or in a PMA application, we do look at the validity of the scale that is used and we do things such as statistical analyses to make sure that the intra- and inter-rater reliability are appropriate, that the differences between the different numbers on the scales are clinically meaningful, that people who are evaluating them can distinguish between a four or a five on that scale, and we make sure that the patients who are part of the validation study are appropriately representative of the patient population.

DR. GONZALEZ: Can you hear me? I don't hear myself.

DR. CHANG: So --

(Cross-talk.)

DR. GONZALEZ: I'm asking -- sorry, I was just asking if they're being correlated with other measures like, say, PROMISE or something like that.

DR. LEWIS: Okay. Can we turn to section (b) of the question? Are there additional measures, resources, or tools that would allow patients and clinicians to compare products for a similar indication and address patient expectations?

One thing that occurs to me is that since these products have different longevities and persistence, it would be a measure over time of continuing effectiveness and how they compare at time intervals: 6 months, 1 year, 2 years. Things like that would be useful since there seems to be fair differences in those.

Dr. Miller.

DR. MILLER: Yes, thank you.

I think some of these things, what we've always needed in plastic surgery and in aesthetic surgery, of course, is some kind of objective measure about what are we actually changing on the patient and how durable is it. Patient-reported outcomes are critical, but even to correlate some objective measure of a change made in the patient to what they perceive their quality of outcome to be, those don't exist very much.

But there are some tools that are out there that can help this, like three-dimensional image analysis. You know, if you are changing the contours of someone's face or other parts of their body with an injectable, well, the patient may say that's fantastic but then how do you correlate their subjective feelings of how wonderful it is to what you've actually done to the patient?

So if you could use some computer analysis of surface contours that's high resolution enough to measure several millimeters of change or something like that and do some image analysis and then show what type of changes have elicited a number five in people's responses of the durability, those type of objective measures, I think, would make a big difference in all of these things and -- because if we -- the patient-reported outcomes are very important, but there's so much subjectivity involved, so much cultural overlay involved, so much personal preferences involved, it becomes hard to really know that what you're doing has made the right kind of differences for somebody, so -- but I think the computer technology exists with image analysis to maybe help with some of this.

DR. LEWIS: Given the sophistication of facial recognition technology these days and the fact that it apparently is being deployed around the world, but especially in China, for recognition of huge populations, there must be quantitative and objective evaluation systems that might potentially be of value here.

DR. MILLER: Yeah, I think so. Adaptive to this purpose. I mean, image --

DR. LEWIS: Correct.

DR. MILLER: -- recognition is one thing, but the kind of detail required to do good facial recognition, that same type of computer analysis can be done to look at differences in one person's face between before and after treatments, and I think this type of information is important in order to understand -- I can't tell if what I do to somebody has benefited them, necessarily. All right, I'm limited in what I know I can do, I can change the shape of something by a certain amount or whatever, and if I could somehow correlate what I know I can do to a patient with how they're going to feel about their outcome, that would be very helpful to have and that requires some good objective measures of changes in appearance, changes in the contours, things like that.

DR. LEWIS: Thank you.

Dr. Alam.

DR. ALAM: Sorry, I just want to make sure -- yeah.

I think one thing to keep in mind, technology is very alluring, obviously, because it reduces cost and it doesn't get tired, no one has to fill out a form or a questionnaire, that's wonderful. I think one of the limitations of technology is we have to make sure that some of these algorithms aren't sort of a proprietary black box where we don't necessarily know what they're measuring.

And I think another issue is that we need to make sure there's a correlation between what the machine detects and what a person sees. So if a machine can detect a difference reliably, that's precise and accurate, but if it doesn't make a difference for the patient or anyone that they know, then even if there's been an improvement, it's clearly not a clinically relevant improvement and I think that's one danger we run into when we find these minute differences, we don't know how to interpret them. So we still have to rely on the patient to interpret them for us. Thank you.

DR. MILLER: Can I make another comment about that? I don't mean to derail our discussion, but I think this is important because this shows up the deficit of where we are with a lot of these aesthetic procedures. For example, I can do an operation to change the location of someone's nipple on their breast, okay, like I have things I can do to move it certain distances, but whether that's going to lead to a patient satisfaction is difficult for me to know because I don't know what that's going to correlate to.

Like, if I knew that if a patient's asymmetry of their nipples was 5 mm, they're fine with that. If it was 7 mm, well, you start to bridge over into where people are not happy. We know if it's 5 cm out, that's not acceptable. So somewhere in there there's a crossing point where I can do something that they're going to be happy with, but I don't know where that crossing point is, I'm just guessing all the time. The same problem as with all these fillers.

And so I think that if I knew, it would just help, I think, if we had some objective measures which were correlated to patient-reported outcomes, that would help guide our therapies instead of just guessing. I hope that makes sense, what I'm saying.

