FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM) AND THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC)

Monday, May 5, 2025

8:00 a.m. to 4:25 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. BATEMAN: Good morning, and welcome. I'd first like to remind everyone to please mute your line when you're not speaking. All members of the public are reminded to silence their phones and other devices, and otherwise refrain from disrupting the meeting. Loud talking or applause may make it difficult for the meeting participants and observers to hear the proceedings.

My name is Dr. Brian Bateman, and I'll be chairing this meeting. I will now call the May 5, 2025 Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee meeting to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We will start with the FDA to my left and go around the table.

DR. DAL PAN: Good morning. I'm Gerald

Dal Pan. I'm the Director of the Office of Surveillance and Epidemiology in CDER at FDA.

DR. McANINCH: Good morning. Jana McAninch, Associate Director for Public Health Initiatives, Office of Surveillance and Epidemiology, CDER, FDA.

DR. MEYER: I'm Tamra Meyer. I'm the Associate Director for Nonmedical Drug Use. I'm in the Office of Surveillance and Epidemiology in the Division of Epidemiology.

DR. KORNEGAY: Good morning. I'm Cynthia Kornegay. I'm an epidemiologist on the Nonmedical Use Team in the Division of Epidemiology.

DR. LEE: Good morning. Hana Lee. I'm a statistical reviewer at the CDER FDA in the Office of Biostatistics.

CDR CRISAFI: Good morning. I'm Leah Crisafi. I am the Director of the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, Office of Neuroscience, Office of New Drugs, CDER, FDA.

CDR LIBERATORE: My name is Mark Liberatore. I'm the Deputy Director for Safety in the Division

of Anesthesiology, Addiction Medicine, and Pain Medicine, Office of Neuroscience, Office of New Drugs, CDER, FDA.

DR. McCANN: Good morning. I'm Mary Ellen McCann. I'm a pediatric anesthesiologist at Boston Children's Hospital in Harvard Medical School and Professor of Clinical Anesthesia.

DR. SHOBEN: Good morning. I'm Abby Shoben. I'm a biostatistician at The Ohio State University.

MR. PHILLIPS: Good morning. I'm Rick Phillips. I'm a patient representative representing the Arthritis Foundation, the Spondylitis Association, and Global Healthy Living, and I'm from Noblesville, Indiana.

DR. JONIAK-GRANT: Good morning. I'm Elizabeth Joniak-Grant. I'm a sociologist, and I've also been a chronic pain patient for 21 years. I am here today as one of the patient representatives, and I do work with the UNC Injury Prevention Research Center in Chapel Hill.

DR. FRANK: Good morning, everyone. My name is David Frank. I'm a medical sociologist at New

York University School of Global Public Health and also a long-time person on methadone maintenance treatment; and I'm one of the patient representatives.

DR. BATEMAN: Good morning. Brian Bateman. I'm Professor and Chair of the Department of Anesthesiology, Perioperative, and Pain Medicine at Stanford.

DR. SEO: Good morning. I'm Jessica Seo, Designated Federal Officer, FDA.

DR. HUYBRECHTS: Good morning. I'm Krista Huybrechts. I'm an epidemiologist at Brigham & Women's Hospital, Professor of Medicine at Harvard Medical School.

DR. BICKET: Good morning. My name is Mark Bicket. I'm an anesthesiologist and pain medicine physician, and an associate professor at the University of Michigan where I co-direct the Overdose Prevention Engagement Network.

DR. BECKER: Good morning. I'm Will Becker, Professor of Medicine at Yale School of Medicine and Chief of General Medicine at VA Connecticut

Healthcare System.

DR. GORDON: Good morning. My name is Adam Gordon. I'm a Professor of Medicine and Psychiatry at the University of Utah, an internal medicine and addiction medicine physician, and Chief of Addiction Medicine at the VA Salt Lake City Health Care System.

DR. DEJOS: Good morning. My name is Mike Dejos. I'm the System Medication Safety Officer for Methodist Le Bonheur Healthcare, overseeing our opioid stewardship program, and I'm also Assistant Professor at University of Tennessee Health Science Center.

DR. REBO: Good morning. My name is Elizabeth Rebo. I'm the Executive Director of Medication Safety for Kaiser Permanente.

DR. AMIRSHAHI: Maryann Amirshahi. I am an emergency medicine physician, medical toxicologist, clinical pharmacologist, and addiction medicine physician here in the DC area. I'm a Professor of Emergency Medicine at Georgetown University.

DR. REICH: Good morning. I'm Jeffrey

Reich. I'm CEO and Co-Founder of Sparian Biosciences. I'm also the industry rep on the DEP [ph] adcomm. Thank you.

DR. SEO: Thank you. And just a quick update, Dr. Carlos Blanco, who's on the meeting roster, will not be able to participate today due to a personal emergency, and Dr. Floyd is on his way.

Dr. Bateman?

DR. BATEMAN: 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 is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. 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 public 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 breaks or lunch. Thank you.

Dr. Seo will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Bateman.

The Food and Drug Administration is convening today's Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees, or SGEs, or regular

federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government

may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interests of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of the findings of the completed extended-release/ long-acting opioid analgesic postmarketing requirements 3033-1 and 3033-2. The link to the release and reissue letter can be found at https://www.fda.gov/media/95546/download. These postmarketing requirements are prospective for 3033-1 and retrospective for 3033-2 epidemiologic studies that examine the serious risks and predictors of misuse, abuse, addiction, and fatal

and non-fatal opioid overdose in patients with long-term use of opioid analgesics for management of chronic pain, including patients prescribed extended-release/long-acting opioid analgesics. This is a particular matters meeting during which specific matters related to extended-release/ long-acting opioid analgesic postmarketing requirements will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the products at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jeffrey Reich is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Reich's role at

this meeting is to represent industry in general and not any particular company. Dr. Reich is employed by Sparian Biosciences.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firms at issue.

Thank you, and I'll return the floor to Dr. Bateman.

DR. BATEMAN: Thank you.

We will now proceed with the FDA opening remarks followed by the regulatory background, starting with Dr. Leah Crisafi.

FDA Opening Remarks - Leah Crisafi

CDR CRISAFI: Good morning, Dr. Bateman,

members of the committee, and invited guests. My name is Leah Crisafi, and I am the Director of the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Office of New Drugs. Today, we will be discussing the results of two postmarketing requirements, also known as PMRs, that were issued to NDA holders of extended-release/long-acting opioids. These PMRs are epidemiologic studies to examine the risks associated with long-term use of opioid analgesics for the management of chronic pain, and they included patients prescribed extended-release/ long-acting formulations.

When these PMRs were issued in 2013, we didn't have good data on how common misuse, abuse, addiction, and overdose were in the context of long-term use of opioid analgesics or the main risk factors for these outcomes. Issuance of these PMRs was among many actions taken by FDA and others to understand and respond to a public health crisis that has taken many lives over the last two decades.

During the next few minutes, I would like to briefly review the agenda for today's meeting. First, Dr. Jana McAninch from CDER's Office of Surveillance and Epidemiology will present the regulatory background and evolving opioid landscape. She will be followed by presentations from the Opioid PMR Consortium, also referred to as OPC. There will then be an opportunity for members of the committee to ask clarifying questions, followed by a short break.

After the break, Dr. Hana Lee from CDER's Office of Biostatistics will present on the methodological and statistical considerations for the studies, and Dr. Cynthia Kornegay, also from the Office of Surveillance and Epidemiology, will present the key study findings and FDA's interpretation of those findings. There will be another opportunity for clarifying questions, then we will break for lunch and return for the open public hearing, after which Dr. McAninch will give the charge to the committee.

As you listen to the presentations, I would

like you to keep in mind the topics for consideration that were presented in the briefing document and are the following: how these studies further extend our understanding of the risks of long-term opioid analgesic use; the relevance and implications of the study findings considering the evolving nature of the opioid crisis and prescribing landscape; and whether there are any novel findings FDA should communicate to healthcare professionals, patients, and members of the public.

I would like to thank the committee members for sharing your expertise and your insights with us today. I would also like to thank the members of the public for providing comments. We will take everything discussed today into consideration as we continue to work on these issues.

I will now turn it over to Dr. McAninch.

FDA Remarks - Jana McAninch

DR. McANINCH: Good morning. It's nice to see everyone here today. I'm Jana McAninch, Associate Director for Public Health Initiatives in the Office of Surveillance and Epidemiology here in

CDER. Before we get started with the scientific presentations, I will provide some regulatory background and information on the evolving opioid landscape in the United States. Here's the outline of my presentation.

FDA has convened this joint advisory committee meeting to have a public, transparent discussion and to solicit input on the completed postmarketing requirement, or PMR, Studies 3033-1 and 2. These are epidemiologic studies that examine the risks of and potential risk factors for misuse, abuse, addiction, and fatal and non-fatal opioid-involved overdose in patients with long-term use of opioid analgesics.

For regulatory and labeling purposes, FDA defines misuse as the intentional use, for therapeutic purposes, of a drug in a manner other than which it was prescribed or by an individual for whom it was not prescribed. Labeling defines abuse as the intentional, non-therapeutic use of a drug for its desirable psychological or physiological effects. And addiction is defined in

FDA-approved labels as a cluster of behavioral, cognitive, and physiologic phenomena that may include a strong desire to take the drug, difficulties in controlling use, and possible tolerance or physical dependence.

We recognize that certain language may perpetuate stigma toward individuals who use substances or who have substance use disorders. We note that the abuse-related terminology used in these studies and in FDA materials is based on statutory and regulatory usage of these terms. FDA is committed to reducing stigma and ensuring access to evidence-based treatment for individuals with substance use disorders.

Next, I'll discuss some background and regulatory history of the extended-release/long-acting, or ER/LA, opioid analgesic PMRs.

Beginning in the early 1990s, the medical community began prescribing opioid analgesics more widely for the management of both acute and chronic non-cancer pain. Most prescribing was for immediate-release/short-acting, or IR/SA, products,

but there was also emerging use of several more recently approved ER/LA products. These products were generally available in higher dosage strengths than were the IR/SA products, and on average, they were prescribed at higher daily doses. On average, ER/LA products also had more milligram equivalents of opioid per prescription compared to the IR/SA products.

In the late 1990s and early 2000s, FDA began receiving and analyzing increasing numbers of reports of misuse and abuse of prescription opioids; meanwhile, public health officials were seeing an alarming rise in fatal overdoses involving these drugs. Using regulatory authorities available at the time, FDA responded through actions such as strengthening warnings in labels and issuing warning letters, citing manufacturers' violative promotional materials.

In 2007, Congress passed the Food and Drug Administration Amendments Act, or FDAAA, giving FDA significant new safety authorities. Among these was that FDA could now require safety-related

postmarketing studies. Under FDAAA, postmarketing studies could be required to assess unknown serious risk, assess signals of serious risk, or identify an unexpected serious risk when available data indicate such a potential. FDAAA also authorized FDA to require safety-related labeling changes based on new safety information that comes to light postmarket and to require that manufacturers implement risk evaluation and mitigation strategies, or REMS, when necessary to ensure that the benefits of a medication outweigh its risks.

In July 2012, FDA approved the ER/LA Opioid Analgesic REMS program, which included a requirement for manufacturers to make available to prescribers, for free or nominal cost, training programs on safe prescribing of ER/LA opioid analgesics following an FDA approved blueprint.

The same year, FDA convened a public scientific workshop with NIH and received other stakeholder input that raised concerns about knowledge gaps related to treatment of chronic non-cancer pain, in particular about the safety of

longer duration and higher dose use of opioid analgesics. FDA conducted a literature review and concluded that more information was needed on the serious risks of misuse, abuse, addiction, overdose, and death with long-term use of opioid analgesics for chronic pain. The review also found an association between higher daily opioid doses and the risk of overdose.

In September 2013, FDA issued five PMRs to all ER/LA opioid analgesic application holders to assess the risks associated with long-term use of opioid analgesics for the management of chronic pain among patients using ER/LA opioid analgesics. The overarching goal was to provide quantitative estimates and to identify potential risk factors for these known serious risks.

Acknowledging that all opioid analgesics carried these risks, FDA was concerned about potentially heightened risks for ER/LA opioid analgesics due to the higher dosage strengths available and their being used more at higher daily doses. The ER/LA opioid analgesic companies were

encouraged to work together to fulfill these PMRs, and they formed the Opioid PMR Consortium, or OPC, to collaborate on conducting the required studies.

Now, I'll provide a high-level overview of the ER/LA opioid analgesic PMRs.

The 2013 PMRs specified that the companies conduct one or more studies to provide quantitative estimates and evaluate risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

Three additional PMRs required that the companies conduct studies to develop and validate outcome measures to inform the design and analysis of the main observational PMR. The fifth PMR was for a clinical trial to assess the risk of hyperalgesia in this patient population. This trial is not a topic of discussion at this advisory committee meeting.

To provide guidance and oversight, FDA formed a steering committee comprised of senior

leadership within CDER. Additionally, FDA convened a public scientific meeting to discuss design considerations for the PMR studies. At the meeting, a panel of scientific experts provided input on study concepts and timelines that were proposed by the OPC.

It was also determined that multiple separate investigations would be necessary to fulfill several of the PMRs; therefore, in 2016, the five original PMRs were released and reissued as 11 separate PMRs, which allowed them to be tracked and fulfilled individually. These included two main observational studies, now 3033-1 and 2, as well as eight supportive studies. The individual study protocols were refined by the OPC and approved by FDA scientific review teams.

The first main observational PMR, 3033-1, required a prospective observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics. It

also specified that the study should examine potential risk factors such as product and formulation, dose and duration, and other clinical, demographic and genetic factors.

PMR 3033-2 required a retrospective observational study using patient health records, insurance claims, and death records to measure the incidence and predictors of opioid-related overdose and death, and abuse and addiction. Again, the PMR specified that the study must estimate the incidence of these outcomes and identify potential risk factors.

Although the original focus of these studies was on patients receiving ER/LA opioid analgesics, both of the PMR studies were later broadened to include patients with any new long-term use of Schedule II opioid analgesics for chronic pain.

The first two supportive PMRs, 3033-3 and 4, were for studies to develop and validate a self-reported survey instrument to identify opioid misuse and abuse in patients receiving opioid analgesics for pain. PMR 3033-5 was for a study to

develop and evaluate in a similar population a diagnostic interview tool for what was referred to then as prescription opioid substance use disorder and addiction. Historically, diagnostic criteria were designed in an era when most harmful opioid use involved heroin, and diagnostic interview tools based on these criteria were not evaluated in patients prescribed opioids chronically for pain. More detail on this is provided in later presentations.

PMRs 3033-6 and 7 were for studies to develop and evaluate medical code-based algorithms to identify opioid-related overdose, abuse, and addiction. And finally, PMRs 3033-8 through 10 were to study how doctor and pharmacy shopping were associated with misuse, abuse, and addiction, and to evaluate algorithms based on these data as possible outcome measures for the main observational PMRs.

Instruments and outcome measures developed and validated in PMRs 3033-3, 4, and 5 were used in PMR 3033-1 to ascertain misuse, abuse, and

addiction, which was operationalized as moderate-to-severe opioid use disorder. The code-based algorithm developed and validated in PMR 3033-6 was used in PMR 3033-2 to ascertain opioid-involved fatal and non-fatal overdoses.

PMR 3033-7 found that coded medical data such as from administrative claims had unacceptably low sensitivity for identifying abuse and addiction and were not appropriate for use in the medical code-based retrospective study, 3033-2; therefore, it was determined that these outcomes would be studied only in PMR 3033-1, the prospective study.

PMRs 3033-8 through 10 found that higher levels of doctor and pharmacy shopping were associated with misuse, abuse, and addiction, but algorithms using doctor and pharmacy shopping data were found to misclassify a high proportion of patients and were not used in the main observational studies.

Here, I'll shift gears a bit and spend a few minutes providing a brief overview of the evolving opioid landscape, recognizing that the environment

in which opioids are prescribed and used has changed considerably since these PMRs were issued.

There have been myriad efforts to stem the tide of overdoses and other opioid-related harms. Some examples include FDA regulatory actions such as REMS and labeling changes, which I'll review shortly, as well as others like hydrocodone rescheduling recommendations, removal of reformulated OPANA ER due to abuse-related risks, and approval of non-prescription naloxone.

Other federal efforts are too numerous to name, but notable examples include CDC's 2016 Clinical Practice Guidelines on Opioid Prescribing and the updated guidelines in 2022, as well as many programs to expand access to evidence-based treatment of opioid use disorder.

Many states passed laws on opioid prescribing, stood up prescription drug monitoring programs, and mandated opioid-related education for providers. Health systems and insurance companies instituted opioid stewardship policies to reduce the volume and doses of opioid analgesic

prescribing. DEA and other law enforcement agencies sought to reduce drug diversion and to shut down rogue clinics and pharmacies.

Much of the focus of these efforts, especially early on, was on reducing inappropriate or unnecessary prescribing of opioids, often by limiting the recommended or allowed quantity or daily dose. Some recommendations were misapplied and enforced as hard limits, resulting in patient harms from abrupt tapering or discontinuation of opioids, and even dismissal of patients from provider practices.

Together, these and other efforts resulted in sharp reductions in opioid analgesic prescribing, beginning around 2013. The figure on the left shows the estimated opioid analgesic prescriptions dispensed annually in the United States from 1992 to 2023. Opioid analgesic prescriptions increased from 112 million dispensed in 1992 to a peak of 263 million in 2012, then declining to 127 million by 2023. IR/SA opioid analgesics, shown by the solid line, comprised the

majority of these prescriptions.

The figure on the right shows these same data adjusted for changes in the U.S. population size. The number of dispensed prescriptions for opioid analgesics increased from 44 per 100 U.S. residents in 1992 to a peak of 84 in 2010, before declining to 38 prescriptions for 100 residents in 2023. Again, prescriptions for ER/LA products comprised a small proportion of the overall dispensing. I note that these numbers do not represent the percentage of U.S. residents who received opioid analgesics, as patients could receive multiple prescriptions in a calendar year.

This figure shows trends in total opioid dose as morphine milligram equivalents, or MMEs, dispensed annually. ER/LA products accounted for a substantial proportion of the total MMEs despite their much lower prescription dispensing counts shown on the previous slide. ER/LA products also drove much, but not all, of the increase in MMEs dispensed up until about 2011 when total MMEs for ER/LAs began to decline. The peak in total IR/SA

MMEs followed a couple years later, and by 2023, total dispensing of opioid analgesic MMEs had returned to levels that were similar to those seen in the early 2000s.

As opioid analgesic prescribing fell, as shown here in the blue bars, opioid-involved overdose deaths, of course, continued to rise, with the sharpest increases attributable to illicit opioids, first heroin, shown by the blue dashed line, then synthetic opioids, primarily illicitly manufactured fentanyl, shown in the dark orange.

In 2013, when the PMRs were issued and the number of opioid analgesic prescriptions dispensed was near its peak, there were about 14,000 prescription opioid-involved overdose deaths shown in fuchsia. Most of these had no co-involvement of heroin or non-methadone synthetic opioids. This line is in yellow. Since then, the total number of prescription opioid-involved overdose deaths has remained fairly stable, but as of 2023, fewer than half of these occurred without co-involvement of heroin or synthetic opioids, and the vast majority

of opioid overdose deaths involve synthetic opioids, primarily illicitly manufactured fentanyl.

This figure shows the most recent available data from CDC's Provisional Drug Overdose Death Dashboard, showing a rolling 12-month total of drug overdose deaths from January 2015 through October 2024. What is striking here is the dramatic downturn in opioid overdose deaths, driven primarily by the decline in deaths involving synthetic opioids other than methadone, mostly illicit fentanyl.

Prescription opioid-involved deaths other than methadone declined modestly during this period, as shown by the green line. Overall, opioid overdose fatalities have come down to levels similar to those seen prior to the COVID-19 pandemic, but are still roughly twice as high as a decade ago.

On the next two slides, I'll highlight some of the regulatory actions FDA has taken related to the risks being assessed in the ER/LA opioid analgesic PMR studies. I'll focus on two of our

primary regulatory tools for managing risk in the postmarketing setting, REMS and labeling.

As noted earlier, in 2012, FDA approved the ER/LA opioid analgesic REMS, which was centered around a requirement that manufacturers make trainings available at no or nominal cost with content based on an FDA-approved blueprint. The blueprint focused primarily on safety of ER/LA opioid analgesic prescribing.

In 2016, FDA convened an advisory committee meeting to discuss this REMS, and FDA determined that the REMS must be modified to include all opioid analgesics intended for outpatient use to broaden the focus of the educational program, to target all members of the healthcare team, and to include more information on evaluation and management of pain, including use of non-opioid options, and a primer on opioid use disorder. In 2024, FDA approved a REMS modification to encourage safe disposal of leftover opioids by requiring opioid analgesic companies to make prepaid mail-back envelopes available to pharmacies for

distribution to patients receiving opioids.

This slide shows a high-level summary of major opioid analgesic safety labeling changes since the PMRs were issued. I'm not going to go through all of these in detail, but the timeline provides some examples of how the agency has used its authorities under FDAAA to update and strengthen information on opioid analgesic prescribing and risks based on new safety information.

Next, I'll provide a high-level walkthrough of current FDA-approved opioid analgesic labeling relevant to the risks evaluated in these PMR studies.

This slide shows the current boxed warning language required for opioid analgesic products, highlighting the risks of addiction, abuse, misuse, and potentially fatal respiratory depression that may occur, especially during titration or following a dosage increase. The boxed warning also describes risks from concomitant use of benzodiazepines or other CNS depressants, examples

of which are provided in other parts of the label. These risks, among others, are all described more fully in other sections of labeling as well.

This slide shows excerpts from the indications and limitations of use. The IR/SA label states that the medication is indicated for management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, either because they have not been, or are not expected to be, tolerated, or because they have not provided, or are not expected to provide, adequate analgesia.

