FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE DRUG SAFETY AND RISK MANAGEMENT (DSaRM) AND THE DERMATOLOGIC AND OPHTHALMIC DRUGS (DODAC) ADVISORY COMMITTEES

Virtual Meeting

Wednesday, March 29, 2023

10:00 a.m. to 3:28 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Philip Bautista, PharmD, MPH
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

DSaRM MEMBERS (Voting)

Karim Anton Calis, PharmD, MPH, FASHP, FCCP
Director of Clinical Research and Compliance
Office of the Clinical Director
Division of Intramural Research
Eunice Kennedy Shriver National Institute of Child
Health and Human Development
National Institutes of Health (NIH)
Bethesda, Maryland

Sascha Dublin, MD, PhD
Senior Scientific Investigator
Kaiser Permanente Washington Health Research
Institute
Seattle, Washington

John B. Hertig, PharmD, MS, CPPS, FASHP
Associate Professor and Chair
Department of Pharmacy Practice
Butler University College of Pharmacy and Health Sciences
Indianapolis, Indiana

Collin A. Hovinga, PharmD, MS, FCCP
Vice President
Rare and Orphan Diseases Critical Path Institute
Clinical Associate Professor of Pharmacy
University of Texas at Austin, College of Pharmacy
Austin, Texas

Krista F. Huybrechts, MS, PhD

Associate Professor of Medicine and Epidemiology

Harvard Medical School and Harvard T.H. Chan School of Public Health

Division of Pharmacoepidemiology and Pharmacoeconomics

Department of Medicine

Brigham & Women's Hospital

Boston, Massachusetts

Tao Liu, PhD

Associate Professor of Biostatistics

Department of Biostatistics

Center for Statistical Sciences

Brown University School of Public Health

Providence, Rhode Island

Vincent Lo Re III, MD, MSCE

(Chairperson)

Associate Professor of Epidemiology and Medicine

Center for Clinical Epidemiology and Biostatistics

Center for Pharmacoepidemiology Research and

Training, Perelman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

Mara McAdams DeMarco, MS, PhD

Associate Professor

Associate Vice Chair for Research

Department of Surgery

New York University

New York, New York

Suzanne B. Robotti

(Consumer Representative)

President

MedShadow Foundation

Executive Director

DES Action USA

New York, New York

DODAC MEMBERS (Voting)

Ken Katz, MD, MSc, MCSE

Dermatologist

Kaiser Permanente

San Francisco, California

Brian Green, DO, MS, FAAD

Associate Professor, Dermatology

Medical Director, Teledermatology

Penn State Health Milton S. Hershey Medical Center

Department of Dermatology

Hershey, Pennsylvania

Megha Tollefson, MD

Professor, Dermatology and Pediatric and Adolescent Medicine

Consultant, Department of Dermatology

Mayo Clinic and Mayo Clinic College of Medicine

Rochester, Minnesota

Maria A. Woodward MD MSc

Associate Professor, Ophthalmology & Visual Sciences

Section Chief and Fellowship Director Cornea, External Disease, & Refractive Surgery

University of Michigan

Ann Arbor, Michigan

DODAC MEMBER (Non-Voting)

Ercem Atillasoy, MD

(Industry Representative)

Chief Regulatory and Safety Officer

Jazz Pharmaceuticals

Philadelphia, PA

TEMPORARY MEMBERS (Voting)

Abbey Berenson MD, PhD

Professor of Ob/Gyn

Director, Population and Preventive Health

Department of Ob/Gyn

University of Texas Medical Branch

Galveston, Texas

David A. Chambers, DPhil

Deputy Director for Implementation Science

Division of Cancer Control and Population Sciences

National Cancer Institute, NIH

Bethesda, Maryland

Edward W. Cowen, MD, MHSc

Chief, Dermatology Consultation Service

National Institute of Arthritis and

Musculoskeletal and Skin Diseases, NIH

Bethesda, Maryland

Kort Delost, RPh

Community Pharmacist

Bountiful, Utah

Sonia Hernandez-Diaz, MD, DrPH

Professor of Epidemiology

Harvard T.H. Chan School of Public Health

Boston, Massachusetts

Donna Ludwinski, BSChE

(Patient Representative)

Director of Research Advocacy

Solving Kids' Cancer

New York, New York

Sonja A. Rasmussen, MD, MS

Professor

Department of Genetic Medicine

Johns Hopkins University School of Medicine

Baltimore, Maryland

Brian Salvas, PharmD

Executive Director

Pharmacy Operations

CVS Pharmacy

Woonsocket, Rhode Island

Courtney A. Schreiber, MD, MPH

Stuart and Emily B.H. Mudd Professor of Human Behavior and Reproduction

Chief, Division of Family Planning

Department of Obstetrics and Gynecology

Executive Director, FOCUS on Health and Leadership for Women

Perelman School of Medicine

University of Pennsylvania

FDA PARTICIPANTS (Non-Voting)

Claudia Manzo, PharmD

Director, Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

CDER, FDA

Cynthia LaCivita, PharmD

Director, Division of Risk Management (DRM)

OMEPRM, OSE, CDER, FDA

Jacqueline Sheppard, PharmD

Team Leader, DRM

OMEPRM, OSE, CDER, FDA

Leyla Sahin, MD

Deputy Director for Safety

Division of Pediatrics and Maternal Health

Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

Office of New Drugs (OND), CDER, FDA

Tatiana Oussova, MD, MPH

Deputy Director for Safety, Division of Dermatology and Dentistry

Office of Immunology and Inflammation

OND, CDER, FDA

SeVan H. Kolejian, PharmD, MBA, BCPPS

Director, Division of Mitigation Assessment and Medication Error Surveillance

OMEPRM, OSE, CDER, FDA

C O N T E N T S

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. LO RE: Good morning, everyone, and welcome. I'd like to first remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Ms. Chanapa Tantibanchachai. Her contact information is displayed here on this slide.

My name is Dr. Vin Lo Re, and once again, I will be serving as the chair for this meeting today. I will now call day number 2 of the March 28-29, 2023 joint meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatological Ophthalmic Drugs Advisory Committee to order. Dr. Phil Bautista is the designated federal officer for this meeting, and we will begin, once again, with introductions.

Introduction of Committee

DR. BAUTISTA: Hi. Good morning, everybody. My name is Phil Bautista. I'm the DFO for this meeting. When I call your name, please introduce

yourself by stating your name and affiliation. We'll first start with the standing members of the DSaRM.

Dr. Calis?

DR. CALIS: Good morning. I'm Karim Calis. I am a senior scientist and director of clinical research for the National Institute of Child health and Human Development at the NIH, and also I'm the chair of the NIH Institutional Review Board in the Office of Intramural Research at NIH.

DR. BAUTISTA: Dr. Dublin?

DR. DUBLIN: Good morning. I'm Sascha Dublin. I'm a general internal medicine physician and a pharmacoepidemiologist. My position is as a senior scientist at Kaiser Permanente, Washington in Seattle, and I have an affiliation at University of Washington, and I see patients at primary care and conduct research on federally-funded projects, with a particular focus on medication safety and pregnancy.

DR. BAUTISTA: Dr. Hertig?

DR. HERTIG: Good morning. John Hertig,

pharmacist by training, associate professor and chair of the Department of Pharmacy Practice at Butler University College of Pharmacy and Health Sciences, located in Indianapolis, Indiana.

DR. BAUTISTA: Dr. Hovinga?

DR. HOVINGA: Hello. I'm Collin Hovinga. I'm vice president for Rare and Orphan Diseases at Critical Path Institute. I am also faculty at the University of Texas at Austin College of Pharmacy. I'm located in the Austin, Texas area. My background and interest is in clinical pharmacology, epidemiology, as well as pediatrics. Thank you.

DR. BAUTISTA: Dr. Huybrechts?

DR. HUYBRECHTS: Good morning. I'm Krista Huybrechts. I'm an epidemiologist by training. I have a faculty appointment at Harvard Medical School and co-direct the Harvard program on perinatal and pediatric pharmacoepidemiology, and my research focuses on drug safety during pregnancy.

DR. BAUTISTA: Dr. Liu?

DR. LIU: Hi. This is Tao Liu, associate professor of biostatistics at Brown University School of Public Health. I'm a statistician by training. My expertise is health data science, causal inference, and data-driven decision making. Thanks.

DR. BAUTISTA: Thank you.

Dr. McAdams DeMarco?

DR. McADAMS DeMARCO: Hi. I'm Dr. Mara McAdams DeMarco. I'm an epidemiologist at NYU, where I have an appointment in the Department of Population Health, as well as in surgery, and I'm the associate vice chair for research in the Department of Surgery. Thank you.

DR. BAUTISTA: Suzanne Robotti?

MS. ROBOTTI: Hi. I'm Suzanne Robotti. I'm the founder of MedShadow Foundation. I'm the executive director of DES Action USA. I'm a DES Daughter and a consumer representative in pharmacovigilance. Thanks.

DR. BAUTISTA: Alright. Next, we have the DODAC members. We'll first start with Dr. Katz.

DR. KATZ: Good morning. Ken Katz. I'm a dermatologist at Kaiser Permanente in San Francisco. Thank you.

DR. BAUTISTA: Dr. Green?

DR. GREEN: Good morning. Brian Green. I'm a pediatric dermatologist at Penn State Hershey Medical Center and medical director of our teledermatology program.

DR. BAUTISTA: Dr. Tollefson?

DR. TOLLEFSON: Good morning. Megha Tollefson. I'm a pediatric dermatologist at the Mayo Clinic in Rochester Minnesota.

DR. BAUTISTA: Dr. Woodward?

DR. WOODWARD: Good morning. I'm Maria Woodward. I'm an ophthalmologist and health services research associate professor at University of Michigan.

DR. BAUTISTA: Dr. Atillasoy?

DR. ATILLASOY: Good morning. I'm Ercem Atillasoy. I'm the industry representative to DODAC. I'm a dermatologist by training. I'm the chief regulatory and safety officer at Jazz

Pharmaceuticals. I'm also a voluntary clinical faculty member at the University of Pennsylvania. I'm a long-term member of the American Academy of Dermatology, and I'm delighted to be here. Thank you.

DR. BAUTISTA: Next we'll be going to the temporary voting members, starting first with Dr. Berenson.

DR. BERENSON: Hello. Abbey Berenson. I'm at the University of Texas Medical Branch, where I am professor of OB-GYN and Pediatrics and direct the Center for Interdisciplinary Research and Women's Health. I was selected for this panel because of my expertise in contraception. Thank you.

DR. BAUTISTA: Thank you.

Dr. Chambers?

DR. CHAMBERS: Good morning. I'm David Chambers. I'm deputy director for implementation science within the Division of Cancer Control and Population Sciences at the National Cancer Institute. Thanks.

DR. BAUTISTA: Dr. Cowen?

DR. COWEN: Hi. Ed Cowen. I'm at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and I have faculty appointments also at Georgetown University and the Uniformed Services University of the Health Sciences.

DR. BAUTISTA: Dr. Delost?

DR. DELOST: Yes. Kort Delost, community pharmacist, retired associate professor from the University of Utah College of Pharmacy.

DR. BAUTISTA: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Good morning. I'm Sonia Hernandez-Diaz. I'm professor of pharmacoepidemiology at the Harvard Chan School of Public Health in Boston, and my research focuses on the safety of medications during pregnancy, with a particular interest in birth defects.

DR. BAUTISTA: Donna Ludwinski?

MS. LUDWINSKI: Good morning. Donna Ludwinski. I'm a patient representative, and I work for Solving Kids' Cancer in New York. I'm a

director of research advocacy programs there, and my son was on isotretinoin for neuroblastoma in a maintenance phase. He had a 6-month course.

DR. BAUTISTA: Thank you.

Dr. Rasmussen?

DR. RASMUSSEN: Sonja Rasmussen. I'm a pediatrician and clinical geneticist, and I'm a professor of genetic medicine at Johns Hopkins University School of Medicine. Thanks.

DR. BAUTISTA: Dr. Salvas?

DR. SALVAS: Good morning, everyone. Brian Salvas, CVS Health, pharmacist by training and currently serving as executive director of retail pharmacy for the pharmacy business for CVS.

DR. BAUTISTA: And Dr. Schreiber?

DR. SCHREIBER: Good morning. Courtney Schreiber, professor of obstetrics and gynecology at the Perelman School of Medicine, University of Pennsylvania, chief of family planning here at Penn, and a clinical and public health scientist in reproductive health. Thank you.

DR. BAUTISTA: Thank you.

Finally, we go through the FDA participants, first starting with Dr. Manzo.

DR. MANZO: Good morning. I'm Claudia Manzo. I'm the director of the Office of Medication Error Prevention and Risk Management within the Office of Surveillance and Epidemiology in CDER, FDA.

DR. BAUTISTA: Thank you.

Dr. LaCivita?

DR. LaCIVITA: Good morning. Cynthia LaCivita, director of the Division of Risk Management in the Office of Surveillance and Epidemiology in CDER at FDA.

DR. BAUTISTA: Dr. Sheppard?

DR. SHEPPARD: Good morning. Jacqueline Sheppard, team leader at the Division of Risk Management.

DR. BAUTISTA: Dr. Sahin?

DR. SAHIN: Good morning, everybody. I'm Leyla Sahin, and I'm the deputy director for safety in the Division of Pediatrics and Maternal Health, in the Office of New Drugs, in CDER at FDA. Thank

you.

DR. BAUTISTA: Dr. Oussova?

DR. OUSSOVA: Good morning. I'm Tatiana Oussova. I'm the deputy division director for safety for the Division of Dermatology and Dentistry, Office of New Drugs, CDER, FDA. Thank you.

DR. BAUTISTA: And finally, Dr. Kolejian.

DR. KOLEJIAN: Good morning. I'm SeVan Kolejian, director of the Division of Medication Assessment and Medication Error Surveillance within the Office of Surveillance and Epidemiology at CDER, FDA. Thank you.

DR. BAUTISTA: With this, I'll hand it back over to Dr. Lo RE.

DR. LO RE: Thanks, Phil.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal with this meeting is to be fair and an open forum for discussion of these issues and that individuals can express their views without

interruption. Therefore, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during any breaks. Thank you.

We will now proceed with FDA opening remarks from Dr. Cynthia LaCivita.

Dr. LaCivita?

FDA Opening Remarks - Cynthia LaCivita

DR. LaCIVITA: Cynthia LaCivita, FDA, and

thank you, Dr. Lo Re.

Good morning. I want to thank the committee members for their questions and comments yesterday. I'm going to try and summarize the modifications that were proposed by the IPMG and the FDA during yesterday's meeting. I'm going to start with the IPMG's proposal.

In addition to the modifications approved by the FDA on March 24th, which included the reintroduction of the patient calendar function to the patient profile screen for patients who can become pregnant, and the ability for designees to take on certain patient enrollment functions, the IPMG proposed to extend the monthly confirmation of counseling for patients who cannot become pregnant to 120 days.

The IPMG stated that they would also like to preserve the abstinence switch, which requires a 30-day wait for patients switching from abstinence to birth control for patients who can become pregnant; the 19-day wait for patients who can become pregnant and missed their first prescription

window; and also maintain laboratory confirmed pregnancy testing, although the IPMG later mentioned that they could align with allowing pregnancy testing in prescriber offices.

The FDA's proposal included revising or laminating the documentation; a monthly counseling for patients who cannot become pregnant; removing the requirement to only use CLIA-certified laboratory pregnancy tests; and permit pregnancy tests to be performed in the prescriber's office.

The FDA did not recommend continuing allowance of home pregnancy testing after the expiration of the public health emergency, and we recommended maintaining the current contraceptive requirements, the 7-day prescription window, and the 30-day dispensing limits for all patients. In addition, we were seeking advice from the committee on how to streamline the pregnancy registry and encourage more participation to yield high-level data.

In addition to the proposals from the FDA and the IPMG, the members of the committee brought

up the following topics and recommendations. They wanted us to consider different dispense limits greater than 30 days for patients who cannot become pregnant, taking into consideration Dr. Katz's thoughts on patient care, that dermatologists would want to see their patients monthly to monitor treatment or adverse events; tailoring the REMS requirements, depending on the patient's choice of contraception, and also to consider if there are additional ways to persuade patients to choose contraceptive methods that are not user dependent. This was caveated by patients may have different circumstances that contribute to their contraceptive choices or lifestyle choices, such as abstinence.

They also suggested to expand the 7-day pickup window for patients who can become pregnant and are picking up their first prescription of isotretinoin; seek information to determine if the REMS contributes to healthcare disparities; and also consider the use of home pregnancy testing after the public health emergency ends with methods

to mitigate falsification.

They wanted us to leverage technology to reduce burden and integrate REMS requirements into existing systems when possible, and reconsider requirements that may preclude telehealth visits, such as the requirement for in-office pregnancy testing, and enable system reminders to stakeholders and patients when REMS requirements have a time limitation.

Hopefully, I've captured the main topics. I'm sure that I've missed a few, but I think these are the main topics that were communicated during yesterday's meeting. I also wanted to thank the committee members for their suggestions on how to improve the implementation of some of the REMS requirements. These were all good thoughts.

I did have one point that I wanted to clarify. We did receive several questions about donating blood, and I just wanted to add that the Red Cross does include isotretinoin as a drug on the blood donation medical deferral list, and it asks that the patient wait until the drug has

cleared from their system to donate blood.

So moving forward, the agency is seeking advice of the committee on potential modifications to the iPLEDGE REMS to minimize burden without compromising safety. From a systems standpoint, we want to avoid changes in the REMS that would inadvertently shift burden from one stakeholder to another, or create unintended consequences that could result in a greater number of fetal exposures.

Specifically, we are asking the committee's advice on the 7-day lockout that occurs when the first prescription window is missed for a patient who can become pregnant, should this be retained or modified; whether pregnancy tests should be done in a medical setting; revising or eliminating the documentation of counseling for patients who cannot become pregnant so the documentation of counseling occur every 30 days or can that time frame be adjusted.

Regarding the pregnancy registry, we are seeking advice on ways to streamline the pregnancy

registry to encourage more participation and yield high-quality data, and whether the collection of the pregnancy and fetal outcome data continues to be necessary, as well as other recommendations to reduce the burden in the iPLEDGE REMS.

I want to thank the committee members for their time yesterday and today, and the agency is looking forward to today's discussion, so thank you very much.

Open Public Hearing

DR. LO RE: Thank you, Dr. LaCivita.

We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the 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 please advise the committee of any financial relationships that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, your lodging, or other expenses in connection with your participation in 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.

The FDA and this committee place great importance in the open public hearing process. The insights and the comments provided can help the agency and this committee in their consideration of the issues and questions before them.

That said, in many instances and for many topics, there will be a variety of opinions. One

of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson, and thank you for your cooperation.

Okay. Speaker number 1, can you please unmute and turn on your webcam? Will speaker number 1 begin and introduce yourselves? Please state your names and any organizations you are representing for the record. You have 10 minutes

DR. GRABER: Good morning. I am Dr. Emmy Graber. I am a director of the American Acne and Rosacea Society, and I have no financial relationships relevant to this meeting.

DR. ZAENGLEIN: Good morning. I'm Dr. Andrea Zaenglein, president of the American Acne and Rosacea Society, and a pediatric dermatologist at the Penn State Hershey Medical Center. I have no relevant conflicts of interest for this meeting.

Today Dr. Emmy Graber, an AARS director, and

I are here representing the millions of patients with acne who are impacted by the overly complex and restrictive isotretinoin REMS program, iPLEDGE, yet they do not have a voice in the process. We will share real-life cases where acne patients, given the hope of this life-changing medication, isotretinoin, are subject to barriers to access that the current program structure imposes all too often, and will propose common-sense changes that preserve the mission of the program, which is to prevent pregnancy while on the medication.

DR. GRABER: Jessica is a 15 year old with severe nodular acne. She waited 3 months to see her dermatologist. Already on a combined oral contraceptive pill, she was enrolled in iPLEDGE, waited 30 days, and was ready to finally start treatment; however, her insurance required prior authorization, which took several days; then Medicaid required a specific brand of isotretinoin that was not in stock at her pharmacy.

Due to no fault of her own, she missed the 7-day window period and was forced into an

additional 19-day waiting period despite the fact that she had two negative pregnancy tests, adhered to the two forms of contraception mandated by iPLEDGE, and was not at greater risk of pregnancy at that point than at any other time in her treatment course.

It took Jessica almost 5 months to start isotretinoin. In the meantime, she went to school, faced her peers, and experienced all the insecurities of being a teenager, compounded by her severe acne. Can you imagine her distress at learning she had to wait even a day longer to begin this life-changing treatment.

The 19-day lockout period is excessively punitive and is not scientifically based. While we understand the concept of the mid-cycle fertile period that applies to patients on abstinence, the IPMG and FDA failed to take into account that these patients are at the same risk of failed abstinence each month. The 20-some pregnancies reported in the 19-day period occurred scattered throughout the entire 19-day period, not in a mid-cycle fertile

period.

In the 19-day lockout, patients were not at greater risk of pregnancy, and therefore you are not capturing a fertile period of pregnancy, but rather the inherent contraceptive failure rate that applies to all patients at all months. With the fertile period reasoning, you could extend the 19-day lockout to 20 days, 30 days or more, and yes, there will be even more documented pregnancies, and yes, decreased exposures.

But patients have already been counseled, agreed to adhere to contraception, waited 30 days, and had two negative pregnancy tests. Additional waiting periods are punitive and unfair to patients who are already abiding by the iPLEDGE guidelines. You are not decreasing any risk, just prolonging the waiting period.

Importantly, patients on combined oral contraceptive pills, as well as those on implants and hormonal IUDs, do not ovulate, and therefore the addition of the lockout for this group to avoid a fertile period is biologically nonsensical, as

there is no mid-cycle ovulation, and thus no distinct fertile period. You are therefore punishing more than half of patients for no scientifically sound reason. This is likely why no other REMS program for teratogenicity have this requirement.

This model is also flawed in that it's based on very strict timing. In reality, patients have highly variable menstrual cycle lengths with even normal cycles ranging from 23 to 35 days. Additionally, the highly specific fertile period rationale fails to take into account the variable timing of patient visits. In clinical practice, we are not able to schedule patient visits at exactly 30 days due to scheduling logistics. We are not seeing patients 7 days a week, we may have multiple practice locations, and patients have their own scheduling conflicts.

All of these factors impose additional variability of days to weeks that the iPLEDGE model does not account for. For these reasons, we propose removing the 19-day lockout period.

Patients can repeat a pregnancy test as they do in subsequent months when they miss the 7-day window period.

DR. ZAENGLEIN: Emily is a 22-year-old college student ready to graduate, and then starting the interview process for her first job in marketing. She's been riddled with acne since a young teenager, and isotretinoin cleared her acne years ago, but recently the acne recurred. Anxious to restart isotretinoin, she responsibly saw her gynecologist and had Nexplanon placed.

She received a baseline pregnancy test and was re-registered in iPLEDGE, but then put into a 30-day waiting period to start treatment. Should this conscientious young woman, knowing her acne may affect her employability and already on a highly effective form of contraception, be forced to wait 30 more days to start isotretinoin?