DR. LEWIS: Do panelists have any other comments?

Dr. Matarasso.

DR. MATARASSO: So when we discover objective measures to correlate with patient-reported outcomes, we will have solved the holy grail of aesthetic surgery. Every one of us --

(Laughter.)

DR. MATARASSO: Every one of us that has treated these patients, the patients that we think have a mediocre result and they're thrilled and unfortunately, vice versa, they have a great result and they are unhappy. But we have the FACE-Q available. Mike, do you want to talk more about that? Or Mary? We have this FACE-Q available that might be

helpful. What do you think about that?

DR. MILLER: I think these are useful things and I think that may be something FDA can do. I saw earlier that they had the BREAST-Q as part of one of their device development tool aspects. Now there are some experts in plastic surgery in patient-reported outcomes.

DR. MATARASSO: Right.

DR. MILLER: And of course, Andrea Pusic.

DR. MATARASSO: Right.

DR. MILLER: And I'm sure the FDA people know about her, but I think there's a small community of people who are really quite expert in this and to get them involved with these discussions and help guide this would be very useful, probably.

DR. LEWIS: Dr. Burke, do you have a comment?

DR. BURKE: Oh, yes. I was just going to say there are so many devices or optical ways of doing these measurements and it's so difficult to conceive of having the exact same device measuring or taking the three-dimensional pictures for many, many doctors in many communities throughout the United States and it's so difficult for these patients because, as we said, everything is subjective and sometimes more than one procedure is done.

A patient usually that has one procedure has multiple procedures and they're not going to wait a year or 2 years to see the durability of one particular injection because they will have moved on to the other most recent development. So number one, the patients are going to have various things and also the ways that we visualize them are different from clinic to clinic or region to region. And third, the technology is expensive and time consuming, so it's kind of difficult to see that this could be done except as specific studies.

DR. LEWIS: Further comments?

(No response.)

DR. LEWIS: Seeing none, Dr. Francis, can we move on to Question 6?

DR. FRANCIS: Yes, we can.

DR. LEWIS: Good. Thank you.

DR. FRANCIS: FDA recognizes the importance of incorporating diverse subject populations in clinical studies, and in the development of validated outcome measures. To this end, FDA has recommended that clinical studies enroll patients with all Fitzpatrick skin types. However, given the diversity of patients with respect to age, race, and gender, as well as differences in individual risk tolerance, i.e. patient preference, we have the following questions:

a. In addition to Fitzpatrick skin types, do you recommend defining any additional patient populations for clinical study enrollment and the development of valid, clinically relevant effectiveness measures?

b. How do you recommend the appropriate patient populations be identified, and what factors or data do you recommend be considered in determining the appropriate patient populations?

DR. LEWIS: Okay. A somewhat complicated question. Could we have thoughts on that issue? Other than Fitzpatrick skin type, what other variables are there that you think should be included and what specific measures would reflect that?

Dr. Alam.

DR. ALAM: Well, one -- and I'm assuming you already have thought about this, obviously, but I think stratifying age is important because what works well for a 25 or 30-year old is very different than what works for a 65 or 70-year old. So obviously, you want to enroll people of different ages, but you also want to be cognizant of the fact that they might respond differentially, so that would be one factor.

DR. LEWIS: Other issues?

Dr. Burke.

DR. BURKE: Yeah. So I think, sort of past medical history and past history of previous procedures. I think we said that possibly even vascular occlusion might be more prevalent in patients who have had past facial surgery. So I think we definitely have to take the past medical history and even sometimes medical conditions into account.

DR. LEWIS: Dr. Alam.

DR. ALAM: I think that's a great point, Dr. Burke. And I think, building on your point, I think another way of differentiating aesthetic procedures that are filler and their using of fillers would be mitigating the visible signs of aging, that's sort of one category. And another category would be fixing some other traumatic or disease related defect.

So I think there's -- you know, because these things are often paid for out of pocket, we don't have a lot of research data on how they can be used to help someone with scleroderma or someone with lipoatrophy or other conditions like that. So those could be maybe separately studied and maybe on a humanitarian basis, companies that make less revenue treating such patients could be encouraged to consider some trials with them.

DR. LEWIS: Further comments?

(No response.)

DR. LEWIS: Okay, so aging but not aging in -- age and gender, obviously. But no other really specific suggestions.

Dr. Chang.

DR. MATARASSO: Prior treatment, prior treatment. Prior surgery. Prior energy devices, also. Energy devices, also.

DR. LEWIS: Thank you.

Dr. Chang.

DR. CHANG: Thank you for those comments. We would also be interested in a little bit more discussion on part (b) of the question regarding how appropriate patient

populations might be defined for a specific indication that might be new, that may be coming in, in the future where perhaps it's in one of the categories that Dr. Alam defined, either for correction of age-related deficiencies or for correction of something related to disease or trauma. Or we would posit another category which is just for augmenting a part of the face or the body, which is truly up to the patient's aesthetic goals. So for a new indication or even for existing ones, are there specific factors that we should be looking for when we try to figure out what is the appropriate patient population?