The ER/LA labels state that the medication is indicated for the management of severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate, also noting that the medication is not intended as a PRN analgesic. It cautions that because of greater risks of overdose and death with ER/LA formulations, the medication should be reserved for use in patients for whom alternative treatment

options, including non-opioids or immediate-release opioids, are ineffective, not tolerated, or would be otherwise inadequate to manage pain.

In the dosage and administration section, opioid analgesic labels advise using the lowest effective dosage for the shortest duration of time, consistent with individual patient treatment goals. It advises that because the risk of overdose increases as opioid doses increase, titration to higher doses should be reserved for patients in whom lower doses are ineffective and in whom the expected benefits of using a higher dose clearly outweighs the substantial risks. It also suggests that many acute pain conditions require no more than a few days of an opioid analgesic and that respiratory depression can occur at any time, but especially when initiating and following dosage increases.

The warnings and precautions subsection on addiction, abuse, and misuse notes that addiction can occur in patients appropriately prescribed opioid analgesics and at recommended dosages, as

well as if misused or abused. It notes that these risks are increased in patients with a personal or family history of substance abuse or mental illness, but that the potential for these risks should not prevent the proper management of pain.

Current labeling also advises that to avoid serious harms, providers should avoid abrupt discontinuation of opioids in patients who may be physically dependent. It emphasizes gradual, individualized dose reductions, as well as the need for ongoing care, shared decision making, and other supports as needed during the tapering process.

We look forward to a robust discussion of the findings and implications of these PMR studies this afternoon. Before closing, I'll briefly review the questions that we'll be asking the committee.

We will be asking committee members to discuss your interpretation of the key findings, both the risk estimates and the analyses of potential risk factors, considering such things as study strengths and limitations; different outcome

definitions; generalizability and relevance to the current opioid landscape; and consistency with other available evidence in your clinical or personal experience. We would also like the committee members to discuss whether there are any important novel findings from these PMR studies that FDA should communicate to healthcare providers, patients, and others. Thank you for your attention.

DR. SEO: Hi. This is Jessica Seo. Apologies for the interruption, Dr. Bateman. I'd just like to take a moment to welcome Dr. Floyd and ask if you could please state your name into the record. Thank you.

DR. FLOYD: Hi. Sorry I was late this morning. James Floyd, Professor of Medicine and Epidemiology at the University of Washington.

DR. SEO: Thank you, and back to you, Dr. Bateman.

DR. BATEMAN: Alright. Thank you.

Thank you, Dr. Crisafi and Dr. McAninch, for your presentations.

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

For this reason, FDA encourages all participants, including industry's non-employee presenters, to advise the committee of any financial relationship that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation 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 presentation, it will not preclude you from speaking.

We will now proceed with the presentation from the Opioid Postmarketing Requirements Consortium.

Industry Presentation - Alexander Walker

DR. WALKER: Good morning, members of the advisory committee and FDA staff. My name is Alec Walker. I am an adjunct professor at Harvard, where I was formerly Professor and Chair of Epidemiology.

The OPC has asked me to coordinate this presentation, which will cover a series of postmarketing studies requested by the FDA to examine the safety of extended-release and long-acting opioids. I readily accepted the OPC suggestion because of my long connection with the design and development of the studies intended to fulfill the FDA's PMRs.

I was formerly a principal of the research firm WHISCON, advising the OPC on study options for postmarketing requirements. Until I retired from WHISCON three years ago, I headed the coordinating center for a large insurance-based cohort study,

which we will discuss shortly as Study 2. I was also the lead investigator for doctor and pharmacy shopping studies, which won't be part of today's presentation.

Let me start with an overview of the PMR studies, and this material repeats some of what you've seen before, and I don't believe any of it's in conflict with what the FDA has presented.

Here are the 11 PMRs that have been issued by the FDA to ER/LA sponsors. The first 10 are observational studies, and the last, at the bottom, is a clinical trial. Among the observational studies, Studies 1 and 2 are the focus of today's presentations. The studies assess the incidence and risk factors for the outcomes of opioid misuse, abuse, addiction, overdose, and death.

Studies 3, 4, and 5 developed and validated measures of misuse, abuse, and addiction for Study 1. Studies 6 and 7 developed and validated methods to identify study outcomes in existing databases. The algorithm for overdose and death was used in Study 2. Studies 8, 9, and 10 defined

and validated doctor and pharmacy shopping as proxy indicators for misuse, abuse, and addiction. They were not incorporated in Studies 1 and 2, so they are not part of today's discussion. Study 11 is the clinical trial. It is also not part of today's discussion, but it was a subject of an advisory committee in April 2023.

Across the development of the PMRs, the OPC partnered with the experienced investigators at independent research institutions to design and conduct the studies, which reflected the input from public hearings and the FDA. The institutions listed here participated in the design, led the data collection, and performed analyses. The institutions hold the study data, and the study investigators will present the results.

The PMRs for Studies 1 and 2 had two overarching objectives: first, to estimate the incidence of misuse, abuse, addiction, overdose, and death associated with the long-term use of ER/LA opioids in patients with chronic pain, and second, to evaluate and quantify risk factors

associated with these outcomes. Note that these objectives are descriptive. Also note that risks, or misuse, abuse, overdose, and death, are described in the boxed warning and other sections of the current labeling, as we heard. The labeling does not provide any quantitative estimates, which is a gap that the successful completion of the PMRs might fill. The heart of PMR 3033 is in these two complementary cohort cities.

Study 1 consisted of a year's in-person follow-up of new initiators of ER/LAs or patients who newly qualified as receiving long-term opioid therapy. To learn about effects beyond one year, the investigators conducted a cross-sectional study of persons with existing long-term opioid use. Study 1 employed measures of prescription opioid abuse, misuse, and addiction that had been refined and validated in Studies 3, 4, and 5.

Study 2 was a large, retrospective, new user cohort study and administrative data. The purpose was to characterize the risks of the comparatively infrequent but severe outcomes of overdose and

death in persons who newly qualified as long-term opioid users. Where Study 1 inferred late effects of the cross-sectional study of a population distinct from the initiating cohort, the automated data of Study 2 permitted long-term observation of the same group for the time of first qualification for as long as members stayed in their insurance plans.

In place of patient questioning, Study 2's outcomes used insurance claims interpreted using the results of Study 6, which provided a chart-validated set of ICD codes for identifying opioid overdose. Study 7 had been intended to produce algorithms for a combined outcome of abuse and addiction using ICD codes. The validation found that the best performing algorithms in health insurance data lacked the specificity to identify these outcomes reliably in chronic use populations. With the FDA's agreement, the investigators and the OPC dropped abuse and addiction as an endpoint in Study 2.

Here we have a chronology of Studies 1

through 7. The study protocols were adapted over time based on scientific guidance from the FDA at collaborative feedback sessions that occurred every 3 months through the conduct of the studies. Studies 3, 4, and 5 preceded Study 1, which they supported by validating the instruments used to measure prescription opioid abuse, misuse, and addiction. Data collection for Study 1 began in 2017 and continued through 2021.

Studies 6 and 7 were needed for the completion of Study 2. Study 6 and 7 both began in 2014 with final report submissions in 2019 and 2018, respectively. Study 2 itself began in 2018 after a year of collaborative protocol development and database preparation. Outcome definitions were folded in as they became available. The retrospective data ran from 2006 through 2017.

The OPC shared interim results for all the studies with the FDA as provided by the investigators. As it received findings, the FDA issued information requests, which have been ongoing. The procedures for gathering information

for the responses were incorporated as protocol modifications, included in stand-alone reports to the agency. The material in this morning's presentations and the OPC's briefing document integrates the responses to the information requests and the protocol specified findings.

In summary, Studies 1 and 2 provided risk estimates associated with long-term opioid consumption and quantified the associated risk factors. Study 1 found one-year cumulative risks for opioid adverse outcomes. Looking ahead, these were misuse in greater than 20 percent; abuse in about 9 percent; and addiction in 1 and a half percent. These one-year outcome risks in patients with new use resemble the prevalences observed in the study of patients with established longer term use. Among the many prespecified risk factors assessed, prior substance use disorders, SUDs, were the most consistent correlates of outcomes.

Study 2 added an estimate of the degree of risk for opioid overdose and opioid-related death, which averaged 2.1 percent after 5 years across the

four study sites. The study further identified baseline dose, prior SUDs, and mental health disorders as the strongest independent risk factors for OOD.

With this background in mind, here is the agenda for the remainder of the presentation. Dr. Yarborough, Senior Investigator at Kaiser Permanente Northwest and Associate Professor at the Bernard J. Tyson Kaiser Permanente School of Medicine, will review the design and results from Study 1. Dr. Seeger, Vice President for Epidemiology at RTI Health Solutions and Adjunct Assistant Professor at the Harvard T.H. Chan School of Public Health, will review Study 2's design and results. I will return to conclude the presentation and begin the question and answer period. All outside experts have been compensated for their time and travel to today's meeting.

With this high-level view in mind, let's turn to the study principles for details. We'll begin with Dr. Yarborough, who will lay out Study 1.

Industry Presentation - Bobbi Jo Yarborough

DR. YARBOROUGH: Thank you, Dr. Walker.

Good morning. I'm Bobbi Jo Yarborough. I'm a clinical psychologist and have conducted health services research at the Kaiser Permanente Northwest Center for Health Research for the past 25 years. My research focuses on centering the experiences of patients, families, and the clinicians who support them to improve care and outcomes for individuals living with mental health and substance use disorders.

Over the last decade, I've studied risks associated with prescription opioid use among patients with chronic pain, including the outcomes of interest in Studies 1 and 2. I've also studied outcomes associated with opioid discontinuation and tapering, including suicide. I'm the principal investigator for Study 1, and today I'll take you through the Study 1 design and results.

As a reminder, Study 1 was intended, first, to estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid

analgesics for chronic pain and to examine the effects of several demographic, pharmacy, and clinical variables; and second, to evaluate and quantify additional risk factors, many that were prespecified in the PMR letter, including demographic, psychosocial, behavioral, medical, and genetic factors.

I'll talk later about how the variables in the PMR were operationalized in the study, but first I want to make sure we're appropriately situated in the study design.

Importantly, Study 1 is not a prospective clinical trial, so when I talk about risk factors here, I'm not talking about predictors that we can then evaluate as part of a causal relationship. The request from FDA was to examine risk factors associated with the study outcomes. I want to make sure it's clear that Study 1 is an observational study.

Now, in addition to estimating incidence among patients who were newly qualified for long-term therapy, we also took advantage of the

opportunity to estimate prevalence among patients who'd been receiving long-term opioid therapy for at least a year. We did this in a cross-sectional study. It was also observational. I'll describe the study sites next.

All participants from Study 1 were recruited from well-established health systems with comprehensive patient management systems, including electronic health records and claims databases. Seven sites were members of the Healthcare System Research Network or HCSRN. These are indicated in the map in blue.

These health systems provide medical and behavioral health care through health system owned clinics and hospitals and/or by contracting out services, so they have a mix of business and care delivery models. Within the HCSRN, specific sites were chosen for the demographic or socioeconomic diversity of their population served. This includes patients with and without insurance and some in rural areas.

An advantage of these sites belonging to the

HCSRN is that they all participate in a common data model, the virtual data warehouse or VDW. The VDW organizes health records and claims data in the same manner across member sites, making multisite research projects like this one more efficient. If we were to conduct this study at various health systems that all had their data organized in individual ways, we would have to spend considerable time finding data sources and making sure that data from all the sites was complete and comparable to one another.

Over the past three decades, HCSRN sites have worked to harmonize all of their data sources in the common data model so that they look like what you see in this figure. The data is routinely cleaned and standardized. This means that we can write one program, or set of programs, and distribute it to participating HCSRN sites, and they can run it with minimal site-specific modification. This makes data collection more accurate, more complete, and quicker than if we were having to write individual programs at each

site.

The point in sharing all of this detail is to help you understand that having these seven sites really made this study and the required study timeline feasible. But we also wanted representation of individuals from very different types of care delivery systems and settings outside the HCSRN, so we also included a U.S. Department of Veterans Affairs site, indicated in the map in yellow; and two organizations were practices participating with the Clinical Directors Network, a primary care practice-based research network. These are indicated in green.

The VA site has a long history of conducting pharmacoepidemiologic research, including research related to opioids. Their potentially eligible population included older African American and Hispanic individuals. The two practice-based research network sites also served populations underrepresented in research and/or low income, minority, and underserved communities.

These additional recruitment settings were

deliberately selected to reflect the diverse population of chronic pain patients prescribed long-term opioids in the United States, while also allowing for adequate and quality data capture. As far as prescribing practices, the states included didn't have the highest or lowest rates of opioid prescribing, but they were illustrative of what was happening in terms of prescribing across the U.S. at the time of study enrollment.

By comparing our study sites to state and county prescribing rates for 2019 from CDC's National Center for Injury Prevention and Control, we were able to confirm that we had included sites with the full range of prescribing rates. For example, in 2019, Washington State had an opioid dispensing rate of 42.8 per 100 persons, and Oregon's rate was 49.2. These rates fall in the moderate range, where 40 percent of states also fell at that time. California was lower at 31 per 100 persons, but when we looked at the county level, the areas served by the participating health systems spanned areas with low, moderate, and high

rates. Michigan State rate was much higher at 58.1, with counties included in the study ranging from 45.2 to 73.5.

For comparison, West Virginia had a rate of 59.6. The states with the highest rates, Alabama and Arkansas, had rates above 80, and while we did not have sites in those states, we did have a Florida site representing Alachua County, which had a rate of 100.3 opioids dispensed per 100 persons.

So we're confident that even though we were not able to include states in the middle of the U.S., some of which you may know would later become known for higher overdose rates, we did include sites with prescribing rates that were similar or even higher than those regions, and we included states with some of the largest increases in overdose rates, making these data clinically informative, even in today's prescribing landscape.

When we were recruiting sites, belonging to the HCSRN was a distinct advantage for the reasons I've already mentioned. Potential sites also needed to have an available interested investigator

with expertise in opioid-related research, pharmacoepidemiology, chronic pain, or substance use disorders. Sites needed to be able to recruit a substantial number of patients prescribed opioids and be able to link to their administrative data.

We sought out sites with efficient survey research teams. We were attempting to fill geographic, including rural and socioeconomic, gaps, including sites with greater Medicaid representation. We explored sites in the Midwest and southern regions of the U.S., including sites in Colorado, Georgia, and Texas. But ultimately these sites were unable to be included because we could not identify an investigator with availability and the required expertise. Together, the HCSRN sites, VA, and PBRN, were selected to maximize efficiency, timeliness, and generalizability.

Why am I spending so much time talking about site selection? I wanted to be clear that this was more than a convenient sample of HCSRN sites and a few others. We understood as we were designing

this study that it was going to be the largest U.S. study measuring incidence of these important outcomes, and it had the potential to be really important to the field, so we took site selection very seriously.

As we were making decisions, we were balancing aspects of internal and external validity. We were asking ourselves how do we assure that we're getting accurate and complete data, particularly pharmacy data, but also important covariates that would come from the health records and claims databases?

How do we recruit sites that are representative of prescribing practices across the country? How can we increase the potential generalizability of our results by including diverse participants who represent the characteristics of patients with chronic pain and new long-term opioid use? There were necessary trade-offs, and we worked with the sites and the FDA as we made decisions.

So with that background in mind, let me

first review the 12-month prospective study.

The prospective study ultimately included two cohorts of patients, ER/LA initiators and long-term opioid therapy initiators or LtOT initiators. Patients were eligible for the ER/LA initiators cohort if they had no ER/LA use within the 6 months prior to their first ER/LA prescription, and then they received at least 28 continuous days of ER/LA opioids with an additional prescription beyond the 28 days for continuation of ER/LA opioid use.

After discussion with an agreement from the FDA, the LtOT cohort was added to the protocol in response to declining ER/LA opioid prescribing during the study. Patients were eligible for the LtOT cohort if after at least 6 months of no ER/LA or Schedule II IR/SA, they received ER/LA and/or IR/SA opioids for at least 70 of 90 days. Because IR/SA products are often prescribed prior to ER/LA products, patients newly initiating ER/LAs in the prospective cohort could also qualify at study entry as new initiators of LtOT from their IR/SA

opioid use prior to initiating ER/LA therapy.

In the event that a subject qualified for both cohorts at sample selection, priority was given to the ER/LA initiators cohort. This was partly because the PMR letter was issued to ER/LA manufacturers and partly because we knew ER/LA use was declining and we wanted to increase that cohort. We were not concerned about not having enough participants qualifying for the LtOT cohort.

Potential participants had to be English-speaking adults between the ages of 18 to 79 who received a qualifying opioid therapy order or dispense and were still taking it at the baseline interview. They also had to be enrolled in their health plan or regularly receiving care in the past year. This was important so that we could collect the baseline covariate data without any concern for missing data.

Additionally, they had to be capable of consenting and completing the study measures. We did not conduct a formal mental status exam, but potential participants were excluded if during any

of the prescreening they had apparent cognitive impairment sufficient to interfere with their ability to provide informed consent or participate in the interviews. Other exclusion criteria were kept to what was minimally necessary for outcome ascertainment.

Potential participants were excluded if they knew they would not be available for the full 12-month follow-up period; if they were receiving hospice care or had a terminal illness diagnosis; had a documented opioid use disorder; or were receiving opioid use disorder treatment.

Study 3033-1 evaluated multiple potential risk factors, approximately 60, that were thought to influence the relative risk for prescription opioid misuse, abuse, or opioid use disorder. Some of these risk factors, on the left side here, were measured using health records or insurance claims data. Patient reported data such as current or past mood and substance use disorders, listed on the right, were collected by interview or self-reported participant survey. The last two

variables shown on the right were derived from an optional saliva sample. All of these were evaluated as independent or multivariate risk factors.

Participation in the prospective study involved a baseline assessment consisting of an in-person or telephone interview and self- or telephone-administered web-based questionnaires. Follow-up assessments and other surveys were conducted at months 3, 6, and 9. Month 12 included a final assessment via telephone interview and a self- or telephone-administered web-based questionnaire. All study materials and the protocol were approved by the Kaiser Permanente Northwest Institutional Review Board.

The primary outcomes of the prospective study were the incidence of prescription opioid misuse, prescription opioid abuse, and addiction, which was assessed as opioid use disorder or OUD. This outcome included both pain-adjusted opioid use disorder by prescription opioids and heroin use disorder. All of these outcomes were assessed

among all participants. Secondary outcomes included an alternative definition of DSM-5 OUD.

Prescription opioid misuse and abuse were determined using the Prescription Opioid Misuse and Abuse Questionnaire, or POMAQ, with modifications for Study 1. The POMAQ assesses the intent and frequency of misuse- or abuse-related behaviors. Addiction was determined using the Psychiatric Research Interview for Substance and Mental Disorders DSM-5 Opioid Version, or PRISM-5-OP, to assess addiction to opioid analgesics among patients prescribed opioids to treat chronic pain. Both the POMAQ and the PRISM-5-OP are instruments that were validated in Studies 3, 4, and 5.

To validate the POMAQ instrument, Study 3 was a qualitative, cognitive interview study to ensure that the content and questions of the draft POMAQ were understandable to patients with chronic pain and relevant to their experiences. Overall, the POMAQ demonstrated content validity and was considered ready for quantitative validation among a larger cohort of patients with chronic pain.

Study 4 was then employed to evaluate the validity and reproducibility of the POMAQ among patients with chronic pain who were on long-term prescription opioids. The POMAQ demonstrated excellent construct validity and test-retest reliability, and therefore was determined to be a valid, reproducible tool to assess the presence of misuse and abuse behaviors in Study 1.

The item responses recorded here reflect misuse intentionality. Two of the responses shown at the bottom of the second two columns, to relax or feel mellow and to unwind after a hard day, were originally attributed to the abuse outcome but were moved to misuse after development of the clinical scoring algorithm. The responses recorded here reflect the abuse intentionality.

Let me move now to the design of Study 5. Study 5 was an observational study to assess the validity of the PRISM-5-OP instrument as a standardized measure of OUD to prescription opioids. This study was needed, as there was little evidence available on how the DSM-5

substance use disorder criteria applied to opioid use disorder, specifically regarding prescription opioids among patients with chronic pain.

Study 5 evaluated 606 patients from pain clinics and inpatient substance use treatment who received at least a 30-day opioid prescription for chronic pain. The goal was to investigate whether a pain-adjusted measure of the DSM-5 criteria improved validity over DSM-5 criteria for opioid use disorder that did not include pain adjustments. Pain adjusted in this context does not refer to statistical adjustment, but rather an adjustment to the DSM-5 criteria themselves. The results supported reliability and validity of the pain-adjusted measures.

Next, I'll review the outcome definitions we used in Study 1

Misuse was defined as the intentional use of a drug for therapeutic purpose to reduce an aversive symptom, or state in a manner that is inappropriately outside label directions, or in a manner other than prescribed by a healthcare

practitioner. This definition includes patients using a drug for a condition different from that which the drug was prescribed, patients taking more drugs than prescribed, or patients using a drug at different dosing intervals.

Abuse was defined as the intentional use of a drug for a non-therapeutic purpose, repeatedly or sporadically, for the purpose of achieving a positive psychological or physical effect. An addiction was determined using the validated Study 5 measure of pain-adjusted OUD when four or more criteria were met while the opioid was taken other than as prescribed and for reasons other than pain relief, or when participants met two or more DSM-5 criteria for opioid use disorder involving heroin.

Let's return to the results of Study 1. A total of 9,601 potential participants were mailed a recruitment letter. Of those who received a letter, more than 6,000 were determined ineligible or did not complete the screening. Common reasons for refusal were lack of interest in participating,

being too busy, and the study commitment being too great.

Of the 3,498 eligible participants who remained and consented to participate, 2,222 were included in the analytic data set, 978 were classified as ER/LA initiators, and 1,244 were classified as long-term opioid therapy initiators, a reminder that these classifications were made on the basis of their qualifying pharmacy prescriptions that made them eligible for the study. Again, participants who met criteria for both cohorts were classified as ER/LA initiators.