Patients on long-acting reversible contraception, also known as LARC, have a risk of pregnancy on par with sterilization methods and are not at greater risk of pregnancy at the initial

visit than at any other time in the course of therapy. When iPLEDGE was first created, LARC methods of contraception were not commonly used, however, hormonal implants and IUD usage have dramatically increased since 2005 and are now employed by many patients ready to start isotretinoin.

These are responsible patients, already committed to preventing unplanned pregnancy, and they should not be subject to delays and access to isotretinoin. Yes, pregnancies have been reported with LARC in the iPLEDGE system, and the reported numbers are reassuringly low. So unless the majority of pregnancies on LARC fall in the first 30 days, there's no rationale for making these patients wait to start treatment.

The IPMG noted in their presentation that differentiating this group would be too complicated for providers; however, as we are able to categorize those who can and cannot get pregnant, I am confident that me and my colleagues can tell the difference between a sponge and an implant. We

propose removing the 30-day waiting period for patients already on LARC, allowing them to start immediately with a negative pregnancy test and use of condoms.

DR. GRABER: McKenna is a 16-year-old junior in high school who came to dermatology with her mother for a second opinion after two years of ineffective treatment by her primary doctor. They live one and a half hours away from the dermatology office, and McKenna is only able to meet the requirements of iPLEDGE through the use of telehealth. Without the telehealth option, the time away would amount to a full week of missed work and school, not to mention the cost of travel. For many Americans, that is half of their yearly allotted vacation time.

The suspension of the CLIA-certification requirement for pregnancy testing permitted by the pandemic exception has allowed patients on isotretinoin to access telemedicine services while maintaining the strict pregnancy testing requirements of iPLEDGE. Home pregnancy tests are

highly sensitive, equal to the ones done in CLIA-certified labs, and highly accurate when interpreted by a dermatology provider, as it is incorrect interpretation of the result, positive or negative, that results in the majority of user errors.

Necessitating CLIA certification results in extra laboratory visits and cost for patients, as most dermatology practices are not CLIA certified, and thus cannot test patients at the time of the visit. Notably, CLIA certification is not required by other REMS programs for teratogenicity.

We recommend removing the CLIA-certification requirement and allowing continued home pregnancy testing so that the 50 percent of patients with pregnancy potential can continue to access telemedicine services. While the IPMG showed publish reports on falsification of home pregnancy testing, they did not discuss the subsequent publication put out by the American Academy of Dermatology iPLEDGE work group that detailed an easy and effective workaround.

To prevent falsification of at-home pregnancy testing, we can require a name and date written on the home pregnancy test as many of us already do. It is a simple fix, much simpler than missing work or school to physically be in a CLIA-certified lab.

The IPMG also states they need data on the safety of home pregnancy testing. As there is no reported spike in pregnancy reported in the last three years, we do have some data to show it is not imposing additional harms. If you remove this option for patients, more specific data on home pregnancy tests cannot be collected.

We recommend continued home pregnancy testing and collecting data. Currently, the online attestation requires providers to document the type of pregnancy tests performed, urine or serum. UBC can add home pregnancy tests as an option to easily capture data on the safety of home pregnancy testing.

DR. ZAENGLEIN: Sophie is a 14 year old starting isotretinoin. She has a history of

migraines with aura and not sexually active. After discussion of contraceptive choices, she chooses abstinence with her mother's support. No 14 year old plans to become pregnant, and Sophie's abstinence ends abruptly. If she had appropriate counseling, she could still prevent pregnancy.

Directly from the iPLEDGE REMS guide for patients who can get pregnant, one of the most common reasons that patients get pregnant is that they are engaged in sexual activity when they plan to be abstinent. Emergency contraception is an FDA-approved, over-the-counter form of contraception currently available in all 50 states, yet it is not mentioned, let alone emphasized, in the iPLEDGE program materials.

We strongly recommend that emergency contraception education be required for all patients who choose abstinence and request considerations for provisioning of the drug at initiation of isotretinoin therapy to allow for quick and affordable access to this last-chance contraceptive option to prevent pregnancy, the

stated goal of iPLEDGE.

DR. GRABER: The American Acne and Rosacea Society recognizes the devastating teratogenic, fetal effects of isotretinoin and acknowledges the importance of an FDA-mandated REMS program; however, the common sense and scientifically based changes that we recommend do not compromise and, in the case of emergency contraception, enhance the stated goals of the program, all the while easing unnecessarily punitive lockouts, ensuring continued telehealth access for patients, and distinguishing highly effective, long-acting reversible contraception from other forms of primary contraception.

In addition to the recommended changes of the AADA, these proposed changes are in line with other REMS programs for teratogenicity created subsequent to iPLEDGE. They preserve the goal of preventing pregnancy, but importantly ease barriers to access and ease the undue administrative burden that this program places on our patients with severe and recalcitrant acne, and it is on their

behalf that we request your thoughtful consideration for these modifications. Thank you so much for your time.

DR. LO RE: Thank you.

Speaker number 2, can you please unmute and turn on your webcam? Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing, for the record. You will have 5 minutes.

DR. SIDBURY: Hi. Good morning. My name is Dr. Robert Sidbury. I am speaking on behalf of the Society for Pediatric Dermatology, and I have no current conflicts. More than five years ago, I served as an expert witness on behalf of Roche, the original manufacturer of the drug Accutane, in cases of alleged inflammatory bowel disease and Accutane, but have not done any such work in the past five years.

I will start by saying, first of all, thank you for this opportunity. This is an incredibly important issue, and everything that you're going to hear from Drs. Frieden and Barbieri, my

colleagues in the future, and that you just heard from Drs. Graber and Zaenglein, apply to my patients, too, and to the pediatric population. So all of those points are valid for our patients as well, but I wanted to take this time to focus my lens on the unique burdens it places on pediatric patients.

This is an incredibly vulnerable time of life. We've all been there. Many of us have kids who are there now. It's a difficult time, and you've seen the cases that Drs. Graber and Zaenglein showed, and just imagine yourself in school with that degree of visible pathology; and that superimposed on this difficult time of life is just an incredible challenge for our patients, and limited access to what is a life-altering medication in these kids just enhances the psychological trauma for these kids.

Many of you may have seen -- just published yesterday in the Journal of American Medical Association and excerpted today in the New York Times, if you haven't -- there was an article

depicting the number of mental health hospitalizations from 2009 to 2019 were up by a quarter. The number that involved suicidal ideation or self-harm had essentially doubled over that period of time. And remember, I said 2009 to 2019. That's pre-COVID. So this is just an incredibly important issue for these kids, so it's incumbent upon us as healthcare providers and systems to improve access for the most effective treatments for these patients.

As I said, this is pre-COVID, that data I just mentioned from the publication yesterday, and we've all seen our kids struggle with COVID, the isolation that it's imposed, and the increased anxiety and depression that that has imposed, so all of that is just amplified.

Now, sort of ironically, as masks are coming off at school, that provided some measure of protection, obscuring the severe acne on the faces of some kids. So the masks are coming off now in many schools, in many areas, and that's actually in some ways been harder on some kids with severe acne

because they have to expose the sorts of pictures that you saw from Drs. Graber and Zaenglein.

So it's just more important than ever -- due to the epidemic of depression and suicide in all teens and tweens, amplified more in patients with this degree of severe acne, plus the COVID issue, it's just more important than ever that we do everything we can to eliminate barriers to the best medications.

The amount of visits, frequent appointments, labs, and administrative hurdles are a challenge for everyone, adults as well; but as you might imagine, even more for kids. And what this also brings along with it is absenteeism. Absenteeism in school, like depression and suicide, has skyrocketed, and this is something that we should do everything we can to minimize. Who does this affect most? It affects the kids with the least amount of resources.

As you've heard before, some of the time spent can exhaust all of the amounts of work leave that parents have and all the amounts of vacation

that parents have just trying to get these kids to their appointments. This is not equitable care. This is something that many patients can't afford, either in terms of the money or time. So it's just critical that we think about every way we can to minimize those barriers, safely of course. It's critical that we maintain the safety that this program is all about, but at the same time make it more user-friendly for all patients, especially those with fewer resources.

The last point I want to make is that if we're not using isotretinoin, if we can't use isotretinoin, and if kids don't have access to that, what alternatives do providers have? There are not a lot of options for kids for systemic therapy for severe nodule and cystic acne, and one that has been used historically, and still is, are our systemic antibiotics.

I think it is incumbent upon all of us as healthcare providers, those of us who use systemic antibiotics, to consider that aspect of care as well, and to minimize the use of antibiotics when

we can to prevent the development of resistance, let alone the potential impacts on patients from side effects of the antibiotics themselves.

In summary, this is just a critical time, and we really appreciate your looking at this issue. I received, unbidden, many emails last night from my membership in the Society for Pediatric Dermatologists, saying please make this case as forcefully as you can because our patients are suffering. That just speaks to the level of investment, engagement, and need that our providers feel on behalf of our patients.

So thank you for listening and thank you for taking up this issue. And again, I appreciate your attention. Thanks very much.

DR. LO RE: Thank you.

Speaker number 3, can you please unmute and turn on your webcam? Will speaker number 3 begin and introduce yourself? Please state your name and the organization you're representing, for the record? You have five minutes, please.

DR. CALLENDER: Good morning. I am Ealena

Callender. I am speaking as senior fellow at the National Center for Health Research. Our think-tank conducts, analyzes, and scrutinizes research on a range of health issues with a particular focus on which prevention strategies and treatments are most effective for which patients and consumers. We do not accept funding from companies that make products that are the subject of our work, so we have no conflicts of interest.

We appreciate the opportunity to express our views today on the proposed changes to the iPLEDGE REMS requirements to minimize the burden on patience, pharmacies, and prescribers while maintaining the safe use of isotretinoin medications. We appreciate the advisory committee making an effort to reduce the administrative obstacles that may delay or interfere with treatment while preserving patient safety.

While patient safety is critical, some current safeguards for patients who cannot become pregnant seem unnecessary. We strongly recommend changing the requirements for patients who cannot

become pregnant. We suggest eliminating the requirement for prescribers to document repeat counseling for women who have had surgical removal of the uterus or removal of both ovaries, and women who are considered post-menopausal. These women will not regain the ability to become pregnant, so there's no medical reason to require repeated confirmation of counseling.

As described in the FDA briefing documents, 72-to-78 percent of denials for these patients are due to a prescriber not completing the counseling confirmation. This requirement has no discernible benefit and its elimination would remove a significant barrier for these patients. If a requirement does not improve safety, why don't we eliminate it?

On the other hand, allowing abstinence alone in patients who can become pregnant raises questions, especially in the setting of widespread restrictions on reproductive rights in the United States. Research indicates that many adolescents report being coerced into having sex. Also, young

adolescents are less likely to tell their healthcare provider that they are sexually active. One study of 169 adolescents found that 25 percent of those between 14 and 17 years old were not truthful with their physicians about being sexually active.

Abstinence is an effective way to avoid pregnancy, and the iPLEDGE counseling seems effective; still, we wonder how often adolescents do not want their parents to know that they have had sex, whether it is coerced or consensual. Therefore, they may withhold this information from their physician. We are not confident that most adolescents would disclose being sexually active even though the iPLEDGE system requires patients to tell their doctor immediately if they decide not to be abstinent, and then wait 30 days before engaging in sexual activity.

As you consider making changes to the iPLEDGE REMS, it is essential to note that researchers have found that these requirements can lead to financial losses for patients, with

55 percent of adult patients, 80 percent of caregivers, and 89 percent of children reporting missing school or work for medication-associated office visits. Female patients are especially likely to incur higher costs due to mandatory repeat office visits, testing, and precise timing of prescriptions.

In summary, we want to be clear that we understand that this medication is a known teratogen, and that it is critical to enforce certain restrictions to prevent fetal exposure. We recommend eliminating unnecessary barriers to equitable patient access when those barriers do not provide any benefits, and considering whether to strengthen contraceptive requirements for adolescents for the reasons outlined above. Thank you.

DR. LO RE: Thank you.

Finally, will speaker number 4 please unmute and turn on your webcam? Will speaker number 4 begin and introduce yourself? State your names and any organizations you are representing, for the

record. You'll have 10 minutes.

DR. FRIEDEN: Thank you. My name is Ilona Frieden, and I'm a board certified dermatologist and outgoing chair of the American Academy of Dermatology Association iPLEDGE work group. I am a practicing pediatric dermatologist at the University of California San Francisco, and I have no other relevant conflicts of interest for this presentation.

Dr. Barbieri, do you want to introduce yourself now or do you want --

DR. BARBIERI: I'll do it now. I'm John Barbieri. I'm a dermatologist and epidemiologist at the Brigham and Women's Hospital and Harvard Medical School, and I'm the deputy chair of the AADA iPLEDGE work group, and I have no relevant financial disclosures.

DR. FRIEDEN: Thank you.

I have been a dermatologist for 40 years, so my career beginning in 1983 almost exactly parallels the life cycle of this particular drug, and I estimate that I have treated, personally,

well over a thousand patients with isotretinoin.

During the past 40 years, it's really striking to realize that no medication has surpassed isotretinoin efficacy for severe and recalcitrant acne vulgaris. In addition, isotretinoin has also been found to be highly effective in a number of other important diseases that we haven't mentioned so far in this hearing, such as ichthyosis, cancer treatments, cancer prevention, and others. And please remember that some of those indications ended up using isotretinoin for years, even decades, greatly increasing the burdens of the iPLEDGE program. The burdens of the iPLEDGE program have caused harms in terms of proven health equity issues for vulnerable populations, which Dr. Barbieri will be discussing in a moment.

One thing that wasn't mentioned yesterday is dosing. In countries other than the United States, lower doses of isotretinoin are standardly recommended because they are equally efficacious for acne vulgaris, but they cause less side

effects. However, because acne outcomes are associated with a cumulative dosage of approximately 120 milligrams per kilogram for more durable responses, there's a tendency in the context of the iPLEDGE program to have a race to the end, so higher doses are used to get through the program, out of the program, and that does result in provably more side effects.

You saw yesterday many timelines, and I really just want to emphasize two dates on this particular timeline. I want to highlight 2016 because that was the year the AAD acne guidelines changed. These guidelines have changed the practice for many of us, including myself. We no longer standardly use oral antibiotics as a long-term treatment, and this is critically important, as Dr. Sidbury said, because it's really about antibiotic stewardship as well as efficacy.

A central aspect of acne management other than isotretinoin has become hormonal therapies, but these are not generally indicated for patients who are in that category of not becoming pregnant;

so for them, there are virtually no other systemic medications other than isotretinoin for the treatment of severe or recalcitrant acne.

Another important timeline is 2019 for us personally. Many dermatologists have written and spoken about the burdens of iPLEDGE before that. We formally that year formed the AAD iPLEDGE work group. We published, as you'll see, a publication which outlines some simple common-sense reforms.

This was a photo of our work group statement. It was published by three of us, but it was on behalf of our entire work group. We had four major recommendations in this proposal: to change the categories to can become pregnant and cannot become pregnant; to reduce attestation just 6 months for those in the cannot become pregnant category; to modify requirements, as was mentioned already and by Dr. Dublin yesterday, for those on LARC; and to allow, which had not been done, explicit acceptance of telemedicine visits as part of the program.

Two of these were accomplished, but they

were not accomplished through the efforts of IPMG at all. Obviously, due to the HHS directives and the FDA, these categories were changed to can become pregnant and cannot become pregnant. In addition was the acceptance of telemedicine visits because of the COVID pandemic. But the other two, until this hearing, we really have not been able to gain traction or adequately address.

The IPMG exists due to the requirement of a REMS program. You might think of it in a way as a kind of an arranged marriage. It's a confederation of currently seven manufacturers who are required to meet and comply with the FDA requirements. And despite many, many attempts to work with the IPMG, we are not aware of any organizational structure or key leaders to communicate with. Instead, we have been given repeatedly a generic email address for trying to establish a working relationship, and we believe that this may explain the inaction of the IPMG since our proposals four years ago in 2019.

This was most graphically illustrated in the crisis of 2021 because despite 6 months of

notification, no prescriber user input was solicited before revamping the website. What the last timeline didn't show, and you couldn't even put on a timeline, were the hundreds of contacts we had tried to make in trying to work with the IPMG, and emails, multiple emails. This lack of transparency and accountability has been a major hurdle in improving iPLEDGE.

The FDA has repeatedly asked us to work with the IPMG, and in the last five years, we have tried our best repeatedly to do so. Even yesterday in the IPMG presentation, most of its presentation, with one exception, was done by their contractors, UBC and Syneos, without leaders of the IPMG coming forward for the presentation, and note that there was not a single dermatologist who presented on behalf of the IPMG, and yet dermatologists are an overwhelming group of prescribers, and directly to work with the IPMG has really not worked out for us. It's just not been possible.

Whatever changes the FDA makes based on this hearing going forward, we really want to find a way

to continue to meet the REMS goals, improve iPLEDGE, and give patients and other stakeholders a voice, and we hope that the FDA will consider these challenges in working with IPMG in a path forward. Thank you so much.

I'll turn it over to Dr. Barbieri now.

DR. BARBIERI: Again, I'm John Barbieri. I'm a dermatologist and epidemiologist at Brigham and Women's Hospital and Harvard Medical School, and I really thank the committee for holding this session, for hearing from these stakeholders, and keeping an open mind.

Isotretinoin, as we've seen in some of the other presentations today, can be an incredibly life-changing medication for many patients. Although there have been concerns about a number of side effects for isotretinoin, more recent data has really supported the safety of this medication. For instance, isotretinoin is actually associated with a reduced risk of neuropsychiatric adverse events like depression and suicidality compared to other acne treatments, which I think is especially

important in this epidemic of mental health problems that we have ongoing.

There were concerns about isotretinoin and inflammatory bowel disease that have largely not held up when studied rigorously. And finally, studies looking at isotretinoin in lab abnormalities have even suggested that lab monitoring may not be of any value for this medication.

We share the FDA's commitment to pregnancy prevention and agree it's critical for the safe use of isotretinoin, but we're concerned that this program is not without inadvertent harms. There are tremendous logistical barriers associated with iPLEDGE. This is just kind of a web of all the different communications needed to just get a patient a prescription, and compared to other acne medications, the time it takes to successfully go from when you prescribe medication to when the patient actually has it in their hand is 5-to-10-fold higher.

Unfortunately, if we look at just the

comparison of the SMART program, before iPLEDGE, to iPLEDGE, there's been a 20 percent decrease in prescribing among people who cannot become pregnant, who have no risk of the outcome that we care about for this program, which is preventing fetal exposure to isotretinoin, and among people who can become pregnant, even greater reduction in prescriptions. So this program has clearly limited access.

In the summary earlier, it's mentioned that the committee was interested in studies on health disparities, and I'd like to summarize a few of them here. This is a study from our group which showed that despite having similar acne severity, non-Hispanic black patients and Hispanic patients are less likely to be prescribed isotretinoin, women are less likely to be prescribed isotretinoin, and those with Medicaid insurance are less likely to be prescribed isotretinoin. In addition, on patients who are of skin of color and patients who are women are less likely to be able to successfully complete a course of isotretinoin,

which, again, I think speaks to some of the barriers that this program creates and the resulting healthcare disparities that may occur as a result of it.

Again, we're committed to safe use of isotretinoin, but it should not come at the cost of healthcare disparities. So what can we do? We appreciate the IPMG trying to work to reduce attestation requirements and confirmation requirements for patients who cannot become pregnant. We believe that this is critical, and we also echo some of the other speakers from today about the 19-day lockup period.

To speak to Dr. Frieden's points earlier, we really need a better relationship, and transparency, and open communication, so going forward we can continue to improve this program to meet the needs of our patients. So when it comes to removing monthly attestation, again, we appreciate the IPMG's efforts to make headway on this. This could substantially reduce access barriers and lessen disparities, but I'm concerned

that what was proposed at this session is not going to improve access.

To all the administratively burdensome practices, the primary issue is not qualifying the patient to receive drug on the website, but the need for monthly visits for counseling and prescription; and many of us on this committee or workgroup would argue we don't actually feel like we need to see patients monthly for this drug.

In the IPMG's proposal, monthly counseling is still required and no refills are allowed. If that's the case, then prescribers will still need to see patients monthly, and access is not going to improve. We're essentially asking patients to come in monthly just to tell them not to share their drug and donate blood for the category of persons who cannot become pregnant.

In contrast, if we pair reducing the qualification frequency to every 4 months, or ideally even less, once a year, in conjunction with reducing the requirements for counseling and allowing for time-limited refills to reduce risk of

diversion or other issues, we can improve access and reduce healthcare disparities.

Additionally, formerly allowing home pregnancy testing and telemedicine is critical, as others have alluded to. I know it was mentioned yesterday, though someone's not a dermatologist or a doctor, that having a patient submit a home pregnancy test with their name and date would be too burdensome. This is already a standard approach in many of our practices, and has been successful, and we're trying to work on collecting data to show this.

In addition, it's certainly much easier to do that than to have the patient come to the office to get the lab slip and travel to another location to have it performed, as many of our offices don't have a CLIA-certified lab associated with them. And then importantly, we kind of know that this is safe; we've been doing it for the past three years during the COVID public health emergency. And the data the IPMG presented yesterday, we haven't seen any statistical increase in pregnancy rate during

this time frame. If home pregnancy testing was such an issue, then why aren't we seeing an effect? Then finally, if we do decide against allowing for continued access to home pregnancy testing, I really would strongly urge the FDA to formally study it, as I do think it's a major step back for our patients.

Moving on to the 19-day lockout period, as has been discussed, most patients when they miss a window period, it is through no fault of their own, and this is just simply not logical. The current programs focused on the menstrual cycles is really an antiquated approach, and has been mentioned in the Q&A yesterday and by others today, many patients do not have a monthly cycle due to medical conditions like polycystic ovarian syndrome, or due to contraception, and those on combined oral contraceptives are not even ovulating at all.

As was mentioned by others, the iPLEDGE program is really an outlier in having this 19-day lockout. And even if we accept this premise about a 28-day menstrual cycle and a fertile period

that's been proposed by some groups and others in other parts of this talk, let's just try a thought experiment. Pick out a calendar either physically or in your mind. Put an X every month on the 15th to be that fertile window. Now pick any day of the month to start isotretinoin and continue it for a standard 6-month course and see how many X's you pass. You'll find if you do this experiment, no matter which day you start, you're going to pass 6 X's.

It simply doesn't matter where in the menstrual cycle you start this drug. No matter which day you start it, it's a continuous medication. You're going to go past six of these fertile windows, as described in this idealized menstrual cycle, which, as many have pointed out, is not really realistic. So by removing this 19-day lockout, and really the archaic timings around the menstrual cycle in general in this program, we can simplify the program, improve it, and better align it with the real-world biology of our patients with acne.

Then has been mentioned, we really need to have a better collaborative relationship together with the FDA and IPMG, and key stakeholders like prescribers, patients, and pharmacists. We would love to work together with the FDA and IPMG to ensure safe access to isotretinoin. We have tried so hard to be able to contact the IPMG to help alert them to problems. Like that debacle in 2021, we warned about every issue that happened and talked about ways to mitigate it, and were largely ignored.