DR. LEWIS: Dr. Alam.

DR. ALAM: I'm not sure I totally understand that question. Are you trying to decide how to find those patients from a pragmatic standpoint or which of these sort of special populations might be relevant to a particular product?

DR. CHANG: We're specifically interested in whether there are additional demographic groups that we should be focusing on, that we should particularly make sure that we are recruiting into the studies and making sure that they're represented in the validation of the effectiveness measures. So right now we have Fitzpatrick skin type; however, you've also mentioned age. However, for a new indication, how would we go about identifying what are the appropriate demographics to consider for a new particular indication?

DR. ALAM: Well, you could have something like a patient focus group or something like that and see what they thought. I think you could ask practitioners who they thought this device might be most applicable to. You could ask the company that was developing it because they probably have a good sense of who they can sell it to.

I mean, one other group I can think of, which we haven't really discussed -- I don't know if it's really one that is appropriate to discuss -- is there are also differences in sort of socioeconomic status and I think sometimes the group that gets the fancy new product

right away is sort of an elite group, so there might be some way to make sure that it's not restricted to just people who are -- have the ability to have excellent beauticians like many of those on this call, but a broader array. But I would just ask around. I think it's very difficult to just, based on a product, to be able to logically deduce the groups that would benefit from it. I think you'd have to have some kind of focus groups and just talk it through with people, explain to them what the product is, what the product does, and then ask them.

DR. LEWIS: Dr. Miller.

DR. MILLER: I think those are great suggestions, but I think if you were to assign me -- if someone were to say go find out, I would review what's been published on this and see what kind of populations this is being done in. I mean, just for example, we talked about the Asian population wanting their radix augmented. Well, that's a pretty specific race and it's a pretty specific problem. So I mean, you could -- if we went through and sort of reviewed where these things are being applied, then you could probably begin to see the populations of individuals who are getting the fillers and then our studies need to reflect those populations to make sure that we're studying them because those are the people who are going to be getting it. Does that make sense? These are probably things you do all the time, so I'm not trying to tell you your business, but it seems like that's one way to go about trying to identify what populations are appropriate to study.

DR. LEWIS: Dr. Burke.

DR. BURKE: Yeah, in looking at different populations and just seeing socioeconomic groups, I mean, then we have to start thinking about smokers, alcohol intake, drugs, obesity and people that were obese, they gained weight or people that were thin -- I mean, people that were obese that lost weight, because their skin texture is entirely different. So there are so many different variables to try to identify.

DR. MILLER: We have to remember, these are aesthetic procedures that people are paying for out of pocket, so that right there focuses the type of individuals who would be candidates to receive these products. So I think we can limit some of our -- the variables we want to consider in what we look at in the studies. Even smokers, I mean, you're exactly right, Dr. Burke, smokers would be important but I mean, most people -- if you have a smoker who wants aesthetic surgery, you tell them stop smoking before I do anything to you.

DR. LEWIS: Dr. Burke.

DR. BURKE: I was just going to say that you can't imagine the number of people that take the new cigarettes, the e-cigarettes. And so I asked one patient who came for various cosmetic things to bring which type he had, at least we could record it, and he arrived with a shopping bag with over 15 kinds of cigarettes that he smoked and I had no concept that he smoked this multiple times a day and this is a very social kind of wealthy, intelligent, educated person. I mean, there are just so many things that we kind of sometimes assume and don't ask.

DR. LEWIS: Dr. Perry.

DR. PERRY: I think the number of variables is obviously going to be infinite and the way to hone it down is to look at the post-approval studies, to look at those annual reports and see what clinicians have been studying on similar drugs and similar implants. And that is, to me, the best way to hone it down, similar to what Dr. Miller said.

DR. LEWIS: Dr. Chang.

DR. CHANG: We thank the Panel for the helpful comments on this question. I believe we have what we need on this. Thank you.

DR. LEWIS: Thank you.

Dr. Francis, let's move to Question 7.

DR. FRANCIS: FDA proposes the proactive incorporation of patient preference information (PPI) into the design of clinical studies and the approval process. This may include the incorporation of study endpoints that query participants regarding the level of risk that is acceptable to achieve various levels of perceived benefit (e.g., filling of an age-related wrinkle, augmentation of the lips, improvement of the profile of the chin).

a. Does the Panel have recommendations regarding how to incorporate patients' preferences of tolerance for risk at different levels of benefit in the benefit-risk assessment of a dermal filler?

b. Since factors such as demographics may affect patient preference, what factors should be considered when incorporating PPI in clinical studies and the benefit-risk assessment of dermal fillers?