Here are select patient demographics for the prospective study. More than 70 percent of patients were greater than age 50 years in either cohort, and just over half were female. Most patients were white, though a representative portion were African American in both cohorts. You can see that in both cohorts, IR/SA opioids are represented as the predominant opioid form at baseline.

Recall that we began recruitment in August

2017, well after opioid prescribing had already peaked. The CDC guideline for prescribing opioids had been released and ER/LA opioids were being prescribed less. Also, predominant opioid form is calculated as the opioid type with the most days' supply, and most patients have IR/SA exposure prior to ER/LA, and many continue receiving IR/SA opioids for breakthrough pain even when they begin ER/LAs, so this was not a surprising finding. Less than 10 percent had a past-year substance use disorder at baseline.

Here are the main results. These are the first robust incidence rates reported using systematic measures and transparent methodology, as the prior literature shows a range of rates, and typically these are prevalence rates, using variable measures. In the ER/LA initiators cohort, the 12-month cumulative incidence rate was 22.8 percent for prescription opioid misuse; 9.4 percent for prescription opioid abuse; and 1.4 percent for pain-adjusted OUD. We observed similar results in the long-term opioid therapy initiators cohort.

Additionally, FDA was interested in looking at incidence rates using different definitions of OUD. Here on the left, I'm showing the pain-adjusted OUD measure that you just saw on the previous slide, which was our primary outcome, as well as the DSM-5 measure on the right, which is a count of the number of DSM-5 criteria that were met where withdrawal intolerance are not rated positive if they occurred among patients who used opioids only as prescribed.

The other objective of the study was to assess risk factors for these outcomes. All analyses of the prospective study were conducted separately for the cohorts. In the interest of time, I'm only showing the ER/LA initiators' cohort, but both sets of results are available in the briefing documents.

In the next series of slides, I'm showing all statistically significant risks with an increased odds of 2 or greater or decreased odds of 0.5 or less for a given outcome. Because there were so many potential risk factors, we chose this

pragmatic threshold, as it represents factors that are either double or half the odds compared to a reference group.

To enter these models, a potential risk factor had to be significantly associated with the particular outcome at the p less than 0.1 level in univariate analyses. As a result, many of the potential risk factors will not be shown on the following slides because either they were not associated with the outcomes in the univariate analyses or they did not meet the significance thresholds for reporting here.

For prescription opioid misuse, having a substance use disorder in the past year, or having an average daily dose of greater than or equal to 120 milligrams morphine equivalent at baseline, both had odds ratios greater than 2. When looking at the outcome of prescription opioid abuse, hydromorphone use compared to oxycodone, and having a substance use disorder compared to not having a past-year substance use disorder, both increased odds of abuse in both the ER/LA and LtOT cohorts.

Here in the ER/LA cohort, those both have odds ratios greater than 5.

Receiving an other active pharmaceutical ingredient compared to oxycodone had an odds ratio of 4.1. Past 3-month prescription opioid misuse at baseline was associated with an increased risk of abuse at follow-up in both the ER/LA and LtOT cohorts. And there are a few other risk factors shown. I'll give you some time to review these.

Finally, the only factor associated with statistically significant increased odds of pain-adjusted opioid use disorder above 2.0 in the ER/LA initiators cohort was use of gabapentinoids. We did observe additional risk factors that increased odds of pain-adjusted OUD in the LtOT cohort. The variables with the largest odds ratios were all related to substance use disorder or problematic opioid use behavior at baseline.

Some factors showed a statistically significant reduction in the odds of misuse, abuse, or OUD, and here we're able to fit all of the outcomes on a single slide. Before we look at

these, I want to emphasize that odds ratios less than 1 do not mean that a given variable is protective because we're not comparing individuals who do and do not take prescription opioids. Everyone in this sample is taking prescribed opioids, so an odds ratio less than 1 means that one subgroup has lower odds of the outcome compared to the reference group.

For pain-adjusted OUD, having an Elixhauser comorbidity score of 1, or greater, or equal to 2, compared to a score of 0 -- so more medical comorbidity -- in those aged 60 and over or 40 to 49, both compared to age 18 to 39, had lower odds of opioid use disorder. For the abuse outcome, having more medical comorbidity compared to none, being obese compared to normal or underweight, and those aged 50 to 59 compared to 18 to 39 had lower odds. Several factors were associated with lower risk of misuse, including those with more medical comorbidity compared to none and those with two or more inpatient hospital stays compared to none.

This concludes the results for the

prospective study. I'll switch now from estimating incidence in the prospective study to prevalence estimates among patients taking opioids for at least a year, as we turn to the cross-sectional study.

I mentioned at the beginning that Study 1 also included a cross-sectional study of patients who had been receiving long-term opioid therapy for at least a year. Because study timelines only allowed for one year of follow-up in the prospective study, the addition of the cross-sectional sample of patients with longer term use provided an opportunity to understand the prevalence of and risk factors for misuse or abuse of prescription opioids or addiction associated with longer exposure to opioids.

Similar to the prospective study, all potential participants needed to be enrolled in their health plan or engaged in care during the prior year. They needed to be able to consent and complete in-person or telephone-administered interviews and self- or telephone-administered

questionnaires, and they needed to still be taking their prescription opioid at the study interview. Exclusion criteria were also similar to the prospective study. Recruitment letters were sent to potential participants, and our recruitment teams followed up by phone to consent, conduct prescreening interviews, and enroll eligible and interested participants.

The primary outcomes of the cross-sectional study were the past 3-month prevalence of prescription opioid misuse or abuse and the past-year prevalence of addiction. The secondary outcomes were the same as in the prospective study. Prescription opioid misuse, abuse, and addiction were again determined using the POMAQ and PRISM-5-OP.

A total of 5,333 potential participants were sent recruitment letters. Of those that received a recruitment letter, 1,936 were eligible and consented. And while 1,325 completed the PRISM-5-OP assessment, 113 did not complete the POMAQ; and therefore, because we could not evaluate

the misuse and abuse primary outcomes, these participants were not enrolled. In total, 1,212 people were enrolled and completed the primary outcome measures.

Among the participants included in the analyses, 80 percent were 50 years of age or older; 57 percent were female; 74 percent identified as white; 12 percent as black; and 5 percent as Hispanic. ER/LAs were the predominant form of opioid prescribed, and 5 percent had a past-year history of a non-nicotine, non opioid substance use disorder.

Here are the results. The past 3-month prevalence was 14.6 percent for prescription opioid misuse and 6.0 percent for opioid abuse. The past-year prevalence of pain-adjusted OUD was 2.7 percent.

As in the prospective cohort, we also looked at the prevalence rate using the DSM-5 definition of OUD. The prevalence of moderate-to-severe OUD was 6.3 percent using the DSM-5 definition, where tolerance and withdrawal were not counted as

positive if the medication was taken as prescribed.

Here, we show the risk factors associated with statistically significant increased odds greater than or equal to 2 of prescription opioid misuse. Again, we see that past-year substance use disorder had the highest odds compared to any other categories.

Next, looking at the outcome of prescription opioid abuse, we see several factors with increased odds compared to the reference groups, but again, the trend continues with past-year substance use disorder having more than double the odds compared to all other factors.

The risk factors with statistically significant increased odds of pain-adjusted OUD compared to their reference groups are shown here. Most notably, being male compared to female and identifying as Hispanic versus not, or black compared to white, were associated with odds ratios greater than 4. Prior to past-year history of major depressive disorder was also associated with increased risk and greater than 2 hospital stays

compared to none.

Here are factors associated with lower odds of misuse, abuse, or OUD compared to a reference group. Factors associated with lower odds of OUD included identifying as other or mixed race compared to white; being overweight or obese compared to normal or underweight; use of an other active pharmaceutical ingredient compared to oxycodone; and those aged 50 to 59 years of age compared to 18 to 39.

For the prescription opioid abuse outcome, those with less than a high school education compared to a high school diploma or GED had lower odds, and those exposed to abuse-deterrent formulations also had lower odds. For misuse, we see that those predominantly using ER/LAs relative to IR/SA and those exposed to abuse-deterrent formulations had lower odds.

Study 1 was conducted in sites illustrative of typical health care by teams with extensive recruitment and retention experience. It used validated instruments to quantify and characterize

the study outcomes among adult patients prescribed long-term opioid therapy. The study was comprised of longitudinal analyses with robust estimations of incidence rates and an extensive list of risk factors were explored.

Limitations included the potential for exposure or outcome misclassification, or selection, recall, or social desirability biases, as these are known limitations of observational studies. Wherever possible, efforts were made to mitigate these design-related weaknesses.

We may not have had statistical power to detect significant differences across small subgroups for risk factors, particularly when the outcome rate was low. And finally, risk factors such as dose changes or discontinuation and the outcome of suicide have been recognized in the literature in the intervening time since the study began, and these were not studied.

When the PMR was issued, there was concern about the known risks of misuse, abuse, and OUD among patients prescribed long-term opioid therapy,

but there weren't clear estimates. There were almost no incidence estimates among patients with new long-term opioid use, and there was a wide range of prevalence estimates reported in the literature. We now have incidence estimates that we can have confidence in because they were measured using validated instruments among patients from typical healthcare settings. We now have more precise prevalence estimates, also rigorously measured.

We know that overdoses associated with heroin use have increased over time, but we now know that heroin use disorder was not prevalent in these studies. We now understand that opioid abuse is more common than opioid use disorder, and many more patients misuse their opioids, somewhere around 15 percent of patients on long-term opioid therapy greater than a year, and around 20 percent of new long-term users by one year.

That information can be useful to clinicians because although the opioid crisis may have shifted to illicit synthetic opioids, opioid analgesics are

still prescribed, and clinicians and patients are interested in this kind of data to inform their risk-benefit discussions. Our results help them to understand how common these risks are, and among many potential risk factors, which to pay closest attention to for specific patients.

We evaluated a number of risk factors previously shown in the literature to have a relationship with problematic opioid use, and we now have more precise estimates of the magnitude of those risks. We found a novel indicator of increased risk for opioid use disorder among patients co-prescribed gabapentinoids. Almost half of the participants in all cohorts and studies for Study 1 had a prescription for gabapentinoids, so this is important.

Finally, we confirm what we already knew, that patients with prior histories of substance use disorder are more vulnerable than those without. That was a consistent and significant risk factor across outcomes. Importantly, the risk factor findings generally align with the published

literature.

Thank you, and Dr. John Seeger will now present the findings from Study 2.

Industry Presentation - John Seeger

DR. SEEGER: Thank you, Dr. Yarborough.

I'm John Seeger, a pharmacoepidemiologist and Vice President for Epidemiology at RTI Health Solutions. I am also an adjunct assistant professor in the Department of Epidemiology at Harvard's T.H. Chan School of Public Health.

I had a 25-year history at Optum, where I eventually took on the role of Chief Scientific Officer for Epidemiology. My research focus has been to address regulatory questions regarding the safety of pharmaceuticals and vaccines. I became a principal investigator for Study 2 once Dr. Walker retired from WHISCON about three years ago.

Now, let me share with you the design of Study 2 and its findings.

Study 2 was designed as a cohort study that was observational and retrospective. The study aimed to address two major objectives of the

postmarketing requirement outlined earlier. Those objectives were to quantify the incidence of opioid overdose and death, OOD, among long-term opioid users and to identify predictors or potential risk factors for OOD.

While Study 1 identified the more commonly occurring outcomes of abuse, misuse, and addiction, the outcome for Study 2, OOD, occurs less frequently; therefore, an observational retrospective study using insurance claims and death records for patients prescribed long-term opioids was selected as the way to provide informative results in a timely manner. Like Study 1, we examined a number of potential risk factors and confounders for OOD, including ER/LA versus IR/SA formulation. Although originally part of the PMR, Study 2 did not search for effect modifiers.

This slide presents how opioid recipients were selected for the study and how they were followed for the outcome of OOD. We identified Schedule II opioid dispensings from pharmacies to

individuals between October 2006 and December 2016. We then checked that the person was enrolled in the data source for 6 months prior to this dispensing and had not received a Schedule II opioid dispensing during that time.

This was our operational definition of new use, and people who received a Schedule II opioid meeting these criteria were further evaluated for eligibility. They had to be adults 18 to 79 years of age, and they had to receive at least 70 days worth of Schedule II opioid in the 90-day qualification period. This was our definition of long-term opioid use similar to the definition used in Study 1.

Persons who met these entry criteria were followed for the study outcome of OOD. In order to identify new or incident cases of OOD, people who had an OOD outcome during either the baseline or qualification period did not qualify for study follow-up. This single cohort was followed for up to 5 years with potential censoring for a number of administrative reasons. At periodic points, the

cohort was characterized using covariates that were also assessed at cohort entry. This allowed us to keep track of the cohort make-up during follow-up so we could see if it changed.

One of the main variables to be assessed was whether the individuals received an IR/SA or ER/LA opioid; however, individuals could have received multiple Schedule II opioid dispensings during the qualification period that were a mix of IR/SA and ER/LA. The way we resolved this was to classify patients according to which of these forms provided the most morphine milligram equivalents, MMEs, during the qualification period. In this way, patients were unambiguously classified as either an IR/SA or ER/LA recipient, and they remained in that group throughout follow-up following the intention-to-treat principle.

This study was implemented in the same way as described in this schematic across four sites that were independent of one another using a common study protocol. Researchers at each site implemented the study protocol with coordination

and pooling of results by Dr. Walker and me. Collectively, the sites implementing the protocol identified 232,106 subjects that met inclusion criteria for entrance into Study 2.

The dark blue boxes reflect exclusion criteria. Of those who met the inclusion criteria, 95 percent passed the exclusions of no opioid overdose during the baseline or qualification period, not receiving non-hospital institutional care, and were alive at cohort start date, leaving 220,249 enrolled into Study 2. This was our sample size.

There are four data sources that contributed to Study 2: two commercial health insurance data sources; one managed care health system; and one Medicaid source. HealthCore and Optum have representation across all regions of the United States, while Kaiser Permanente Northwest, KPNW, and Vanderbilt University Medical Center, VUMC, using Tennessee Medicaid data are regional.

Keeping in mind that the data sources were meant to be informative and diverse, they were

selected for having the following features. They had large size and well-defined demographic and regional characteristics. They had complete or nearly complete information on provider, facility, and pharmacy services, allowing us to capture drug exposure and patient covariates along with outcomes. They had experience working with U.S. claims data and translating them to Sentinel Common Data Model.

All sites were participants in FDA's Sentinel initiative and also conduct their own pharmacoepidemiology research. All sites had the ability to go beyond the administrative data to access medical records for validation or link to the vital statistics data or National Death Index. And finally, the sites provided diversity in healthcare settings, and by this, I mean data included people cared for in outpatient or inpatient settings across the U.S. under a variety of reimbursement types.

The primary study outcome was first occurrence of opioid overdose or death. This was

presented both as risks and rates for the overall cohort and for subgroups. Secondary measures included a characterization of the cohort at baseline and at periodic intervals during follow-up. The OOD risk or rate was determined within strata for the identification of high- or low-risk subgroups of the main cohort.

A sensitivity analysis was conducted where we shortened the period without Schedule II opioids from 6 months to 1 month. Finally, based on FDA feedback, we also included a switch/add substudy to assess OOD risk among people who qualified for the cohort as an IR/SA user and who subsequently switched to or added an ER/LA or a different IR/SA.

An important element in research is confidence in the ability to measure the study outcome, which in this case was OOD. For this reason, I will take a brief digression to Study 6, whose purpose was to provide us with this confidence.

There was a published algorithm that used ICD codes to identify opioid overdose, and Study 6

sought to determine if the algorithm could be used as it was or if it could be improved. The algorithm was based on ICD codes that designated variations of opioid poisoning. The investigators of Study 6 examined additional codes that might be ancillary to opioid poisoning in categories shown here.

As candidates to improve on the sensitivity and specificity of OOD identification, the study applied the multivariable statistical techniques of LASSO and CART, which are commonly used in algorithm-building studies. The researchers found that there was no combination of these additional variables that improved the performance of the original algorithm when compared to the gold standard of medical chart review.

Here are the main results of Study 6. More than 1,000 charts within Kaiser Northwest were reviewed for this algorithm assessment, and the original ICD-based algorithm showed excellent performance on all measures shown in this table.

And there was even more to the study.

Excellent performance in Kaiser Northwest may not transfer to other data sources, so there was a large scale portability assessment involved. This involved a separate sample of more than 1,400 charts from three of the four study sites plus Kaiser Washington, and the results were quite similar to the published algorithm; therefore, we felt confidence in the performance of the OOD algorithm, and it was adopted for use in Study 2.

Study 2 prespecified patient characteristics that might affect OOD risk. These were based on electronically recorded patient information within the data sources in time frames relative to the cohort start date. Prior to the cohort start date, insurance claims bearing codes were used to identify select diagnoses. This included pain-causing conditions clustered into similar types and baseline substance use and mental health disorders. We also identified dispensings of non-opioid medications.

At the cohort start date, we captured demographics including age, sex, calendar year, and

the U.S. census region. You'll note that we collected variables during follow-up that were the same as those collected before cohort entry to describe the cohort composition longitudinally.

Now, let's look at Study 2 accrual across the years of the study. This figure shows the fraction of the cohort accrued by year, with 2006 being a partial year and 2009 being the most common year of cohort entry. There is a decline in people entering the cohort thereafter that corresponds to a general reduction in the use of prescription opioids and which meant fewer opioid recipients met our entry criteria, but there are still people who entered the study in all accrual years. Since study follow-up goes through 2017, people who entered the cohort in later years tended to provide shorter durations of follow-up.

Now, let me show you some features of the cohort. I call your attention to the overall cohort size, 220,249, which matches the flow diagram presented earlier. Two-thirds of the cohort were aged 45 years or older and

approximately half female. Most of the cohort was sourced from the south region of the United States, reflecting that one of the data sources, VUMC, is entirely located there, and about one-third of people in the cohort had received a dispensing of an antidepressant, benzodiazepine or muscle relaxant.

Several medical diagnoses were tabulated for the cohort; first, the pain clusters. The study mapped pain-related diagnoses into 13 different pre-established pain clusters. These are the seven with the highest prevalences, all above 20 percent. Of these, back pain and limb/extremity or joint pain were the most prominent. Close to one-quarter of the cohort had diagnoses of depression or anxiety, and around 5 percent had a substance use disorder diagnosis.

We tabulated the specific opioid that patients in the cohort qualified with. The short-acting opioids at the top of this table are considerably more common, with 84 percent of patients in the cohort qualifying for the IR/SA

subgroup versus 16 percent for the ER/LA shown at the bottom. Once the cohort was accrued, its size declined over time. This figure shows the size of the cohort from start time through the end of follow-up. About two-thirds are followed through one year, one-third through 3 years, and one-sixth, or about 16 percent, through 5 years.

The main reason for loss to follow-up is administrative, such as a change in insurance coverage or the end of the study. Indeed, four of the 11 cohort accrual years could not have had the full 5 years follow-up because they reached the administrative end of the study, December 2017, first. Cohort retention was not uniform across data sources or risk factors. For example, retention was higher in VUMC and Kaiser than in the commercial health insurance data sources, and retention was lower in persons with a baseline diagnosis of OUD.

Now, let's attach some numbers to the cohort whose size I just depicted graphically. This slide shows cohort accrual overall and by data source,

along with the person-years follow-up contributed and outcomes identified during follow-up. There are more person-years than people in the cohort, which tells you that the average follow-up was longer than one year; and if you do the calculation, it comes out to an average of 2 and a quarter years per person.

During this follow-up, there were 3,034 OOD events identified, with 17 percent being fatal. The cumulative risk of OOD was 2.1 percent or 2.1 cases of OOD per 100 people, and the incidence rate was 5.3 cases of OOD per thousand person-years, which translates to 0.53 events per hundred person-years or about half a percent per person, per year. I mentioned this to connect with the next slide that shows cumulative risk per year of follow-up.

The fairly narrow 95 percent confidence intervals around both the risk and rate for OOD, 2.0 percent to 2.2 percent and 5.1 percent to 5.5, show that the study met the objective of estimating OOD risk with good precision. I would also like to

point to the diversity in OOD risk among the healthcare settings contributing to the overall numbers. In particular, VUMC has a crude OOD incidence rate that was about 2 and a half times what it was in the other sites. VUMC is a Medicaid population that has demographic and comorbidity characteristics that correspond to higher OOD risk than the other sites.

On the next slide, I will show the cumulative risk per year of follow-up, but I would like you to remember the average incidence rate, 5.3 per thousand or about half a percent per person per year, which is the incidence rate averaged over all 5 years of follow-up. The OOD risk could vary across the 5 years of follow-up, so the cumulative risk at 5 years might not reveal an increasing or declining risk during that time.

Here is the cumulative risk of OOD by year across the 5-year follow-up, accounting for the changing size of the cohort. You can see the fairly consistent linear increase in OOD risk of about 0.4 or 0.5 percent per year, building to a

cumulative risk of 2.1 percent at 5 years. And while cumulative risk varied across sites, this pattern of linear increase in OOD risk over time was present at all sites.

The study sought to determine whether OOD rate was influenced by patient characteristics. Presented here is the hazard ratio of OOD by age and error of cohort entry. The black diamond shows the reference group. The overall estimates support an age-related decline in the risk of OOD. Younger age groups show higher risk than the referenced age category of 45 to 54 years, while older age groups show lower risk.

The era indicates that people entering the cohort in the last era were at higher risk. While not shown here, we also looked at sex and census region, and there were similar risks across subgroups of these variables. All four of these risk factors -- age, sex, era, and region -- were then accounted for through adjustment when examining other potential risk factors.