Again, with some of the proposals here, as has been heard by groups, many of them really just miss out on some of just the day-to-day practices of how taking care of patients with acne works, and by including dermatologists and key stakeholders in these discussions as we move forward with changes to improve this program, we can make sure that it's patient-centered. So we really ask to have regularly scheduled meetings, including the FDA, IPMG, and other key stakeholders, and have a clear and transparent and, importantly, timely process

for us to raise concerns and address programs with the issue.

With that, I want to thank, again, the committee for listening to us today and for hearing from our groups, and, additionally, to just keep an open mind and be thoughtful about how we can make this program patient-centered to ensure safe access to prevent fetal exposure without creating healthcare disparities and unnecessary burdens. Thank you.

Clarifying Questions to Presenters

DR. LO RE: Thank you for those thoughts.

The open public hearing portion this meeting has now concluded. We will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

As we have additional time, we will take remaining clarifying questions until we break for lunch at 12 p.m. Eastern time.

Can you please display M-1 slide 4, please?

(Pause.)

DR. LO RE: While that slide is coming up, for Q&A, please remember to use the raise-hand function and to state your name for the record before you speak. If you can, please direct your question to a specific presenter. If you wish for a specific slide to be presented, please let us know the slide number and the presenter, if possible.

As a general reminder, it would be helpful to acknowledge the end of your question with a thank you, and end of your follow-up question with, "That's all for my questions," so I can move on to the next panel member.

I've just gotten a messaging that Dr. LaCivita would like to make a point of clarification from the FDA.

Dr. LaCivita, would you come on camera, please?

DR. LaCIVITA: Yes. Cynthia LaCivita, FDA. Thank you.

I think I might have misspoke when I had my

opening remarks. I just wanted to make sure that we were seeking the company's advice on the 19-day lockout that occurs when the first prescription window is missed in the patient who can become pregnant, and whether this should be retained or modified. I can't recall exactly what I said, but I think I might have misspoke then, so just for the record. Thank you so much.

DR. LO RE: Thank you, Dr. LaCivita.

I've also been messaged that IPMG representatives would like to provide additional information in response to a question that Dr. Katz had raised about contraception for those identified 12 pregnancies that were detected during the lockout. I don't know if Mr. Shamp is going to be presenting on behalf of IPMG.

MR. SHAMP: Yes. This is Jim Shamp from UBC. In follow-up, we do have some updated information on the question about the contraception choices that the 10 patients that had gone into a 19-day wait were using.

Ten out of the 12 pregnant patients who

entered that 19-day wait reported contraception choices of birth control pills and male latex condom; one reported vaginal ring and male latex condom; and one reported abstinence, just to clarify that these are the choices as reported to the iPLEDGE system by the patients. Thank you.

DR. LO RE: Okay. Thank you.

So while we're waiting for hands to come up for clarifying questions, let me start off.

We've heard quite a bit at the open public hearing about issues of equity and negative health impacts on disparities and vulnerable populations, particularly with regards to delays in care. My question, I think primarily to IPMG, is there was data that was presented that 15 percent, or approximately 15-to-20 percent, of patients who can become pregnant miss their first treatment because the 7-day prescription window expires.

I don't believe that we saw data with regards to race or ethnicity. I also recall that one of the speakers at the open public hearing had mentioned about there may be disparities with

regards to not completing a course of isotretinoin treatment, and I would be interested to know if there are racial, ethnic disparities, and if you can provide breakdowns according to race and ethnicity with regards to completing a course of treatment. Thank you, and this is Vincent Lo Re at the University of Pennsylvania.

MR. SHAMP: Jim Shamp from UBC. We can appreciate that there is a burden associated with complying with the iPLEDGE REMS and that we are committed to helping ensure access to a isotretinoin, but we do have to do that within the confines of the REMS, and in a way that ensures we're meeting the goals to prevent fetal exposure to isotretinoin. We do not collect, as part of the enrollment of the patient, either race nor ethnicity, so we're not able to provide that data at this time. But as I said, we are committed to helping ensure access to isotretinoin in a way that continues to support meeting the goal. Thank you.

DR. LO RE: I'm going to go in order of the hands being raised.

Dr. Woodward, your hand is up.

DR. WOODWARD: Hello. This is Maria Woodward, University of Michigan, the Ophthalmic and Dermatologic Advisory Committee.

I guess my question, then, is in response to the fact that iPLEDGE is not currently collecting race and ethnicity data. I'd like to add that there's also insurance status data, uninsured insurance, and that data. I think that this data may be available through the AADA, and my question is, to them, do they have this data showing the disparities? I believe that it was highlighted in their presentation, but I'd like to dive into that because it makes common sense knowledge that people who can afford it and have better health literacy are more easily able to deal with this system. So I was hoping the AADA could clarify their data from their research studies.

DR. LO RE: Dr. Bautista, can you clarify if it is permissible for AADA to respond or not?

DR. BAUTISTA: Hi. At this time, we are not taking any clarifying questions from any of the

OPH speakers.

DR. WOODWARD: Well, I apologize. I thought that was our time to ask questions to them. Thank you. Can someone from, then, the FDA -- or is there just not data?

I guess, then, my follow-up question would be, does IPMG have a system for looking at peer-reviewed data to see about these disparities? If they don't have data, it sounds like it's being collected by other institutions. Do they have a process by which to review data for health equity?

MR. SHAMP: Jim Shamp from UBC. The IPMG does not currently have a process to review peer data. Thank you.

DR. LO RE: If I could just follow up from Dr. Woodward's question, then, one of the other key barriers that were mentioned during the open public hearing were prior authorizations, issues of either insurance denial or insurance delays.

Can you just clarify how often these delays are contributing to missing the first treatment because of the window period expiring? Do you have

those data?

MR. SHAMP: Jim Shamp from UBC. If I could just clarify, you're asking if we have data that indicates why the patient missed the 7-day window?

DR. LO RE: Yes, and particularly, if it was related to insurance, lack of prior authorization requests, or other insurance issues.

MR. SHAMP: We do not have data -- we don't collect any data, and therefore don't have it on why the patient missed the 7-day window, but what the system does collect we don't have, again, today. But we do collect data on patients that have discontinued, provided that the prescriber indicates from the system the patient discontinued, and reasons of insurance is one of those discontinuation reasons. Thank you.

DR. LO RE: Thank you.

Dr. Katz, you have your hand up.

DR. KATZ: Thank you. I wanted to thank the speakers of the open public hearing for their comments, and just to clarify something that I said yesterday about prescriptions longer from 30 days,

that I would want to check in with my patients and didn't advocate for longer prescription times. I do think that. I just wanted to clarify that I think that that could be done by telehealth, and certainly would not require an in-office visit for every patient. Thank you.

DR. BAUTISTA: Hi. This is Phil Bautista, the DFO. I really appreciate all the comments we received so far, and some of the questions as well, but I just want a reminder that at this point it's just really to focus in on clarifying questions; so presentations, briefing materials, or any additional information that you might need to inform the discussion later on after lunch.

So if you do have any recommendations or solutions, we ask that you raise these for discussion and voting questions. Thank you.

DR. LO RE: Dr. Salvas, do you have a clarifying question?

DR. SALVAS: I do. Thank you.

Good morning, everybody, and thank you to the members of the public for sharing their

perspective. Two clarifying questions for me, and I'll direct this to the IPMG and the FDA for their perspectives.

What is the proportion of patients leveraging abstinence as their form of contraception, and what is the IPMG's and FDA's perspective on the incremental monthly risk for patients using abstinence? The reason I ask has to do with the 19-day lockout, and it was brought up this morning that that risk does not go away on a monthly basis for folks using abstinence for those that can become pregnant, so I would appreciate understanding that a little bit more deeply.

Then the second is, do we have data to support continued monthly counseling and blood donation, in person, virtual, or otherwise, beyond the hypothetical risk of somebody potentially sharing or potentially donating blood? I understand the hypothetical risk of this, but do we really understand the risk/reward of exerting this much effort for the system? Thank you.

MR. SHAMP: Jim Shamp from UBC. In response

to your first question about the proportion of patients using abstinence, slide up. On this slide, you'll see the 10 most common contraception methods based on the monthly interactions, and you can see here that, based on that, abstinence is the number one choice with over 700,000 monthly interactions choosing abstinence as their choice, which is just slightly more than 46 percent.

As far as the incremental risk of using abstinence, I will ask Dr. Weiss to respond to that question.

Dr. Weiss?

DR. WEISS: Hi. Dr. Herman Weiss. I'm an external GYN consultant. As a paid consultant to the sponsors, I have no financial interest in the outcome of this meeting.

The incremental risk associated with abstinence as the primary choice -- indeed, you are correct -- doesn't go away, but it shouldn't change in terms of the way that the program is run if abstinence is their true method.

Now, I know it was mentioned earlier about

the fact that adolescents have been shown to potentially lie to their caregivers as a way to cover up sexual activity. That should be, indeed, taken into account when making recommendations for the continued program. Thank you.

DR. SALVAS: Thank you.

I guess where I'm going, gentlemen, is if we're to consider potentially removing the 19-day lockout in a system where half of the patients are not benefiting on the subsequent months, should we also be considering adding the 19-day lockout for those patients on a monthly basis? And if we have an allergic reaction to a system designed like that, might that be an important consideration for whether or not the 19-day rule, or whatever we want to call it, should exist in the first place?

MR. SHAMP: Jim Shamp from UBC. The purpose of the 19-day lockout, or wait in this case, is to prevent fetal exposure to isotretinoin, so this is the last opportunity to prevent the exposure. After the patient has received their drug, then the goal is then to try to minimize the exposure. So I

don't think the 19-day wait would be best serving that purpose, but like I said, the purpose of it at the first prescription window is to prevent fetal exposure. Thank you.

DR. SALVAS: Understood.

Alright. That's enough for me. Thank you.

DR. LO RE: Dr. Calis, you have your hand up.

DR. CALIS: Yes, thank you very much. Actually, that's a good segue to my question because I'm kind of getting a good understanding of all the issues that we're deliberating on today. The one thing that I keep coming back to is the 19-day lockout. I've heard a lot of discussion and kind of partial presentations about it from various individuals, but I'm still unclear, including even the statement just a second ago about what is truly the rationale of the 19-day lockout, and what evidence is there [inaudible - audio gap] -- I heard a little bit of the history that there was a 23-day lockout, et cetera, so there was some thought put into this, and I would just like to

have someone kind of elaborate on it. I understand the physiologic parts. Are there technical administrative reasons as well? I haven't heard it clearly articulated, so I'd appreciate some thoughtful discussion of that because I think that's a critical issue that we have to consider.

MR. SHAMP: Jim Shamp from UBC. I'll ask Dr. Weiss to elaborate on the 19-day wait.

Dr. Weiss?

DR. WEISS: Thank you. Dr. Herman Weiss, external GYN consultant. As has been presented by both the agency and by the IPMG, indeed it's true that there's limited strong medical rationale for this legacy 19-day wait period, but from the data presented, it is quite evident it has successfully identified 12 pregnancies.

Now, we understand that menstrual cycles vary given the average 28 days, but as mentioned earlier by Dr. Barbieri, if you go into any 6-month period of time, you're going to have 6 ovulations in an untreated patient. But the fact of the matter is, abolishing this legacy 19-day wait would

have risk exposing these 12 patients to the drug.

So although there's no strong medical rationale, as we've gone over, and I think as your question has identified, as we said earlier, the proof is in the pudding and I think that that would be part of the rationale. Thank you.

MR. SHAMP: Yes. And if I can just add, pregnancies from this 19-day wait are likely unreported because they are not required to be reported to the registry, because they are not exposed. Thank you.

DR. LO RE: Can I ask Dr. LaCivita, just maybe from the agency's perspective for Dr. Calis, if they can provide some additional either insights or thoughts as to the medical basis for the rationale. I know it was presented by Dr. Crist in the past, but Dr. Calis is looking for a little clarification.

DR. LaCIVITA: Thank you. This is Cynthia LaCivita, FDA. I'm going to ask Wenjie Sun to answer that question, and then she may need assistance by Dr. Crist. Thank you.

DR. SUN: Hi, everyone. Wenjie Sun, FDA.

DR. LaCIVITA: Dr. Sun, we can't hear you very well.

DR. SUN: Can you hear me now? Is that better?

DR. LaCIVITA: Yes.

DR. SUN: I'm going to speak on the biological rationale for the 19-days. The failure to obtain a prescription during the initial 7-day prescription window will lead some patients to enter into the fertile time of their menstrual cycle, and a wait period is necessary to detect any pregnancy for that particular population during this time.

For those who fail to pick up their first prescription prior to initiation of treatment, the 19-day lockout is just an added layer of screening for everyone to prevent exposure, and that's our rational for the 19 days. Thank you.

DR. LO RE: Thank you, Dr. Sun.

Dr. Calis, was that clarified for you?

DR. CALIS: No, not yet. I have a quick

follow-up.

So I understand what was just presented, and I appreciate the responses. I guess what I'm gathering is that the 19-day lockout is affecting the initial phase when we start prescribing this drug, but it obviously does not continue on, and somebody can get continued treatment.

Additional pregnancy testing early on in that phase, could that be substituted as a method to help us prevent the 19-day lockout? Is there some kind of alternative administrative method that can help ensure that we could limit embryo-fetal exposure to the drug? Thank you.

DR. SUN: Thank you for that question. The 19 days apply to everyone, and it is designed to prevent exposure for everyone before they start treatment. This is the last chance for us to have this layer of screening to prevent exposure.

The reason it requires 19 days and not less than 19 days, for a particular group of patients who do ovulate regularly, if they follow that 28-day menstrual cycle, when they fail to pick up

their prescription, they are entering into that fertile phase, and it takes time for pregnancy to develop at implant before it can be detected. So screening for that particular population prior to 19 days will fail to detect that, those pregnancies that might occur during that cycle, and that's the reason why a wait time is needed for that population.

Does that answer your question?

DR. CALIS: Somewhat. Thank you.

DR. SUN: Thank you.

DR. LO RE: Thank you, Dr. Sun.

Dr. Dublin?

DR. DUBLIN: Thank you. I have a couple of questions. One of them is I guess for the FDA, and I'm just wondering, is it within the scope of the advisory committee and of the FDA to require that IPMG develop a robust process for assessing the impact of iPLEDGE on health disparities and health equity? This could include features such as requiring that iPLEDGE collect some of the data about race ethnicity or that IPMG access outside

databases to study this.

Is this within the scope of FDA's ability to recommend, based on the advisory committee?

Then a follow-up question to IPMG would be, what are the barriers to, and would you have an objection to, beginning to collect information about data that would allow you to study health disparities within iPLEDGE, such as race data, ethnicity data, socioeconomic status, and other rural world versus urban location? Thank you.

DR. MANZO: Hi. this is Claudia Manzo from FDA. I'll try to address that question. We certainly have the ability to require sponsors to assess the impact on patient access. I can't say that in the past we've look specifically at socioeconomic status or race. That is, of course, additional information that we might be requesting of a patient that really, in general, would go beyond the scope of what's necessary for the safe use of the product, but we can take that back and think about ways in which they might be able to look to see whether there's greater impact in

certain populations of patients than others.

Does that help answer your question?

DR. DUBLIN: That's great. Thank you.

Then the question for IPMG, would you be opposed, or what barriers do you see, to beginning to collect the data that would allow you to understand the differential impact on the requirements on patients in more vulnerable situations?

MR. SHAMP: Jim Shamp with UBC. We appreciate this thinking, and we are certainly happy to discuss those changes with the agency, as well as stakeholders. I do want to just state that as with any change to the REMS, this change would require a proposed modification to be submitted to FDA, FDA's review, and approval of that, as well. Thank you.

DR. DUBLIN: I have a follow-up comment and a question. I just want to comment that one of the speakers, in responding to a question recently, used the language of "adolescents lying to their caregivers" to cover up sexual activity, and I just

want to highlight that I find that language concerning. I think it shows a lack of empathy and compassion towards our adolescent patients. I'd like to ask that speakers make every effort to speak about the patients we're serving in a way that respects the difficult choices they face.

Third, I have a comment or question about the fertile window, and I wonder if we could put one of the calendars or the pictures back up. I just want to reason out loud and ask FDA to respond.

It looked to me, from one of the pictures that showed the different dates, someone might have a pregnancy test on days 1 through 5; and then they might miss their pickup in the next 7 days; and then they might have the 19-day lockout. I mean, it actually looks to me like if someone did get pregnant during the lockout period of 19 days -- so during the fertile window -- that we've seen a variety of different kinds of data. We did see data that the pregnancy tests are able to detect, say, 70, or 90, or something, some really high

percent of pregnancies, after 19 days, but that's after 19 days from conception.

So I think we may be conflating some different things because it seems to me like if someone got pregnant right at the end of the fertile period, like day 16, the odds of the pregnancy test on day 20 detecting that pregnancy, that's 5 days from the date of the conception. That would be very, very low. So, in a way, I feel like the 19 days it takes to detect the pregnancy successfully, that's the 19-day lockout. The 19-day lockout has the fertile period right in the middle.

So I'm just wondering if FDA could react to the idea that maybe this is sort of false reassurance, that if a pregnancy occurred on day 16, the pregnancy test is not really helping us in the way we believe it is; and thus, I guess I would say I'm not convinced it's fully justified. But I really would appreciate your thinking about whether I'm thinking through this properly.

DR. LO RE: Dr. LaCivita, could you or

someone in the group, in the agency, respond?

DR. LaCIVITA: Yes. This is Cynthia LaCivita, FDA. I'm going to ask Dr. Sun if she could respond to that question, and I'm not sure she has a backup slide for that, or even from her presentation.

DR. SUN: I do have a slide from the presentation. Give me one second. Wenjie Sun, FDA. If you'd like, you can pull up my slide for slide 15.

(Pause.)

DR. SUN: Okay. I'm going to talk about it while you're pulling up the slide. The slide I'm referring to is a graphic representation of detection of pregnancy for patients with regular cycles, and thank you for pointing it out. You are correct; testing patients 19 days after the confirmatory pregnancy test takes a patient to roughly day 20 to day 24 later of their cycle, and this represents the earliest time where pregnancy conceived during the cycle can be detected. That percentage is roughly around 40-to-66 percent;

therefore, if you wait longer, you could potentially detect a greater percentage of pregnancy.

Does that address your question?

DR. DUBLIN: Thank you. I think that's really helpful. I think everyone on this call is united to our commitment and passion about preventing pregnancies, but I really take the points that were raised earlier about people who don't even ovulate because of the contraception they're on. And I think that to really follow this logic to its end, we'd have to require something like a 25-, or 30-, or a 35-day lockout, or something where I think we wouldn't really -- as the previous speaker said, if we have an allergic reaction to that, we should listen to that feeling.

That concludes my questions. I appreciate the FDA's and IPMG's answers. Thank you.

DR. LO RE: Great. Thank you.

Ms. Robotti, you have your hand up.

(No response.)

DR. LO RE: Ms. Robotti?

MS. ROBOTTI: Sorry. I clicked hastily. Thanks. I'm sorry. Very quickly, an easy question is, how many people get locked out in a year? I've forgotten the number.

MR. SHAMP: Jim Shamp from UBC. Approximately 15 percent of the patients go into a 19-day wait after their first prescription.

MS. ROBOTTI: Thanks. Perfect; just what I was asking.

Secondly, I'm asking this question because I am not a doctor, and oddly as a consumer rep, I'm not allowed to consult with doctors ahead of the meeting. It's just one of those roles they have for us. So you all know this, but I would like to know it.

The counseling, the initial counseling that a doctor goes through with a patient, I mean, I've seen the checklist of what needs to be covered, but not the detail of it. So does it include the discussion of the consequences and the options available to the patient? So a specific discussion of, if you should become pregnant on this, your

options are you could seek an elective abortion, which most do, but what are now becoming increasingly more difficult to choose, or pray for a spontaneous abortion or you will give birth to a child with incredible difficulties, challenging it with huge amount of expenses to out of pocket, and to society, and the damage.

Is that all covered in these initial conversations that require it to be? I just want to understand that young teenagers really understand the consequences of choosing abstinence and making mistakes.

MR. SHAMP: Jim Shamp from UBC. The education materials provided to the prescriber to be used with the patient does provide specific counseling on the choices, the available contraception choices, that are approved for the iPLEDGE REMS program. In the situation if a pregnancy occurs, the patient should be referred to an expert in the situation to be counseled on possible choices following that pregnancy. Thank you.

MS. ROBOTTI: Well, thank you.

DR. LO RE: Thank you.

Dr. Atillasoy, you have your hand up.

DR. ATILLASOY: Hi. Can you hear me?

DR. LO RE: Yes, we can hear you.

(No response.)

DR. LO RE: Now I don't think we can hear you.

(No response.)

DR. LO RE: Okay. While you're sorting out the connectivity -- wait; now we can see you.

DR. ATILLASOY: Oh, sorry. Can you hear me?

DR. LO RE: Yes, we can hear you and see you.

DR. ATILLASOY: Ercem Atillasoy. I can forego the questions. I could ask them later.

I would just ask if the FDA or IPMG could remind us -- two quick questions -- the number of prescriptions for isotretinoin in the last 5 or 10 years in the United States, number one; and then perhaps comparing or contrasting the rates of unintended, or the number of unintended,

pregnancies in the United States versus a country like Canada that doesn't have a REMS.

I ask that in the context of trying to determine -- there's been lots of commentary about lack of access to the medication, so I just wanted us to see some data around this topic. Thank you.

MR. SHAMP: Jim Shamp from UBC. Slide up. From my presentation, we do have this slide that shows the number of prescription risk management authorizations from year 16, and that is just a little more than 1.8 million just from year 16 alone. I want to just point out that year 16 was a shorter year. This was the bridge assessment report, so it covered 10 months instead of the typical 12 months. But you can see the volume from this, cumulatively, that over the first 16 years of the iPLEDGE REMS, there have been almost 21 million authorizations.

I believe your second question, if you wouldn't mind restating that. I just want to clarify what it was.

DR. ATILLASOY: The question there was also

just to compare and contrast the number of unintended pregnancies in the United States versus a country like Canada, which does not have a REMS program. There's been lots of discussion about contraception and our potential reliance upon consideration for in-home testing and things like that, so I'd appreciate seeing unintended pregnancies in the U.S. versus Canada or other countries that may not have a REMS program in place.

MR. SHAMP: Yes. Slide up. This is Jim Shamp from UBC. This slide shows the unintended rate of pregnancies in the U.S., which was 45 per 1,000 women, or young women, and this is data from 2011. Then you can see, on the right-hand side, the general Canadian population rate of 50 pregnancies per 1,000 women, and that is from data of 1996 through 2011. In comparison, the same year of 2011 for the U.S. population, the iPLEDGE pregnancy rate in that year was 1.2 per 1000. Thank you.

DR. ATILLASOY: Thank you.

DR. LO RE: Dr. Woodward, you have your hand up.

DR. WOODWARD: Yes. I just had another clarifying question for IPMG.

I understand that we've been saying this number about 12 people affected because of the lockout period, but that's a cumulative number. As I look at the data tables that are presented in the briefing document, there's only three in year '16, and similarly between 0 and 5 it looks like, over the 12-to-16-year period. I'm just thinking when I compare that to table 14 in the briefing document that says the number of exposed iPLEDGE pregnancies by isotretinoin exposure over the lifetime of people taking the medication, it's 177 after that lockout period during the monitoring phase.