DR. LEWIS: Dr. Bressler.

DR. BRESSLER: I am clearly not an expert on dermal fillers, but I've done a lot of designing of clinical trials and endpoints. So I want to just emphasize, as the FDA is thinking of this, that I would recommend they strongly consider emphasizing that these are exploratory endpoints until the clinical relevance of these endpoints is understood. You're going to be developing these, they haven't been tested across diverse populations in diverse uses, so I think it's very important. But when you use the term endpoints, I just would not want some failed outcome of something in these endpoints to dissuade other primary or important secondary endpoints that were found that may be beneficial. So I would hope, or I'm just advising that you keep that in mind, call them exploratory until there's general consensus that you're confident that they have strong clinical relevance.

DR. LEWIS: Yes, Dr. Sepulveda.

DR. GONZALEZ: Yes. So I guess what I was going was that both in terms of determining endpoints and establishing effect sizes for those, I think it will be important to

make sure that you're not just considering patients who are participating in the trials. These patients are obviously in some ways self-selected and so in terms of risk tolerance and review about the right balance of benefits and risks, it could be skewed and so I think it will be critical to consider the views of patients beyond the trial when doing these assessments.

DR. LEWIS: I do think you're setting yourself an extremely difficult challenge here, Dr. Chang, because it's been well shown that people's personal acceptance, people's personal belief in relative risk for a given event is highly variable relative to the actual risk that's present, and their perception of it is often quite different from the reality. So trying to achieve a scale which has reliability, I think, would be extraordinarily difficult, but perhaps it could be done.

Dr. Ballman.

DR. BALLMAN: Thank you.

Yeah, I mean, I agree and I find it a bit sort of interesting, I mean, again -- and I'm sorry, I go back to oncology, but we have tradeoffs between sort of the toxicity of a treatment and whether they might just get additional disease-free survival, not even talking about overall survival as the endpoint. And basically, we don't try to incorporate patient preferences there, but we just sort of capture what the risks are and what the benefits are and then that's a discussion with the physician and the patient to make that sort of individual type decision. I mean, I think this is going to be a very hard thing to quantify for a group as a whole because I think each patient is going to make that tradeoff for him or herself.

DR. LEWIS: Dr. Alam.

DR. ALAM: I agree with a lot of the previous speakers. I think there is complexity here. First of all, you also -- if you're studying something in a clinical trial, it's going to be

difficult to communicate risk levels because you might not know yourself, until the trial is concluded, what the differential risk levels are. So that's one complexity.

I think if you do want to do this, I would use large sort of measures. I don't know how to describe that better. In clinical context, we often do that. For instance, if you look at dermatologists and plastic surgeons, I'm going to make a broad generalization, there's a little bit of a divergence. People often come to a dermatologist because they want something minimally invasive and they're not quite ready for that facelift, which sometimes they need, and sometimes I have to say you need to see one of my colleagues because really, what I can do for you is not really going make you get what it is that you seem to expect. And then there are other people who look about the same, who are happy with that lesser thing.

So I think if you had two or three big categories like do you want any inconvenience, downtime of a day or two or less, and if they say yes, okay, they have a super low risk, and on the other hand there are the people who money and time and inconvenience are no object, they want to go the whole hog, then you might be able to. But if you try to slice it very finely, I think you'll get into trouble.

DR. LEWIS: Dr. Sepulveda.

DR. GONZALEZ: So two comments on that. I agree, this is a very complicated problem and I think it's great, but it's going to take quite a bit of effort to get it right. That said, I think a couple of comments. First, even though tackling the whole thing might be too much, we can definitely partition this into smaller tasks that might lead us to something closer to where we want to be. We could certainly look into prioritizing the kind of information that patients would like to get from trials, right? And so that's an exercise that can easily -- relatively easily be done with a large cohort, if you want nationally. And as long as you have some standard in terms of how you're informing the participants in a study like

that, about what the tradeoffs are, there's evidence that suggests that that is doable.

The other thing to keep in mind, and it just makes the problem a bit more tricky, is that preferences don't necessarily correspond with personal risk levels, right? You can have someone who is going to benefit the most in a net basis from a specific intervention but happens to be the most risk-averse person, right?

And so I feel like shooting at individual level tradeoffs is going to be nearly impossible, I agree with what has been said before, but perhaps a way to operationalize this is to look more broadly at what becomes acceptable or unacceptable and then compare the actual data against those thresholds that we've elicited from the patients and that might be a way to simplify the problem to make it a bit more manageable.

DR. LEWIS: Dr. Miller.