Looking at subgroups adjusted for these

demographic covariates, we identified prior SUD, particularly OUD, and prior psychiatric diagnoses as predictors for increased risk of OOD. This aligns with literature and current opioid utilization recommendations. We also see that a range of psychiatric diagnoses prior to start of long-term opioid use predicted increased OOD risk, and medications used to treat OUD or psychosis corresponded to similar increased OOD risk as being highly correlated with the condition for which they are prescribed.

This figure shows the same cumulative risk as the earlier slide, but now broken out by those with and without a baseline diagnosis of OUD. A history of OUD was the only baseline characteristic that affected the retention in the respective insurance plan. If I can draw your attention to the numbers at the bottom of the slide, you see there is a modestly more rapid decline in follow-up associated with the history of OUD, so that at the end of 5 years, the OUD subset of 961 patients is 12 percent of its starting size, while the

corresponding number, 36,050, for the non-OUD subset is 17 percent. As might have been expected, there was a substantial difference in the cumulative OOD risk according to this baseline variable, where it was close to 5 times higher among those with OUD than those without it.

Turning to the outcome of OOD by other subgroups, we also see that most opioids predicted increased OOD risk relative to the reference category of hydrocodone, methadone used for pain being the highest. Of interest, patients treated with an ER/LA as the principal molecule had a hazard ratio of just over 2 for OOD compared to short-acting opioids, which makes sense, as ER/LA opioids are often used with a higher dose or in conjunction with IR/SAs. In fact, dose accounts for much of the increased risk identified. While not shown here, when these factors are adjusted for qualifying dose, most hazard ratios move closer to 1, and the hazard ratio associated with ER/LA formulation becomes 1.0.

So how does opioid dose affect OOD risk?

This figure sums up the MME of Schedule II opioid dispensing during the 90-day qualification period preceding cohort entry and stratifies OOD hazard ratios by approximately quintile cutpoints. As already recognized in the current ER/LA labeling, higher doses equal higher risk, and the data collected in Study 2 further support this. What you can see is that those who are in the highest quintile of opioid dose, 67 MME or more daily, had a rate of OOD that was more than 4 times the rate in those who qualified in the lowest quintile, 17 MME or less daily.

Further, this highest quintile is disproportionately comprised of ER/LA opioid recipients. Two-thirds of those receiving a qualifying opioid dose in this quintile were on ER/LAs. I should note that as a consequence of the study design, this qualifying dose, or the baseline MME, could be the opioid the patient received months, or even years, before the OOD event occurred; however, the sizeable hazard ratio shows how strongly this baseline measure of opioid dose

effects OOD risk.

To address a secondary study objective, we formed a cohort comprised of people who entered the primary cohort as IR/SA recipients and who subsequently either switched to or added a different opioid. This new cohort allowed us to observe the effect of switching to or adding an ER/LA form to switching to or adding an IR/SA form. The dose and covariate status immediately preceding cohort entry were noted and adjusted for. The dose immediately after was monitored but not adjusted for.

Here we have the opioid doses in MMEs before and after the switch/add cohort start date. The top line shows that members of the ER/LA added cohort had already been receiving higher doses before the introduction of the new opioid than did the IR/SA added cohort, illustrated in the lower line. Introducing an ER/LA was moreover associated with much higher dosing after the introduction. The high subsequent doses reflected clinical choice to introduce ER/LA medication.

The switch/add cohort was less than one-quarter the size of the full cohort. The OOD events observed lead to a higher rate of OOD than in the full cohort, suggesting that switching or adding an opioid is in itself an OOD risk factor regardless of the formulation. Recall that the full cohort rate of OOD was 5.3 events per thousand person-years, while here it is 11 and 7.3.

There was an elevated hazard ratio for OOD in the ER/LA added cohort. Adjusting for the preswitched dosing did not affect the hazard ratio to any meaningful degree. Also, the adjustment was based on preswitched dose, and the dose these patients were on during follow-up was considerably higher.

To wrap up our discussions of the findings from Study 2, like Study 1, Study 2 included a large sample to produce precise estimates of risk using a validated outcome in a new user cohort design from which the evolution of risk over time could be assessed across four data sources, giving a broad-based picture of long-term opioid risk from

the point of initiation.

Study 2 limitations included exposure measurements based on recorded pharmacy dispensing, while actual opioid use was not observed. The study did not account for opioids obtained outside of insurance, and patients medical characteristics were inferred from the diagnoses accompanying services but may not correspond to the actual conditions.

It appears that initiation of long-term opioid use predicts continued opioid use, at least through 5 years. In these people, the risk of OOD increases linearly over time at about half a percent per year. The factors most associated with an increased risk were higher baseline opioid dose and having a baseline diagnosis of substance use disorder or other mental health diagnoses, or receiving medications to treat one of these conditions.

Other important predictors include having a baseline diagnosis of psychosis or taking antipsychotic medication. There was a higher risk

of OOD observed among persons who began with or switched to ER/LAs versus IR/SAs, which was closely correlated with a higher dose that accompanies that switch. These risk factor findings overall align with what has previously been reported in the literature for long-term opioids and already included in the opioid labeling.

Thank you. I'll now turn the presentation to Dr. Walker.

Industry Presentation - Alexander Walker

DR. WALKER: Thank you, Dr. Seeger and Dr. Yarborough.

In summary, Studies 1 and 2 provided risk estimates associated with long-term opioid consumption and quantified the associated risk factors. I shared this slide previously, as it provides an overview of the study outcomes. Study 1 found one-year cumulative risks for opioid misuse in 23 percent, abuse in about 9 percent, and in addiction, in about 1.6 percent. These one-year outcome risks in patients with new use resembled the prevalences observed in the study of patients

with longer term use. Among the many prespecified risk factors assessed, prior SUDs were the most consistent correlates of outcomes.

Study 2 added an estimate of the degree of risk for opioid overdose and opioid-related death, which averaged 2.1 percent for the overall population across four studies. That estimate varied by subgroups with baseline dose, prior SUDs, and mental health disorders as the strongest independent risk factors for OOD.

To conclude, the opioid PMR program was designed in conjunction with external expert advisors and healthcare organizations in agreement with the agency to address evidence gaps related to the risks associated with the long-term use of ER/LAs. The studies used the best available scientific resources. Two validated research measures were developed, one for misuse and abuse and another for addiction. Ad hoc validation studies confirmed the appropriateness of an existing database algorithm for OOD.

The ER/LA opioid postmarketing observational

studies employed rigorous data collection and well-tested methodologies. They quantified the incidence of and identified the strongest risk factors for five outcomes of interest among chronic pain patients receiving long-term opioid therapy in routine care. While the opioid prescribing landscape has changed over time, prescription pain management continues to be needed by patients. These data add to the existing body of evidence to help further inform scientific knowledge and support patient safety.

Thank you for your attention. We have additional experts with us today to help answer your questions. They are Dr. Ning Smith, Lead Biostatistician for Study 1; Dr. Karin Coyne, Principal Investigator of Studies 3 and 4; Dr. Deborah Hasin, Principal Investigator of Study 5; Dr. Sandra Comer, an opioid abuse liability expert; and two clinical consultants, Dr. Charles Argoff and Dr. Richard Rauck.

With that, we're happy to take your questions.

DR. SEO: Hi. This is Jessica Seo. I apologize for interrupting again, Dr. Bateman. I'm happy to report that Dr. Blanco has been able to join the meeting. He will be participating virtually today.

Dr. Blanco, if I could ask you to please introduce yourself into the record.

DR. BLANCO: Yes. Thank you for inviting me. My name is Carlos Blanco. I'm a practicing psychiatrist. I am also the Director of the Division of Epidemiology, Services and Prevention Research at the National Institute on Drug Abuse.

DR. SEO: Thank you.

Back to you, Dr. Bateman.

Clarifying Questions

DR. BATEMAN: Okay. Thank you.

We will now take clarifying questions to OPC. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if

possible. Finally, it would be helpful to acknowledge the end of your questions with a thank you and the end of your follow-up questions with "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for OPC? And maybe I'll just start while people are thinking of their questions. This question would be for Dr. Yarborough.

The question is about the inclusion criteria for Study 1, the perspective component, and I guess it also applies to Study 2. For the LtOT component, there was an exclusion of those who used any opioids during the sixth month of baseline before they got the 70-plus days supply. I think, from clinical experience, it's a quite common pattern that patients will be prescribed short courses of opioids before intensifying to daily or near daily use.

So I'm wondering if you can just comment on this design choice and how it might affect interpretation or generalizability. I would think,

as I understand it, it would exclude patients who are prescribed shorter courses of opioids, may have a high degree of opioid liking and actually seek out longer term opioids, which would be potentially a high risk group for misuse, abuse, or addiction.

DR. WALKER: That's Dr. Yarborough. Could you comment on the effects of the exclusion of prior opioid use?

DR. YARBOROUGH: This is Dr. Yarborough. Yes. The goal with the long-term opioid therapy cohort was to identify new users who would go on to become long-term users. So we intentionally excluded people who might have acute episodes like you were just talking about, recognizing that that is a group that there's a hazard in doing that.

DR. BATEMAN: And do you have information on the number excluded for short-term use before --

DR. YARBOROUGH: I don't at hand.

DR. BATEMAN: Okay.

Dr. Gordon?

DR. GORDON: Thank you. Adam Gordon, and this is about 3033-1 to Dr. Yarborough.

With regards to the inclusion criteria, actually the exclusion criteria, I note that in your presentation and in the briefing document that an exclusion was a documented OUD diagnosis and were on medication treatment for opioid use disorder.

I'm interested, though, on the briefing document, page 40, that the baseline characteristics indicated that about 3 percent of people had OUD in the past year, and almost 6 to 7 percent of those patients at baseline had OUD prior to the past year. And I'm just trying to reconcile why these patients were then included in the trial in the subsequent outcome evaluation, and if they were, how they were accounted for because they evidently had OUD at baseline.

DR. WALKER: Dr. Yarborough on an apparent contradiction between the exclusion criteria and interview results, and how that was handled.

DR. YARBOROUGH: This is Dr. Yarborough. So participants were enrolled; if they had the outcome at baseline, they couldn't be considered for that

outcome at follow-up, but they might be considered for the other outcomes. So participants who had OUD at baseline, if they did not have abuse, for example, were included in the abuse analysis but not the OUD analysis.

DR. GORDON: Could I just follow up? So they were not included in the outcome of OUD, but they could have been included for the outcome of abuse and misuse.

DR. YARBOROUGH: Presuming they did not have those at baseline, yes.

DR. GORDON: Thank you.

DR. BATEMAN: Okay. Dr. Bicket?

DR. BICKET: Thank you. This is Mark Bicket. I had a question about Study 3033-1. I know for the other study, 3033-2, we saw the examination of calendar time or the cohort entry, and examined outcomes for that. For 3033-1, I'm not sure I saw that, and I just wondered if that was a consideration, if calendar time or the date of cohort entry was considered for that, and if that data was available.

DR. WALKER: Dr. Yarborough and the effects of calendar time in Study 1, or Dr. Smith, Dr. Smith, the study statistician.

DR. SMITH: This is Ning Smith. For Study 1, the cohort entry time period is shorter, much shorter than Study 2, so cohort entry time was not considered as a risk factor in the study models.

DR. BICKET: The other question I had was about slide CO-25 on the definition of misuse. One of the criteria here is that someone reports that they had more pain. It seems likely that persons who have chronic pain are quite likely to experience acute on chronic pain some time during the year. So I'm just wondering if there could be some discussion about a patient who does experience acute on chronic pain.

Were they to engage with their clinician and come up with a plan, it's my understanding that that interaction would not be counted as an example of misuse here versus someone who was using their prescription in ways that they had not necessarily

counseled with their prescriber to do so. Thank you.

DR. WALKER: I think that would be appropriate for Dr. Coyne to discuss acute on chronic pain.

DR. COYNE: Hi. This is Dr. Coyne. That is a great observation and quite accurate. When we developed the clinical algorithm, which took -- we did two separate ongoing studies to validate patient responses, and that very precise observation of acute on chronic pain was taken into account.

The way the POMAQ is worded is the first question is about a specific behavior, and then about the intentionality, and then about the frequency that it occurred and like number of doses. So within the algorithm, it will account for the number of times that it may have occurred, as well as the frequency within a day and month, et cetera. So that is accounted for, so it would not be counted against them.

DR. BICKET: Thank you.

DR. BATEMAN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. I'll start with my questions for the dash-1 study. Do you have any numbers if misuse was pain adjusted? I think it kind of speaks a little bit to the point that Dr. Bicket was saying.

Later on in our discussion, I can talk more about why I'm curious about those, but were there any numbers ever run to basically say, here we may have misuse, but it's for therapeutic reasons, and what the statistics would look like if it was a pain-adjusted score similar to how it was done for OUD?

DR. WALKER: For the possibility of doing a pain adjustment for misuse, I think it would be Dr. Coyne again who should respond.

DR. COYNE: If we go back to slide CO-25, which has the reasons for misuse --

DR. JONIAK-GRANT: I'm sorry. It's hard to hear you.

DR. COYNE: Okay. Sorry.

If you look at some of the intentionalities

in here, we have direct attribution: to treat my pain faster, I had more pain, I need more pain medication. So there are very specific intentionalities that reflect the reason and the intent for using additional medication or whatever the behavior may have been.

Again, we did account for some of this by quantity and allowing a certain number of times to be acceptable. Within Study 1, and I'll let Dr. Yarborough speak to that, I don't think they looked at the individual reasons, per se, to adjust that score because it's a complex analysis of multiple behaviors to account for, and every single behavior has different intentionalities as well. But they do have attribution to the reasons for misuse.

DR. WALKER: My understanding is that the misuse outcome was not further pain adjusted in Study 1.

DR. BATEMAN: I'm going to ask the panelists to just ask one question, and then if you have multiple questions, we'll circle back around to

you. We have many people with questions and limited time.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I'll start in with my question with respect to the first study, and it's related to interpretation. In both introduction and in the summary, it was sort of mentioned that there are the estimates for incidence, and then the prevalence estimates were similar. But looking at the numbers, for example, misuse, the incidence estimates were around like 21-22, and then the prevalence estimates were closer to like 15 percent.

I was just wondering whether you could comment a little bit on why that interpretation. And I was wondering whether it had to do with the fact that for the prevalence study, it asks for the past 3 months, if my understanding is correct, and for the incidence, it goes up to 12 months. Does that explain the difference, or why else do you think that the prevalence estimates in a higher risk population were lower than the incidence

estimates?

DR. WALKER: I'm probably responsible for the term "similar," so let me say that, really, what I was referring to is the order of magnitude jumps from misuse, to abuse, to OUD, and seemed to me largely similar. The cross-sectional cohort, as we had said, was intended to fill in the gap left by the impossibility of doing more than one-year follow-up of the original cohort, so it's variable. I'm not sure that we have the data to make a more in-depth interpretation of effects over time on the basis of the cross-sectional cohort.

Would Dr. Yarborough like to add anything?

No. So what we had was a stop-gap measure to try and get the studies done within a reasonable time period, and that precluded a real-time-to-event sort of analysis.

DR. HUYBRECHTS: Thank you.

DR. BATEMAN: Dr. Reich?

DR. REICH: Thanks. Jeff Reich. A clarifying question for me is on the abuse-deterrent formulations, the ADFs, which

seemed to me, for obvious reasons, to be potentially a major confounder. I recognize that most of them weren't really launching onto the market until about 2015-2016, but even so, for 331, or even 332, do you have a number for the percentage of patients that were prescribed the ADFs in terms of the incidence of abuse, misuse, and addiction for that specific cohort?

DR. WALKER: In Study 2, we do not have a separate analysis of abuse-deterrent formulations. In Study 1, you'll recall that they were associated with a reduced abuse outcome measure, but there's not further information available. Those were the rates in the follow-up study.

DR. BATEMAN: Dr. Shoben?

DR. SHOBEN: My question is about the selection of the reference group for, really, all categorical variables, but specifically age because that was different between Study 1 and Study 2. Age 18 to 39, or something, was referenced in Study 1, and then 45 to 54 was referenced for Study 2. And I was wondering, one, if you could

comment on this overall selection process for the reference, and two, why those were different between the two studies.

DR. WALKER: The studies were done independently so I think the separate investigators need to respond. For age, in Study 2, we simply took the large middle group as the reference group and took care to present the full range of age categories.

I could ask Dr. Yarborough or Dr. Smith to address reference categories in Study 1.

DR. YARBOROUGH: And we simply took the youngest age category as a reference group.

DR. WALKER: That was Dr. Yarborough.

DR. BATEMAN: Okay. Dr. Amirshahi.

DR. AMIRSHAHI: Maryann Amirshahi. I had a question for Dr. Seeger with regard to, I believe, slide 58.

As a medical toxicologist, when we talk about opioid poisoning, not all opioid poisonings are the same. So when we were evaluating these ICD-9 codes, did we, for example, look at the

difference between somebody who intentionally overdosed with their opioid analgesic versus somebody that had a therapeutic mishap by combining medications, or someone who was intentionally abusing it? Because those overdose populations are very, very different, and what we would do with that data might be helpful for mitigation. Thank you.

DR. WALKER: With permission, I'll answer for Study 2. The study encompassed the transition from ICD-9 to ICD-10, in which the categorization is quite different. We had a separate validation study for the ICD-10 codes. The ICD-9 codes, the term for overdose in the language of the ICD code is poisoning. That's not the clinical term that appears in the record, but if you want to put in an overdose, the code will appear as poisoning.

The original Green proposition was basically to take everything that was an opioid poisoning and count it as a poisoning, and that had been based on a chart review as well. The additional study looked at -- remember, we're trying to create a

claims diagnosis -- is there anything about hospitalization history, other drugs being used, other opioids being used, diagnoses of things we know are risk factors? Do any of these predict better a chart review diagnosis than simply those opioid overdose, quotes, "poisoning codes." And there was no combination that did better than that.

So for taking OOD as a -- now, these are all insurance claims diagnoses -- claims diagnosis, no other combination seemed to be better than simply going simple.

DR. AMIRSHAHI: Thank you.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: James Floyd. This question is about slide CO-69, so I think this is for Dr. Seeger.

It's pretty well established that benzodiazepines and other sedating meds can potentiate the adverse effects of opiates. I was interested in the associations for antipsychotics and antidepressants, and ADHD therapies, because we're tasked with asking -- there are a lot of

findings in this really great work that you've done. Are there any findings that have relevance for labeling?

One question I have is if you've done some analyses adjusting for the prior psychiatric diagnosis, and then estimating associations for the medication class. I suspect a lot of this confounding by indication, but if you have kind of a novel association that persists after adjusting for psychosis or other mental health disorders, that would be an especially interesting and informative finding.

DR. WALKER: You're right. These would be especially interesting. I've just conferred with Dr. Seeger and agreed that I'll take the question.

The first thing to bear in mind is these are all baseline characteristics. These aren't concurrent therapies later on when the overdose actually occurs, so we're looking at these as predictors of of opiate overdose. We have to be careful not to put too fine a clinical interpretation on the interactions. Presumably,

they have their effect by carrying forward in time that use in the baseline predicts use later, but it may predict other things as well.

The tight association between, say, an antipsychotic use and a diagnosis of psychosis is why we took as our principal analysis the analysis which adjusted for demographic factors only; because if you ask the effect of psychosis, conditional antipsychotics, or vice versa, it's a very refined question. It's not impossible, and to do a fully covariate adjusted analysis could make sense, but not in a simple way. So these are simple predictors.

DR. FLOYD: Yes. And let me follow up. A causal inference for many of these findings is very problematic.

DR. WALKER: Correct.

DR. FLOYD: This work is very high quality. You've taken a lot of attention to apply good study designs, a lot of rigor, so it's not a criticism of the work; it's just the nature of epidemiology. Still, if you can share those findings, it's a

simple analysis adjusting for prior psychiatric diagnoses, and then sharing the effect estimates. If there's time to do that, I'd be curious to see that result later.

DR. WALKER: There's not time to do that particular analysis before the day is over. There are fully adjusted analyses. We've included everything as a predictor with some limitations because the sites are not all large enough to include all the predictors --

DR. FLOYD: Sure.

DR. WALKER: -- and we will be able to show that. And I believe if you look at the results in the FDA briefing document, they primarily focused on the fully adjusted results, which do do the kind of analysis that you're asking for.

DR. BATEMAN: Dr. Becker?

DR. BECKER: Will Becker. A question for Study 1. I wanted to ask about the decision to use patient-reported data for current past mood disorder and current past substance use disorder, the considerations that went into that; was EHR

data not available, was it found to be problematic, and so on. Thanks.

DR. WALKER: So on the use of patient-reported data on mood disorder, I'd ask Dr. Yarborough to comment.

DR. YARBOROUGH: This is Dr. Yarborough. I wasn't sure who was speaking. I'm not sure who to look at. Thank you.

We did have EHR data, but because we could do this structured clinical diagnostic interview, we preferred that over HR data, which can sometimes over- or underestimate rates of various diagnoses.

DR. BATEMAN: Dr. Dejos?

DR. DEJOS: Mike Dejos, System Medication Safety Officer for Methodist Le Bonheur Healthcare. I recognize on slide 25 that it was mentioned, and there were two statements: to relax or feel mellow, as well as to unwind after a hard day. And they were moved over to this misuse category, and they were originally on the abuse category. We see numbers of about 23 percent were in misuse, about 9 percent in abuse. I'm just curious. If they

were to be retained in the abuse category, what would those numbers be?

DR. WALKER: Let me ask Dr. Coyne to comment on the rationale and effect of that switch into the misuse category.

DR. COYNE: The rationale for switching them over was because it was more of a therapeutic effect, and in some positions they could use these as misuse categories. In terms of attributing each and every intentionality to the misuse, we ended up within the validation study just counting up all the misuse flags and not the specific intentionalities at the time. There was very little shift when we switched them over in terms of our abuse flags to our misuse flags within the validation study. And I'll let Dr. Yarborough speak if they did not have an opportunity to examine that yet in Study 1.

DR. BATEMAN: Okay. We'll do one more question before we take a break. We'll circle back to remaining questions if we have time later in the day.