So I just want to make sure I understand because when you said 12, I couldn't find the 12. I could only find just year by year. Thank you.

MR. SHAMP: Jim Shamp from UBC. So those 12 pregnant patients are from years 12 through 17, and you are correct that they are not all in one

year, so that is the cumulative for those years. And I think we've said this before, but just want to restate, that this number is likely underreported because these pregnancies are not required to be reported to the registry because they are non-exposed pregnancies. Thank you.

DR. LO RE: Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I just had a clarifying question related to access. It was my understanding, based on data that were shared yesterday, that over time, the number of patients on treatment had increased. But I seem to remember from data that were presented earlier today, that since the introduction of the iPLEDGE program, the number of patients that have been treated was much lower than before the iPLEDGE program, and I'm not sure I fully understood it or interpreted the data correctly. But I was wondering, given that the public commenters can't respond, that maybe IPMG can speak to that.

Is there any evidence that since introduction of the iPLEDGE program, with all of

its restrictions, that access has decreased? Are there data to support that or not at this point?

MR. SHAMP: Jim Shamp, UBC. I don't think we have data over the life of the program that would support this, but what we do have is data from the past, I believe, 4 or 5 years.

Can I get the data that has the enrollment?

(Pause.)

MR. SHAMP: Bear with me while I'm having this pulled up.

(Pause.)

MR. SHAMP: Yes, slide up.

DR. LaCIVITA: Dr. Lo Re, maybe when Mr. Shamp is done, we also have some drug utilization data that might be helpful.

DR. LO RE: Will do, Dr. LaCivita. And Dr. Pham's hand is up, too. Is that all related?

DR. LaCIVITA: (nods yes.)

DR. LO RE: Very good.

MR. SHAMP: This is the data we have available today. Unfortunately, it only shows year 12, but as you can see, we had nearly

300,000 patients enrolled in iPLEDGE in year 16 alone and just over 1.8 million authorizations to dispense. Thank you.

DR. LO RE: Dr. LaCivita, do you and Dr. Pham want to respond for utilization?

DR. LaCIVITA: Yes. I'm going to turn it over to Dr. Pham for that question. Thank you.

DR. PHAM: Hi. Good morning. This is Tracy Pham, FDA. Backup slide number 8, please?

(Pause.)

DR. PHAM: So while we're waiting for the slide to show up, I just want to make a comment. We're looking at a proprietary drug-use database to look at the number of isotretinoin prescriptions dispensed from the U.S. outpatient retail and mail-order specialty pharmacies, and we look at this monthly data. As you can see from this graph, the monthly dispensed prescriptions for isotretinoin is it fluctuates, but it's follows a very similar pattern where there is a dip around October and November, but then it's picked up again after that, usually around January, February, and

March. So as you can see, there's no decrease after that modification. There's that usual dip in October and November, and then the trend picked up again. So based on this data that we're showing, we didn't really see a decrease in use.

Then if you can go to slide number 9, just to go back to one of the questions that was raised earlier of how many prescriptions and how many patients are taking isotretinoin in the last couple of years, we did look at also the number of prescriptions and number of patients for isotretinoin from the retail and mail-order pharmacy since 2010, and as you can see, the number of patients and prescriptions basically doubled over that time period that we analyzed.

Let me know if there are any other questions or additional clarification?

DR. HUYBRECHTS: No follow-up from my end. Thank you.

DR. PHAM: Okay. Thank you.

DR. LO RE: Thank you, Dr. Pham.

Dr. Calis, you have your hand up.

DR. CALIS: A quick question. I'm following up actually on the question from one of my other colleague panelists with regards to the patient education. Can someone describe the nature of the patient education as it relates to the extent of the discussion of the embryo-fetal toxicity and teratogenicity issues? Is that something that is emphasized in the education? That could obviously influence compliance with various methods of pregnancy prevention.

MR. SHAMP: Jim Shamp from UBC. Bear with me as I find the material.

(Pause.)

MR. SHAMP: Your question is specific to the information and materials that have to do with embryo-fetal toxicity; is that correct?

DR. CALIS: Correct. Thank you.

MR. SHAMP: Looking in the prescriber guide, there is a section on birth defects that discusses that there is an extremely high risk that a deformed infant will result if pregnancy occurs while patients who can become pregnant take

isotretinoin in any amount, even for short periods of time. Potentially any fetus exposure during pregnancy can be affected. Not every fetus exposed to isotretinoin has resulted in a deformed child; however, there is no accurate means of determining which fetus has been affected and which has not been affected.

While isotretinoin is taken during pregnancy, it has been associated with fetal malformations, and there is an increased risk for spontaneous abortions and premature births. The following human fetal abnormalities have been documented and, slide up, the remaining materials match what is on this slide here.

(Pause.)

DR. LO RE: Dr. Calis, any other questions?

DR. CALIS: No. Thank you very much. I appreciate it.

MR. SHAMP: Thank you.

DR. LaCIVITA: Other questions? Dr. Liu, you have your hand up.

DR. LIU: I have a question about the 7-day

pickup window. I heard several reasons that can lead to the patient missing the 7-day pickup window. The reasons include insurance, patient's schedule, and prescriber's schedule. I wonder if there's any detail statistics, like a summary, about the reason why patients are missing this 7-day window. This may be a question for IPMG. Do we have any data for that?

MR. SHAMP: Jim Shamp from UBC. We don't collect specific reasons for missing the window -- I'm looking for the data that shows the reasons for denial -- but what we do is we do have data on some of the reasons that the authorization was denied, which might give us some insight into why this is happening.

While I'm waiting for that data to come up, there are a couple reasons why a patient may miss the 7-day window outside of just not getting to the pharmacy and picking it up. If they fail to demonstrate their comprehension in that time frame, that would cause a denial. So if they never demonstrate the comprehension, it would not matter

if they were able to get to the pharmacy. In looking at reasons for denial, 44.6 percent of the denials are because the patient has yet to demonstrate their comprehension, and that is the number one reason for denial.

DR. LIU: I'm talking about the 7-day prescription window. That means they can pick up the medication but miss the window.

MR. SHAMP: Once the prescriber enters the pregnancy test and confirms the patient in the system, that's what creates the 7-day window, and then within that 7-day window, the patient must also demonstrate her comprehension before she's qualified to receive drug. So if she does not demonstrate her comprehension, she will not go to pick it up at all. But beyond these denial reasons, we don't have specific reasons why the patient was not able to get their drug in that 7-day window. Thank you.

DR. LIU: Okay. Also, do we have any data that suggests for patients who miss the 7-day prescription window has a higher chance to become

pregnant than those who didn't?

MR. SHAMP: Jim Shamp from UBC. We don't have data that shows an increased risk to these patients, but what we do know is that this is the last opportunity to prevent fetal exposure, and that's directly tied to one of the goals of the iPLEDGE program. Thank you.

DR. LIU: Alright. Thanks.

DR. LO RE: Dr. Tollefson, you have your hand up.

DR. TOLLEFSON: Yes. I have two questions about emergency contraception that I think may be directed towards the experts at the FDA for the first part. I'm trying to get a sense for the availability of emergency contraception, in general, and are there regional variations in that. Second, is there a reason that, so far -- this could be for IPMG or the FDA -- that specifically hasn't been considered in the education part of the iPLEDGE program?

DR. LaCIVITA: Cynthia LaCivita, FDA. I'll start the question, and then I'm going to probably

ask Dr. Crist to help me. I'm not aware of any regional issues with regard to the availability of emergency contraception. There may be some; I'm just not aware of anything like that.

What was your second part of the question? Can you repeat that again? Oh, where is the emergency contraception located in the materials?

DR. TOLLEFSON: Yes.

DR. LaCIVITA: Okay.

DR. TOLLEFSON: Is it located, and second, is there a reason it just hasn't had more attention?

DR. LaCIVITA: It is located in the materials. I'm going to turn it over to Dr. Crist.

DR. CRIST: Hi. Thank you. Lindsey Crist from the FDA. Related to your question about emergency contraception in the REMS materials, there is information in the Contraception Counseling Guide, so it is recommended. The requirements in there state that these patients should receive emergency contraception counseling. In the patient enrollment form, the patients also

attest to stating they've received information on emergency birth control.

Does that answer your question?

DR. TOLLEFSON: Yes, I think in part. It seems that there's probably some more opportunity for focused, I guess, counseling, and kind of calling it out in a situation where someone might find themselves unexpectedly in a potential unexpected pregnancy situation. So I'm just looking to reasons for why that might not be more specifically counseled or called out in the process, instead of just being a part of a list of recommendations.

DR. CRIST: Thank you.

DR. LO RE: Just to clarify, though, Dr. Crist, it sounds like -- so just clarify this for me -- emergency contraception education is included in the monthly counseling that patients who can become pregnant receive at the time of picking up their prescription, or not?

DR. CRIST: The documents state that the patient should receive emergency contraception, and

that this message should be conveyed by a prescriber. There's not like a separate document that goes over emergency contraception details. It's all combined in this contraception counseling guide, which is intended for the prescriber to utilize to counsel the patients monthly.

DR. LO RE: And this counseling is uniform across prescribers? It's sort of scripted?

DR. CRIST: The counseling guide just gives general information for the prescribers to counsel on.

DR. LO RE: Okay. So is there potential for variability, then, across prescribers?

DR. CRIST: There could be variability across the prescribers; absolutely.

DR. LO RE: Okay. Thank you; appreciate it.

Other clarifying questions?

(No response.)

DR. LO RE: If there aren't any other clarifying questions, I'd like to ask a question. One of our charges for the discussion is ways to streamline the pregnancy registry, and I just note

that we haven't had many questions that are directed towards that.

So just that this committee can be most effective in trying to address that particular aspect, can I just ask from Mr. Shamp at IPMG, can you give me a sense, or one of your colleagues, in terms of the consenting process for inclusion in the pregnancy registry, could you just take us through the procedure of that? Because if we're going to try to consider ways to streamline, I'd just like to get some sense as to how is that done, and are there potential barriers that could be removed.

MR. SHAMP: Jim Shamp from UBC. I'll my colleague, Dr. Ephross, to respond to the question.

Dr. Ephross?

DR. EPHROSS: Sara Ephross, Syneos Health. This is something that we are actively investigating, possible ways to streamline, but it is important to note that there is patient confidentiality, a patient consent form that includes information about confidentiality, and it

takes about 15-to-20 minutes, is my understanding , to administer by phone. Thank you.

DR. LO RE: Just one other follow-up question, Dr. Ephross.

MR. SHAMP: Dr. Ephross?

DR. LO RE: Just one other clarifying question for you, Dr. Ephross. So this consent occurs at the time that a pregnancy is identified; correct?

DR. EPHROSS: That is correct.

DR. LO RE: I just am wondering, is there any thought to do consenting for all the participants in the program, or would that just simply be too burdensome? Let me rephrase my question to you.

DR. TOLLEFSON: Thank you very much.

DR. LO RE: My question is, since it seems like identifying potential patients who become pregnant for consent is a challenge, are there other times at which consent could occur perhaps earlier?

DR. EPHROSS: Yes. Thank you for that

clarification. Slide up, please.

I did want to clarify -- I think your questions have to do with the registry data collection flow --

DR. LO RE: Yes.

DR. EPHROSS: -- and this slide shows that. So at the time -- excuse me. I want to clarify one thing first, which is that at the time of initial iPLEDGE consent, everyone in iPLEDGE attests that they know that in the event of a pregnancy, their pregnancy information may be shared with the registry. So that is a time where there is consent in terms of just being included in the registry; that is given.

Later, as this slide shows -- slide up -- this is Appendix A from the actual protocol, and although the slide is small and hard to read, it shows the different places where different kinds of information are collected. On the left side what I was talking about is the initial information that's given at the time of the initial iPLEDGE program consent. That's on that first line on the

left side of this slide, where it says that "This is consent to report pregnancy to the iPLEDGE pregnancy registry." So your information may be shared with the pregnancy registry.

Then the second line on that same left side says that there's maternal consent to participate in the iPLEDGE registry, and what that means is once the information is shared with the pregnancy registry, which consent is given to at the time of the initial iPLEDGE program consent, that everyone gives consent for, and what the second maternal consent to participate is, is to collect additional information in the pregnancy registry.

DR. LO RE: Okay.

DR. EPHROSS: At long last, I've clarified, the difference between those two time points.

DR. LO RE: Okay. Thank you very much.

DR. EPHROSS: Thanks for your patience.

DR. LO RE: A question for Dr. Bautista; it's 12:00. There are three additional hands up for clarifying questions. Point of procedure, can we break and have those questions answered at

12:30 pm?

DR. BAUTISTA: Yes, that's fine.

DR. LO RE: Is that ok?

DR. BAUTISTA: Yes, that's ok.

DR. LO RE: Alright. So I'm going to just take a note that that is Ms. Robotti, Dr. Katz, and Dr. Hernandez-Diaz.

We'll break now, and return at 12:30 for those last three clarifying questions, and then we'll move to the questions to the committee and the discussion. Thank you.

(Whereupon, at 12:00 p.m., a lunch recess was taken.)

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

(12:30 p.m.)

Clarifying Questions to Presenters (continued)

DR. LO RE: We are going to resume the clarifying questions.

Sorry. I got a note that FDA requests one additional minute to provide a point of clarification.

Dr. LaCivita, did you or a member of the agency want to provide that?

(No response.)

DR. LO RE: Dr. LaCivita?

(No response.)

DR. LO RE: Alright. We're going to hold off, then. Wait.

Dr. Manzo --

DR. MANZO: Yes. Hi. I don't know. I think she's having some issues.

DR. LO RE: No worries.

DR. MANZO: We wanted to make sure that it was clear. With the drug-use data, we thought we heard there were some discrepancies or disparities

in women not being prescribed isotretinoin, so we're going to have Dr. Pham present some information on use by age and by sex. Thank you.

DR. LO RE: Thank you.

DR. PHAM: Thank you, Claudia.

This is Tracy Pham, FDA. Backup slide 11, please?

(Pause.)

DR. PHAM: On this slide, we're looking at the number of isotretinoin prescriptions that were dispensed from the retail and mail-order pharmacies in year 2022, and as you can see from this slide, the number of prescriptions dispensed to female and male patients are very similar, 50 percent. Even though we didn't show the age for the male patients, the data also show that the majority of both female and male patients were age 12 to less than 46 years old. We just wanted to make that clarification, and I can take any questions if there are any additional questions from this slide.

DR. LIU: Can I ask a quick question?

DR. PHAM: Yes.

DR. LO RE: Dr. Liu?

DR. LIU: Yes. A quick question. Based on the description, I remember that the drug's given to 20 years and older. Why is this less than 20 years? Just a quick clarification.

DR. LO RE: Dr. Pham, I think the question was the indication for the drug was 12 years or older. Why less than 12?

DR. PHAM: These data, we don't have a way to clarify whether there is a data error, so we don't have access to the medical record to confirm. So there might be some dispensing to this age group, but it could be a data error where it's erroneously being captured, but we see that it's very small. It's 0.1 percent.

DR. LO RE: Dr. Epps, you had your hand up. Did you want to clarify?

DR. EPPS: Yes. Thank you very much.

There are exemptions for oncology indications, high-risk neuroblastoma, as one of our expert panelist can attest to, as well some inborn or congenital ichthyosis and some other

indications, and those are the patients who are under 12 years of age.

DR. LO RE: Great. Thank you, Dr. Epps.

Are there questions related to this slide, Dr. Salvas?

DR. SALVAS: Yes.

Dr. Pham, first of all, thank you for sharing this. I think the data gap that I just want to continue to highlight for us is that, while we have this on a gender basis, the lack of race ethnicity data overlaid on this. I feel like it's holding us back from really being able to understand if the program design is restricting access in a way that is disproportionately hurting specific populations.

Another panelist earlier also mentioned managed care as something I think would be interesting, too. Understanding the breakdown by Medicaid exchange commercial, for example, would really help us understand, as we try to contemplate future changes to this program, whether there are certain groups that are disproportionately impacted

from an access perspective.

DR. LO RE: Ms. Ludwinski?

MS. LUDWINSKI: Yes. Thank you. Donna Ludwinski, patient representative. To the point that was just made about the under 12-year-old set, it did make me wonder why the actual indication isn't captured, because if the whole purpose of iPLEDGE is to prevent pregnancy exposure, and yet you have these oncology conditions that are -- I mean, high-risk neuroblastoma affects 3, 4, and 5 year olds. Isn't that an unnecessary burden to even have them have to register? By my calculations, the past 16 years have been somewhere between 3[000], 4[000], 5,000 high-risk neuroblastoma alone, aside from these other indications that were mentioned earlier.

So I'm just curious. What is the point of having to register these particular indications in the iPLEDGE because it may be creating an unnecessary burden for those oncologists that are prescribing it, and those families. Thank you.

DR. LO RE: Dr. Pham, or Dr. Manzo, or

Dr. LaCivita, do you want to respond?

DR. MANZO: I can try to address that question. We set up the program and, again, these off-label indications are off-label. We do recognize them. We have worked with the company -- the companies -- to allow certain aspects of the program to be exempt for serious medical conditions.

For example, some of these patients would fall into the category of cannot get pregnant, so it might be categorized that way. They may also not have to wait if there's a serious medical condition. So they may not be subject to the 30-day waiting period if they are a person that can become pregnant. That being said, it is a program that's intended, at this point, for all patients, but we do try to ensure that access for those serious conditions are addressed.

DR. LO RE: Thank you.

Dr. Katz?

DR. KATZ: Thank you. Two questions about the pregnancy registry. First, patients who don't

give their consent, are they asked the reason why they're not consenting for their data to be collected? And the second question is, you mentioned it takes about 15 minutes to ask someone to consent. If you were to take out the part about fetal outcomes, I wonder how much that would decrease that time and the complexity of the request for consent. Thank you.

DR. LO RE: Is this to IPMG?

DR. KATZ: I guess so. Thank you.

MR. SHAMP: Jim Shamp with UBC. I will ask Dr. Ephross to respond to the questions.

Dr. Ephross?

DR. EPHROSS: Sara Ephross, Syneos Health. Regarding your first question about the reason why the patient doesn't give consent, I don't believe that that's something we've looked into yet. The second question about the time for consenting either by phone or the patient consent form by mail, I don't know whether removing the fetal pregnancy and fetal outcome section would reduce the time needed because there is the basic consent,

including confidentiality and all the information that we all know that needs to be in a consent form that would still be there, but we are happy to look into both of those suggestions. Thank you.

DR. LO RE: Thank you.

Just continuing the questions that were left over from the last period, Ms. Robotti, you had your hand up. Do you still have a clarifying question?

MS. ROBOTTI: I do. Thank you.

I know that recently, this morning, somebody said that half of those that get denied treatment and thereby go into the 19-day hold, half the time the reason is patient comprehension. And I'm wondering -- this is for IPMG -- have you tested the test itself? Have you tested different types of tests to ensure that the issue is really with patient comprehension, or do you just have a test that's not particularly working well, and a different test would result in much higher comprehension numbers and fewer problems?

MR. SHAMP: Jim Shamp from UBC. I just want

to clarify, the data I gave about the denials was not specific to the reason they did not get their drug in the 7-day prescription window; it was just simply data that showed why when the pharmacy attempted to obtain the RMA, that they were not able to. So that data did not show whether or not the patient did go on to get drug later in that same 7-day window or in a subsequent 7-day window.

MS. ROBOTTI: I still would suggest that a close to 50 percent failure of comprehension rate is indicating we have a real problem with education in America or there might be an issue with the test.

MR. SHAMP: Yes. Allow me to clarify. That denial reason is not because they failed it; it's because they had not done it. So it's not because they failed it. They just had not completed it.

MS. ROBOTTI: You had said that they had the whole 7 days in which to get it right or to pass it, so I took the implication to be that they were failing it, not that they were refusing or not getting around to doing it.

MR. SHAMP: Let me just give you an example. A patient goes into the prescriber's office, is counseled, the pregnancy test is entered, the confirmation of counseling is entered, and it increased the 7-day window.

MS. ROBOTTI: Yes.

MR. SHAMP: The same day, the prescriber electronically sends the prescription to the pharmacy. They may try to obtain the RMA as soon as they receive it. The patient has not even gotten home and to a point where she could have completed the demonstration of comprehension. So at that point, the pharmacy would have received the rejection. So it's not that she didn't take it and failed or took it and failed; it's just that the denial occurs when that has not been completed.

MS. ROBOTTI: And is the denial automatically lifted when it is completed or does the pharmacist have to reapply?

MR. SHAMP: The pharmacist has to obtain the RMA subsequent to that to ensure that all other safe-use conditions are still met at that moment.

MS. ROBOTTI: So there has to be communication back and forth between the patient and the pharmacist to say, okay, I did the test.

MR. SHAMP: Um --

MS. ROBOTTI: Yes.

MR. SHAMP: -- yes, that is if they want the attempt to be completed at that time, yes.

MS. ROBOTTI: They certainly do. Okay. Thank you.

DR. LO RE: Thank you.

The last clarifying question that we had from the prior session was Dr. Hernandez-Diaz. Do you still have a clarifying question?

DR. HERNANDEZ-DIAZ: Thank you. It was answered by Dr. Ephross. Thank you very much.

DR. LO RE: Okay.

These are going to be the last two clarifying questions that we have up because we're going to have to go to -- we have five questions. So please try to keep them brief and direct them to the appropriate parties.

Dr. Calis?

DR. CALIS: Okay. Just a quick question to follow up on the characteristics of the patients using isotretinoin. You showed the slide with the age groups lumped together, the 12 to 46 year olds. I'm wondering if you have a breakdown of maybe by 12 to 16 years of age. I think you would all agree that this is an entirely different population from the standpoint of education programs. And the follow-up question to that would be, is the educational program tailored to a particular age group or is it just all the same?

DR. LO RE: I think is Dr. LaCivita, either you or anyone in your group.

DR. LaCIVITA: I'm going to ask Dr. Pham to answer the question regarding the breakdown of the age, and then IPMG may need to answer the second part of the question.

DR. LO RE: Thank you.

Dr. Pham?

DR. PHAM: Tracy Pham, FDA. I'm sorry. We did not break down that age group from 12 to less than 46 years old, but that would be something that

we can take back and analyze in the future.

DR. LO RE: Last clarifying --

DR. CALIS: The follow-up would be the education program that was described earlier; is that tailored to a particular age group or is it one educational program?

MR. SHAMP: Jim Shamp from UBC. If I can have slide up, please?

To answer your question, the demonstration of comprehension questions is not tailored to the age group, but as you can see here and from the data that FDA presented, the largest age group in iPLEDGE is the 16-to-29 years of age. The questions are tailored to the contraception choices made by the patients. Thank you.

Dr. Green, last clarifying question.

DR. GREEN: Mine was more along the lines of emergency contraception, and I'm not sure who best to direct this to. But earlier, someone had said that it's available on the iPLEDGE website. I spent a little time over lunch looking through, trying to figure this out because, I don't know, I

probably have a couple hundred people on isotretinoin right now. We used to get books, and the books had the consent forms in them. Now it's all mainly online unless you print it out.