DR. MILLER: I think it's more clear if we can just define the risks and I think to try and develop a tool to assess an individual's risk tolerance, that is a major task. I mean, it's some kind of psychometric thing which can score someone's risk tolerance. I mean, it seems like that's a moving target, someone's risk tolerance in their twenties who's jumping across canyons, you know, that they could die if they didn't make it across, they're different than the same person and a couple years later has got kids and the family and the risk tolerance changes and that's a really difficult thing, I think, to get a handle on objectively and I think if we just -- our primary task is to spell out the risks for somebody and the benefits and then it's really kind up to them what -- how they do that calculation.

DR. LEWIS: Dr. Alam.

DR. ALAM: But to that point, when you -- I completely agree, telling them what the risk level is, is the key. But you might consider some slightly more patient-understandable ways of conveying what the risk level is, because sometimes I think we use kind of obtuse arguments and statistics and likelihood of adverse event and those make less sense to

people than something a little more organic.

DR. LEWIS: I think the general consensus, Dr. Chang, is that you set yourself a really tough task there because you're asking to take two variables that are each highly subjective and personal and ask how you can correlate them. It's like asking how can you correlate two random numbers with each other and the answer is probably you won't be able to. I don't think there is a lot of direction around the Panel about how to go about that.

Why don't we move on to Question 8?

DR. FRANCIS: FDA believes that it's important for patients to be appropriately informed of the benefits and risks of dermal fillers.

a. Are the current methods of informing patients adequate, or are additional strategies needed to appropriately convey risks of dermal filler injections to patients, particularly for areas with more reports of vascular occlusion-related events?

b. FDA has identified the following examples that may be useful strategies to communicate the benefits and risks of dermal filler injections to patients:

    i. Patient labeling with consistent presentation of benefits and risks, with specific structure and content

        1. Patient labeling that includes additional information on increased risks for areas with more reports of vascular occlusion-related events

    ii. A boxed warning regarding the risks of intravascular injection

    iii. A patient decision checklist that, among other information, may include:

        1. information and risks for dermal filler injections
        2. specific mention of risks of soft tissue necrosis, blindness, and stroke
        3. additional information and acknowledgment of risks for areas with more reports of vascular occlusion-related events, if these areas are

approved through the PMA process

4. an approach for patients and providers to affirmatively acknowledge that each item was read and discussed

If you believe that additional strategies are needed, would you recommend that the example strategies above be implemented or that alternative or additional strategies be implemented?

DR. LEWIS: Thank you.

Well, that's an excellent question and I think there are some really positive answers to that. So would the Panel like to begin?

Dr. Perry.

DR. PERRY: Regarding the first question, I think that a checklist could be a good idea. I think the two sub-questions there about additional information of areas of increased risk is probably not so good an idea because the risk is low for all of them, but it's there. And so I think, you know, providing that extra risk that's still very low, my thought would be that that might just confuse patients and many people get it in multiple areas of the face, anyway. So I would say part (i)(1) and part (iii)(3), I would say no.

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: Yeah, I just want to follow up on that because we don't even know what the denominator is, so we don't know if the areas where we're seeing increased risk might be because those are areas that are being targeted more and because it is so low, it could almost -- and it's been shown to happen in many different places. So I agree, I don't think that the labeling should have additional information of increased risk for areas with more reports unless we're sure that that really is reflective of an increased risk.

DR. LEWIS: Dr. Alam.

(Off microphone response.)

DR. LEWIS: You're muted, Dr. Alam.

DR. ALAM: Oh. I agree with that, I don't think we have enough data to convey, with any reliability, differential risk.

DR. LEWIS: I do think that one point you raised, and which I think is a significant issue, is the lumping of all risks in a single list, implying that there is some equivalence to them, whereas mostly the transient effects, swelling, redness, tenderness, etc., all of which are likely to be reversible compared with visual disturbances, neurologic disturbances, skin necrosis, which are not reversible, are in totally different categories. And so I think the significance of that and simply reading a laundry list of things, patients might not perceive the relevant significance of those different things.

And I think the more severe complications need to be singled out and highlighted in specific discussions with the patient so that they do understand that. It's still going to be hard for them to deal with that because the incidence is so low but it's so catastrophic when it does occur that they should've been warned about it and if they're all simply lumped together and not singled out by explicit discussion, I don't think that would be adequate.

Dr. Burke.

DR. BURKE: I think it is important to mention all of these things, but I think that you could have one argument that says these are transient and usually resolve within days to weeks, and then when the specific catastrophic items are mentioned, you could say this is 1 in 500,000 in the United States. So I think you can -- I mean, you must say that this happens, but I think it is important to cite the rarity of the event. And I'd suggest to be sure the patients read it and we could kind of take as a model the iPLEDGE method of consent that every item the patient has to initial. Now, some patients just sort of go down the page and initial it and don't read it but, I mean, we should stand with the patient, as we know

when we -- if a medical assistant asks a questionnaire and asks the patient question by question, we learn more information than when we just give a patient a document to complete. So perhaps a medical assistant could kind of read it. But maybe the in-between is to have every item itemized and say that this, it might happen 10% of the time that people get bruises or edema or transient complications that resolve relatively rapidly and that there's this 1 in 500,000 incidence of something highly serious, so they have to know that can happen, but that could be especially initial circumstance and it's sort of like saying when you buy a car, that you could get killed by traffic or whatever, but it's -- I mean, that's not as -- that's more common than just consequences we're discussing here.