Dr. Rebo?

DR. REBO: Elizabeth Rebo. I had a question related to race. I saw in Study 1 about 75 percent of the participants were white. I did not see that data for Study 2, so a question about what that looked like. Then also, I'm curious as to concerns about applicability to other races based on the predominantly white, at least in Study 1 that I'm aware of.

DR. WALKER: Alright. So we have two questions, one for Study 2. Could you just say again what the question for Study 2 is?

DR. REBO: Right. I didn't see the data for race by breakdown.

DR. WALKER: Study 2 did not have data on race.

DR. REBO: Okay. But it did have results related to -- I see it. I think this was Study 2 saying something that being black had more of a higher incidence.

DR. WALKER: But that was Study 1.

DR. REBO: That was Study 1? Okay. So no

race for --

DR. WALKER: There was no race data. The insurance claims data do not carry race with them --

DR. REBO: Oh, I see.

DR. WALKER: -- so that wasn't available.

DR. REBO: Okay. And any concerns with Study 1 about the applicability since 75 percent of participants were white?

DR. WALKER: Let me ask Dr. Yarborough to comment on race and the applicability of the study results.

DR. YARBOROUGH: Yes. I think when we have small representation of any racial subgroup, we have to be careful about interpretation and how those results may or may not apply.

DR. BATEMAN: Okay. We will now take a quick 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with members of the audience. We will resume at 10:45.

(Whereupon, at 10:30 a.m., a recess was taken, and meeting resumed at 10:45 a.m.)

DR. BATEMAN: Okay. Welcome back. We will now proceed with FDA's presentations, starting with Dr. Hana Lee.

FDA Presentation - Hana Lee

DR. LEE: Good morning, everyone. My name is Hana Lee. I'm a statistical reviewer at the FDA. I'm going to talk about key methodological and statistical considerations for extended-release/long-acting opioid analgesic postmarketing requirement studies 3033-1 and 3033-2, which I'm going to refer to as Study 1 and Study 2. I'll provide an overview of the study design and highlight key considerations for interpretation of the study findings. I'll start from the review of Study 1.

Study 1 consisted of two studies, prospective and cross-sectional studies, with the goal of estimating the incidence and prevalence of, and identifying risk factors for misuse, abuse, and opioid use disorders, OUD. The prospective study

considered two cohorts, ER/LA cohort comprising patients of new extended-release, long-acting opioid analgesic use or ER/LA OA use, and LtOT cohort comprising patients with new long-term use of an ER/LA or Schedule II opioids.

The cross-sectional study considered patients regularly using opioids for at least one year with at least one ER/LA opioid prescription. Data sources were electronic health records, EHR; claims; patient questionnaires; and interviews from 10 study sites in the United States. Study periods went from August 2017 to October 2021 for the prospective study and from September 2017 to February 2019 for the cross-sectional study.

Primary outcomes were survey- and interview-based opioid misuse, abuse, and OUD. Past 3-month misuse and abuse were measured by a questionnaire called POMAQ, and past 12 months OUD was captured from patient interview called PRISM-5-OP. In the prospective study, misuse and abuse were measured at baseline, then every 3 months during the 12-month period, and OUD was

measured at baseline and at 12 months. In the cross-sectional study, outcomes were only measured at the time of interview.

Here are some key eligibility criteria for the prospective study. For the ER/LA cohort, patients were eligible if they had a record of at least 28 days' supply of an ER/LA opioid followed by a subsequent ER/LA opioid prescription, and this had to occur within a 90-day period before the patient's baseline interview. Patients were excluded if they used an ER/LA opioid in the 6 months prior to their initial 28 days' supply.

For long-term opioid therapy, LtOT cohort, patients were eligible if they had at least 70 days' supply of an ER/LA or a Schedule II opioid within a 90-day period before the baseline interview. Patients were excluded if they used an ER/LA or Schedule II opioid in the 6 months prior to their initial 70 days' supply.

For both ER/LA and LtOT cohorts, patients were excluded if they had an OUD diagnosis or were receiving treatment for OUD based on their EHR and

claims data. For both prospective and cross-sectional studies, eligibility required at least 12 months of health plan enrollment or with evidence of receiving health care as determined by EHR and claims. Patients were excluded if they were in hospice or had a terminal illness per chart review or self-report.

Now, I'll start with background on a key change in the eligibility criteria for the prospective study. Initially, the prospective study planned to recruit only the ER/LA cohort, which includes patients with new long-term ER/LA opioid use; however, a decline in ER/LA opioid prescribing during the earlier study period made it clear that Study 1 wouldn't meet the recruitment goals.

To address this, eligibility criteria were revised to include a second cohort, the long-term opioid therapy LtOT cohort. With this refinement, the initial plan was to combine the ER/LA and LtOT cohorts if they are sufficiently similar with respect to various patient characteristics;

however, substantial differences were observed, and the two cohorts were analyzed separately. Therefore, in the next presentation, Dr. Kornegay will present the results by outcomes stratified by the two cohorts, ER/LA and LtOT cohorts, and by prospective and cross-sectional studies.

Here's an overview of the statistical analysis. The primary outcome measure was incidence for the prospective study and prevalence for the cross-sectional study. Both studies also included risk factor analysis to identify factors associated with the risk of outcomes. Please note that at the time these studies were designed, there was limited information on risk factors; therefore, the risk factor analysis was designed to be exploratory, not intended to evaluate prespecified causal relationships between specific risk factors and outcomes.

The risk factor analysis examined various potential risk factors, including social demographics; opioid-related factors; substance use disorder or SUD history; health and pain-related

factors; mental health and social factors; as well as genetic factors for a subset of patients with available genetic data. These factors were collected from EHR, claims, questionnaires, and interviews. They were measured at baseline for the prospective study and at the time of the outcome assessment for the cross-sectional study.

Logistic regressions were used to assess relationships between risk factors and outcomes measured on the odds ratio scale. Three types of analyses were performed. Unadjusted analysis assessed individual risk factors. Demographically adjusted analysis examined each risk factor while controlling for age, sex, race, and ethnicity. Fully adjusted analysis included significant factors from the unadjusted analyses along with demographic variables, age, sex, race, and ethnicity.

In the next few slides, I'll highlight two key considerations for interpreting findings from Study 1. I'll start from cohort retention and impact of loss to follow-up. Second, I'll cover

overarching considerations related to risk factor analysis. Additional considerations for outcome definitions and measurement will be covered in Dr. Kornegay's presentation.

I'll now discuss cohort retention in the prospective study. As described before, past 3-month misuse and abuse were assessed at baseline and every 3 months thereafter. Past 12 months OUD was assessed at baseline and at 12 months. For misuse and abuse, the final analysis sample at 12 months was restricted to patients who did not have the outcome of interest at baseline assessment and completed at least one follow-up assessment. Accordingly, the misuse analysis, for example, excluded patients who had misuse at baseline but could include those with abuse at baseline and vice versa for the abuse analysis.

For the OUD analysis, the final sample was restricted to patients who had no OUD at baseline interview and completed both baseline and 12 months assessments. As a result, the analyses for misuse, abuse, and OUD did not have the same number of

patients. Retention rate at 12 months ranged from 81 percent to 93 percent, which are reasonably high. Although some bias from differences between patients lost to follow-up and those who remain is possible, the low attrition rate makes it unlikely that this had a substantial impact on outcome estimates or risk factor analyses.

I'll now discuss considerations for risk factor analysis, which apply to both Study 1 and Study 2. Let's start with the strengths.

The risk factor analysis evaluated comprehensive sets of potential risk factors, some of which are rarely captured or evaluated in published literature. For example, the prospective study was able to assess patient-reported information on history of substance use disorder, mental health, pain severity, and pain interference that are often missing or incompletely captured in claims-based studies. Additionally, various modeling approaches were conducted to examine different types of associations.

Now, limitations and considerations. First,

statistical power analysis for Study 1 suggested that the power to detect true risk factors could be insufficient for outcomes with low prevalence and incidence such as OUD or for risk factors with small sample sizes, such as morphine for misuse. Also, no multiplicity adjustment was considered due to the exploratory nature of the analysis. Given the large number of analyses conducted, some statistically significant results could have been due to chance.

Additionally, FDA focused on fully adjusted results for the purpose of risk factor identification. Some cautions are warranted when interpreting the findings. First, the speedy attempt to reduce number of variables in final analysis, fully adjusted analyses included many risk factors likely reducing power and precision of the estimation. Second, final risk factors were selected based on statistical cutpoints rather than known or suspected causal relationships, which may have led to the exclusion of important risk factors and/or inclusion of mediators, leading to observe

and attenuated associations between risk factors and outcomes.

For example, in the cross-sectional study, the number of reported adverse childhood experiences, ACE, was significantly associated with outcomes in unadjusted analysis but not in fully adjusted analyses. This does not necessarily mean that the adverse experience is unrelated to the outcomes; rather, a substantial part of the effect of ACE may be mediated by factors such as adult mental health. So, when adjusted together, the direct effect of ACE may appear minimal even when the total effect, including both the mediated and direct effects, is significant.

In summary, some true relationships may have been missed, while some observed significant results could have been due to chance; therefore, FDA's interpretation of the findings from risk factor analysis considered the direction, strength, and consistency of findings, as well as regulatory interest. Finally, we also considered findings from other studies that emerged during the conduct

and review of these PMR studies.

Next, I'll provide an overview of the design and key considerations for Study 2.

Study 2 was a retrospective cohort study with the primary objective of quantifying the incidence of and risk factors for opioid-involved overdose or opioid overdose-related death, OOD, in patients with new long-term Schedule II prescription opioid use. Data sources included EHR, claims, and National Death Index, NDI.

Eligible patients were identified from four study sites: one Medicaid, one non-profit managed care system, and two nationwide commercial insurance databases. Non-fatal overdose events were identified by a code-based algorithm, and fatal overdose events were identified or confirmed through NDI linkage. The study period spanned January 2006 to December 2016 with a follow time of 5 years for the primary analysis.

Since the previous presentation covered a similar visual, I'll briefly highlight some of the key eligibility criteria, including the OOD

exclusion requirement as it relates to one of the key considerations in Study 2.

As a reminder, Study 2 evaluated the baseline and qualification periods of the first eligible Schedule II opioid dispensing record to determine whether it qualified as new long-term opioid use.

Patients were excluded if they had any Schedule II opioid dispensing during the 6 months baseline, and they had to have at least 70 days' supply of a Schedule II opioid dispensed during the 3-month qualification period. Additionally, patients were excluded if they had a record of OOD in their EHR or claims, or a death record in the NDI during the baseline or qualification periods. Therefore, the primary cohort consisted of patients with new long-term opioid use who had no OOD for at least 9 months prior to the start of follow-up.

The primary outcome measures were cumulative incidence estimated from the complement of the Kaplan-Meier OOD-free survival and incidence rate calculated as the total number of OOD events per

1,000 person-years. Both measures were calculated at each site and, overall, adjusting for site population size. Cox proportional hazardous models were used for risk factor analyses. The same risk factors as in Study 1 were considered, except for genetic factors. These factors were obtained from EHR and claims.

Three different analyses were conducted, again using a slightly different adjustment and selection process compared to Study 1. Unadjusted analysis assessed each risk factor the same. Demographically adjusted analysis assessed each risk factor along with age, sex, calendar era, and U.S. census region. Fully adjusted analysis included all risk factors simultaneously with stepwise selection for the final model. Age, sex, and opioid formulation variables were forced to be included in the final model.

Lastly, site-specific hazard ratios from the fully adjusted models were summarized via meta-analysis, accounting for variabilities across sites. Additional statistical analysis was

conducted for a subgroup of patients called switch/add cohort. This subgroup comprised patients dispensed immediate-release, short-acting, or IR/SA opioid during the qualification period, and then switched to or added an ER/LA or a new IR/SA medication.

In this presentation, patients who switched to or added an ER/LA opioid are referred to as ER/LA switch/add patients, and those who switched to or added a new IR/SA opioid are called IR/SA switch/add patients.

The goal of this exploratory analysis was to examine the risk of OOD between ER/LA switch/add patients and IR/SA switch/add patients. These two groups differed in various characteristics around the time of switch/add event. To adjust for the imbalances, propensity score weighting was conducted. All risk factors were balanced after weighting, and therefore a Cox model, including a binary indicator for ER/LA switch/add patients versus IR/SA switch/add patients was applied to the propensity score weighted populations.

I'll now discuss key considerations for Study 2.

The ICD code-based algorithm to identify OOD outcomes was initially developed and validated in PMR 3033-6, or Study 6, using data from patients with an elevated risk of an overdose at Kaiser Permanente Northwest, or KPNW, site. The algorithm's performance was evaluated using manual chart review as the gold standard.

In the validation study, the OOD algorithm demonstrated high performance. The algorithm was further validated across different settings, including commercial, insurance, and Medicaid setting, and also revalidated in Study 2. In addition, linkage to the NDI data to capture fatal overdoses was a key strength of Study 2, as this is rarely done in claims-based studies due to cost constraints.

03:36:45 [indiscernible] these strengths, Study 2 has limitations associated with using medical documentation. OOD events had to be recognized by a healthcare professional, meaning

some events reversed by a bystander or not resulting in a medical claim were not captured. Linkage to NDI allow for capturing fatal overdose events, but some fatal opioid-involved overdose events may have not been recorded as such by the death certifier.

Additionally, this study focused only on the incident OOD among patients with new long-term opioid use who had no OOD at least 9 months prior. This may limit generalizability of findings because such patients are likely at lower risk of OOD than general population initiating new opioids. Also, follow-up was censored at the first OOD event, so subsequent OOD events, including a fatal overdose following non-fatal overdose, were not captured. Lastly, FDA focused on the overall OOD and did not cover the intentional OOD because of the poor performance of the intentionality algorithm.

Another key consideration is cohort retention. The overall cohort retention was 91 percent in the first 3 months and gradually decreased over time, with only 17 percent remaining

at year 5.

Lost to follow-up was expected given the longitudinal nature of the study and health insurance turnover; therefore, at design stage, Study 2 considered outcome measures that can account for such loss and potential bias. First, cumulative incidence was calculated using Kaplan-Meier estimator, which considers only the patients who remained at risk. Also, incidence rate using person-time denominator accounts for actual times that patients are at risk. However, bias may arise if patients who were lost had systematically different risk of OOD than those remained.

I'll now discuss risk factor analysis for Study 2. As a recap, the goal of risk factor analyses is exploratory, aiming to identify factors associated with risk of opioid-related outcomes. These analyses were not designed to test specific hypotheses, nor to evaluate prespecified causal relationships.

With that in mind, I'd like to emphasize

that the switch/add analysis is truly exploratory. This analysis was added after the recruitment challenges, necessitating the addition of the long-term opioid therapy cohort in Study 1. A similar expansion was applied to Study 2 to include patients using Schedule II IR/SA opioids long term. While this allowed for comparisons between ER/LA switch/add patients and IR/SA switch/add patients in Study 2, some of the key covariates such as changes in dose that occurred with the switch/add event were not adjusted for. Dr. Kornegay will provide a more detailed review of this issue.

Next is about heterogeneity and generalizability. Study 2 included multiple sites in various healthcare settings to enhance generalizability, so some level of site heterogeneity was expected at design stage; however, we observed substantial heterogeneity mainly due to a small number of study sites -- only four -- with Medicaid site being notably different than the other sites. This limited interpretability of the overall incidence

estimates, leading FDA to focus on site-specific estimates.

Site heterogeneity also complicated interpretation of the meta-analysis, warranting caution for results with substantial heterogeneity. Still, some of such findings remain meaningful, particularly when the direction of association is consistent across sites. A key example is diagnosis of alcohol use disorder.

As shown in this figure, meta-analysis result indicated statistically significant increased risk of OOD; however, the heterogeneity value was 0.70, indicating the result is subject to substantial heterogeneity across sites. One of the key sources of the heterogeneity was the KPNW site, where result was I significant due to higher uncertainty.

Despite this, the direction of association across all four sites remained consistent, supporting a strong association between alcohol use disorder and increased risk of OOD. Other similar findings include lower opioid dose category,

antidepressants, or benzodiazepines use, and diagnosis of psychosis.

I'll wrap up this presentation with a few concluding remarks.

During the development and refinement of these PMR studies, competing priorities influence the designs and methods of choice. The findings from these PMR studies must be interpreted in light of the key considerations discussed in this presentation.

Thank you. Next, Dr. Kornegay will walk us through the key findings and interpretations from these PMR studies.

FDA Presentation - Cynthia Kornegay

DR. KORNEGAY: Good morning. My name is Cynthia Kornegay, and I will be presenting some of the key study findings and FDA's interpretation of them for the ER/LA PMRs 3033-1 and 2. I will cover the prospective and cross-sectional PMR 3033 studies, Study 1 first, followed by PMR 3033-2. After reviewing the study findings, I will discuss our summary and interpretation of

these findings. First, the PMR 3033-1 studies.

Recall that these consisted of two studies, a 12-month prospective cohort study and a cross-sectional study of misuse, abuse, and OUD. The eligibility requirements and study design have been described previously, so I am not going to repeat them here; however, I did want to provide a reminder of the outcomes of interest.

There were three primary outcomes in these studies -- misuse, abuse, and addiction -- operationalized as moderate-to-severe opioid use disorder. Misuse and abuse were measured using the POMAQ and are aligned with the definitions that FDA uses for regulatory purposes. The patient recall period for these outcomes was the past 3 months.

Moderate-to-severe OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid therapy, or two or more criteria related to heroin use. We refer to these as moderate-to-severe pain-adjusted DSM-5 OUD. The recall period for OUD was the past

12 months.

The PRISM-5-OP modifies the previously validated PRISM-5 to include additional information on the reason for opioid use. The pain-adjusted criteria used as a primary OUD outcome in Study 1 incorporated this additional information into the standard DSM-5 OUD measure. Specifically, the pain-adjusted measure counts the desire to quit or cut down as positive only if there are unsuccessful attempts versus just a desire to quit or cut down on prescription opioid use. Also, symptoms are counted as positive only if they occurred for a non-pain reason.

PMRs 3033-3, 4, and 5 were conducted to validate the POMAQ and PRISM-5-OP. For the POMAQ, the two validation studies assessed the face and content validity and reproducibility of the questionnaire. The approach for the PRISM-5-OP was a bit different in that the validation sought to provide evidence that the changes made to the PRISM-5 instrument for this population did not affect the previously shown validity. This was

accomplished using several different approaches, including test-retest reliability; exploratory factor analysis; expert review; and a multitrait-multimethod measurement using selected external validators.

FDA concurred that the POMAQ and PRISM were acceptable for use in Study 1 and that the PRISM validation results were an improvement over the PRISM-5 in this population. To further understand the pain-adjusted DSM-5 OUD metric, we requested analyses using both pain-adjusted and standard OUD definitions.

The next two slides will present a brief picture of the Study 1 populations. As a reminder, all patients in the cross-sectional study had been dispensed at least one ER/LA prescription in the past 12 months. The majority of patients in both studies were 50 years of age or older, and there is a slightly higher percentage of women.

When selected mental health, SUD, and general health risk factors were examined, the prospective and cross-sectional studies were

generally similar. Having four or more adverse childhood experiences, use of antidepressants in the past year, and a comorbidity score of 2 or greater were common in all cohorts. Between 5 and 10 percent of patients were classified as having a non-opioid, non-nicotine, substance use disorder in the past year. In the prospective study, between 1 and 3 percent of patients were classified by the PRISM-5-OP as having an OUD in the past year.

In terms of opioid-related risk factors, having an ER/LA as their predominant opioid formulation was common in the ER/LA cohort and the cross-sectional study but uncommon in the long-term use cohort. Oxycodone was a predominant opioid moiety for approximately one-third of patients. Morphine was a fairly common predominant opioid moiety in the ER/LA cohort and the cross-sectional study but had little use in the long-term use cohort.

Hydrocodone was the most commonly used predominant moiety in the long-term use cohort. Other Schedule II opioids were used by 10 percent

or fewer patients in both studies. The distribution of average daily dose at baseline was different in the two studies. Most patients in the prospective study had an average daily dose under 90 MMEs compared to about half of the patients in the cross-sectional study.

Now, I will move on to provide an overview of the incidence and prevalence of misuse, abuse, and OUD in Study 1.

This slide shows the one-year incidence and prevalence findings. About 22 percent of the prospective study patients developed misuse during the 12-month study, and about 15 percent of cross-sectional patients had prevalent misuse. Approximately 9 percent of the prospective cohort study patients developed abuse, while 6 percent of cross-sectional study patients had prevalent abuse.

As a reminder, the misuse and abuse questionnaire had a 3-month recall period. It was measured every 3 months in the prospective study, but only once in the cross-sectional survey.

Incident moderate-to-severe, pain-adjusted

DSM-5 OUD occurred in approximately 1.5 percent of prospective study patients during the 12 months of follow-up, while the condition was prevalent in 2.7 percent of patients who had used opioid analgesics for at least a year. The last column shows the incidence and prevalence of moderate-to-severe OUD using the standard DSM-5 criteria. These estimates were 2 to 4 times higher than estimates using the pain-adjusted criteria.

Not shown on this slide, but included in the OUD outcome, were a small number of patients with heroin use disorder: 0 patients in the ER/LA cohort, 3 patients in the long-term use cohort, and 2 patients in the cross-sectional study. Also not shown on this slide, estimates for any OUD defined as meeting two or more criteria for either prescription opioid use disorder or heroin use disorder were higher, as described in our briefing document.

The estimates observed in these studies fall within range of those in the published literature; however, those ranges are quite wide. Vowles, in a

widely cited 2015 meta-analysis, including patients with chronic non-cancer pain using oral opioid analgesics, found a range of misuse estimates between 2 and 56 percent and an estimate of abuse prevalence of 8 percent, and a range of addiction prevalence estimates from less than 1 to 23 percent.