But I took a look at iPLEDGE's website, which is, essentially, if you pull up the one guide, what used to be the book is the guide for patients who can get pregnant, and then in there, there are two consent forms to sign. One is informed consent about birth defects, and line 10, in there it says, "I have received information on emergency birth control."

But we don't give out the books anymore because they're no longer printed and mailed, and there's nothing on the website, on the iPLEDGE website, about emergency contraception other than this little throwaway line in one of the consents. So I'm curious where that information might be found so that if we're going to direct patients to it -- outside of our own counseling, if we're going to direct patients to the website, where we would find that.

DR. LO RE: Mr. Shamp, I think the question is just one with regards to specific information on emergency contraceptive counseling and information. Can you clarify that, please for Dr. Green?

MR. SHAMP: Yes. Jim Shamp from UBC. There is information about emergency contraception in the contraception counseling guide, and that is available to prescribers behind the login. Thank you.

DR. GREEN: I'll have to look more for it. I can't find it.

Questions to the Committee and Discussion

DR. LO RE: Okay. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We're now going to proceed with the questions to the committee and the committee discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the request of the panel.

Dr. Phil Bautista, the designated federal officer, has some instructions for our voting members.

DR. BAUTISTA: Thanks, Dr. Lo Re.

This is Phil Bautista, the DFO. We have two voting questions today, questions number 1 and 3. Voting members will be using the Zoom platform to submit their vote for this meeting. If you're not a voting member, we'll be moving you out to a breakout room while we conduct the vote.

After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote questions are completed, he'll announce that the voting will begin. For voting members, you'll see a voting window appear where you can submit your vote. As a reminder, there will be no discussion during voting.

In order to vote, please select the radio button, which is a round circular button in the window that corresponds to vote, yes, no, or abstain. Please note that once you do submit your

vote, you will not be able to change it, so please submit carefully. Once all voting members submitted their vote, I'll announce that the voting has closed, and there will be a momentary pause as we prepare the results and return all non-voting participants into the meeting room, so we ask for your patience at that time; after which I'm going to be displaying the vote results and reading the results from the screen into the record, so the number of yeses, noes, and abstentions; after which the chairperson would go down the list and ask each of the voting members to state their name and how they voted, for the record. Voting members can also state the reason why they voted as they did; however, you should address any subparts of the voting question, if there are any.

Are there any questions about the voting process before we begin?

(No response.)

DR. BAUTISTA: I see none. Since there are no questions, I'll be handing it back to Dr. Lo Re so we can begin with question number 1, our first

voting question.

DR. LO RE: Great. Thank you.

Question number 1 is a voting question. Can we bring up the slide, please?

Question number 1 reads as follows. The REMS currently requires a 19-day lockout period for patients who can become pregnant and do not pick up their first prescription of isotretinoin within the 7-day prescription window.

Question. Should the iPLEDGE REMS retain the 19-day lockout period requirement before patients can take an additional pregnancy test to be eligible to receive isotretinoin? Response is A, yes, or B, no, and if you voted no, please provide your rationale and recommendations on when the additional pregnancy test should occur before starting treatment.

Are there any questions about the wording of the question?

(No response.)

DR. LO RE: If there are no questions or comments concerning the wording of the question, we

will now proceed with the voting on question 1.

Phil?

DR. BAUTISTA: Thanks, Dr. Lo Re.

We'll now move all non-voting participants to the breakout room.

(Voting.)

DR. BAUTISTA: Hi, everybody. This is Phil Bautista, the DFO. The vote is now complete. We have 4 yeses, 17 noes, and 1 abstention.

I'll hand it back over to Dr. Lo Re.

DR. LO RE: Great. Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish to. We'll go in order, so Dr. Katz is at the top of the list.

DR. KATZ: Ken Katz. My vote was no. I think this places an unduly high burden, physically and psychologically, on our patients. There's likely some, but very marginal benefit to this additional period, and a lack of clear medical incentive and rationale for it, as was stated by

many, including the consultant to the IPMG, and it seems arbitrary. Likely, we will miss some pregnancies, and we are missing some already, but the burden is not matched by the benefit. I would support testing it at 7 days, and then 7 days after that to pick up the prescription. Thank you.

DR. LO RE: It looks like I am next on the list. I voted yes, based on the data that was presented to the committee and the recommendations by the iPLEDGE sponsors that the 19-day wait remain in place. My consideration is that the benefits of this criterion outweighed the burden.

I consider that the 19-day lockout period ensures that patients who can become pregnant do not receive and start taking isotretinoin during their most fertile period. The iPLEDGE sponsor's briefing document and the both the agency's and the sponsor's presentations highlighted for me the important medical rationale for this period and how essential this lockout period is to preventing fetal exposure to isotretinoin.

The data presented by the FDA briefing

document from one of the studies, and discussed in the roundtable discussion, found that testing for the pregnancy 19 days after conception can detect up to 66 percent of the pregnancies, and I felt that since iPLEDGE year 12, the total of 12 pregnancies, having been detected during the 19-day waiting period to prevent fetal exposure, and we discussed how low this number was, for me, since treatment with isotretinoin is elective, I felt it was valuable to avoid potential exposure to isotretinoin exposure as much as possible to avoid fetal malformations, spontaneous abortion, or premature birth.

Since 15 percent of the patients who can become pregnant missed their first prescription because the 7-day prescription window has expired, mainly during days 3 to 7, this committee discussed interventions like text reminders that could potentially reduce the numbers who miss their first prescription. And finally, I didn't hear any evidence to necessarily consider an alternative time frame as a lockout. Thanks.

Next on our list is Dr. Woodward.

DR. WOODWARD: This is Maria Woodward. I voted no as well to keeping the requirement for a 19-day lockout period. My rationale is that the evidence from the FDA does not align with my understanding of medical knowledge about fertility windows, nor has it been applied broadly as a policy for all teratogenic medicines, so I don't know why the rationale is for this specific medication.

The evidence provided by the patient advocacy group really implies to me this is really not an elective need for some patients, as this really improves quality of life not only for their physical health, but also their psychological and mental well-being.

I also have concerns that this policy will affect people who have less resources to effectively get to pharmacies to access their medical doctors in timely fashions and to go through the process of an online system rapidly and effectively if they have limited resources. And

since we do not have data, my understanding from Health Services Research and from social determinants of health is this will likely affect those most vulnerable to these policy changes, these policies that feel inequitable.

I do not have a specific recommendation for the window, but I agree that it's possible that repeating the test immediately would be more conducive, but I do not have a strong opinion on that, as it's not my area of expertise.

DR. LO RE: Dr. Dublin?

DR. DUBLIN: Thank you. My name is Sascha Dublin from Kaiser Permanente, and I voted no that I do not favor retaining the 19-day lockout window, and I share many of the reasons for that expressed by Drs. Katz and Woodward. It feels arbitrary and not well aligned with current medical knowledge about the fertility cycle.

But I think in particular, that it's not tailored, really, to the lived experiences and the physiology of the people who could become pregnant, where some may be on long-acting reversible

contraception and others on combined oral contraception, where they're not ovulating, so this whole idea of differential periods of high fertility doesn't apply to them. Then for those who have chosen abstinence, they're equally at risk for all cycles during the treatment window of 5-6 months or longer, so it seems arbitrary to single out the very first exposure.

I recognize the importance of preventing pregnancies, but I think it's a slippery slope, where the longer you make the lockout period, the more pregnancies you will detect, and that could be stretched into a sort of ridiculous argument about a very, very long lockout period.

I think the one option is to completely drop the 19-day lockout period for everyone and allow a pregnancy retest right away. I would also be supportive of a pregnancy retest at 7 days. I also think that if people were very concerned, you could retain the 19-day lockout only for a certain group of users who it feels more relevant to, such as those with contraceptive methods most likely to

fail.

But pulling all of it together, I felt that considering the health equity issues, the issue about being able to take time off and have resources to navigate complex systems of care, and to have insurance that either generously covers prescriptions or requires prior authorization, that the overall and the best outcome in terms of the balance of the benefits achieved versus the burdens imposed, that the burdens outweighed the benefits. And with a simple yes or no choice, I would vote no to retaining the 19-day lockout.

DR. LO RE: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Hi. Sonia Hernandez-Diaz, and I voted no. In terms of recommendations, I will say the same as Dr. Dublin. I agree that this lockout window, not giving the drug, and doing the pregnancy test, would prevent exposed pregnancies, but it also then prevents exposure to non-pregnancies that would benefit from initiating the drug.

So the question is, where do we set the benefit-risk balance? I found that the current period is inconsistent with the rest of the program because the pregnancy rate doesn't seem much higher during those 15 days and during any other 15 days during the program, and we seem to accept the pregnancy rate during other months.

Also, those that are totally given the drug and are going to be exposed are not required to have this other pregnancy test, even if they have post-fertility window. So for these reasons, I voted no. However, I do appreciate FDA's intention of having the aim of do not start if pregnant, and therefore avoiding and preventing exposure versus discontinue as soon as possible to minimize exposure in other months, so I understand, their amendments [indiscernible] make sense.

I also have knowledge that this stricter first screening might set what's the standard for the rest of the program, so that if we modify, we may have consequences beyond this initial period. So I would suggest that if FDA decides to modify

the current program, it will be important to follow up in one or two years, and actually look at the pregnancy rate per month from prescription before and after implementing this change.

Finally, I totally agree with whatever we do, that they need to facilitate that a larger proportion does get their prescription within the 7 day window. Thank you.

DR. LO RE: Thank you.

Dr. Liu?

DR. LIU: This is Tao Liu. I voted no for two reasons. The first reason is I regard the 7 days as a trigger, missing the 7-day prescription window as a trigger for the 19-day lockout. It's not very effective for identifying a subpopulation without a higher risk of pregnancy. Actually, a patient can meet the 7-day prescription window for several reasons, many reasons not related to the pregnancy. That's the first reason. The second reason is during this period, as the data suggested, the pregnancy risk is very low, less than 0.07 per thousand, which is lower than the

general population and lower than the yearly applied program. So for these two reasons, I vote no.

DR. LO RE: Thank you.

Dr. Hertig?

DR. HERTIG: John Hertig. I voted yes. I've been listening intently to all these presentations and really am appreciative of especially the public commentary. Yet, despite this, I've yet to hear evidence of a real better alternative to the 19-day lockout or waiting period. We were presented evidence this lockout has prevented fetal exposure to isotretinoin in the past. I voted to continue this approach until the time comes that evidence of a more efficient and equally safe, if not safer, process is presented to us for consideration. Thank you.

DR. LO RE: Thank you.

Dr. Tollefson?

DR. TOLLEFSON: Megha Tollefson. I voted no for many of the reasons that were already stated, but primarily it is one of the largest sources of

burden and the biggest impact, I think; a large impact on people not being able to get the medication, especially those that are probably the least resourced. While it has prevented some pregnancies, I think the rationale and the scientific evidence behind that is not strong for the amount of burden that it carries; for example, variability of the menstrual cycle and different methods of contraception. It also cannot account for the instances where someone might fill the prescription but not necessarily start it right away, so there are many variables that fall through in the 19-day period.

I think the amount of effort that is directed towards overcoming that burden could be well spent in other more effective ways of preventing pregnancy, such as a focus on emergency contraception, which there's very minimal at this time. I also don't have a very strong opinion on when the pregnancy should be tested again, pregnancy testing, and I think right away would seem reasonable. I also echo that whatever changes

we make, I think this is a good opportunity to study the impact, and be more nimble with future potential adjustments. Thank you.

DR. LO RE: Great. Thank you.

Dr. Hovinga?

DR. HOVINGA: I voted no largely for much of the reasons that were already stated. I think it does, particularly for adolescents, induce a significant degree of healthcare burden just because, obviously, this is one of the populations that is most sensitive to acne and the social and the long-term effects of disfiguration, but they also have to rely on multiple other people to help them sometimes get care. So by introducing this with a short period of time, I think that really does impact their access to treatment.

The other things that I think are, really, as we were listening to the conversations and the information that was shared, the failure to include different types of contraception and the determination of whether or not there needs to be a waiting period is also a concern, and the lack

of -- I mean, I have three daughters, and cycles are highly variable, even in our house. So our understanding of fertility and cycles is limited, and I think that a guesstimate of the waiting period is a little bit more of an assumption rather than a fact, so thank you.

DR. LO RE: Thank you.

Dr. Green?

DR. GREEN: Hi. Brian Green. I voted no for the reasons mentioned. I would support immediate retesting if you miss the 7-day window, and the reason I'm saying that is it was mentioned that, I believe -- and I wrote down -- that 15 percent miss that initial 7-day window.

Just my experience, I think most people miss that 7-day window for issues completely out of their control, namely insurance issues; waiting to get that prior authorization; as well as pharmacy issues and waiting to order the medicine and it not come in, in time. I think it's completely unfair to hold the patient responsible for things that are completely out of their control. And again, I

would support if they missed that 7-day window, just an immediate retest and provide that that is negative, allowing them to pick up the medication.

DR. LO RE: Thank you.

Ms. Ludwinski?

MS. LUDWINSKI: Yes. Donna Ludwinski. I also voted no and agree with all of the points made so far. The only thing I'd reiterate, though, is it said "laudable effort to prevent exposure." As Dr. Liu pointed out, out of 173,000 patients over a 5-year period, it did prevent exposure in 12 cases, which is, as he alluded to, a very, very small number.

So I agree with what the majority have said already, that this does represent a burden that's probably unreasonable. The other thing I support is immediate retesting before picking up the medication, provided its negative.

DR. LO RE: Thank you.

Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I voted no for reasons that have already been well

explained. What has not been said, or that I didn't hear, is that if we had the research, the understanding of why people are missing the 7-day window that pushes them into the 19 days, that would help us make a better decision. I'm unimpressed with the depth of the research that's been offered today. Thanks.

DR. LO RE: Thank you.

Dr. Cowen?

DR. COWEN: Hi. I voted no as well for many of the similar reasons. I think there is a very compelling data-driven case that was made for the burden that this lockout puts on 15 percent or more of individuals who can become pregnant, and I was less convinced by the physiologic discussion of the 19 days as a specific time period. I don't feel strongly about when retesting should be done, but it would be reasonable certainly to do an immediate retest.

DR. LO RE: Thank you.

Dr. Rasmussen?

DR. RASMUSSEN: Yes. I voted yes. I am

committed to reducing barriers and burden of getting people onto this medication, and I know that it can be life-changing, but I feel like this is a last opportunity. I know that the number of pregnancies appeared to be low, 12, but we know that that may be an underestimate.

I felt like the reminders have not been yet maximized, and we realize that a lot of it is people not completing the comprehension test, or at least that was what I heard, is that that was a frequent reason for the lockout being put in place. I wouldn't be opposed to tailoring that lockout to persons with different methods of contraception if you're on a method of contraception that has a lower risk of pregnancy.

To me, it would be really helpful if we had more information from the root cause analysis. Having so little information from that, I guess I agree with Dr. Robotti that I'm concerned that we don't have all the information that we need to make some of these decisions. Thanks.

DR. LO RE: Dr. Salvas?

DR. SALVAS: Thank you. I voted no. I want to echo the comments of the folks that went before me around the lack of depth and breadth of the data provided today to help make informed choices. I will say on this specific point, it does appear that we do have data to support a change. The limited strong quantitative and medical evidence here, as well as what we do know about the patients -- mainly the significant proportion of treated lives that are using forms of contraception that manipulate the fertile window -- support changing this particular rule to help ensure access.

I would be open to further dialogue in a data-driven sense around other devices that could be the same or more impactful here, while also delivering on the commitment to ensuring access.

DR. LO RE: Thank you.

Dr. DeMarco?

DR. McADAMS DeMARCO: Hi. Mara McAdams DeMarco. I voted no, and I agree with the points that have already been raised. I would also like

to remind everyone that the absence of data that was presented on disparities does not mean that they're not present, and that any changes that are made to the iPLEDGE program should be made in parallel to new data collection on race and social determinants of health. This way we can ensure that the changes we're discussing today, as well as any future changes, are not exacerbating potential disparities. I would also support immediate retesting, as has been previously described by other colleagues.

DR. LO RE: Thank you.

Dr. Schreiber?

DR. SCHREIBER: Thank you. I also voted no. I considered the data and the narratives holistically that were presented and the risk factors for pregnancy while on treatment. Similar to Dr. Tollefson, I would consider, and recommend considering, that investment into the attention of different risk factors for pregnancy be a focus as opposed to this wide swath that all individuals who can become pregnant are being treated the same way,

because risk factors for pregnancy are not the same, and I worry about that being sex and gender discriminatory in this setting.

I think that one approach for retesting could be immediately before starting treatment, and that a less paternalistic approach to that would be to enable patients to complete a home pregnancy test before initiating treatment. Thank you.

DR. LO RE: Thank you.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I voted no for, actually, all the same reasons that have already been mentioned. To me, it felt that the biological rationale behind the 19-day window seems weak. As was pointed out during the discussion, if conception occurs towards the end of that fertile window, we would most likely not be able to pick it up because it's really the earliest time, giving us a little bit of a false sense of reassurance, and this coming at the cost of reduced access for a substantial proportion of patients -- 15 percent was mentioned -- and often through no fault of the

patient himself.

So it was mentioned a number of times that the main reason, or one of the major reasons, is really not completing the comprehension questions. Given that that's just a small list of questions, it seemed that it's really a matter of the patient remembering to do it before going to pick up that prescription. So solutions maybe like a text reminder or so, I'm wondering whether that could help with getting that proportion down.

The main reason I lean towards no, it's been pointed out a number of times that this is the last opportunity to prevent exposure but, to me, the risk of pregnancy is no greater with that first prescription as it is to when patients are already on treatment. And if they've had negative pregnancy tests during treatment, like with each renewed prescription, that risk to become pregnant would be the same. So I really failed to really grasp the difference between a differential treatment for that first prescription versus subsequent prescriptions.

That's also why, in terms of when to do the testing, I would be leaning towards doing it the same way as it's done during the treatment, and that is right away, when they missed a window, do another pregnancy test and reopen the 7-day window. Thank you.

DR. LO RE: Thank you.

Dr. Berenson?

DR. BERENSON: Yes. I voted yes. The reasons for have already been stated by Dr. Hertig and Dr. Rasmussen. I will say that it was a difficult question to vote on because of the way it was worded. We were only given two choices -- or three -- yes, no, and abstain. It seems to me that there are many different ways that this problem could be solved with a more personalized approach to who the patient is and what type of method they are using. But given the lack of that detail, it was either keep the rule or throw out the rule altogether, and it is clearly benefiting some patients, more likely those that are using abstinence or birth control pills that can be less

reliable. So I voted yes so we could benefit those patients, although I do feel it creates a barrier, and other solutions should be examined.

DR. LO RE: Thank you.

Dr. Calis?

DR. CALIS: Karim Calis from the NIH, and I voted no. Quite frankly, I was very skeptical about the rationale for the 19-day lockout. I think it's somewhat arbitrary and a rather archaic concept. I think that any purported benefits of a 19-day lockout can likely be replicated by optimizing the pregnancy testing window, and I also agree with Dr. Schreiber's comments specifically about home pregnancy testing prior to initiating treatment.

DR. LO RE: Thank you.

Dr. Delost?

DR. DELOST: Kort Delost here. I voted no for the same reasons most of the others said, but I also took into account all the prior comments before our meeting, as well as the organizational comments that were listed today from the day-to-day

practitioners that come across this and see the problems that have developed from that.

I also believe in the law of diminishing returns, and only 12 makes me wonder if that would have never been in place, if there would have been a large difference between that and what we actually see now as far as the number of pregnancies. So I believe if the burden was higher on the people trying to get the medication than the program was helping, I would probably retest if that 7-day window was going to be passed.

DR. LO RE: Great. Thank you.

Lastly, Dr. Chambers?

DR. CHAMBERS: Yes. As the only one to abstain, I just wanted to check did you want the rationale behind the abstention?

DR. LO RE: Yes, please.

DR. CHAMBERS: Okay. I think Dr. Berenson said it quite well, that confronting the discrete choice between removing something altogether or maintaining it without considering alternatives left me motivated, both by all of the wonderful

reasons for the program and the limitations and potential inequities that result from it. I also thought that the lack of data on the specific reasons why people missed that 7-day window might lead us to better concentrate on our efforts on making the lockout window as rarely used and rarely seen as possible, rather than choosing either to focus on its continuation or its removal.

So that's where I ended up feeling most comfortable, based on my limited expertise in certain matters, with an abstention.

DR. LO RE: Great. Thank you.

So I will summarize. Those voting no felt that the burden outweighed the benefit, particularly an undue burden for adolescents; that the pregnancy risk was deemed to be very, very low; that there was a lack of clear scientific and biological rationale, and that in some instances, it felt arbitrary. There was acknowledgement that this approach only picks up 66 percent of pregnancies and it may miss pregnancies, and particularly there was a feeling that this

disproportionately affected people with less resources and those who were most vulnerable.

There was a feeling it was not aligned with medical knowledge of fertility cycles and didn't take into account the different risks experienced by patients who can become pregnant. There was a number of comments about the timing of retesting; that it should occur immediately if the patient misses the 7-day window. There was a question about where should the risk-benefit balance be. There was a comment that the pregnancy rate was really not much higher during that 19-day -- it was very low during that 19-day period, and that any changes that would potentially be implemented really may have important consequences, and that it will be important to general important data to look at the pregnancy rates per month before and after if any changes are implemented.

There was consideration regarding examining differences in the risk factors for pregnancy, better understanding the amount of effort in examining emergency contraception use and

counseling, and there were two comments about enabling patients to be able to complete home pregnancy testing during this period, and in essence, that there really was a lack of data and more research was needed on this 19-day lockout period.

Those who voted yes felt that the lockout has prevented fetal exposure; that there was no evidence in support of a better alternative; and that this was a last opportunity to assess exposure. The one abstention commented that really confronting this discrete choice was challenging, and that there were numerous data limitations on the inequities and a lack of data on the reasons for the lockout.

We will now move to question number 2. Question number 2 is a discussion question. Could we have question number 2 up? Thank you.

It reads as follows. Discuss whether the REMS should require pregnancy tests be completed in a medical setting, such as an office or a laboratory, rather than at home.

May I ask, are there any questions about the wording of this question?

(No response.)

DR. LO RE: If there aren't any questions or comments -- two questions I see.

Dr. Hovinga?

DR. HOVINGA: Sorry. This is Collin Hovinga. My question about this one was that there was a lot of discussion previously about CLIA versus non-CLIA testing. Does it matter here or is that something we're concerned about now?

DR. LO RE: Can I direct this to Dr. LaCivita, the question about consideration of CLIA testing.

DR. LaCIVITA: Correct. So regarding whether it could be completed in a medical setting, most prescribers' offices do not have the ability to do CLIA testing, so I think you could consider that; whether it should or should not be CLIA testing required, then also consider whether it's a medical setting or at home. Thank you.

DR. HOVINGA: Thank you.

DR. LaCIVITA: Does that help?

DR. HOVINGA: Yes. Thank you.

DR. LO RE: Okay. Seeing no further questions, if there are no other questions or comments, we'll now open this question for discussion.

Dr. Atillasoy, do you want to start us off?

DR. ATILLASOY: Sure. Thank you, Dr. Lo Re.