DR. LEWIS: Yes, Dr. Bressler.

DR. BRESSLER: Thank you.

I was going to, I think, agree with what you said, Dr. Lewis, in terms of pulling out this intravascular risk separated from the others and I do think there should be a strong warning about that, the severity of it, the irreversibility of it, and of course the rarity of it. Not so much so far for what I've seen from the United States in the clinical trials, but many of our colleagues anecdotally, who are retina specialists around the world, have all seen this in Asia and so it just seems more common than what we have here.

Now, by having that on the box, so to speak, and of course that's going to be up to regulatory agencies elsewhere in the world, as well, but at least it's there and it's of no harm truly for the patient in the U.S. who will see that there's this very rare event, they can confirm that with their physician and be told look, this is extremely rare, I've never seen it, but it could happen and we do things to mitigate against it. But at least to the world population, it will be there so that if there is someone who wanted to know about it, it's not mixed up with all those other, I think, less catastrophic, although perhaps more common indications. So I think it could be done in an appropriate way with greater emphasis on that

intravascular risk and those items.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: Thank you, Dr. Lewis.

Undoubtedly, these untoward sequelae, edema, erythema, ecchymosis, must be separated. Those are consequences of an injection that probably occur to a greater degree than not and they should not be confused with complications and certainly the tragic complications that we're referring to. So I absolutely agree with what the last two speakers have said. The question is how to present it. You know, when you put smoking causes lung cancer on the side, people are going to smoke if they want to. If you give them the incidence of blindness as one in whatever, they'll say it's not going to happen to me. So the question is how to make it effective.

As Karen talked about, a checklist. Karen Burke. You know, the problem with a checklist is somebody may just fill it out in the waiting room and just check everything off. Does the doctor have to do it? The question is how to have -- I think we all agree that this needs to be presented to the patient and the untoward sequelae which occur in most people and the severe complications which occur rarely have to be well separated and distinguished. The question is how to make it impactful so that people really think about it. And I don't have the answer to that.

DR. LEWIS: Dr. Alam.

DR. ALAM: I want to make two points. First of all, I think we are -- I agree with you completely, Dr. Lewis, it does need to be clearly mentioned. I would like to differentiate between intravascular occlusion that results in vision loss and the much larger percentage, the 99% that don't. So I think we have to be careful about not lumping those two together because I think an FDA number, it seemed like maybe there are four times as many non-visual related events, but I don't think that's correct. Based on our research, there are

many, many more. It's just that ascertainment for those minor occlusion events is much less good. If someone goes blind, it's hard to like not report that, but if someone has a little bruise and a little red spot -- it might not. So differentiate those two. With regard to complicating the risk of the worst possible outcome of blindness, I think we have to be careful because it is quite rare. So to Dr. Matarasso's point, on the one hand we want to highlight that this risk, like you said, Dr. Lewis, is different than the other risks but we don't want to make it so alarming that people think it's really likely to happen to them.

So to FDA's previous points about trying to need tools to make risk adjustment easier for patients, but I know this beyond the scope of our current discussion, FDA might consider coming up with some comparisons, some examples of what the risk level might equate to. Like this is the same as if X number of people in your state get filler, it's like one of them every year would have this complication or it's the same as having a head-on car accident or whatever, but something that people can understand that there's a difference between stubbing your toe on the side of your bed, which can happen pretty easily, and a plane crashing into your bathtub, which is possible but quite unlikely. So I don't know if you want to do that sort of thing, but I think if you are going to alarm people, which -- or at least highlight this risk, you have to avoid alarming people unduly.

DR. LEWIS: Yes, Dr. Sepulveda.

DR. GONZALEZ: Yeah, I want to echo that last point because it is well known that people don't understand the level of risks that we're talking about. People are going to -- to the extent that we are going to highlight this, we're going to overestimate the probability. That's just a well-known issue with our psychology. Another point that I wanted to raise was that, from the decision science standpoint, what matters when it comes to decision making is how can this vary from one PRO to another and it may be something to consider that, you know, the label doesn't -- the label can be explicit about

this being a risk for a family of products, not just a specific product, because it is more relevant really on the decision of whether I will pursue any of these interventions at all, not so much about whether I pursue one versus another.

DR. LEWIS: Dr. Burke.

DR. BURKE: Thank you.

Well, I agree with everything that has been said. I think that, also, the ophthalmologic possible blindness should not be lumped with the soft tissue necrosis because some degree of soft tissue necrosis is far more common than the blindness. And that also can be devastating and it can require major surgical correction. So I think that should be a special item.