The wide range of estimates in the literature may be due to variable study populations, outcome definitions and ascertainment, and time periods when studies were conducted. It is important to recall that the estimates from these PMR studies apply to patients starting or continuing long-term opioid therapy. They do not inform the risks associated with short-term opioid analgesic use.

There are some caveats to keep in mind related to OUD measurement. The incidence of pain-adjusted DSM-5 OUD was 2 to 4 times lower than standard DSM-5 OUD. This is not unexpected given the narrow criteria of the pain-adjusted OUD definition; however, both measures could still

misclassify patients.

For example, the pain-adjusted measure could miss OUD if a patient reported using opioids for pain, but this pain occurred as part of withdrawal associated with an opioid use disorder. Standard DSM-5 measures could misclassify a patient as having OUD, for example, if the patient had continued use of opioids to manage pain despite physical problems related to the medication or if attempts to taper or discontinue opioids were unsuccessful due to uncontrolled pain related to the underlying condition.

These findings highlight the complexity of identifying OUD in patients using opioid analgesics long term for pain. We will be asking the committee members to discuss the different definitions and how they affect the interpretation of the OUD estimates in these studies.

The next section will provide highlights of the risk factor analyses for Study 1. I will present selected risk factor associations describing the strongest and most consistent

factors, those related to opioid analgesic use, as they are of particular regulatory interest, and several other results that illustrate the variable findings across models, outcomes, and study designs.

This table shows the fully adjusted associations between the non-opioid/non-nicotine substance use disorders and the primary outcomes, as well as how misuse, abuse, and OUD were associated with each other in the prospective study. A non-opioid/non-nicotine substance use disorder in the past year was the strongest and most consistent risk factor for misuse and abuse in the prospective study, and although it's not shown on this slide, the cross-sectional study as well.

The association was not seen for the OUD outcome, possibly due to the low number of patients with incident pain-adjusted DSM-5 OUD. The long-term use cohort results did show a strong association between a prior to past-year non-opioid/non-nicotine substance use disorder and OUD.

Although it is not shown here, there was a strong association with an increased risk of standard DSM-5 OUD in the ER/LA cohort but not in the long-term use cohort. Having misuse at baseline was also strongly associated with an increased risk of incident abuse, as well as baseline abuse with subsequent misuse and OUD in the long-term use cohort.

These are the fully adjusted results for selected opioid-related risk factors in the prospective study. When it was included in the fully adjusted model, opioid formulation was not associated with any of the primary outcomes. Use of an ADF did not meet the criteria for inclusion in any of the fully adjusted models.

A higher average daily dose during the baseline period was associated with an increased risk of incident misuse in the ER/LA cohort and incident abuse in the long-term use cohort but was not included in the model for pain-adjusted OUD. When individual opioid moieties were examined, hydromorphone was associated with an increased risk

of abuse in both cohorts compared to the reference group of oxycodone.

Although the substance use-related findings in the cross-sectional study were similar to the prospective study findings, the opioid-related risk factor results for the cross-sectional study were notably different. Having a predominant formulation of an ER/LA opioid was not associated with any of the primary prospective study outcomes but was associated with decreased odds of prevalent misuse in the cross-sectional study.

Although use of an ADF was not included in the fully adjusted models for the prospective study, it was associated with a decreased odds of prevalent misuse and abuse in the cross-sectional study. Finally, there were no observed associations between opioid moiety and the outcomes of interest, as evidenced by the two examples shown.

These are the demographically and fully adjusted estimates for selected mental health risk factors of major depressive disorder, or MDD;

generalized anxiety disorder, or GAD; post-traumatic stress disorder, PTSD; and an adverse childhood experience, or ACE, of four or more in the prospective study. Demographically adjusted analysis results showed risk factors of greater magnitude compared to fully adjusted findings. Although not shown, a similar pattern was seen in the cross-sectional study.

As discussed previously, this does not necessarily mean that these risk factors are unrelated to the outcomes; instead, part of the risk factors' effect may be mediated by other factors in the model. When adjusted together, the risk factors' direct effect may appear minimal, even though the total effect of the mediated and direct effects is significant. The magnitude of these risks found in a demographically adjusted model could also have been magnified by leaving out other risk factors.

Another notable difference between the prospective and cross-sectional risk factor analyses was that sex was significantly associated

with misuse, abuse, and especially strongly with OUD in the fully adjusted models for the cross-sectional study but not the prospective study. The reasons for this divergent finding are not entirely clear but may involve differing inclusion of variables in the models or power to detect the various associations.

Synthesis is challenging because as we've seen in several examples, the observed associations for many risk factors varied widely across designs, cohorts, models, outcomes, and outcome definitions. Risk factors were included in the final model based on statistical cutpoints rather than known or suspected causal relationships. Over- or under-adjustment was possible by, for example, controlling for factors that were highly correlated, or that could be mediators in the causal pathway, or not including important variables and models.

In addition, the risk factors that were included in the models differed by study design, cohort, and outcome. Many risk factors were

studied, and there may have been insufficient statistical power for some associations. Associations could also have been observed due to chance.

A history of a non-opioid/non-nicotine SUD was the strongest and most consistent risk factor for the primary outcomes. A past-year or prior to past-year history of an SUD was fairly common at baseline in both the prospective and cross-sectional studies. A higher average daily dose at baseline was associated with a higher risk of misuse in the prospective ER/LA cohort but was not associated with abuse or OUD, and was also not associated with the primary outcomes in the cross-sectional study. The dose risk factor was not included in all fully adjusted models, particularly in the cross-sectional study, and the small number of OUD outcomes per dose category may be a reason why there was no association noted with OUD.

Baseline hydromorphone therapy was associated with a higher risk of abuse in the

prospective study. In general, individual opioid moieties were not associated with the primary outcomes in the cross-sectional study; however, the low baseline prevalence of some moieties, such as hydromorphone and oxymorphone, may be why these associations were not consistently seen.

While multiple mental health conditions were associated with the primary outcomes in demographically adjusted analyses for both the prospective and cross-sectional studies, these associations were attenuated or not observed in fully adjusted analyses, possibly due to the inclusion of mediators in the fully adjusted model.

A baseline history of a mental health condition, or social risk factors associated with the primary outcomes, was common in both the prospective and cross-sectional studies. A predominant formulation of an ER/LA opioid or an ADF formulation was associated with lower odds of misuse in the cross-sectional study but was not associated with any of the primary outcomes in the prospective study.

Because the analytical approach focused on the predominant rather than the exclusive ER/LA use, and all the patients had at least one ER/LA prescription, the interpretation of these findings are unclear. In addition, the temporal relationship between formulation, use, and development of the outcome cannot be established in the cross-sectional study.

Next, I will present highlights of results from PMR 3033-2. This was a retrospective cohort study of opioid-involved overdose or opioid overdose-related death, referred to as OOD, using medical claims data linked to the National Death Index. Patients were followed for a 5-year period, between January 2006 and December 2016.

These are selected demographic, mental health, substance use, and pain-related risk factors that were included in Study 2. The age distributions for HealthCore and KPNW were similar. There were fewer patients aged 55 and older in Optum, while VUMC, which was exclusively Medicaid, had a higher proportion of patients in the

18 to 44 year old range.

The baseline prevalence of an OUD diagnosis was similar at HealthCore, KPNW, and Optum. The proportion of patients with an alcohol SUD at baseline was highest at KPNW, while VUMC had the highest percentage of patients diagnosed with an OUD or other SUD. Depression and anxiety diagnoses were fairly common at all sites. A psychosis or other mental health diagnosis had a higher prevalence at VUMC compared to the other three sites. Limb/extremity or joint pain and back pain were the two most common pain diagnoses at all of the study sites.

This table shows the baseline distributions for opioid-related and concomitant non-opioid medication risk factors. Across all sites, IR/SA hydrocodone and oxycodone were the most common predominant opioid moieties.

Dose was measured using quarterly or qualifying QMME, defined as the total MMEs contributed by Schedule II opioids in the 3 months prior to the patient's cohort entry. The

data-derived dose categories resulted in approximately 20 percent of patients in each category, except for KPNW, where one-third of patients were in the lowest category.

For reference, 1500 QMMEs is about 17 MMEs per day or 2 to 3 5-milligram oxycodone tablets. HealthCore and Optum had higher QMMEs medians compared to KPNW and VUMC. VUMC had the highest percentage of patients dispensed antipsychotic medications and gabapentinoids at baseline, while HealthCore had the highest percentage of patients dispensed a benzodiazepine.

Next, I will present the cumulative incidence and incidence rates observed in the study.

The cumulative incidence of OOD increased at a fairly steady rate over the follow-up period at all the study sites. At 5 years, HealthCore, KPNW, and Optum all had rates between 1.4 and 1.6 percent; however, the rate at VUMC, the Medicaid site, was just over 4 percent. Due to this difference, we did not focus on an overall

incidence estimate.

The incidence rates per 1,000 person-years were highest at the 3-month mark, declined through the first two years, and then stabilized through the end of the study. The 5-year rates for HealthCore, KPNW, and Optum were similar, between 3.1 and 3.3 per 1,000 person-years. In contrast, the rate for VUMC followed the same temporal pattern but was substantially higher at 8.3 per 1,000 person-years. As with the cumulative incidence, due to this difference, we did not focus on an overall rate.

Similar to Study 1, these estimates apply to patients starting long-term opioid therapy and do not inform risks associated with short-term use. The study population may also reflect a lower risk group of patients starting long-term therapy since those with recent opioid overdose were excluded. The higher incidence rates during the first 90 days of follow-up could reflect a truly higher risk early in therapy, or simply that patients at highest risk were more likely to have an overdose

early and be censored, leaving a cohort consisting of lower risk patients.

As previously described, attrition was substantial and could bias estimates if patients who left the cohort differed in their risk of OOD compared to those remaining in the cohort. The notable differences for VUMC, which was exclusively Medicaid, versus the other sites supports a range of OOD estimates rather than a single value. These cross-site comparisons do not account for differences in the underlying populations, and some risk factors, including baseline prevalence of OUD and other SUDs, were more prevalent in VUMC.

The estimates observed in this study were generally similar to those seen in the published literature, although methodological differences make direct comparisons challenging.

Next, I'm going to discuss the risk factor findings. Although I focused on the meta-analysis results here, results from each of the study sites were considered in interpreting these observations.

This is the forest plot for the

meta-analysis of fully adjusted results for demographic and opioid-related risk factors. In association with age, the association with age showed a pattern of patients younger than the referenced ages of 45 to 54 years having an increased risk of OOD, while older patients had a lower risk. There was substantial heterogeneity observed in the association between age and OOD.

Interestingly, the risk of an OOD in the fully adjusted model decreased across calendar time from 2006 to 2016, while opioid-involved overdose death rates in the general population continued to rise during that period. Compared to the reference of hydrocodone, predominant baseline use of methadone, morphine, and oxycodone were associated with an increased OOD risk at multiple sites and in the meta-analysis. The association with predominant formulation of an ER/LA versus IR/SA opioid was not observed in the fully adjusted results either at individual sites or in the meta-analysis. At all sites, a higher QMME at baseline was associated with a higher OOD risk

during the study period.

This slide shows the meta-analytic results for the concomitant medication use, SUDs, and mental health conditions. Baseline use of antipsychotics, antidepressants, and benzodiazepines were associated with an increased risk of OOD at multiple sites, as well as the meta-analysis. The antidepressant category included SSRIs, SNRIs, tricyclic, and other antidepressants.

Although gabapentinoids use was included in the final fully adjusted model only for VUMC, it was significantly associated with an increased OOD risk at that site. A diagnosis of limb/extremity or joint pain was associated with a decreased OOD risk at multiple sites and in the meta-analysis. A diagnosis of other pain was associated with an increased risk of OOD. The other pain category was a heterogeneous group of conditions that included, for example, trauma, arthritic diseases, and cancer pain. Increased OOD risks were observed with alcohol, opioid, and other substance use disorders,

as well as with psychosis and depression.

Study 2 included an exploratory analysis of switching to or adding an IR/SA or ER/LA opioid and risk of subsequent OOD. This cohort consisted of patients who were exclusively on a Schedule II IR/SA opioid regimen prior to the switch/add event. Dose was defined as daily mean MME, or DMME, calculated for the 3 months before and after the switch/add event, the pre-switch and post-switch DMME.

Approximately 20 percent of 53,257 eligible patients switched to or added an ER/LA opioid. Patients who switched to or added an IR/SA opioid had a median decrease in dose, while those who switched to or added an ER/LA opioid had a median increase in dose. Of note, while the pre-switch dose was included in the analysis, the post-switch dose was not.

As previously described, propensity score weighting was used to adjust for risk factor imbalances between the two groups; then a Cox proportional hazards model was used to estimate the

hazard ratio. The meta-analysis indicated that there was a significantly increased risk of OOD in patients who switched to or added an ER/LA opioid, a group who also experienced an increase in dose, compared to patients who switched to or added an IR/SA opioid. As the model did not adjust for the change in dose, the observed results should be interpreted with caution.

The interpretation of the meta-analysis was not straightforward and faced similar challenges as Study 1. There were many risk factors studied. There was the potential for chance associations and insufficient statistical power for some analyses. The final risk factors were selected based on statistical cutpoints, which led to including different variables in fully adjusted models across sites.

For example, sedative, hypnotic, and gabapentinoid use were associated with increased OOD risks at VUMC but did not meet criteria for inclusion in the final fully adjusted models at the other three sites, and observed associations for

individual factors varied widely across models and sites.

Having a substance use disorder diagnosis and having a higher opioid dose at baseline were the strongest and most consistent risk factors for OOD at each study site and in the meta-analysis. For dose in general, the OOD risk increased as the baseline dose increased. Both of these associations are known and generally consistent with the published literature.

Baseline diagnoses of depression or psychosis and baseline benzodiazepine, antipsychotic, and antidepressant use were all associated with increased OOD risk at multiple study sites and in the meta-analysis. Use of benzodiazepines and antidepressants was quite common, although the antidepressant category was heterogeneous, including both CNS and non-CNS depressants.

Baseline formulation was not associated with OOD in the main analysis. In an exploratory switch/add analysis, patients who switched to or

added an ER/LA opioid had a higher risk of an OOD compared to patients who switched or added an IR/SA opioid, but there were some important caveats to this finding.

First, dose changes within predominant opioid moiety were not included in this analysis, so the risk associated with increasing from 20 to 40 milligrams of IR oxycodone per day could not be compared to switching from 20 milligrams IR to 40 milligrams ER oxycodone per day as an example.

Second, the change in dose from the switch/add event was not included in the model. This analysis was not able to disentangle the increased risks due to changing dose from the risks associated with the inherent properties of ER/LA formulations; however, the results suggest that the increase in dose may have been the primary driver of the increased OOD risk in patients who switched to or added an ER/LA opioid, although some contribution of the ER/LA formulation cannot be ruled out.

The last part of my talk will provide an

overall summary and interpretation of the Study 1 and Study 2 results.

These studies had substantial strengths, but the interpretation and communication of findings must be balanced by considerations when understanding the results, including generalizability and what the studies were and were not designed to do. Some key strengths of the study were that there were large multisite studies with broad geographic and sociodemographic coverage, including some Medicaid and safety net sites.

The study was guided by external experts and had validated outcome measures, as well as prespecified protocols and analysis plans. Study 1 included prospective longitudinal patient-reported data on misuse, abuse, and OUD collected at prespecified time points and linkages that allowed capture of fatal overdoses.

Some of the key limitations were that the studies were not designed to examine the risks associated with shorter term, non-prescribed, or

changes in opioid therapy over time, including tapering or discontinuation. It is unclear how estimated incidence and prevalence compared to groups without long-term opioid analgesic use, and the studies were not designed to evaluate outcome interdependency, for example, OUD and OOD.

There was limited generalizability. For example, Study 1 recruited heavily from integrated and managed care populations, and the study data were captured during a specific time within an evolving opioid landscape.

To summarize the high points of the prospective and cross-sectional studies, the 12-month incidence of misuse in new long-term opioid therapy patients was just over 20 percent, while the 3-month prevalence in patients on opioid therapy for at least 12 months was approximately 14 percent. The incidence of abuse was approximately 9 percent, while prevalence was 6 percent. The incidence of addiction, measured as moderate-to-severe OUD, varied by definition and by cohort, ranging from 1.4 to 5.8 percent, with

prevalence ranging from 2.7 to 6.3 percent.

These risks are within ranges described in the published literature. They are described in the boxed warning and other sections of opioid analgesic labeling.

In Study 2, the 5-year cumulative incidence of OOD in patients new to long-term Schedule II opioid therapy was between 1.4 and 4.1 percent, while the 5-year OOD incidence rate was between 3.1 and 8.3 per 1,000 person-years. These results may underestimate overall OOD risk in patients with new long-term opioid use due to cohort exclusions, potential attrition bias, limiting the analysis to the first OOD event only, and the potential for incomplete capture of OOD events.

The intentionality codes performed poorly, limiting our ability to distinguish suicide attempts from other types of overdoses. These estimates were within ranges reported in the literature but direct comparisons were challenging. These risks are described qualitatively in the boxed warning and other sections of opioid

analgesic labeling.

Regarding the risk factor findings, there were a large number of analyses from multiple models, cohorts, outcomes, and outcome definitions, making synthesis and interpretation of findings challenging. The risk factor analyses were exploratory, as the models were constructed based on predetermined statistical cutpoints instead of known or suspected causal relationships.

The strongest and most consistent risk factors align with opioid labeling: a personal history of a substance use disorder; higher opioid doses, particularly for the risk of overdose; mental health disorders; and use of CNS depressants. Other associations were also observed but were not consistent across models, cohorts, or outcomes. Examples include sex, age, opioid moiety, ADF use, comorbidity score, number of adverse childhood experiences, and gabapentinoid use.

These studies provide a range of quantitative estimates for misuse, abuse, OUD, and

overdose in a specific patient population with long-term opioid analgesic use, and these risks are qualitatively communicated in the current opioid labeling. The main risk factor findings generally align with current opioid labeling, namely that individual patient characteristics -- for example, substance use history and mental health conditions -- are important considerations when assessing risk. And if opioid analgesics are indicated, it is important to prescribe the lowest dose and for the shortest time needed, with extra caution at dose increases and in patients using other CNS depressants.

These concepts are also included in opioid risk evaluation and mitigation strategy-compliant continuing education, and other educational programs and guidelines.

Despite some important limitations, the ER/LA opioid PMR studies add to the body of evidence on risks associated with long-term use of opioid analgesics, particularly by incorporating prospectively collected data, validated outcome

measures, and database linkages. Thank you.

Clarifying Questions

DR. BATEMAN: Okay. Thank you.

We will now take clarifying questions to the FDA. When acknowledged, please remember to state your name for the record before you speak and direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up questions with, "That is all for my questions," so we can move on to the next panel member.

We have about 15 minutes for these questions, so again, we'll limit panelists to one question to begin with, and then circle back around if we have time for additional questions.

Are there any clarifying questions for the FDA? Dr. Amirshahi?

DR. AMIRSHAHI: Hi. Maryann Amirshahi. My question is for Dr. Kornegay, and specifically

slide 66 for Study 1. When we looked at how we define moderate-to-severe OUD, it says that we included patients with adjusted criteria for OUD related to prescription opioid use or those for OUD related to heroin.

My question is that during this study period, the heroin wasn't really heroin anymore in a lot of areas, and there were a lot of patients that didn't report using heroin, and they would say that I'm using fentanyl. So is there a way that we can, or did we try to capture specifically illicitly manufactured fentanyl as a drug of abuse when assessing the OUD criteria? Thank you.

DR. KORNEGAY: Dr. Cynthia Kornegay, DEPI, FDA. I am not aware that illicitly manufactured fentanyl or illicitly manufactured products of any kind were captured separately, or separately probed, during the OUD classification; however, the OPC may have more information on that specific question. Thank you.

DR. AMIRSHAHI: Thank you. I appreciate it because during this time, really, we're not seeing

heroin abuse; it's all fentanyl. So it's something that I think is important to capture.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: Mark Bicket. On slide 68, it mentions about the outcome validation with the FDA concurring about the measurement tools used in 3033-1, and my question is about the FDA's thinking about the primary outcome of moderate-to-severe OUD and its relationship to abuse.

One of the questions is, what would be the FDA's thinking about the relationship of the two, and was there consideration for viewing any opioid use disorder, whether it was mild, moderate, or severe, as an important outcome for 3033-1?

DR. McANINCH: Thanks. Jana McAninch, OSE. We did ask the OPC to include data on any opioid use disorder, so two or more criteria, and that is in the briefing document. The primary definition of moderate-to-severe opioid use disorder was a way to operationalize the outcome of addiction, which of course is not a diagnosis per se but is generally discussed as aligning reasonably well

with moderate-to-severe symptomatology of opioid use disorder, so that's why that decision was made.

Abuse was measured separately using the POMAQ, and I think one of the challenges of the way the study was designed was that those three outcomes were measured separately, as kind of separate concepts; although, of course, they're highly related. There was a composite measure also that was a secondary outcome, but we didn't look, really, at the interrelatedness of those outcomes, specifically, as part of the study design --

DR. BICKET: Thank you.

DR. McANINCH: -- or we didn't require that to be done. Thanks.

DR. BATEMAN: Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. My question is actually for Dr. Hana Lee related to the second study. You mentioned a couple of times that there was concern about potential selection bias due to attrition. And in the presentations earlier from Dr. John Seeger, it was emphasized that actually when they were looking at the

characteristics of patients over time, that there was no evidence of a change in the population over time, other than SUD.

So what I was wondering is are there remaining concerns at the end of FDA, or is it more raised as a theoretical concern? And if there are remaining concerns, would an analyses that adjust for censoring would, for example, address the concern?

DR. LEE: Hana Lee, Office of Biostatistics at FDA. We did not have data on differences between those who were lost and those who remained, and I believe what OPC presented is the characteristics over time among those who remained in the cohort.