I just want to first say as the non-voting industry rep, I wanted to comment that my opinions are my own. I don't mean these to reflect the opinion of IPMG nor of Jazz Pharmaceuticals, where I'm the chief regulatory and safety officer, and Jazz does not manufacture isotretinoin; nor those opinions represent the University of Pennsylvania Department of Dermatology, which is where I trained, and I have a voluntary teaching appointment; nor those opinions of the AAD, and I've been a proud member for almost 30 years.

As I mentioned yesterday, I've had the pleasure of prescribing Accutane for a few decades. Now, it may not be the thousands, but it's been in

the hundreds. I just want to also preface my comments that I think it is a wonder drug in many ways, but I'm also very much aware of the risks and the severe consequences, and the dangers of the product, as we've been discussing. And I'd like to remind everybody about the other dangers and risks of isotretinoin, and I welcome everyone to review the U.S. prescribing information in great detail.

So in terms of this issue, as a dermatologist, I remain very concerned about some of the movements, which I find personally somewhat irresponsible. I've heard lots of comments, including the public forum and from my fellow dermatologists. I fully understand the frustrations and issues; however, a lot of what I'm hearing is talking about logistics, about convenience, about insurance. I think we all need to remind ourselves this is really all about safety.

For those of us that have been in the industry and focused on the development of new medicines, new vaccines, and to focus of course on

safety, in terms of REMS, I need to remind everyone -- and Dr. Crist from the FDA brought it up as well -- the intent is that there will be some burdens with REMS. So people are conflating and commingling the issue of benefit-risk versus the burdens that are associated with the REMS.

I personally want to commend the FDA, and the manufacturers, and the academy because when I look at the data that's been in front of us, I think that this program has been a tremendous success. The rates of unintended pregnancies are extremely low relative to other countries. The prescriptions I am seeing, the data that was shown, we have gone from 1 million to 2 million prescriptions, and yet we maintain this low rate, so I find it to be very successful.

I do agree, by the way, with the prior comments that you made, Dr. Lo Re, and others in terms of why it should be retained, the 19-day wait, but regardless, I agree with the comments that there should be a testing immediately if someone misses the 7-day window.

In terms of the home pregnancy tests, I remain concerned. From my own experiences, there's a tremendous benefit for patients being seen ideally in person, not only for the pregnancy testing and the REMS requirements, but also to assess for suicidality, depression, potentially liver testing and other chemical panels. These are things that are best deciphered in person, again, understanding the benefits of telemedicine.

So I want to make sure that we retain this successful program and that this product can be distributed. In fact, for all the reasons that have been stated for the last two days, it's important that we maintain the REMS program so that the product can be available with those 2 million prescriptions to serve the public and serve patients.

I do think some of the discussions about disparities and inequities, those are really important. I want to make sure that we're not conflating and commingling issues. As a dermatologist, I would ask others to really

consider how much of this is directed at the REMS versus other ways that there can be access, not only for isotretinoin, but to dermatologists and others that should be able to adjudicate the benefits and the safety of their products.

So for all those reasons, I strongly encourage us to -- post-pandemic, post-COVID -- not allow for in-home testing. I am totally fine with in-the-office testing as well. Thank you.

DR. LO RE: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Hi. Sonia Hernandez-Diaz. I was going to actually follow up this point of discussion. When we started the meeting yesterday, I had in mind that to prescribe this medication, that dermatologists and other healthcare providers were going to actually want to see the patients once a month to evaluate and counsel. And then, of course, that's a great time to have a pregnancy test, better than having to have another extra visit to a lab. That I have no question.

But as we were listening to the

presentations today and yesterday, there seems to be a tendency to have more remote contacts, and telemedicine seems to be a reality and seems to be very useful, at least for some patients. So if that's the case, if we cannot ignore that telemedicine is going to happen, should we consider smart ways to have the pregnancy test at home that would still make it unlikely to be falsified?

With COVID, we learned from the COVID tests themselves; not from the pregnancy tests during COVID, but from the COVID tests, we were able to do remotely with supervision to be allowed to travel and so forth, and if there is something not as ideal as having it in the office but that could be done with supervision and with assurance.

Like, for example, could the prescriptions be provided with a pregnancy test that has a barcode on the name that could be shown to a system remotely before and after taking the test that might be considered sufficient for reassurance to the prescriber, or could we allow pregnancy tests being conducted at the pharmacy before picking up

the prescription, and not to transfer the burden to the pharmacists in this case.

I think discussing ways where the pregnancy tests can be inserted in a plan, like telemedicine that is going on, and it is a reality, it could be useful to consider.

DR. LO RE: Thank you.

Dr. Katz?

DR. KATZ: Ken Katz. I would support continued home pregnancy testing. I think office testing has a high burden that's disproportionate on lower income people, and people who are farther away from a place where they can get tested, that would really restrict access to the medicine.

I think that there was no uptick during the public health emergency was important, and although there was some falsification reported, there does not appear to have been an uptick. There was a comment made that it would be difficult for providers, dermatologists or others, to interpret home test results, and I think we've heard that that's not the case.

The proposed workarounds with names and dates sound reasonable. There are other technological fixes that are possible, including barcodes or other possibilities that could be studied or implemented. The IPMG could break out the data on home versus other testing, and if it turns out that there's an uptick, this issue could be revisited.

I think it is ok to study it over time, but just to give you a sense of timelines at which things happen, I just want to bring up the example of the gender-neutral language issue, which is something that I proposed in an article that was published in January of 2016. There was a meeting with FDA about this issue in April of 2016. There was no substantive opposition by FDA or other stakeholders to that suggestion, and it took about five and a half years to implement that change, and that was just a language change. I can't imagine how much time it would take to study and implement something more complicated like this. I think it's not worth the wait. A much lower second choice

would be to allow for testing in a CLIA-waived environment. Thank you.

DR. LO RE: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I have to advocate for continued strong oversight for pregnancy testing. So many of the people -- the young women and those who can become pregnant who are taking this drug -- are at ages where they potentially take risks that would not seem appropriate to somebody who's perhaps more mature. And I think that the consequences of risk taking, even if it is age-appropriate -- people do take risks at certain ages that they wouldn't at others -- the consequences are severe.

I'm going to say it again. In the America that we live in today, elective abortions are becoming more and more difficult, and that is the, by far, number one choice of action, according to the information we're given in this meeting, of people who find themselves pregnant while taking this drug.

That said, there are other ways that have

not been explored to make pregnancy testing less difficult. We're getting offered very black-and-white choices here, or left-and-right choices, however one wants to show the dichotomy. We've all agreed, I think, that CLIA-certified pregnancy tests are probably not necessary, but home tests are way too easy to falsify. So what are the other options? I don't know. Why can't a walk-in clinic provide the oversight for appropriate testing, even using a home testing kit? It's just the oversight that you need and the freshness of it, or can someone develop home pregnancy tests that are extremely difficult to falsify or more difficult to classify than seem worth it?

Regarding telemedicine with this particular drug, I had not realized until Dr. Atillasoy -- I hope I said his name correctly -- spoke, which I find him very compelling, about the particular risks of this drug on other side effects, psychological side effects, and how important it is to see patients, with drugs that have this effect,

in person, on a regular basis. And that's what I have to say. Thanks.

DR. LO RE: Thank you.

Dr. Green?

DR. GREEN: I just wanted to support being able to continue to do home pregnancy tests. Any system you put into place, you can find a way around. There are people all the time in the military, when they're being brought in, who bring in bags of urine just so they don't fail their drug tests so they can actually come through MEPs.

We are not following these people into the bathroom to watch them actually pee on the stick or in the cup. We're not doing any of that, and at some point we have to say, we've done what we can and patients are going to do what they're going to do. At Hershey, what we have people do for telemedicine is take the stick, write their name, write the date on it, and then send a picture of that the same day as their visit. That way we have the pregnancy test the same day that we've ok'd them on iPLEDGE, assuming it's negative. That

seems to be a pretty good way, as was mentioned this morning in a follow-up article that was published, as a way around the issue with people trying to falsify these things.

This system, as has been pointed out, has done a great job of keeping the pregnancy rates extremely low, but it has not driven them down to zero. People's behavior is what it is. People are going to do what they're going to do, and a lot of the people we rate this medicine for are teenagers. All of us either have teenagers or at some point were once teenagers. Teenagers do not make the best decisions.

I think allowing this to continue to happen at home is important, to continue with the benefits of telemedicine, and I definitely think that we're never going to come up with a foolproof system. So, again, bringing people in is burdensome, and it's costly. I can tell you, at our hospital, unfortunately, some people get a bill for $35 for a pregnancy test. That's one done in the office, not done at the lab. Depending on their insurance, you

can get a pregnancy test at the dollar store that's every bit as sensitive, and I think it should be allowed to be continued to be done at home.

DR. LO RE: Thank you.

Dr. Rasmussen?

DR. RASMUSSEN: Yes. I'm in support of allowing home pregnancy tests with some of the caveats; for example, Dr. Green's recommendation, having the person's name on it and having the date so that it decreases the risk of falsification.

My sense is -- we don't have data on this -- but people are not wanting to pay for another home pregnancy test or didn't have one at home. If they have one there, I'm hoping that will make it less likely they would want to falsify it. I think that's reasonable. I think with the use of telemedicine, it decreases barriers that people might not be able to get to the doctor to do a pregnancy test and to pay for it. Thanks.

DR. LO RE: Great. Thank you.

Dr. Salvas?

DR. SALVAS: The first comment I have is

related to what I think feels to be a lack of data shared around this particular topic for us to be able to weigh in. I think it would be helpful to really understand the performance of the at-home testing versus the traditional. I don't believe the breakdown of our experience over the last few years with the iPLEDGE program was provided around which patients were using at home versus an office. Maybe it was all, but it wasn't covered.

The second thing I just want to share is that some of the managed care elements that we should consider are particularly around the financial burden of at-home testing. The coverage of this is going to vary, and if we're talking about socially vulnerable populations, their ability to afford monthly testing is something that we should consider.

DR. LO RE: Thank you.

Dr. Tollefson?

DR. TOLLEFSON: I also support continued use of home pregnancy tests with caveats as well, for many that have already been stated. I have to

admit that it makes me slightly uncomfortable, and probably all of us, given the teenage population and what's been stated accurately about teenagers, but I think the data reassures me that over the time of the pandemic, we didn't have any higher pregnancy rates. Even though we don't know how many home pregnancy tests were used, I think collectively from our experience, we know it was commonly used.

So I would support its continued use with the caveat that we now actually capture what type of pregnancy test was done, and then we can more effectively study the rates of pregnancy moving forward, and with mitigation falsification strategies.

DR. LO RE: Thank you.

Dr. Hertig?

DR. HERTIG: John Hertig. As others, I support home and other CLIA-waived testing options, including those office-based testing options. As others have mentioned, the iPLEDGE administrators, the agency should explore and test our telehealth

and remote options for patients not only to support their increased access to health professionals but also decrease burden, while still maintaining the integrity of the process, and really ultimately patients' safety. So I think we're headed in this direction. If we can continue to provide access while maintaining the integrity, that's going to be key because, ultimately, the patient's going to benefit. Thank you.

DR. LO RE: Great. Thank you.

Dr.. Woodward?

DR. WOODWARD: Thank you. Maria Woodward. I agree with many of the panelists and committee members that the availability of pregnancy tests are more widely [indiscernible] than CLIA-certified labs is important. Certainly, number one, having it available in providers' offices who do not have access to CLIA testing is reasonable, and I agree with that as a recommendation, but beyond that, also that telemedicine delivery of testing can be done safely and effectively. But as others have alluded to, this should be evaluated by analysis.

I will also say that I have a hat as the director of an ehealth program, and I run a large telemedicine program at our Veterans Administration. I'm not representing neither of those bodies during the call, but I want to be clear that telemedicine is just a care delivery method, and it's a safe and effective care model, so the counseling that was discussed and the monitoring of patients can be done very safely and effectively with telemedicine.

As a matter of fact, we usually get better adherence to visits for certain populations who can afford the access of telemedicine capabilities. And as many physicians know, most of psychiatry has gone to a telemedicine model, so I disagree with the assertion that an in-person visit for safety and communication is necessary because I think, as our psychiatry colleagues have really now moved almost exclusively to telemedicine for their care, administering safe and effective communication and monitoring can be done through a telemedicine platform.

I do want to briefly comment on the cost analysis that's coming up. I don't think that's a primary argument here, as we do really focus on safety for these committees. But if a cost analysis is done about monthly cost testing at home, that analysis should also look at the co-pays and the high deductibles that come with having to come into a doctor's visit for a monthly test. The pregnancy test at home is probably very low compared to how much you have to pay for an in-office visit. I don't know the details around this, but I think if a cost analysis is done, it should be reflective of the entire scope of cost. Thank you. I'm done.

DR. LO RE: Thank you.

Ms. Ludwinski?

MS. LUDWINSKI: Yes. Thank you. Donna Ludwinski, patient representative. I support the home pregnancy tests as well, and the one issue I want to point out we discussed a little bit yesterday was the low rates of post-treatment pregnancy tests. The FDA review team recommended

continuing that, but we really didn't come to any conclusion on how to encourage that, especially given that pretty close to 10 percent of the pregnancies in 2021 were in that category, even though only 5 percent completed both pregnancy tests.

So my question would be, could that be incentivized? Clearly, home testing could be much less burden and perhaps an incentive by itself. I don't know who would pay for it, but a $25 gift card to the second one might increase that compliance to that requirement. Thanks.

DR. LO RE: Thank you.

Dr. Dublin?

DR. DUBLIN: Thank you. I support the continued availability of home pregnancy testing as an option for patients who choose that, for many of the reasons that have been discussed. I especially want to highlight the issues with logistical difficulties and accessing even a CLIA-waived provider's office; the story we were shown during the public comment of a teen who lived one and a

half hours drive away from the office of the provider. Then in addition, there can be challenges with teenagers, even if they live close to a provider, being able to physically get transportation and a parent having to take time off work to drive them to the office, even if it's in the same city. Those are burdens that really need to be considered.

I really appreciate the points that were made about the risk of falsification, and I think that many people have put out really great ideas about how to mitigate those. I think one option would be to do a pilot program for a smaller group of patients and study it, but I also appreciate the comment that was made about the risk of long-term delays.

I think we clearly heard from patients in the written comments that were available in the docket about how much more pregnancy testing meant to them, and I think we need to be aware and respectful of the burdens. I totally agree that it's ok for REMS to place some burdens on people,

but I think that home pregnancy testing can be done in such a way that it can balanced, reducing the burden to some degree while adding some mitigation measures.

I think that the concerns about suicidality or depression, those were very briefly touched on in one of the presentations with public comment this morning, and evidence was presented that this really is an issue that has been considered and evaluated, and shown not to be a valid issue; that in fact suicidality and depression rates were lower in people who received appropriate treatment.

I think, again, we've just heard from many people on this panel about the rise of telehealth, which you've seen in many aspects of care, including psychiatry, and including, in my primary care setting, the cat is really out of the box in terms of telehealth, and I think we need to adapt, and the REMS needs to sort of recognize how care is being delivered in the current era. I also am influenced by the fact, as other people have mentioned, that we didn't see a big spike in home

pregnancies reported on this drug during the time period when we all believed there was a big move towards home testing in this population. Thank you.

DR. LO RE: Thank you.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I'd like actually to pick up on the last issue that Dr. Dublin just mentioned, and I agree. Several of the committee members have made a very strong case for continuing the home testing in light of the shift that we see towards telemedicine, but the reassuring data have been mentioned a number of times that during the pandemic, we haven't really seen an uptick in terms of unwanted pregnancies in that regard.

I'm just wondering whether we also need to take into consideration that the pandemic was a very different unusual time period, and I'm not a hundred percent sure that we can extrapolate that towards the post-pandemic period. I mean, there was much less social contacts and so forth.

I think if we're continuing to provide the option of home testing, I think what will be really important is to use that as an opportunity to collect data and find out from those that do the home testing versus those that opt to go to the physician's office -- monitor over time whether we really see the continued trends that seemed to be there during the pandemic -- that there is no difference in terms of pregnancies being reported; then use that time period as well to explore other ways, such as the one that have been mentioned already, like can we provide a little bit more oversight, and maybe it is being done right now; and can we learn from some of the COVID testing itself and so forth.

So I definitely see a strong case for continuing the home testing, but I really think that continuing to collect data and really understand its implications will be important in the coming years. Thank you.

DR. LO RE: Thank you.

Dr. Calis?

DR. CALIS: Karim Calis from the NIH. I think that home pregnancy testing is a very effective tool, and I think that FDA should not require that pregnancy tests be completed exclusively in a medical setting.

Now, having said that, I would say that home pregnancy testing should be used to help supplement, not replace, in-office testing for some of the reasons that were articulated earlier with regards to medical monitoring, and education, and what-have-you, and I think that's very, very important. So it should be used to help fill in the gaps, especially in the context of what we talked about earlier.

If FDA were to eliminate the 19-day lockout, that would necessitate, to my mind, in-home testing as an additional tool to help fill in the gaps there. So I think we should find creative ways to use pregnancy testing at home in a way that might complement testing in a medical setting.

DR. LO RE: Thank you.

Dr. Cowen?

DR. COWEN: Thanks. Ed Cowen, NIH. I also agree that home testing with appropriate safeguards in place, to minimize what is going to be human nature to, in some cases, alter tests, be accounted for.

The other point that I want to bring up, which I had brought up yesterday as well, is I think we need to be as forward-thinking as possible about how medicine is evolving, and have our eyes open that we're not going to go back to the year 2000 and 2005.

The other thing that I think is relevant perhaps for the non-dermatologists to understand is laboratory monitoring has changed dramatically for Accutane prescribing, so there's now good evidence that monthly laboratory monitoring of things such as LFTs is not necessary. It used to be that a CLIA-certified urine pregnancy test was part of a monthly trip every month for the patient and their parents to have their blood work done. That's not necessarily the case anymore. So we're talking about having them come into a laboratory

specifically in some settings for just a urine CLIA test.

DR. LO RE: Great. Thank you.

So let me summarize this discussion by the committee. I'll start off by saying that there were concerns that there was a general lack of data on performances of home pregnancy testing versus testing in the medical setting. There was really a strong feeling that the rise of telemedicine makes home pregnancy testing more accessible, more feasible, particularly for marginalized vulnerable individuals and those who are far away from clinical settings.

There were a number of discussions that were centered around workarounds to make the pregnancy testing at home a bit more rigorous, acknowledging concerns about falsification. There were discussions about including names and dates, and photographing that, providing pregnancy tests with barcodes, and then having those uploaded onto the iPLEDGE website.

There was acknowledgment that what was seen

as reassuring, that despite the availability of home pregnancy testing during the COVID-19 public health emergency, there really was no increase in pregnancy rates observed. There really was a sense that it was important to continue home pregnancy testing, acknowledging the benefits of telemedicine as a care-delivery method and the financial burden of having patients having to come in to the medical setting, and whether that would be covered, depending on insurance, and that that might vary, and that telehealth will increase access and reduce barriers and disparities.

There was some disagreement on in-person visits and patient safety. There was a comment that there was a tremendous benefit for patients being seen in person in the medical setting to assess other factors like mental health, but it was also brought up that psychiatrists currently use telemedicine quite extensively, and that as a consequence, in-person visits may not necessarily being necessary for patients' safety.

I will note that cost analyses were

recommended, and that consideration for costs in-person and in-office visits versus home testing would really be important, and that, additionally, any changes going forward in home pregnancy testing, or if it's maintained, really need to understand and get data on the pregnancy rates outside as we emerge from the public health emergency because the data within the COVID-19 pandemic may not necessarily generalize. I'll just conclude that there was a general sense that, really, we need to be forward-thinking about how medicine is evolving with telemedicine to allow increasing access to medical therapies.

I'll stop there, and we will proceed to question number 3. Can we have question number 3 up? It's a voting question.

Thanks, Dr. Bautista.

I will read question 3. For patients who cannot become pregnant, when should the REMS require the prescriber document counseling the patient in the iPLEDGE system? So again, this is for patients who cannot become pregnant, and the

options are, A, only with the first prescription as part of patient enrollment; B, monthly, which is the current requirement; C, every 120 days; or D, some other frequency, and provide the frequency that you think, and a rationale.

Are there any questions about the wording of this question?

(No response.)

DR. LO RE: If there are no questions or comments concerning the wording of this question, we will begin the voting on question 3.

DR. BAUTISTA: Thank you. We will now move non-voting members to the breakout room.

(Voting.)

DR. BAUTISTA: Okay. The vote's now displayed. It's 10 members who voted for the first choice; 1 member who voted for the second choice; 6 members who voted for C, the third choice; and 5 members who voted for D, the final choice.

Dr. Lo Re, I'll hand it back to you.

DR. LO RE: Thank you.

We will now go down the list and have

everyone who voted state their name and vote into the record. Again, you should provide justification of your vote. We will start with Dr. Hernandez-Diaz, at the top.

DR. HERNANDEZ-DIAZ: Hi. It's Sonia Hernandez-Diaz. I voted for 120 days. My intention was to reduce the burden because I think these patients have no risk but still get the burden, so I think that's unbalanced.

I think the logistics of how to do it depends a little bit on the telemedicine, and under the requirements that we were discussing before in the sense that when we got information, we had a sentence saying, "Prescribers will still be required to counsel all patients monthly," and then there was some discussion of if that is still necessary or not because that would affect the issues that were mentioned as a drawback of not having this monthly visit, one of them being the unrecorded prescriber potentially sending the prescriptions.

So I think, depending on whether we are

opening the door of having not only the lack of the recommended RMA, but the potential of opening the door to refuse and not needing an in-person visit, that might create different logistic issues and ways to solve them. Thank you.

DR. LO RE: Thank you.

Dr. Liu?

DR. LIU: This is Tao Liu. I voted for D, some other frequency. Here's what I think. Every 120 days seems arbitrary to me, that's why I'm not fully convinced that's the best choice, based on the histogram plots, and other information.

Unfortunately, we do not have data, like the the outcome related to blood donation and also shared medication, to assess which one will be the best choice. What I think here is, for women who can become pregnant, we have this comprehension and the knowledge testing every month and, unfortunately, we do not have just a test for patients who cannot become pregnant.

I think maybe we can take this opportunity to do like a shorter version test to test the

general knowledge of the medication, like the consequences of sharing drug and blood donation, and use these testing results to do a personalized counseling schedule. For example, if the patient passes maybe the first two tests, first months and second months, and pass the tests both times, then it may be safe to say the patient has a good understanding of the medication and retains the knowledge pretty well, and it's safe to do, say, the documentation in another 3 months.

So that's my thought on this. Instead of doing a one size fits all every 120 days, or every month, maybe we should do this based on patients' test results, recognizing there's a big patient [indiscernible] reasons. Some patients may need monthly documentation and counseling, and some patients may not need that. Thank you. That's my choice.

DR. LO RE: Thank you, Dr. Liu.

Dr. Katz?