And my second point is, I think that I would really appreciate seeing a kind of universal consent that we all use. I mean, we all kind of write our own or modify some template, but I would look forward to particularly this consent being discussed in detail and then disseminated to all physicians doing these filler procedures because it would be so excellent that we all use the same consent in our practices.

DR. LEWIS: Dr. Perry.

DR. PERRY: I'd just like to add briefly that anecdotally, I've consented many, many patients who have had fillers previously and when I bring up blindness, they're incredibly surprised. So I think it's a very important issue that needs addressing.

DR. LEWIS: Yes, Dr. Miller.

DR. MILLER: Yeah, I think I agree with that last comment that it's critical that patients understand this is a possibility for them and they can weigh the risk-benefit. It's the task of the clinician to put perspective on the level of risk, that's critical as well, but the most important person besides the patient to understand the possibility of this is the person who's doing the injecting. I mean, I would -- I think every person who wants to do

one of these things needs to have a little bit of anxiety as they're putting that needle in, that -- you know, that they could make this person blind. And so that level of awareness and intensity and to do all those things we talked about to minimize the possibility of this and do it safely, that has to be forefront in a person's mind as they go about doing this.

DR. LEWIS: Okay. I think maybe that's enough.

Ms. Brummert, I'm sorry. Go right ahead.

MS. BRUMMERT: I'm just wondering if -- I mean, patients do want a checklist and they do want as much information as they can get, but I don't know that it has to be a scary thing. Can there be phrasing in there that says there's been an uptick in ocular whatever or stroke? I don't know if you necessarily have to say you're going to go blind from this, you're going to -- you know, I don't think you have to scare somebody, but I just wonder if you can put more prevalence on the things that are coming to light and then also have a way for the physician or medical assistant to verbally go over that list with the patient so that they're kind of both on the same page about what they're listening to. Did it make sense?

DR. LEWIS: I'm not seeing any other hands up. I think that's about all the Panel has for this, so I believe we should move on to Question 9.

DR. FRANCIS: Would you recommend that a patient device card be part of the patient labeling? Does the proposed mock-up card example below have sufficient information?

DR. LEWIS: Dr. Alam.

(Off microphone response.)

DR. LEWIS: You're muted, Dr. Alam.

DR. ALAM: I'm sorry again, Dr. Lewis.

I have a question. I don't quite understand how this patient device card would work. Would this be something that the patient would retain, the physician would retain, that

would need to be turned in to FDA? I'm not exactly sure how this would work. If you could explain that, that would be very helpful.

DR. LEWIS: Dr. Chang.

DR. CHANG: Yes, Cynthia Chang.

The patient device card we are envisioning is something that would be given to the patient for the patient to keep as a record of the implants that they've received. I believe there are some other implants, implantable devices that also have patient device cards.

DR. LEWIS: What would the primary benefit of this be, Dr. Chang, in terms of carrying information? What do you envision would be the benefit presumably of the next physician who might be asked to treat the patient who looks at this?

DR. CHANG: So we are interested in the Panel's thoughts on this. Some possible benefits may be that it's easily accessible, a centralized location for the patient to have that record of what was injected, how much, when, who did it, and that sort of thing and that way they could refer to that when they're going to the next injector, for example. It may be something that they could refer to if there is some sort of safety communication that goes out about a particular product. And in terms of other benefits, another one may be that if there is an adverse event that the patient experiences, they could perhaps choose to report to our MDR system or to the manufacturer on their own with the relevant details.

DR. LEWIS: Dr. Burke.

DR. BURKE: I think this would be absolutely fabulous. I mean, we all have had patients that came to us with nodules and the patient doesn't know what was injected, they're kind of vague about when it was, and I just think this is so great for a patient to at least know what they had and when they go to another physician, we will know what we are treating if it's an adverse effect and we will know what was successful with the patient, if the patient was very happy with the previous filler. So I just think this would be fabulous

for every patient to have and the physician obviously could keep a copy in the office so if the patient lost their little identification card or history card, we could resend it to them and -- but I just think this is a fabulous idea.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: Yeah, I would agree with that on a lot of levels. I would tell you that it's -- when you're looking at about 2% of -- if there's five million injections a year and there's 350 million people in the country, you're talking about a lot of things. But the advantage to it, I think, is that one of the things we could do is educate patients to go to a provider that provides this card. Just like we do with the breast implant, we want patients to have breast implants with people that register them with the NBIR. Every single day I -- and it will weed out the list of practitioners that are using unknown products in people's faces. I'm treating a patient tomorrow whose practitioner was put in jail and she has multiple problems and nobody has any idea what's in there.