So if the patients who were lost and patients who remained in the cohort are substantially different in terms of risk of OOD, then still the bias could arise, and we did not have data to empirically check whether the characteristics are different or not.

DR. HUYBRECHTS: Thank you.

DR. BATEMAN: Mr. Phillips?

MR. PHILLIPS: Thank you. Rick Phillips, patient representative. Throughout this data, the misuse and abuse have been lumped together, and that in particular is difficult for the elderly population because misuse could mean no use, meaning that they had an undesirable result and stopped taking the medication or took it less often than prescribed.

Do we have a breakdown of misuse and abuse, particularly in the over 55 population? I think misuse is very, very different than might be implied with that general label. Thank you.

DR. MEYER: This is Tamra Meyer, Division of Epidemiology. Can I make sure I understand your question? So I think you were asking about misuse and abuse prevalence, separated prevalence or incidence. Was that one part of your question?

MR. PHILLIPS: That's correct.

DR. MEYER: Okay. And then I heard you also asking about the incidence and prevalence in certain age groups. Is that correct?

MR. PHILLIPS: In particular, the over 55 or over 50 group?

DR. MEYER: Okay. Give us one moment, and we can pull up a slide to help with the first part of the question.

Could we pull up page 62 of the briefing document, please?

(Pause.)

MR. PHILLIPS: I noticed in the first presentation that constipation was a reason for misuse. If we're measuring misuse in terms of constipation at over 50, lumping it with abuse implies that the patient was doing something wrong. And frankly, if constipation is one of the reasons for misuse, then we really have to separate it because it looks as if those older categories are misusing their medication by taking too much. In fact, they're not misusing it by taking too much; they're misusing it by taking too little.

DR. MEYER: Yes. Mr. Phillips, this is Tamra Meyer, Division of Epidemiology. Thank you so much for your comments on that, and we're very

interested in hearing the advisory committee's discussion and opinion on the way that these were measured. Thank you.

DR. BATEMAN: Okay. Thank you.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Hi. Elizabeth Joniak-Grant. First, I really applaud the inclusion of pain-adjusted DSM-5 criteria for OUD. I think that's been kind of missing for a long time in the data that comes out.

I wanted to ask a little bit about the reasoning behind not including it for misuse. There are a number of misuse reasons, and could really signal more poorly managed pain versus potential for OUD. For example, "The dose my healthcare provider prescribed wasn't strong enough; to sleep better; I had more pain," those types of things. So I was wondering what the rationale was to include it in the one category or outcome and not in the misuse outcome. Thanks.

DR. McANINCH: Jana McAninch, OSE. Thanks for that comment. I think that the terminology in

this field is always challenging, and misuse is often used as kind of an umbrella term. In these studies, misuse and abuse were meant to be mutually exclusive categories separated by the intent of use. So the misuse was use not as directed, but with therapeutic intent, whether it was for pain or to manage some other symptom. So although it didn't separate out use to manage pain specifically, that is the intent of separating the abuse and misuse behaviors, if that helps.

DR. JONIAK-GRANT: Okay. So if I'm understanding you correctly, basically we can presume when it's flagged as misuse, it was for therapeutic purposes and by extension for pain management --

DR. McANINCH: Correct.

DR. JONIAK-GRANT: -- versus abuse would then be not.

DR. McANINCH: Non-therapeutic purposes.

DR. JONIAK-GRANT: Okay. Thank you.

DR. BATEMAN: Dr. Reich?

DR. REICH: Thank you. Jeff Reich.

Clarifying questions, and maybe suggestions, around some of the subgroups that I think can help clinicians as this data rolls out and is integrated into practice, and clinical thought can help.

For example, in the substance use disorder categories, sometimes you spike out alcohol. You lump together cannabis and stimulant use. I wonder if those could be parsed separately; and more importantly, also parsing out the pain subgroups because you parse it by anatomy, but I think the way clinicians think about it now, maybe always, is by process.

For example, you have other including trauma, arthritic pain, I think you said, but you also have a category for joint/limb, so that's a little muddled. Neuropathic pain; where does that fit in? Cancer pain looks like it's been lumped into other. For example, you call out gabapentin as kind of a separate risk but, really, what's driving that is the use of gabapentin in complex regional pain syndrome or difficult-to-control pain, and that's really what's driving the risk.

So understanding, I think, the mechanisms there would be really helpful.

DR. MEYER: This is Tamra Meyer, Division of Epidemiology. The questions I heard you asking were whether the substance use disorders and the pain subgroups could be parsed more.

DR. REICH: A little finer and a little bit more mechanistically.

DR. MEYER: And then I heard you ask a second question about where neuropathic and cancer pain fit.

DR. REICH: Well, that would be part of parsing out the categories of pain.

DR. MEYER: Okay. I think we can at least answer where those were categorized, those types of pain could be categorized, so turning that over to Dr. Kornegay. And then the OPC might have more information on being able to parse things more substantially. Thanks.

DR. KORNEGAY: Dr. Kornegay, DEPI, FDA. The substance use categories are actually parsed out further in the demographic and unadjusted analyses.

For some of these, substance use -- and they're parsed out very finely -- cannabis, stimulant, cocaine, et cetera, et cetera -- there were some small numbers in those cells. So for the fully adjusted analyses, we just rolled them up into the larger categorical groups.

The pain categories were based on a literature standard, and at FDA, we do not have the data to parse those out further or differently; however, the OPC might be able to shed some more insight on how those could be managed in a different manner. Thank you.

DR. MEYER: And, Dr. Kornegay, do you remember or recall where the neuropathic and cancer pain fit? Thanks.

DR. KORNEGAY: Yes, I'm sorry. Dr. Kornegay, DEPI, FDA. Neuropathic pain was its own category within the pain categories that were used as risk factors in these analyses. Cancer-related pain was in the other category, so unfortunately it was grouped in with all of those other various diseases. Thank you.

DR. BATEMAN: Dr. McCann?

DR. McCANN: Hi. Mary Ellen McCann. I have just a very quick nomenclature question. The OPC consistently used the term "addiction," and the FDA used "opioid, uh, use disorder." And I guess my question is, was that intentional by the FDA?

DR. McANINCH: Thank you. This is Jana McAninch, OSE. The language used in the PMR language was addiction, and actually the original PMR in 2013 was issued the same year that the DSM-5 came out, if I'm remembering that correctly. So the terminology shifted from abuse and dependence to opioid use disorder.

I think that the terminology has evolved over the time that these studies were being conducted, so I think that's one issue; and then I think the OPC is likely trying to use the terminology that was in the PMR language itself. But the addiction in the studies themselves was operationalized using the DSM-5 criteria, either pain adjusted or not pain adjusted, for opioid use disorder, mild, moderate, severe. So I think we

tended to use the opioid use disorder terminology more just based on the outcome definition.

DR. McCANN: Thank you.

DR. BATEMAN: Okay. Thank you.

We will now break for lunch. We will reconvene again in this room at 1:00 pm Eastern Time. Please take any belongings you may want with you at this time. Panel members, please remember there should be no discussion of the meeting topic during the lunch break amongst yourselves or with any member of the audience. Additionally, you should plan to return around 12:55 pm to ensure that you are seated before we reconvene at 1:00 pm. Thank you.

(Whereupon, at 12:13 p.m., a lunch recess was taken, and meeting resumed at 1:00 p.m.)

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

(1:00 p.m.)

Open Public Hearing

DR. BATEMAN: 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, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the industry group. For example, this financial information may include the industry group's payments of your travel, 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 on the open public hearing process. The insights and comments provided can help the agency and this committee in their considerations of the issues 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 that this open public hearing be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

For those of you presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder,

please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please state your name and any organization you represent for the record. You have 10 minutes, speaker number 1.

DR. ABRAMS: Hi there. Good afternoon. Can I be heard ok?

DR. BATEMAN: We can hear you.

DR. ABRAMS: Excellent.

Hi. I'm Dr. Michael Abrams, a senior health researcher with Public Citizen, a nonprofit, consumer advocacy organization founded in 1971. We currently have over a half a million members and supporters throughout the country. Our health research group, of which I'm a member, uses research and advocacy to address regulatory issues that are the responsibility of the HHS and, of course, the Food and Drug Administration, including assessing the safety and effectiveness of prescription medications. I and Public Citizen at-large have no financial conflicts of interest related to today's meeting.

The committee, as you are well aware, is reviewing the results of two postmarketing studies conducted by industry and designed to quantify the incidence of opioid use disorders and overdose events that follow the initiation of long-term opioid analgesic use for medically supervised non-cancer pain control. Combined results from both studies also report on various demographic, healthcare, genetic, and other factors that may correlate to use disorder or overdose incidence.

The primary results are, I think, well summarized in table 22 of the FDA briefing document. That table shows that among persons initiating long-term use of opioids for non-cancer pain, the 12-month incidence of abuse, defined as intentional repeated or sporadic use for the purpose of the psychological or physical effects, was 6 to 9 percent, and the 5-year incidence of moderate-to-severe DSM-5 opioid use disorder was 3 to 6 percent. So-called "pain adjustment," quote/unquote, of the DSM diagnostic criteria yielded 5-year incident rates of 1 to 3 percent.

The FDA briefing material notes, we think appropriately, that these ranges, like those generated before them, are quite variable, and the more conservative estimates may well miss valid signs of opioid use disorder. In fact, results from these new studies show that substance misuse, defined by intentional inappropriate use of one's prescription, is evident in a full 15 to 23 percent of opioid initiators within 12 months.

Despite complexities in the misuse to formal use disorder continuum, that high misuse estimate we believe marks one of many substantial risks associated with extended opioid use for non-cancer pain. Such high risks of misuse, we think, should be quantitatively and prominently stated on all opioid product labels.

Table 22 also shows that the 5-year incidence of overdose events, including fatalities, range from 1 to 4 percent. These results are consistent with previous estimates according to the FDA reviewers. Our concern about the validity of these results is that only 17 percent, just under

one-fifth of the original study cohort, was traceable for the entire 5-year study period.

A curious result also emerged from this analysis. Overdose and death rates were apparently highest for the first 3 months of the 5-year follow-up study. FDA reviewers on page 96 of their public briefing document proffer three explanations for the surprising finding.

First, during the first 3 months of long-term opioid use, it may be that it is the most intensive period of use, and second, that there may be a quote/unquote "depletion of susceptibles or vulnerables with time," or three, that early titration of the medication may increase unexpected overdose risks.

It is concerning to us that these explanations seem biased towards the notion that risk of overdose is transient and short-lived among those using opioids for chronic non-cancer pain, when we know from much empirical data that increased tolerance, withdrawal, and previous overdose events are distinctive risk factors for

future events. Accordingly, we encourage the FDA and others to interpret this tenuous finding cautiously.

Despite such limitations, these overdose results do reinforce the prospect of major harms associated with long-term opioid use in non-cancer patients. Accordingly, the FDA should require that all opioid product labels clearly and quantitatively, such as it can be done, state these risks for consumers and prescribers.

We agree that the findings for various other factors that appear to influence opioid use disorder and overdose risks in these studies are exploratory and underpowered to assess the effects of the many factors considered. Nonetheless, right now I want to make three cautionary observations about those findings.

First, significant effects were observed with gabapentinoid use, showing that these seizure medications, widely used off label for neuropathic pain, correlate with increased risk for opioid use disorder and overdose. Public Citizen has an open

petition from 2022 to the DEA and the FDA to schedule gabapentin and gabapentin enacarbil, which currently are unscheduled, even as they closely resemble the gabapentinoid pregabalin, a substance that has been on the DEA Schedule V for some time.

Caution number two, formulation, including abuse-deterrent formulation, generally does not correlate in these studies with either the incidence of opioid use disorder or overdose. These findings support the fact that full opioid agonists are nearly universally associated with a heightened risk of opioid use disorder and overdose.

The suggestion, as was made by the FDA in the packet, that hydromorphone is more pernicious than other opioids, or that abuse-deterrent formulations are effective as reducing opioid-related morbidity and mortality, are, we think, tenuous inferences from these and other data.

A final caution about these analyses, the three gene specific burden scores reviewed in these

postmarketing studies were not significant correlates of future opioid use disorder. These negative findings are consistent with the limited predictability of genome-wide association studies regarding the variance and expression of the opioid use disorder phenotype. We thought it was important to point that out.

Overall, the two new postmarketing studies thus would conclude and we think are confirmatory of substantial risks, and of a few mediators associated, or not, with long-term opioid analgesic treatment for non-cancer pain. These studies, however, we think reveal little new information, and they do not address the overall risks to benefits of opioids for pain relief as such.

Moreover, these postmarketing studies represent what we think is an off-the-mark response to a 2012 petition that Public Citizen submitted to the FDA with collaboration from Physicians for Responsible Opioid Prescribing, and you'll hear from Dr. Kolodny later today. That petition requested that the label of all opioid analgesics

be changed to unambiguously state that non-cancer pain treatment with such drugs should be limited to the treatment of severe pain, and that dosing should be limited to 100 morphine equivalents or less per day for a maximum period of 90 days.

We believe that our requests from 2012 continue to be appropriate, and the results of these long overdue postmarketing studies that we're talking about today do not eliminate the need for these labeling changes. It is in fact disturbing to us that the FDA has yet to fully respond to our 2012 petition, even as there is still no new data showing that long-term use of opioid analgesics for non-cancer pain is overall, and in comparison to other existing therapies, reasonably safe and effective. Thank you.

DR. BATEMAN: Thank you.

Speaker number 2, please state your name and any organization you are representing for the record. You have 15 minutes.

DR. KOLODNY: Thank you. My name is Dr. Andrew Kolodny. I am the President of

Physicians for Responsible Opioid Prescribing, PROP. I've been working on the opioid crisis for the past 20 years as a former health official for New York City; as an addiction psychiatrist treating opioid use disorder; as the medical director of a university-based research collaborative; as an advocate pursuing more forceful FDA regulation of opioid manufacturers; and as an expert witness in the opioid litigation. My statement today is on behalf of PROP. PROP has no financial relationships with pharmaceutical companies or other life science corporations, nor do I personally. I have paid for my own travel to the meeting.

The FDA's decision to require opioid postmarketing studies in 2013 stemmed from an effort launched in 2012 in which health officials, medical experts, and public health advocates filed an administrative request, a citizen petition, to FDA seeking changes to opioid labels. We wanted long-term and high-dose opioid use to become explicitly off label so that FDA would be able to

prohibit manufacturers from promoting aggressive opioid use.

Essentially, we were asking FDA to correct a terrible mistake, a mistake that led to a massive loss of life and an epidemic of opioid use disorder impacting millions of families across the country. This mistake I'm speaking about was approval of a label on opioid analgesics that gave manufacturers a green light to claim that long-term and high-dose opioid use is safe and effective for common chronic pain conditions, conditions where we know that opioids are more likely to harm patients than help them. We requested removal of moderate pain from the indication, and we asked for duration of use and an upper dose on labels such that long-term and high-dose use would become off label.

In September 2013, FDA responded with a partial acceptance. It removed moderate pain from the label. For our other requests, FDA agreed that evidence of long-term safety and efficacy was lacking, but rather than changing the label, it requested PMR studies on efficacy and safety; and

it said that those studies should be completed by 2018. Yet, in 2025, we still don't have an efficacy trial, and today for the first time we're receiving results on the safety trials.

So what have we learned? This table is from page 44 of the industry briefing document. I've highlighted in orange the figure showing 22.5 percent of patients started on extended-release opioids met DSM-5 criteria for opioid use disorder within the year. You see that again highlighted in orange.

We have known for many years that about a quarter or more of patients on long-term opioids suffer from OUD, but these have been prevalence estimates. To my knowledge, this is the first study to determine an incidence. The findings are striking and disturbing, and they raise ethical questions because so many study subjects were harmed.

OUD, including mild OUD, is not benign. OUD is a devastating, life-altering, and life-threatening condition. For obvious reasons,

the 22.5 percent figure is not a finding that opioid manufacturers would want to highlight. The numbers they seek to highlight appear in bold on this table, again which comes from page 44 of their briefing document. The number they like better is 1.4 percent.

To whittle down 22.5 percent to 1.4 percent required some very fancy footwork, including altering the actual DSM-5 criteria to invent the so-called pain-adjusted DSM-5 criteria. But DSM-5 did not require these changes. It already has baked into it an adjustment for diagnosing OUD in patients prescribed opioids. The adjustment is the exclusion of the tolerance and withdrawal criteria for patients who take opioids as prescribed.

The DSM-5 work group that created the DSM-5 OUD criteria did so with an understanding that the criteria would be used for patients, patients who use opioids medically and non-medically. The criteria was not created exclusively for users of illicit opioids. Concern that DSM-5 needed a so-called pain adjustment did not come from the

medical community. It did not come from professional societies or addiction specialists. It did not come from NIH-funded research. The call for a pain adjustment came from opioid manufacturers, and it is supported by only one industry-funded study.

I have never heard a complaint from addiction specialists that the DSM-5 overdiagnosed OUD in patients with pain and needed an adjustment. To the contrary, I have heard clinicians complain that the criteria can underdiagnose OUD because pain patients receiving regular prescriptions do not need to engage in the DSM-5 drug-seeking behavior criteria.

The OPC would have you believe that the pain-adjusted DSM-5 criteria are validated, but their pain adjustment lacks face validity. This is not the first time that we are hearing from opioid manufacturers that patients on long-term opioids who engage in addictive behaviors should not be considered addicted. For many years, the industry pushed the false, dangerous, and thoroughly

debunked concept of pseudoaddiction, which claimed that addictive behaviors were caused by underdosing opioids; that patients who appeared addicted needed a higher dose of opioids.

But really, all of this gets worse. The OPC appears to expect us to believe that mild OUD is clinically unimportant. This is false. Mild OUD is not benign, it does not easily resolve, and without treatment, it is unlikely to remain mild. Any results from Study 1 that are included on opioid labels should not exclude the large number of patients who developed mild OUD.

The work group of experts that created the actual DSM-5 OUD criteria determined that a patient meeting two or more criteria, not four or more criteria, should be diagnosed with OUD. They came to this conclusion because patients meeting two or more criteria are expected to be experiencing clinically meaningful distress.

As you consider the disturbing results from Study 2, which found that thousands of patients in the sample experienced overdoses, and hundreds died

from overdose, please keep in mind that this was likely to be a large undercount because of missing data from patients who had changes in insurance. Also keep in mind that beyond the 5 years reported on this graph, it is likely that overdoses continued to mount.

This study, which is cited by the CDC guideline, was done in Canada, where a single-payer system allowed for easier, long-term tracking of outcomes. They found that deaths continued to mount beyond 5 years. For men, deaths were still mounting 12 years later. Another finding in this study was that one in every 32 patients on long-term, high-dose prescription opioids lost their life to overdose within two and a half years.

Study 1 and 2 demonstrate what we have long known that long-term opioid use is dangerous, and that the higher the dose, the more dangerous it becomes. So is the substantial risk of starting a patient on long-term opioids worth taking? In other words, do we have adequate evidence that long-term opioid use helps many patients? The

answer is no.

In the AHRQ evidence review that was used to inform the development of the 2022 CDC guideline, AHRQ concluded, quote, "Evidence on long-term effectiveness is very limited, and there is evidence of an increased risk of serious harms that appears to be dose dependent."

In a CDC statement published in the New England Journal of Medicine CDC wrote, "The science of opioids for chronic pain is clear: for the vast majority of patients the known, serious, and too-often-fatal risks far outweigh the unproven and transient benefits." In that same paper, the CDC also wrote, quote, "We know of no other medication routinely used for a non-fatal condition that kills patients so frequently."

I think we're missing some of the remaining slides. Is there another slide after the CDC? No? That's ok. The 2022 VA DoD guidelines stated, "We recommend against the initiation of opioid therapy for the management of chronic non-cancer pain."

In the discussion today, you will be asked

by FDA to comment on opioid labels and on how FDA should communicate what it learned from these studies. I don't have the slide to show you, but I was going to put up a slide indicating the current label on extended-release opioids. I'd like you to consider the current label and the current indication.

The label is an FDA stamp of approval that communicates that long-term opioid use is safe and effective. And since the label continues to omit a recommended upper dose, it implies that opioids are safe and effective, even when dangerously high doses are prescribed. The existing label also gives opioid makers a green light to promote opioids for conditions where they are more likely to harm than help.

You have an opportunity today to help FDA correct a terrible mistake. In your discussion on how the study results should inform labeling, I urge you to let FDA know that opioid labels should reflect the scientific evidence. On-label use should be limited to short-term acute pain and to

palliative care, the conditions where benefits are likely to outweigh risks. Thank you.

DR. BATEMAN: Speaker number 3, please state your name and any organization you are representing for the record. You have 10 minutes.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman, President of the National Center for Health Research. We do not accept funding from pharmaceutical companies or any entities that have a financial interest in our work, so I have no conflicts of interest.

Thank you for the opportunity to share our views at this very important meeting. I'm speaking as a scientist trained as a postdoc in psychiatric and psychosocial epidemiology at Yale Medical School, and as someone who has worked extensively to train patients to understand the risks and benefits of medical products.

On a personal note, a few years ago, I was prescribed 3 months of opioids after two different surgeries with absolutely no warnings about long-term use; and just 2 days ago, I was with a

hospitalized relative who was told nothing about the risks when she was prescribed opioids after surgery. When I was prescribed opioids, I knew to switch to acetaminophen very quickly, but I know from these experiences how important FDA labeling and warnings are, and the harm that's done when those aren't up to date and changes are delayed.

Today, I'll focus on the three studies that are discussed at this meeting, as well as the impact of current labeling that continues to mislead patients and physicians about the benefits and risks of opioids for long-term use.

Regarding labeling, if the FDA does not improve the accuracy of its labels on all opioids, patients will continue to spiral into opioid addiction through no fault of their own. I want to thank the FDA for previously changing the labeling indication from, quote, "moderate-to-severe pain," which now includes only, quote, "severe pain." However, the current labels are still much too broad because they don't restrict use for chronic pain, and they imply that these drugs have benefits

that have never been proven. Labels should have clear warnings to help ensure that the benefits outweigh the risks for all patients included in the indication.