DR. KATZ: This is Ken Katz. I voted for only with the first prescription as a part of

patient enrollment. It's a pretty high burden on the prescribers for which I see little to no benefit. And we're not being asked whether there's benefit of counseling regarding diversion or blood donation, but rather whether there's any benefit of documenting that on the website, and I see that there's little to no benefit -- or data, there's little to no data suggesting there's any incremental benefit to that. Diversion and blood donation seem to be pretty low risk in and of themselves. So I don't see a benefit of confirming counseling in the system at any point, including 120 days, which seems quite arbitrary to me.

Regarding the question of whether an unregistered prescriber would take advantage of this, I think that's very unlikely in my experience, clinically, with the knowledge about the issues with isotretinoin and prescribing among non-dermatologists or even some dermatologists who elect not to prescribe it. So that seems very low risk, and that can also be studied over time, and if that's a problem, it could be revisited. Thank

you.

DR. LO RE: Thank you.

Dr. Hovinga?

DR. HOVINGA: Hovinga, yes. I voted for C, 120 days. Given that I still felt torn with this, I could have easily said only with the first prescription. The rationale for that is that I think 120 days for me was a bit of a compromise in between the two, so I leaned towards the all or nothing.

The reason for this is that given the courses of therapy and distribution of treatment, it seemed like a point in which the majority of cases where we would have sufficient coverage of time, that if the patient were going to be diverting medication, that might be a reasonable time. But that might have happened, and every reinforcement of not to divert or give therapy to others would be reasonable. I think also with the transfusion issue, I think there are other safety nets there as well, so I was less concerned about that. Like I said, I was torn between the two

responses, and I went with the 120. Thank you.

DR. LO RE: Thank you.

Dr. Green?

DR. GREEN: Hi. Brian Green. I voted for only with the first prescription. The system exists to make sure that people don't get pregnant. The stats I think showed somewhere around 20 million prescriptions recently on one of those slides somebody had, and there were 4 or 5 cases total of someone sharing the medication resulting in a pregnancy. That's an extremely low rate of that happening.

When you look at what we're doing on the iPLEDGE system versus what we're doing when the patient comes in, we'll talk about that when we give them the prescription, and I don't see the need to go back and put it on the iPLEDGE website. Again, like I said earlier with the pregnancy and home, people are going to do what they're going to do. We can take reasonable steps to stop them from doing it. I think bringing it up and mentioning it when we see them make sense. I think doing it on

the website more than once is unnecessary.

DR. LO RE: Great. Thank you.

Dr. Rasmussen?

DR. RASMUSSEN: Yes. I went with every 120 days. To me, the monthly prescriber documentation seems extra burdensome on the prescriber. I do know that prescription medication sharing, when we did a study several years ago, showed about a quarter of men, about 25 percent of men, share prescription medications sometimes, and we know that is a concern. So I would hope that there would be a requirement of continuing to do that counseling monthly, but I just don't know that it needs to be documented on the website. Thanks.

DR. LO RE: Thank you.

Dr. Cowen?

DR. COWEN: Yes. I recommended only with the first prescription as part of enrollment. I was not convinced that there is compelling evidence that having to make the prescriber go in at a second, somewhat arbitrary, date, two-thirds of the way through the typical course, is going to

meaningfully affect the two major concerns that were raised regarding blood donation, which is already screened, as mentioned, and sharing of medications.

Certainly I'm not in favor of longer term prescriptions, and I think with 30-day prescriptions, it's unlikely that there's going to be a lot of sharing of medications given the other patient visits required. But given what we just heard, I would be very interested to get follow-up studies on the level of prescription sharing that does occur with this medication.

DR. LO RE: Thank you.

Dr. Calis?

DR. CALIS: Karim Calis from the NIH. I voted for option D. I felt that doing it with just the first prescription may not be sufficient, especially if you're going to continue treatment for a longer period of time, and I thought that monthly is, to my mind, clearly excessive. So I would think that if you're going to continue treatment, for example, for another 6 months or

something in that order, then you would repeat that. It's not a bad thing to do. I don't think it's prohibitive and burdensome. It's to help with the general education, misuse, diversion, et cetera, so that's my vote.

DR. LO RE: Thank you, Dr. Calis.

Dr. Berenson?

DR. BERENSON: Abbey Berenson. I voted only with the first prescription as part of patient enrollment. These patients cannot become pregnant, which is really the main overwhelming reason for iPLEDGE to begin with. There were two reasons that were presented to us for why the patient would need to go through this more than the first time. One was to remind them not to give blood. I believe there are many reasons that people are not eligible to not give blood, and at the blood centers, they screen patients for that; that it is not up to the patient to figure out all of those reasons.

The second thing is sharing of medication. They're only getting a 30-day supply, so to share their medication, they're going to have to give up

their own medication, and given how severe the cystic acne is, I don't think many of them want to give away their own tablets, and the data that we were presented I believe showed us that this was rather uncommon. So I felt that the burden on the provider and the patient just did not merit doing this more than the first time. Thank you.

DR. LO RE: Thank you.

Dr. Delost?

DR. DELOST: Yes. Thank you. Kort Delost. I voted D for some reasons for the future possibly. I was going to ask the rest of the staff, or the voters here, about what they felt about doing it 90 days in the future. I know we can't vote on that now. I know there's some pushback on that, but for ease of use and less burden for patients, I figured I'd throw my vote for D, at a 90-day rate because we live in a 30- and 90-degree world as far as providers and pharmacists when it comes to medication, as well as patients. So I thought maybe a 90-day establishment now with the thought that maybe in the future, 90-day prescriptions

would align with those, and that's why I voted that way. Thank you.

DR. LO RE: Thank you.

Dr. Dublin?

DR. DUBLIN: Thank you. This is Sascha Dublin. I voted for D, some other frequency, and the frequency I had in mind was something like every 6 months. I also found choice A appealing and think it could be reasonable. I agree with what's been said in terms of I'm not particularly concerned about blood donation because I think there's, as Dr. Berenson just said, safeguards in place.

I do really appreciate what Dr. Rasmussen said about drug sharing. I think it's a lot more common than we know, and I think the small numbers we heard about of reported cases are probably just what happened to be spontaneously reported, so there could be a lot more sharing out there. This is an area where I wish we had more data.

I think the issue to me is that sometimes when a person is starting a new course of

treatment, they get so much information, it can be a bit overwhelming, and there may be some people who don't fully take in and retain the information about, really, don't share this medication, much differently than you should think of your other medications, and I think that people might benefit from repeated counseling.

I know that although it's a great idea that everyone will do the repeated counseling every time they contact the patient, it is possible that it could somewhat fall through the cracks, and knowing that it's measured and you have to report it every 6 months could be helping make sure that counseling does continue to take place.

So I think what I had in mind would be every 6 months was that for most patients who have a relatively short course of treatment, they'll learn about it in the beginning, and that will be sufficient, but for those rare patients who are having a significantly longer course, or even lifelong use, there could be value to making sure it happens periodically, but I think A is a very

reasonable choice as well.

DR. LO RE: Thank you.

So I'm up next. Vincent Lo Re. I voted A. I recognize that this was a huge burden on providers and for patients who cannot become pregnant. I acknowledge that 72-to-78 percent of risk management authorization denials were due to the monthly requirement for confirmation. I didn't really hear compelling evidence that issues related to blood donation, which as we heard is already screened, and diversion, aside from a few case reports and a case series -- and I thought to remove the burden further; that only counseling at the first prescription as part of enrollment was sufficient.

Dr. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I voted A, only with the first description as part of patients enrollment, for reasons well spoken before.

DR. LO RE: Thank you.

Dr. Hertig?

DR. HERTIG: John Hertig. I'll go on record, and as others have said, I also found choice A reasonable. I didn't vote for 120 days because there is value, demonstrable value, to educational reinforcement, and there was some data presented to support a 120-day cadence. But as others have noted, once a month does seem overly burdensome, and I'd like to reduce that burden. Thank you.

DR. LO RE: Dr. DeMarco? Dr. McAdams DeMarco?

DR. McADAMS DeMARCO: Hi. Mara McAdams DeMarco. I, too, voted C, every 120 days for a lot of the reasons that have been presented already. I, too, was convinced by the data showing that a number of patients that are using it around this time point would make this an appropriate time frame for a kind of re-education and reinforcement of these safety concerns. Thank you.

DR. LO RE: Thank you.

Dr. Ludwinski?

MS. LUDWINSKI: Hi. Donna Ludwinski,

patient representative. I completely agree with what Dr. Hovinga said at the beginning about really kind of leaning toward A, but I picked C as well kind of as a compromise. I agree with what Dr. DeMarco McAdams just said. It does seem reasonable to serve as a reminder, but I appreciate that maybe the contact all along is enough of a reminder; it doesn't have to be formally entered into the iPLEDGE, so if I could change my vote, I'd change to A, but I voted C.

DR. LO RE: Thank you.

Dr. Woodward?

DR. WOODWARD: This is Maria Woodward. I voted A, only with the first prescription with the patient enrollment because of things that other people have said. If the goal of the iPLEDGE is to prevent pregnancies while on the medication, I do not see the benefit of preventing pregnancies to the individuals who cannot become pregnant.

That being said, I do hear the committee members' voices about every 120 days, and I think the question is, is iPLEDGE the best approach for a

more holistically look at public education? We are talking about individuals having to attest to prescriber-documented counseling when, really, what we are concerned about is a holistic education program about diversion and education. So maybe this is an area that needs to be studied about how to best educate people on these issues and at what frequency, and whether prescriber-documented counseling is the best method to do that; then maybe in a study, you can see that every 120 days is most appropriate to really get that education, or maybe there's a whole other mechanism for public health education on this issue. Thank you.

DR. LO RE: Thank you.

Dr. Salvas?

DR. SALVAS: Brian Salvas here. I voted A, for reasons others have shared. It makes sense to only do this as part of the enrollment. I will say this is not a litigation of what's covered here being clinical pearls, but more about the provider enrollment requirement that led me to answer this way.

DR. LO RE: Thank you.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I voted A, at the time of the first prescription as part of the patient enrollment. I do want to emphasize I very much recognize the potential risks associated with blood donations and medication sharing, and therefore think the monthly counseling is important, but I voted on the need for the documentation in the iPLEDGE system, not the need for the counseling itself.

In terms of the documentation in the system itself, that seems to me more of an administrative step with few benefits. In terms of a potential other cadence like the 120, I didn't really see a good scientific justification and sort of linking it somehow to an average prescription duration. So I want to emphasize I think monthly counseling is important; documentation itself I think is not necessary through the treatment. Thank you.

DR. LO RE: Thank you.

Dr. Tollefson?

DR. TOLLEFSON: I voted D with the suggestion of possibly yearly; however, I will say I'm completely comfortable with A as well, but my thought process was along the lines of Dr. Dublin. As a part of this, prescribers have to provide monthly counseling, as was just mentioned, this is just a documentation requirement into the iPLEDGE system. I think most prescribers do document their monthly counseling in their own medical records. I would say that it would be ok not to re-document that in iPLEDGE for a standard length course of isotretinoin, which very well, in most cases, is more than 120 days.

The reason that I consider the yearly is as for the few patients in which they might want it for extended periods of time. Even though the monthly counseling is still happening, if overall it was felt to be more reasonable or better accepted to have this done yearly in those situations, I would be ok with that, but I'm also very comfortable with A.

DR. LO RE: Great. Thank you.

Dr. Chambers?

DR. CHAMBERS: Hi. David Chambers. I did vote A as well, only with the first prescription as part of patient enrollment, for many of the reasons that others have suggested, that this is about the requirement of documentation as opposed to specifically focusing on counseling. So given the potential to reduce burden while still maintaining the importance of focusing on ongoing communication of risks, I thought A was the right choice.

DR. LO RE: Thank you.

Dr. Schreiber?

DR. SCHREIBER: Hi. Courtney Schreiber. I voted B, monthly, and the only one I believe. As others have stated, I agreed with the description that we really didn't have data to assess any other interval for comparison with monthly, so I was unable to make a decision, given that the other options were for arbitrary.

While I understand that this is about documentation and not counseling itself, we weren't given an opportunity to vote on a change in

documentation versus counseling for patients who can become pregnant. And in both of these settings, we are talking about the potential, though rare, possibility of harm to others, whether it's a patient who can become pregnant or who can't become pregnant. So from an equity perspective, my belief is that the systems should be the same, and maybe the documentation for both populations is excessive, although the counseling should be similar. Thank you.

DR. LO RE: Thank you, Dr. Schreiber.

Let me attempt to summarize here. I think that the responses were all over I think mainly because there really was a lack of data on this, in this area, and it was a general consensus that we really needed more study, more research into prescriber documentation, whether it is important, whether it is impactful, so let me go through the responses.

In terms of supporting only with the first prescription as part of patient enrollment, there was a general sense that every-month documentation

is simply too burdensome on both providers and patients who cannot become pregnant; that acknowledging 72-to-78 percent of denials are due to the inability to have monthly documentation; that there was limited compelling evidence that monthly documentation would either affect blood donation, which is already screened, or diversion, which was felt to be, though without data, rare, based on case reports and a case series.

There was really little to no data on the benefit of confirming, counseling, documenting beyond any of the initial visit, and there was acknowledgement from those who voted for this that other intervals really seemed fairly arbitrary.

In terms of supporting monthly, again, acknowledgement of no data to express support for any other interval beyond monthly, which is the current approach, which limited decision making; and from a health equity standpoint, given the rare possibility of harms to others, a monthly system should be maintained because that applies to all individuals in the iPLEDGE program.

The every 120 days, for those who chose this, there was an acknowledgement that some additional check-in for counseling about the need not to divert or donate blood was appropriate. There was concern that monthly seemed too burdensome. For those in favor of some other frequency, there was an acknowledgment that, again, there was no necessary data on what the appropriate time period was. There was a recommendation to consider personalized schedules, based on knowledge of risks of blood donation or sharing.

There was concern, particularly for prolonged durations of isotretinoin, that some additional counseling may be necessary. Some suggested 30, some suggested beyond 120 days, but there was concern in this group that doing it simply with only the first prescription would not necessarily be sufficient, but that monthly was too burdensome.

So I think the lack of data on what is the appropriate timing here limited somewhat the responses, in they were all over.

We are going to go on to the fourth question. May I have the fourth question up? I'm going to read the fourth question.

The fourth question, a discussion question, reads as follows. The iPLEDGE pregnancy registry collects information on fetal exposure, pregnancy outcomes, fetal outcomes, and root cause analysis. Please discuss recommendations on the pregnancy registry requirement and the ways in which it could be streamlined to encourage more participation to yield high-quality data.

Are there any questions about the wording of this discussion question?

Okay. There's a question from Dr. Schreiber.

DR. SCHREIBER: Apologies. Maybe this isn't exactly about the wording, but I am wondering if the goal is more participation, for sure, or is that up for debate, whether or not this is of value to continue the registry or all aspects of the registry as it is? Because I thought I understood that from prior, that maybe there was an

opportunity to change it, as opposed to just increase participation.

DR. LO RE: Dr. LaCivita, it looks like you came on. Do you want to help to clarify that discussion question, please?

DR. LaCIVITA: Sure. Cynthia LaCivita, FDA. Thank you.

I think we're looking at any advice that you give us with regard to we know the participation is low, so if we could streamline some of the activities and get some feedback or advice on that so that maybe more people would participate. Also, some of these outcomes are information that we have years of experience on. Is it necessary to collect information on the fetal outcomes moving forward? So I think any of your thoughts on that would be greatly appreciated.

Does that help you at all?

DR. SCHREIBER: Yes. Thank you.

DR. LaCIVITA: Sure.

DR. LO RE: Thank you, Dr. LaCivita.

Opening comments on this discussion

question?

Dr. Delost, will you lead us off?

DR. DELOST: Yes, I will. I think that there are ways to follow up and do a better job. Since people are so used to answering surveys on their phones and things like that, maybe the FDA could reach out using a platform by using those surveys directly to the patient once they're discovered there's a pregnancy issue, and maybe following up on that.

I know it's voluntary and things like that, but it doesn't really violate a HIPAA because they've already signed up for it, and I think using the electronic follow-up poll and data on the outcomes might help get more involvement. Thank you.

DR. LO RE: Dr. Rasmussen?

DR. RASMUSSEN: Yes. I believe being able to get information on the root cause analysis is really essential. To be honest, the rest of it is a little less important, but where has the program failed, that the person ended up being pregnant I

think would really help us to know how to change the program in the future.

I think whatever we can do to try to -- whether it's an app on a phone, or whether the concerns are about confidentiality, I think whatever sort of reassurance that can be given -- I know there are things called certificates of confidentiality that say that even if you're given a court order, that you would not give that information, which are more concerns about the inability for women to have the choice of having pregnancy terminations. I think we're going to have an even harder time getting people to report the pregnancy registry. But I really feel like this is essential, and we need to think creatively about ways to improve the likelihood of getting information about root cause. I actually don't know that we need more information about fetal outcome. I think we've finished [indiscernible] that for fetuses. That's it. Thanks.

DR. LO RE: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Hi. It's Sonia Hernandez-Diaz. I agree with Dr. Rasmussen, in the sense that I see this study presented [indiscernible] in two parts. One is the detection of pregnancies and the analysis of causes, which I will keep, and then the other one is a follow up, which is more tying in.

For many reasons, I would suggest that it can be discontinued. One is because most of the outcomes that we have seen are either losses to follow-up or terminations, therefore we will have little information. Second, with that little information, there is no result of the registry that would change our [indiscernible] prior over the teratogenic [indiscernible] effect. So the benefit in terms of the amount of useful information are very small, and it is a burden to follow them. If they're pregnant, pregnant women know that they are going to be asked to do about what they are going to do after being pregnant. That might actually maybe affect their willingness to participate in the first part, which is not

going to ask them about what they are going to do afterwards. So for those three reasons, I will keep only the first part, and then focus on improving enrollment participation on that first part.

One thing is we need to streamline the information that is collected, but it seemed from the presentation that it's already very short and it's not the time of answering the questions that might be a challenge or might be affecting participation and completion, but maybe the confidentiality, as Dr. Rasmussen said.

Also, if this is an interview, still that's not what the new generations are used to. So moving to more friendly platforms that they like and they use, if possible, with the apps that they know how to use very well, that might be a way.

I don't have specific recommendations for ensuring complete confidentiality, but maybe once they don't have to report what they are planning to do, that might lower their concerns. Thank you.

DR. LO RE: Thank you.

Dr. Katz?

DR. KATZ: Thank you. Ken Katz. Keeping in mind that the purpose of iPLEDGE is to prevent fetal exposure to isotretinoin, it seems like the only important aspect of the registry is really the root cause analysis. The other aspects of it might provide useful information regarding other things, but not toward preventing fetal exposure to isotretinoin. So I'd recommend keeping the root cause analysis and maybe discarding the other parts, and maybe by making it a simpler survey, people would be more willing to participate.

For those who aren't going to participate, maybe asking them why so that the survey might be a change or the approach might be changed to encourage future participation moving forward, with some data to support that. Thank you.

DR. LO RE: Thank you.

Dr. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I have no way to make this simple or to streamline it; in fact, I want more information. Without information

on race, socioeconomic status, insurance that can be overlaid on the pregnancy registry, we don't know who is not getting access to treatment versus who is in the large picture. People lost to treatment and people who discontinue treatment is something that is very important because we don't know why they're lost to treatment.

We should note is it the burdens of the iPLEDGE program? We should note is it the harshness of the side effects? It implies there's also a risk that some of those patients became pregnant and did not want to report it, so just stopped going to the doctor's office and responding.

We have their information, their contact information, to do follow-up, phone calls, reachouts, and find out what happened to them. It would give us so much more information, and without it, we have no basis on which to make decisions. That's all.

DR. LO RE: Thank you.

Dr. Hovinga?

DR. HOVINGA: Hello. This is Collin Hovinga. When I think about this, getting people to complete any survey or follow-up data in clinical trials, or any other element of this, is very, very difficult. I think one of the things that was done really well with the CDC is when everyone got their COVID vaccine, where they got a push to say, "Hey. How are you feeling?"

So having some kind of structure where if there's a triggering event, that you have a pregnancy, then that triggers additional follow-up, it's only done as a follow-up measure. I do think the important element here is going to be the root cause analysis, and I think that the pregnancy outcome, or fetal outcome, is probably less important here, given what we already know.

The only other caveat I would mention is that I think the more questions that you ask of people -- in pregnancy registries, after that, it's hard to get good responses or complete responses. Also, I think given our current climate for abortion and whatnot in many states across the

United States, it raises more concerns of what you're going to be using with your information, even if people are told that their data or their information is going to be held in confidence. Over.

DR. LO RE: Thank you.

Dr. Schreiber?

DR. SCHREIBER: Yes. Courtney Schreiber. Just to expand on that last point, this could potentially be putting patients at risk if they are in states where abortion is illegal or practically illegal. So that would be a major disincentive to report a pregnancy that is going to likely end in a pregnancy termination, and something that we should consider for the safety of the population of patients using the therapy. I agree with what's been said, that there doesn't seem to be utility to continually collect neonatal outcome data.

In terms of the RCA, again, weighing that against the risk to individuals who are reporting pregnancies in the current political climate, if the RCA data were being utilized, I would put more

weight on that benefit to outweigh the risk of asking patients to report pregnancy, but I haven't seen too much evidence of the RCA data being utilized, at least not in these last two days.

We know that abstinence is a major risk factor. For a pregnancy during treatment, and abstinence isn't really considered a contraceptive method but a lifestyle choice, and it's not considered in all the ways in which patients who are stating that abstinence is their lifestyle choice might need ready access to emergency contraception or quicker referral for contraceptive care should that change; not to mention that not all sex is voluntary, 1 in 6 women in this country are raped.

So all of these components are parts of the program that are difficult to address without more mandated and potentially coercive counseling around contraceptive methods used, my point being that if there isn't a plan to really utilize the data on risk of pregnancy through the iPLEDGE program, to make changes to the iPLEDGE program, and to the

recommendations for contraceptive use during isotretinoin therapy, then is it really worth collecting the data? Thank you.

DR. LO RE: Thank you.

Dr. Calis?

DR. CALIS: Karim Calis form the NIH. I actually kind of have a little different perspective on the pregnancy registry maybe than some of my colleagues. I don't believe there's such a thing as excessive amounts of data on pregnancy outcomes, as well as all the other aspects that are collected in the pregnancy registry. I think this is vital information that can inform us about the extent of the exposures and what outcomes may occur.

So I actually feel that it's a really important tool to continue, and we should encourage participants who want to. It's certainly something that they would choose to participate in freely, and the default should be actually to participate, and somebody can opt out of that if they so choose, if their situation is such that they don't want to

share that kind of information, but I think it is vital information.

I think it would be a mistake to not collect this type of information. The process certainly can be streamlined, but I actually think that there's even an ethical imperative to collect pregnancy outcome data. We do that all the time in clinical trials of various types of substances and medications that are used, where we don't know enough about teratogenicity, et cetera, and I think that that can apply even in this particular case, where we do know a lot of information but not quite everything.

DR. LO RE: Thank you, Dr. Calis.

Dr. Robotti, you have your hand up. Did you have a follow-up? No? Okay.

MS. ROBOTTI: No, my mistake.

DR. LO RE: No worries.

Dr. Dublin?

DR. DUBLIN: Thank you. Can you hear me?

DR. LO RE: Yes.

DR. DUBLIN: Great.