So I do think it's a good thing because it (a) gets the public, if we publicize this, to go to practitioners that provide this so that right away it lessens the group of people that are doing bad things. It allows, as Karen pointed out, the patient never wants to know what's been put in there, when it was put in there and so on. I mean, short of an injection registry, not a complications registry, short of an injection registry, that's probably the next best thing.

DR. LEWIS: Yes, Dr. McGrath.

(Off microphone response.)

DR. LEWIS: You're muted, Mary.

DR. McGRATH: It takes a minute.

Adding on to that, it would be even better if this were digital and since most physicians' offices and even a lot of medical spas now have electronic records, the trick

would be to have this recorded electronically in the record, which patients can access now, obviously, and to tell them that this is where it will reside, because I think giving out cards is not so effective anymore, except maybe with COVID vaccinations, we want our cards. But other than that, patients don't tend to hang on to these, I've noticed, even with breast implants, but they do like to have it in their electronic record because then they or their primary care doctor and everybody can access it.

So what I don't know is whether most physicians' offices across the country now have electronic records that they could be doing this, but I think that really would be, in the future, the way to go with it.

DR. MATARASSO: If I can add to that. I agree, I think that's the ideal way to do this, as a registry for every injection, as we're doing, for example, with breasts. I think that one of the stumbling blocks will be that many of the cosmetic practitioners don't have EHRs. But if we can form some form of a registry, it's by far the best thing, and then publicize to the public that they should be using a practitioner that inputs their data and they should have an opt-out for the patients if they don't want it. But I can tell you, a day doesn't go by that every one of us sees someone who has no idea what's in their face, when it was put in and so on. So that would be the ultimate solution.

DR. LEWIS: It seems, Dr. Chang, that -- well, one further comment.

Dr. Perry.

DR. PERRY: Oh, yeah. I was just going to say I agree and also, I agree with Dr. McGrath, the card is going to get very long very quickly for a lot of patients, but it is great information to have.

DR. LEWIS: Yeah. So the consensus, Dr. Chang, is a fair amount of enthusiasm for the idea and admonition that a card per se would be useful, but even more useful would be some sort of an electronic registry or electronic record which the patient could access, as

well as other people, that would not be subject to getting lost.

Dr. Alam, did you have a further comment?

DR. ALAM: Yeah, I agree with what you're saying and also what Dr. McGrath was saying, but I'm just a little concerned. I like the electronic thing in your medical record, but I'm just concerned we might be reinventing the wheel. We already have medical records and now there's a federal law that allows patients to access their medical records. So I think this is important and I think we should maybe redouble our efforts to ensure that providers write all of this stuff down in their medical record in some form so it's easily accessible, but I would hesitate to create another level of complexity beyond that medical record, which we all know where it resides, whether it's on paper or electronic. But I would just encourage practitioners, require them to note this information, if necessary. Thank you.

DR. LEWIS: Are there further comments?

Dr. McGrath.

(Off microphone response.)

DR. LEWIS: You're muted, Mary.

DR. McGRATH: It takes three clicks to make it unmute.

I agree with you, Murad. You know, for 20 years I've been putting this information into my medical records. Well, it's by paper records and then eventually electronic records. But there could be a way -- it could be less accessible if it's just buried. There might be a way to do both. I agree with you, you don't want to increase the burden by having to record the information twice for the patient, but there must be a way to perhaps have a different kind of form or something that we could use, use only once, but the patient could get it and have it be a lot more concise without just duplicating work.

DR. LEWIS: Dr. Perry.

DR. PERRY: I would just add that many patients see multiple providers for their fillers and so that's where I think the card would really come in handy.

DR. LEWIS: Well, not seeing any further comments, I believe we're at the end of our day.

Dr. Chang, did you have some remarks to make?

DR. CHANG: Yes. So I would like to thank the Panel on behalf of my FDA colleagues and myself for all of the very thoughtful comments that you have provided throughout the day, your excellent questions to us and to the speakers, as well as your recommendations for our questions.

We have covered quite a number of different topics related to dermal fillers today, ranging from specific items regarding the risks of intravascular injection and visual impairment, on to some very challenging questions regarding patient preference information, demographics and the like. And then finally, we wrapped up with your helpful comments on the informed decision making. And so we will be taking your comments into consideration and we just really appreciate your time and thoughtfulness today.

DR. LEWIS: Thank you, Dr. Chang. And thanks to all the staff, Dr. Ashar and all of the staff at the FDA who actually integrated a large variety of electronic media today and pretty seamlessly. I thank you all a great deal for doing that.

I specifically want to thank the Panel, the Open Public Hearing speakers, industry representatives, the patient representative, the consumer representative, the sponsors, and the FDA for their contributions to today's meeting.

And I now pronounce the March 23rd session of the General and Plastic Surgical Panel adjourned. Thank you, all.

(Whereupon, at 4:49 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:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

March 23, 2021

Via Zoom Videoconference

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.

_____

BRAD WEIRICH

Official Reporter

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