So I agree with the points that have been raised about the potentially most valuable and potentially actionable part of this data collection is the root cause analysis. I agree with previous speakers who said that they don't feel that it's a benefit to continue collecting data about pregnancy outcomes or infant outcomes because it's hard to imagine how that would change our recommendations or our practice. I think it's important in collecting data to really ask what decision needs to be made from the data, what analyses am I going to do to guide those decisions, and that should inform what data are being collected.

I think we heard over and over again in the earlier discussions that we really want to know why are people saying no to the registry, and I don't think we got an answer. To me, it wasn't clear from IPMG if they aren't even asking at all, they don't collect the data, or if they just haven't analyzed them, or if they don't know if they have the data. So I think that a fresh start would be to try to find a sensitive and acceptable to

patients way to ask about, tell me about your decision not to participate to understand the barriers.

I think there are these huge concerns about potential legal liability, and I think that I agree with the idea of not asking people about their intentions about termination or not, to be protective of women.

I think what we saw in terms of the data about the causes of failure, it didn't give me a lot of confidence in the current depth or analytic rigor of a root cause analysis that's being done to date. All we saw were things like what contraception were they on or the stated reason being things like contraceptive failed, but there are so many more interesting and important questions of why did the contraception fail. Did someone forget to take her birth control pill? Did someone decide to stop it due to side effects?

I think we really need a lot richer understanding of the context and the potentially modifiable factors that led to the pregnancy, and I

think sometimes the way you get those is actually through qualitative data collection such as semi-structured interviews, or at least really big sections for people to write free text information. And I think to do that work, it would really help if you could reassure people that you were going to somehow de-identify or de-link the data you collected as soon as feasible, to take away any link to identifiers so that you could really try to ensure the data couldn't be traced back to individuals. I think that might be very reassuring.

I want to speak briefly to the idea about a mobile app. There actually was a project funded by the Patient-Centered Outcomes Research group, and it was funding that came in through FDA's Sentinel Initiative that created it. I was part of a project where we developed a mobile app to collect data directly from participants, including from pregnant women. It's a customizable app, and it's open source, and it's available.

The challenge we had when we piloted at

Kaiser Permanente was we reached out to something like a thousand pregnant women, and only 7 percent decided to take up the app and participate and report on their medication exposure. So having an app that we were sending them out little questionnaires, people who did participate stayed in for a long time and were very enthusiastic, but the participation rate was very low.

I know that in traditional research studies, we get much higher participation when we pay people and we give them a financial incentive. I think there are ethical issues around would it be coercive. We don't want to coerce people to participate, but I do think that, from a purely research standpoint, a financial incentive does help people feel like it's worth the time and energy if that's the concern that they're having.

So I'll stop there, but I do favor trying to keep and improve that first part, that root cause analysis, and really getting more usable and more rich detail about how pregnancies are happening in this program. Thank you.

DR. LO RE: Thanks, Dr. Dublin.

So let me try to summarize the comments from the committee. I think there was consensus that the information collected from the pregnancy registry on the root cause analysis was the most important, the most actionable, and would give important information on the factors that led to a patient's pregnancy, although there was acknowledgement that we may need better data on this, particularly why did contraception or abstinence fail, and qualitative surveys were recommended that potentially could fill in those gaps and provide reassurance that data might be de-identified.

There were lots of comments about electronic -- either smartphone applications, texts, pushes -- and more user-friendly platforms to increase participation in the pregnancy registry. There was a general sense that, really, more information on fetal outcomes and follow-up would not be valuable. These data are already known. The data would not be actionable and may

actually discourage individuals, particularly when asking about plans for the pregnancy in a climate and in states where abortion may be illegal.

There were concerns raised about whether and how the root cause analysis data was currently being utilized, and there was a suggestion that potentially the registry should be the default with an opt-out available, and that we need far more data on why people are saying no to the registry to understand the barriers to participation, and particularly there was concern about potential legal barriers.

Then there was a suggestion about an open-source app that was funded by PCORI, but even that had very little uptake in participation and a suggestion about potential financial incentives, which might be valuable.

Okay. I'm going to move now to question number 5. That's our last question. Can we bring question 5 up, please? Thank you.

This is a discussion question. Discuss any additional recommendations to minimize burden in

the iPLEDGE REMS. Any questions about the wording of this?

Dr. Green?

DR. GREEN: I didn't have any questions about the wording. I had some additional recommendations, so I can hold off if you want to see if anybody has questions.

DR. LO RE: Yes. Leave your camera on and leave your hand up, and I'll just see if there are any other questions from the advisory committee on the wording of this question.

(No response.)

DR. LO RE: It doesn't look like it.

Dr. Green, please.

DR. GREEN: I brought a few things up yesterday. The app we just talked about I think is specific to people who have gotten pregnant and sort of what happened. I do think iPLEDGE should exist as an app because most people go to their phones rather than their computers, particularly teenagers and younger people, early 20s, so anything that they had to do, it would be wonderful

if there was an app that was developed.

I brought up the idea yesterday on the dropdown menu when you're entering patients' contraceptive methods. There does not need to be hormonal IUD and non-hormonal IUD. I would love to just have that say "IUD." And I think entering the date every time that we counseled people and when we just check the box that said I have counseled people on this, is redundant as well. I think that would streamline things quite a bit if there were an app. It's going to be less clicks if we don't have to enter the date every time.

The potential for contraceptive mismatch will be less if there's only one IUD there, because if we select hormonal IUD and the patient selects non-hormonal IUD, it's going to be a mismatch, and it's going to cause a delay of them picking up their medications.

I'd also like to suggest a change on this consent form for consent about birth defects. Number 7 is, "I may receive a free birth control counseling session from a doctor or other family

planning experts." There's a form, and then it says, "Fill out this form for a free consultation." I've never had anybody ask me about this, but I have no idea where they're going to get this free consultation from a doctor or other family planning expert, so I think that's something we need to look at in the sign the consent form. And maybe IPMG knows where this is going to happen, but I certainly do not.

DR. LO RE: Thank you.

Dr. Salvas?

DR SALVAS: Thank you. Brian Salvas from CVS. To me, all my recommendations come down to technology. Recognizing I represent some 9[000]-10,000 pharmacies and a significant portion of the isotretinoin dispensing in the U.S., I've seen a significant change in the way that the IPMG supports my pharmacy providers with technology.

It's been a consistent theme across a lot of folks' testimony, and questions, and comments over the last two days, whether that's facing digital capabilities, whether it's improved EHR

integration, or platforms for providers. But for pharmacies, I think it's important to recognize that when that change happened at the end of 2021, we actually took a really significant step back, and all of the interoperable connections required in order to enable that RMA, that dispensing authorization happened.

It used to happen in an automated way through the adjudication network for retail pharmacies because McKesson was involved at that time. Now that they're not, every pharmacy, every day, in order to dispense the stuff has to stop, has to leave their dispensing workflow and access a portal that is only designed for this distinct purpose. And it is not something that they're doing in the normal course of their business for the other products that they're dispensing, other products that, thus, this change dangerous in different contexts.

So what I would love to see continued work on is how we can still deliver on our commitment for safety, limiting the adverse events associated

with this product, while also ensuring that we're able to maximize the effectiveness for the provider networks.

DR. LO RE: Thank you. That was the change, Dr. Salvas, that was in 2021 that you're referring to; is that correct?

DR. SALVAS: That's right. When they speak the moving from one REMS administrator to another, that was the change, and it had significant impact for everybody.

DR. LO RE: Dr. Berenson?

DR. BERENSON: Just to clarify, we're open now to discuss this question; is that correct?

DR. LO RE: Yes, that's correct.

DR. BERENSON: Okay.

I had two comments. One was whether you're talking about the 19-day lockout or redoing the iPLEDGE every 30 days, I do think that we need to take into consideration that LARC methods, the rate of failure is extremely low. So while it is true, as it was pointed out, that all methods can fail, when they're over 99 percent effective, I think

that we can treat those methods differently than we treat methods such as birth control pills or abstinence, that fail far more often, and that is one way we could minimize burden on the providers and the patients.

The other point that I would like the FDA to consider is if there are some creative ways that we can use more members of our healthcare team. As more and more time goes by, the burden on the physicians just keeps increasing, especially since the beginning of the EMR, where physicians now have to do all their own documentation. So if it is the case that the physicians have to do all the counseling, there is a possibility that others in the office, like an RN, could be trained to do that, or perhaps, as we saw during COVID, the pharmacists could pick up some of that burden. These are just some ideas of how to decrease the burden.

DR. LO RE: Thank you.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I had a

couple of thoughts related to missing that initial 7-day pickup window, and the first one is something that I believe Dr. Green brought up yesterday, and we haven't really had a chance to discuss these two days, like the rationale behind the 7-day window. I think Dr. Green brought up that the need for prior authorization is often just insurance not being able to approve that prior authorization in time, and is often a reason for missing the window there.

So I was just wondering in the future, moving forward, whether there's any possibility of reassessing whether that 7-day is really the right window or whether that could maybe be extended with a couple of days to avoid those kind of delays.

The second one, also related to this, is it seems that there is a lot of opportunity for the patient just to miss that window for no particular reason other than that they forget the things that they need to do. The issue was brought up that now the calendar would be brought back into the system, but it still requires the patient to log on to the

system, and to then look at the calendar and see where they are. And I was just wondering -- we talked about technology -- that if there was a simple text reminder to the patient -- we're getting reminded for our doctors' visits all the time -- sort of saying, "Remember, you still need to complete your comprehension questions," or "Remember, your window to pick up the prescription at the pharmacy is closing," I'm wondering whether that could reduce the number of missed 7-day window, which then has repercussions for the provider, and the pharmacy, and so forth. So those were just two thoughts related to missing the window. Thank you.

DR. LO RE: Thank you.

Dr. Katz?

DR. KATZ: Thank you, and a couple of suggestions. One is having emergency contraception and making that information more prominent and more easily accessible. I think it's now in the prescriber guide but not in the information that's meant for patients themselves, and I think it

should be included there more prominently and more easy to access.

The second has to do with telemedicine, to make it explicit in the prescriber's guide which activities are acceptable and not acceptable. In telemedicine, I think with all the concerns about iPLEDGE, people are probably going to be conservative on what they will employ, what methods they will employ, so just to be explicit about what they can do to make it easier for everyone would be useful.

My final comment has to do with the definition of patient categories and trying to be more respectful to our transgender patients, and to encourage prescribers to use language that respects where they're coming from. Currently the language states, for example, for cisgender females, it says, "born a female and transgender males born female -- cisgender males born a male." That's not language that I think is usually used with our transgender patients, but rather the sex assigned at birth and then current gender identity. I think

that's the language that most people are using.

So this idea that a transgender female was born a male I think is not respectful to that community, and I would encourage IPMG to solicit input from stakeholders who are transgender to make sure they get it right. Thank you.

DR. LO RE: Dr. Rasmussen?

DR. RASMUSSEN: I just wanted to make the same comment that Dr. Katz just made about enhancing awareness among patients about emergency contraception. I do feel like whether that's through getting more information to the patients or whether clinicians are including that in their monthly counseling, I think it really is important to remind persons that that is something that is available to them and could actually lead to pregnancy prevention in a time when access to pregnancy termination might be decreasing. Thanks.

DR. LO RE: Thank you.

Dr. Woodward?

DR. WOODWARD: Thank you. Maria Woodward. I wanted to recommend that to minimize the burden

of iPLEDGE REMS, really, we should be communicating with our dermatologic colleagues and professional societies who are thought leaders and experts in this field more directly, as well as the patient advocates. I had serious concerns that the method of communication with IPMG is not an open forum.

Specifically, I would recommend that there is a representative from both patient and dermatologic societies that are appropriate, where maybe a task force can be designed to figure out who those people or roles of those people would be, so there is representation in the build and design, rather than concerns after the fact. I think many of the issues with the rollout could have potentially been mitigated had there been better communications, and that really worried me when I heard that that is not an open line of communication.

Mounting on to that is really just that there is some mechanism to regularly review the peer-reviewed literature. We are in medicine, and evidence-based guidelines are critical; so

understanding there's a lot of research and interest in this space that is clinical and well peer-reviewed literature that should be reviewed regularly, and maybe those dermatologic colleagues could lend light to those and give context to those. Thank you.

DR. LO RE: Thank you.

Dr. Tollefson?

DR. TOLLEFSON: Thank you. Megha Tollefson. My comments mirror any of the recent ones that have been said. I also think that there's an incredible opportunity, one, to study outcomes that can be used to inform the future. I was, quite frankly, surprised at the lack of some data that was available, and part of that involves including the key stakeholders, such as the prescribers and also the dispensers, as decisions are being made, and I think not just dermatologists, but dermatologists that are actively prescribing isotretinoin often.

I also want to echo, I think, the importance of an app in iPLEDGE. This is medicine that is used by young people. Young people interact with

their very expensive handheld devices the most. They don't respond to email, they don't necessarily go on to web pages, and I think if we're going to be effective, as effective as possible, it's going to have to be through an app-based system.

I'd like to see that monthly counseling be standardized through that. I think there's a lot of variability in what counseling is given when it's left to the individual prescriber or practice. And if our goal is to minimize pregnancy, that would be the best way, certainly with a large emphasis on emergency contraception on a monthly basis. Thank you.

DR. LO RE: Dr. Dublin?

DR. DUBLIN: Thank you. I really appreciate all the wonderful suggestions my colleagues have made. Things I'd like to highlight and maybe lend a little more detail or a new twist to is I think the importance of recognizing the incredible effectiveness of LARC, as Dr. Berenson pointed out, and treating it differently.

Specifically, one thing that seems like it

was worth debating is whether to remove the 30-day waiting period after the initial consultation about starting isotretinoin. It's not clear to me why someone who's already been successfully on LARC for months needs to wait 30 days before their second pregnancy test. This could be a very concrete way of recognizing the difference between LARC and other forms of birth control, or the need for someone to go out and get birth control that doesn't have it.

Like one of my colleagues, I was really concerned to hear about the difficulty that dermatologic societies have had in establishing open lines of communication with IPMG, and I think the issues that were raised about transparency and communication are very, very important.

I think, if possible, the FDA should really require that IPMG hold periodic, regularly scheduled stakeholder forums, which could either be, to some degree, open to the public or could be scheduled meetings with representatives from obvious major stakeholder groups who are eagerly

awaiting a chance to interact with them to help reduce burden; because I think those of us on the committee, we could come up with some good ideas right now, but a lot of the best ideas are going to emerge as things go forward in the future, seeing when problems come up, there has to be a mechanism in place for IPMG to listen to those concerns in real time, and respond, something like every 3 months or every 6 months. I think that should just be an expectation.

Again, that requirement that IPMG should be regularly reviewing the literature that's relevant about patient experience, patient health disparities and satisfaction, I know we've talked about it in other settings, but since this is a moment when suggestions are asked for, I would like to just get on the record the suggestion that there be some kind of expectation or requirement that IPMG be collecting data in a way that allows the examination of health disparities, including by race, and ethnicity, and insurance status, and also some requirement to access, either reasonably well,

accessible outside data to understand the health disparities, both in initiating isotretinoin in the first place and successfully completing a course. I think this could be done in a way that isn't incredibly burdensome and expensive, but I think there should be an expectation of generating some data.

I really like the idea of trying to automate and standardize the counseling. There will never be a replacement for that provider-patient relationship and contact, but to supplement with some kind of one-time online counseling that is well done, designed for the way teenagers and younger people are interested in hearing the information, I think would be a real strength, and especially the emphasis on emergency contraception.

I really like the idea that was raised at some point during this two days that there really should be a lot of -- it could almost be the default, that for most patients, you're going to provide the prescription for plan B, and supply it at the time of their first isotretinoin

prescription, and then they'll have it for the whole course of treatment. They don't have to buy it, but to make it available at the very beginning sets the expectation that it would be good to have in your medicine cabinet, particularly if the choice is abstinence or birth control pills. Thank you.

DR. LO RE: Dr. Ludwinski?

MS. LUDWINSKI: Hi. Thank you. Donna Ludwinski, patient representative. My question really just has to do with looking at other indications and seeing about off-label use and which groups absolutely shouldn't be required to be enrolled in iPLEDGE. I feel a good perhaps exercise would be engaging some of the pediatric oncologists who deal with it and feel it's really not helpful in their situations. So that's my only suggestion. Thanks.

DR. LO RE: Thank you.

And lastly, Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Well, thank you. Just to emphasize, this is going to be an opportunity

for evaluation and also emphasizing the importance for technology for the integration of a system and sending texts, the apps, and the counseling for this new generation. We can do some type of gaming; that's what I think they like.

But I had a specific comment, following up from Dr. Woodward, regarding the interaction with dermatologists and prescribers. This is an idea we do for other areas like epilepsy and neurology, to have a pregnancy session around or during the dermatology meetings, where the updates of their results briefly can be presented every year, and then it's an opportunity to get also input and an exchange of information for how it's working. Thank you.

DR. LO RE: Dr. Atillasoy?

DR. ATILLASOY: Yes. First, I just want to thank everyone for a robust conversation. Actually, in terms of an additional recommendation, I wanted to just take this quickly in another direction. There's been discussion about the benefits of telehealth versus in-patient. I think,

ironically, one of the concerns I've seen is that it appears, to me, over the last 10 years or more, that the duration of dosing isotretinoin seems to be getting more and more prolonged and extended.

Again, I recommend everyone to take a close look at the U.S. prescribing information. The drug is supposed to be dosed, generally, for 5 months, 20 weeks, and there's been some discussions about testing 6 months later and beyond, so I take issue with that.

I also want to emphasize while I don't disagree regarding that someone can make an assessment in, let's say, a psychiatric context, the benefit, for example, of having in-person visits in the office, in the clinic, is that dermatologists can make assessments of how the patient's responding to the isotretinoin. So ironically or paradoxically, I myself worry and wonder that with the advent of more telemedicine and not seeing the patient, we may be inadvertently extending the duration of dosing.

So actually, recommendations that really

reinforce the benefits, if you want to call me old school, fine, but the benefits of seeing a patient, examining the patient, evaluating the cysts, the nodules, et cetera, and how they're progressing, may actually allow us to stay within label and, in general, complete a 5-month course as opposed to 6, 7, 8, or 9 months. And I would say that in those cases, that actually can further reduce the burden that I'm hearing about from prescribers, so I wanted to also emphasize those points as well.

Again, I still hear comments about IPMG, and in terms of disparities, I understand all that. I would ask others and the specialty to look at other areas for disparity, including the number of dermatologists, for example, in medical dermatology. There are other things that are being done. So not opposed to additional information being sought from the manufacturers in this case; however, let's bring in the entire context as to what may be leading to that kind of disparities and how we can make this more inclusive. Thank you.

DR. LO RE: Thank you.

Dr. Katz?

DR. KATZ: Thank you. I appreciate Dr. Atillasoy's comments. Just to respond to that, when I talk about telemedicine, that includes photographs or videos as well, which are other very good ways, I think, of examining a patient, and not just asking questions by phone or by email, for example, but getting some visual data as well. Thank you.

DR. LO RE: Let me summarize the discussion for this question. There were comments about iPLEDGE considering existing, at least in some form, with better tech integration, be it apps or texts, to appeal better to the younger patients who are utilizing the program.

There were comments regarding specific questions on the counseling questionnaire on entry of dates, IUD use, and consent regarding completion of free consultation forms. There was an acknowledgment that the change that occurred in 2021 may have led to more challenges for pharmacists, prescribers, and patients, and ways to

potentially mitigating that in the future, be it with better tech integration or other interventions that should be considered.

There were several comments that there should be better consideration that long-acting reversible contraception failure is very low, and that, potentially, there should be special considerations for these patients or ways to make the program a bit simpler.

There was a consideration about reassessing if the 7-day window is appropriate or if it should be extended because of prior authorization delays or other issues in accessing prescribers. There was acknowledgment that the electronic calendar that was just recently reimplemented requires logging onto the system and whether there should be other alternative tech solutions that may be easier considered.

There were several comments about increasing input from stakeholders, be it from professional societies, patient advocacy societies, with the iPLEDGE system. And particularly IPMG, there were

suggestions that maybe FDA should require regular IPMG stakeholder forums to listen to input to gather greater integration mechanisms, to review medical literature regularly, and to have the specialty societies and patient advocates shed light on issues.

There was consideration for enhanced awareness on emergency contraception to make this information more accessible for counseling, which could lead to enhanced pregnancy prevention. There were considerations for increasing the use of telemedicine, making it explicit in the provider guide about what is acceptable and what is not. That was countered by the value of in-person visits; that in-person assessments could potentially identify how patients are responding and may enable improvement in retention in the iPLEDGE program.

There was consideration for a lack of data overall on the iPLEDGE program and the need for more data on studying the outcomes, the variability in counseling that was present, the need for

potentially qualitative studies, and especially more data on the disparities. Disparities in access, disparities in counseling, equity, race, insurance status, and potentially the use of outside data supplemented with improvements in the iPLEDGE platform may enhance this.

There was a lack of data also highlighted on other indications for isotretinoin and which groups potentially should not necessarily need to be enrolled, such as those with ichthyosis or neuroblastoma. There was also a suggestion for research dissemination by IPMG or others on a yearly basis at national meetings for transparency and input.

Are there any final comments from FDA at this time?

DR. LaCIVITA: Dr. Lo Re, thank you. I would like, with your permission, to give Dr. Manzo a second just to kind of update the committee. We've heard a lot about technology and the use of technology, and I think she has a few points that would be helpful to share with the committee, and

then I'd like to be able just to wrap up with a few, thank you, if that's ok.

DR. LO RE: Sure.

Dr. Manzo?

DR. MANZO: Thank you, all. I heard Brian Salvas and others talk about potential solutions, technological solutions, and I just want to make the committee aware that FDA is actually working to reduce the burden of REMS, generally, not only the iPLEDGE program but other REMS programs.

To that end, we've been working with a number of external stakeholders on the development of an open-source, proof-of-concept REMS integration prototype that leverages data standards, such as data standards used within EHRs and electronic prescribing, and technology to allow for certain REMS activities to be integrated in the workflow of both prescribers and pharmacists.

If there's an interest in participating in this, it is open to participation, and we can provide information about how to get involved in that. Thank you.

DR. LO RE: Dr. LaCivita?

DR. LaCIVITA: Cynthia LaCivita, FDA.

On behalf of the FDA team, I want to thank Dr. Lo Re and the committee members for your time that you devoted to the advisory committee meeting over the last two days. We know it's a significant amount of time that you've provided to us. In general, we've heard the committee say that there is a need for more data for some of the metrics. There were lots of good recommendations and suggestions that we'll be taking back for further discussion. And as Dr. Manzo mentioned, the agency is aware of the burden associated with REMS, and we are exploring ways to use technology to reduce burden associated with REMS requirements.

So in closing, I just want to mention that we really do appreciate your advice regarding the iPLEDGE REMS, and we hope you have a great afternoon. Thank you.

Adjournment

DR. LO RE: Great. Thanks very much, Dr. LaCivita.

We will now adjourn the meeting. I want to thank everybody for their participation and for their help, and have a wonderful rest of your day. Bye bye.

(Whereupon, at 3:28 p.m., the meeting was adjourned.)