As you all know, almost all medications, whether over the counter or prescription, include a maximum recommended dose, but opioids do not. That must be changed, even if the maximum recommendation dose does include exceptions in specified rare cases.

I've taught courses in training and study design, and data interpretation, and I have two major criticisms of the studies that we're reviewing today. The first is the definition of opioid use disorder as used in these studies.

As you've heard, the DSM-5 has a very good definition of mild, moderate, and severe OUD. The criteria include physiological and psychological symptoms, as well as the impact on a person's social functioning and daily living. These DSM-5 criteria are widely accepted by experts in the field, but they do create a problem for those

interested in selling or prescribing opioids. For example, as you've heard, and you've seen on the Consortium document on page 54, it states that the DSM-5 criteria show a 22 and a half percent incidence of OUD among patients prescribed ER/LA opioids in Study 3033-1.

To reduce that disturbing finding, the Consortium worked with researchers to modify the definition of OUD in two ways. Number one, it includes only moderate and severe OUD, eliminating mild OUD; and number two, it adjusts for pain, and this will bias the results of the study in two inappropriate ways.

First, mild OUD is a very negative outcome, and it often does worsen over time with more severe opioid dependence and dysfunction in daily life. Any clinician will tell you and will give you many examples of mild OUD becoming moderate or severe over the years, and I challenge any unbiased researcher to provide evidence that contradicts that.

Number two, the DSM-5 criteria are already

adjusted for pain, as you've heard, so it makes no sense to revise it to add another so-called adjustment for pain. If you adjust for pain when measuring OUD, you are undermining the validity of the OUD outcome measure.

The Consortium's adjustment for pain in their data analysis reduces the number of patients categorized by them as having OUD, but it does not reduce the number of patients who actually have opioid use disorder, which, as the FDA noted today, can be related to the desire to avoid withdrawal pain, as well as the desire to feel euphoric.

There are other problems as well. For example, the retrospective study had an extreme amount of missing data, making the results difficult to interpret. We know that Medicaid patients often go in and out of Medicaid, and patients with private insurance change policies. And that's why it's so difficult to study U.S. opioid patients over long periods of time, and it's much easier to evaluate that in other countries.

So again, I would mention, as Dr. Kolodny

did, the study by Kaplovitch, et al., of more than 32,000 patients in Canada. They found that the number of opioid-related deaths continued to grow over the years. They didn't just grow the first, and second, and third year. They continued to grow, ending up at about 2 and a half percent deaths for the men up till 12 years after starting opioid therapy for chronic pain, and plateauing just below 1.5 percent for women in the 8 years after starting opioid therapy for chronic pain. That's a small percentage, but it's a lot of patients; and we need to consider the percentage of deaths and OUD in the context of the unproven benefits of long-term opioid use.

As you know, research indicates that many of these patients would have managed pain without long-term opioid use if they had been encouraged to use non-opioid medications when the pain first started after their surgery or accident. Given the lack of evidence of the benefits of using opioids for chronic pain, 22 and a half percent of people with OUD, and 2 and a half percent of men, and

1 and a half percent of women dying from long-term opioid use should be considered unacceptable because FDA law requires that there is evidence for safety and efficacy for the specific indication on the label.

I want to just say a few words about the U.S. Agency for Healthcare Research and Quality, known as AHRQ, which reviewed 115 randomized-controlled trials and 40 observational trials on opioids' benefits. That federal agency's report concluded, and I quote, "In observational studies, opioids were associated with increased risk of an opioid abuse or dependence diagnosis; overdose; all-cause mortality; fractures; falls; and myocardial infarction compared to no opioid use," and that the risk was dose dependent for almost all those outcomes.

The report also concluded that no randomized-controlled trial evaluated immediate or long-term benefits of opioids compared to placebo; and that, quote, "Limited evidence indicated no difference between long- and short-term acting

opioids ineffectiveness, but long-acting opioids were associated with increased risk of overdose." In conclusion, we should more seriously consider what the AHRQ review stated as we weigh the implications of the Consortium data today.

Many years ago, the FDA promised to revisit the evidence regarding the risks and benefits of extended-release and other long-term opioid use, and despite black boxed warnings, these labels do not quantify risk. And as a result, FDA is not providing physicians or patients with all the information they need to make informed decisions.

On Saturday, I heard medical staff tell my hospitalized relative upon discharge after surgery, "Don't worry about the pain. We can give you medication to control the pain." I then picked up her prescriptions, which included opioids. At the hospital pharmacy, I was not told about the risks and benefits of opioids for long-term use, and there were no written warnings on the bottle of pills. I respectfully ask this committee to urge the FDA to rectify that situation. Thank you.

DR. BATEMAN: Thank you.

Speaker number 4, please state your name and any organization you're representing for the record. You have five minutes.

DR. ALEXANDER: Hi. Good afternoon. It's Caleb Alexander. Can you hear me?

DR. BATEMAN: We can.

DR. ALEXANDER: Great. Thank you.

I'm a pharmacoepidemiologist and practicing internist, and a Professor of Epidemiology and Medicine at Johns Hopkins. By way of disclosures, I'm former Chair of the FDA's Peripheral and Central Nervous System Advisory Committee. I co-direct an FDA-funded Center of Excellence, and I've served as a paid plaintiff's expert in opioid litigation.

I'm also a developer of a patent-pending platform, Stage CARES, that supports opioid abatement, and I co-direct the Opioid Industry Documents Archive, which is a digital archive co-created by UCSF and Johns Hopkins that contains millions of documents that shed light on the root

causes of the opioid crisis. The opinions expressed herein are my own and not necessarily the views of Johns Hopkins.

Today, we're asked to consider whether the results of two recently completed industry-funded observational studies should prompt changes in opioid regulation. Candidly, it's hard not to be a little jaded when opining on these matters because the FDA's historic response to the epidemic has been so muted relative to its regulatory authority and its typical careful exercise of evidence-based medical product regulation. With that said, here we are, so let's consider the facts.

There's a mountain of evidence regarding the risks of long-term opioid use. We don't have one or two studies; we have hundreds, unequivocally demonstrating non trivial risks from long-term opioids. Many of these have been well designed, non-industry-funded investigations, with carefully developed protocols to maximize causal inference.

The conclusions from these studies are abundantly clear. The risks of opioids, which are

dose and duration dependent, are deadly serious, and they're hard to mitigate through clinical prediction rules, abuse-deterrent formulations, or other risk mitigation approaches despite the clinical appeal.

The new studies we're asked to consider don't refute any prior work, nor are they inconsistent with it. Of course, one should not be surprised that different studies yield different estimates of the frequency of harms given that studies vary in their inclusion and exclusion criteria, exposures and outcomes, analytic approaches, and so on. I must also say that the concept of pain-adjusted addiction is a little curious. It does remind me a little of industry's enthusiasm for the debunked concept of pseudoaddiction.

While I will leave it to others to disentangle these concepts, I will point out that there are incredibly high rates of pain among those with opioid use disorder, and it's not clear, to me at least, that the presence of pain with a

diagnosis of addiction makes the diagnosis any less severe or the prognosis without treatment anymore benign.

Another important point is that when it comes to the value of a drug, of course it's not just about risks. It's about risk-benefit balance, which raises another elephant in the room, which is more than 25 years after the epidemic began, the striking paucity of evidence about the benefits of long-term opioid therapy.

Opioid manufacturers have not performed such a suitably designed trial to gain approval for dozens of new products. And why would they? Who could blame them if the FDA hasn't required this as a criteria for market access? Nor have manufacturers fulfilled the FDA's postmarketing requirements by demonstrating long-term efficacy, more than 12 years after such an expectation was established.

The FDA has also queried today about the relevance of the findings given market declines in opioid prescribing and soaring deaths from

fentanyl. It's true that opioid oversupply has decreased and that fentanyl takes far too many lives, but none of this diminishes the importance of aligning the drug label with evidence. And while the FDA briefing helpfully included lots of data points, I'm not sure it emphasized, or frankly even mentioned, that thousands upon thousands of individuals continue to die every year preventable deaths from prescription opioids in the United States.

It's easy to get lost in the data, and indeed at meetings like these, the amount of scientific information can be overwhelming. But let's not lose the forest from the trees. For a product with crystal-clear, dose-dependent harms and unclear benefit, why do we still have a label that omits a recommended upper dose limit and that suggests opioids are safe and effective for long-term use?

For all the regulatory actions that the FDA has taken to help address the epidemic, it has yet to undertake the single most effective step fully

within its authority, which is to align the label with scientific evidence. The label should be revised to include a recommended upper dose limit and to clearly stipulate that outside of palliative care, use should be short term. As millions of Americans know all too well, there's not a moment to lose. Thank you.

DR. BATEMAN: Thank you.

Speaker number 5, please state your name and any organization you're representing for the record. You have five minutes.

DR. CONNOLLY: Good afternoon. Thank you for the opportunity to speak today. My name is Dr. Nancy Connolly. As an internist, I have spent the bulk of my career practicing primary care. I have fellowship training in infectious disease, integrative medicine, and I am board certified in addiction. Last year, I studied policy with the Robert Wood Johnson Health Policy Fellowship and had the opportunity to give a briefing at the National Academies on illicit drug policy, past, present, and future.

I'm here to ask the committee to carefully consider the effect on my patients and all the people in this country of continuing to support a label on opioids that implies that long-term, high-dose opioid use is safe and effective, when we all know the opposite is true. Other people here will tell you about the robust body of data that exists to support my assertion that opiates used to treat chronic non-cancer pain are both ineffective, toxic, and too often deadly.

I'm going to share a personal story. In roughly 2001, my mother, who had suffered from severely deforming rheumatoid arthritis from her early 20s, was just past 60. She was newly widowed, and was working as a clinical psychologist, having earned her PhD after she finished raising her kids. This was the height of the Purdue marketing blitz, and her primary care doctor seeing her pain started her on opiates. Of course, in the short term the opiates relieved the pain.

There is no such thing as a heritage poppy.

The history of humans' relationship with opiates goes back to before written history. They are effective, powerful, and both useful and extremely dangerous. The concept of an opiate without side effects is similar to having love without the inevitability of grief.

Gradually, my mother's tolerance grew, and her doctor gradually increased her dose. The side effects that emerged were treated as additive conditions rather than predictable effects of the drug. She had constipation and stomach pain, anorexia and nausea. She had mood issues, balance issues. She ultimately had falls, which invariably resulted in increased doses of opiates and a spiral of treating the adverse effects of drugs with other drugs.

The fact that this happened to my mother perhaps just makes it more tangible to me. I have seen this also with mine and my colleagues' patients. In my residency as a cohort, we took care of a group of young sickle cell patients who unquestionably suffered from iatrogenic addiction.

In my current job, I provide urgent care to people suffering from homelessness, and in this cohort, I've seen tolerance, addiction, and pain in every shape and size. Any doctor who has taken care of patients with chronic pain, both on and off opioids, knows that chronic daily opioid use causes significant adverse effects.

I've taken care of thousands of patients over the course of my career. I rarely say never or always, but I can say definitively that I have never cared for a patient on long-term, round-the-clock opioids who did not also have daily pain. In short, long-term opioids do not consistently reduce pain, but they do cause tolerance requiring escalating doses; dependence within weeks; opioid-induced hyperalgesia; reduced physical and psychological function; and a dramatically elevated risk of overdose, addiction, and death.

The FDA label communicated to my mother's doctor that these drugs were safe and effective for daily long-term use. She trusted the FDA, and the

FDA violated that trust. My mother died following a fall in January of 2020. At the time, she was on a 75-microgram fentanyl patch, on hospice with no limits on her dose, and still, her last cogent act was to ask for more. She died in terrible pain.

The studies will never reflect these types of stories, but of course there must be thousands, if not tens of thousands, of similar cases based on prescribing patterns. Without a change to the label, how many more compassionate, harried doctors will believe that the benefits of long-term use outweigh the risks?

We cannot undo the past, but we can prevent more harm from being done. I urge the committee to act decisively. Let FDA know that opioid labels should include a duration of use and an upper dose limit so that they are consistent with the science; that there is no reliable evidence supporting long-term efficacy; that the risks increase substantially over time; and that patients and prescribers deserve clear, unambiguous language that guides safer decision making.

Thank you so much. I don't represent anyone but myself. Thanks.

DR. BATEMAN: Thank you.

Speaker number 6, please state your name and any organization you are representing for the record. You have five minutes.

DR. GUPTA: Good afternoon. My name is Ravi Gupta, and I'm a primary care physician, health policy researcher, and an assistant professor at Johns Hopkins University and Bloomberg School of Public Health. As part of my clinical practice, I care for patients who suffer from chronic pain, as well as those afflicted by opiate use disorder. In my research, I examine FDA regulatory processes, brand name pharmaceutical companies, anti-competitive behavior such as reformulating or tweaking existing drugs, as well as the political, social, and commercial underpinnings of the opioid epidemic. I'm speaking today on behalf of myself, and I'm not representing any institutions or organizations that I am a part of. I have no financial conflicts of interest pertinent to

today's session.

As we are all well aware, hundreds of thousands of people have succumbed to overdose in the opioid crisis, along with the countless friends, families, and communities that have been affected by the epidemic. And as has been well documented, the opioid epidemic began with the promotion and prescription of opioids.

The role of different parties -- including manufacturers, distributors, pharmacies, prescribers, agencies, and civic organizations -- in promoting the sales of prescription opioids has also been described in detail and been subject to numerous lawsuits and settlements.

The fact that at today's convening, three decades after the approval of OxyContin, we continue to discuss the potential safety of long-acting opioids for the treatment of chronic non-cancer pain is remarkable. The promotion of prescription opioids relied on a number of claims that were unproven and directly led to the opioid

crisis. Several of those claims are pertinent to today's discussion.

The first claim, which has been repeatedly made for decades and thus far has been unfounded, is the subject of ongoing postmarketing studies and at issue today: the safety and efficacy of extended-release opioids for the treatment of chronic non-cancer pain.

Going back at least as far as 1986, case reports, poorly designed trials, and observational studies were used to buttress the claim that opioids were safe and effective for chronic non-cancer pain. Many of these studies suffered from basic but vital issues: small sample sizes; lack of control groups; lack of blinding; and incomplete data collection, not to mention conflicts of interest among the studies' authors.

In addition, many of the randomized trials followed patients for short periods, often no more than 3 months, but results were extrapolated far beyond the short period. The paucity of evidence supporting the approval of long-acting opioids, in

particular, for the treatment of chronic non-cancer pain itself, is a travesty, but these studies do not allay concerns of their safety for several reasons.

First, in the prospective study, 3033-1, the inclusion criteria of participants only required 6 months without an ER/LA opiate prescription prior to the first ER/LA opiate prescription. Thus, the included participants were not opioid naive and may already have some tolerance to opioids.

Second, in both ER/LA and LtOT initiative cohorts, 8.4 percent and 5.8 percent of participants developed any incident OUD using the pain-adjusted DSM-5 measure. I will speak on the pain-adjusted DSM-5 measure in a moment; however, using the DSM-5 measure, a remarkable 22.5 percent of ER/LA initiators and 14.8 percent of LtOT initiators developed any incident OUD.

These are non-trivial numbers. Any OUD is OUD. In my clinical practice, I would be exceptionally cautious of prescribing any medication with adverse event rates this high, even

if it's not a deadly condition like OUD.

Another common claim made by the opioid industry was that individuals who appear to be developing addiction to prescription opioids from a doctor may have pseudoaddiction, requiring more opioids to treat what is actually continued pain. Pseudoaddiction was a fictitious new disease stemming from a 1989 case report of a single 17-year-old patient with leukemia.

Despite the absence of a single study validating the creation of this new disease, the use of pseudoaddiction to justify prolonged treatment with opioids from chronic non-cancer pain was widespread. The use of the pain-adjusted DSM-5 criteria to measure OUD in Study 3033-1 is reminiscent of this condition and we believe should be interpreted with caution relative to the DSM-5 measure. Rates of OUD were far higher when the DSM-5 measure was used in this study.

Finally, it's difficult to reconcile the ongoing reliance on ER/LA opioids for chronic non-cancer pain when we have safer and effective

alternatives like buprenorphine and methadone. These medications have the potential to reduce harm and improve lives, yet they remain underused, held back by political hurdles, regulatory constraints, and the deep stigma that still surrounds them.

As a primary care physician, I regularly care for patients who suffer from chronic non-cancer pain. My goal always is to treat their pain, but in the safest and most effective way possible. And as is the case with treatment decisions for any disease, I rely on the FDA's careful evaluation of the safety and efficacy of the treatment. I urge the committee and the FDA to interpret the results of these studies cautiously and to revise the labels of approved ER/LA medications accordingly. Thank you for the opportunity to offer comments.

DR. BATEMAN: Thank you.

Speaker number 7, please state your name and any organization you are representing for the record. You have five minutes.

DR. MAZLOOMDOOST: Good afternoon. My name

is Danesh Mazloomdoost. I'm a dual board certified anesthesiologist and pain physician, trained at Johns Hopkins and MD Anderson. I practice in Kentucky, one of the epicenters of the opioid epidemic, and have treated thousands of patients both with and without chronic opioids.

The PMR studies are important reiterations of the risks to chronic opioid therapy, or COT, but they fall short in capturing the full scope of harms. The use of the pain-adjusted screening for OUD significantly underestimates the true incidence of opioid use disorder. DSM-5 does not require the so-called pain adjustment to avoid false positives; in fact, DSM-5 criteria are more likely to underdetect OUD in patients prescribe opioids for two key reasons.

First, patients on prescribed opioids rarely experience absence, which is needed to exhibit behaviors reflecting OUD; and second, among chronic opioid therapy, DSM-5 explicitly excludes tolerance and withdrawal, two of the most prevalent indicators counting towards OUD. These exclusions

severely limit diagnostic sensitivity, let alone if there's further pain adjustment to them.

Opioid harms are not isolated to use disorders. Chronic opioid therapy disrupts the endogenous opioid system, or the EOS, which is a neuroendocrine system that governs far more than pain. Chronic opioid exposure destabilizes many organ systems, often irreversibly. Consider the evidence.

In immune dysfunction, during the COVID-19 pandemic, patients on chronic opioids had significantly higher rates of ICU admissions and mortality. The immune suppression from opioids increases the rates of cancer and reduces the likelihood of survival. In endocrine, the androgens insufficiency caused by opioids impairs tissue repair and bone density, accelerating degenerative joints. Among 06:22:47 [indiscernible] patients like the one Dr. Connolly mentioned, [indiscernible] 06:22:54 in fractures and a marked rise in all-cause mortality. Opioids are also linked to higher rates of obesity and

diabetes, showing further endocrine disruption.

Cardiovascular risks. 06:23:04 [indiscernible] opioids increase the relative risk of a cardiac event by about 2 and a half times, which is 40 percent higher than the risk posed by Cox 2 inhibitors, medications that were withdrawn from the market because of their cardiac concerns.

Respiratory compromise. Chronic opioids suppress respiratory drive chronically, which increases sleep apnea and impairs immune functions within the lung, contributing to increased mortality during infections.

Gastrointestinal harm. Chronic constipation is often a side effect discussed, but bowel dysfunction from opioids leads to longer hospitalizations, more complications, and a tenfold increased cost of care for GI events. Mood dysregulation. Studies show, and I have seen among my own chronic opioid patients, increased rates of depression; emotional blunting; suicidality; cognitive decline; and impaired decision making.

And finally, and most importantly to me, is

pain sensitization. Ironically, the chronic opioids worsen chronic pain. The endogenous opioid system adapts to opioids like a compressed spring. Each dose provides relief followed by rebound sensitivity, increasing baseline pain and promoting disability long term. Early exposure, higher doses, longer duration all correlate with worse outcomes. This point cannot be overstated.

Opioids blur the line between pain caused by structural pathology like arthritis and the amplified perception of pain driven by a disrupted nervous system. When patients on chronic opioids report uncontrolled pain, it may reflect progression of disease, but more often it signals a broken pain processing network.

This very property of opioids, the amplification of pain over time, was exploited to drive sales and escalate prescribing through concepts like pseudoaddiction; yet, these outdated concepts still cloud medical judgment and policy today, including, with all due respect, some of the questions raised within this committee.

The endogenous opioid system was never designed for continuous saturation. When flooded by exogenous opioids, it adapts at a cost. Tolerance, withdrawal, emotional flattening, hormonal suppression, hyperalgesia, these are not side effects; they are predictable expressions of a system dysregulation, which is dose dependent, duration dependent, and often irreversible.

This committee must not view opioid use disorder and overdose as the only meaningful harms to chronic opioid therapy. Opioids themselves are a marker of neuroendocrine compromise tied to a decline in both quality of life and longevity. Thank you.

DR. BATEMAN: Thank you.

Speaker number 8, please state your name and any organization you are representing for the record. You have five minutes.

(No response.)

DR. BATEMAN: You're on mute, Dr. Ballantyne.

DR. BALLANTYNE: Sorry.

My name is Jane Ballantyne. I'm a Professor of Anesthesiology and Pain Medicine at the University of Washington in Seattle. I have been a pain physician looking after chronic pain patients for over 30 years. I have no financial relationship.

Dependence is a consequence of round-the-clock opioid use. I'll explain later what I and others consider dependence to be. FDA stipulates that ER/LA opioids are prescribed round the clock, and safety considerations actually support this.

The 2016 CDC guideline and other measures vastly reduced prescribing of opioids for chronic pain, the peak being at the beginning of the 21st century of the opioid epidemic and the prescribing of opioids. Nevertheless, clinicians are still faced with millions of patients who are stuck on opioids. That means they can't get off a treatment that's not actually helping them.

Clinicians know this because in our everyday practice, particularly in primary care, we come

across these patients, but a recent study documented the scale of this problem for the first time. This study uses data from the National Household Survey. It finds 3 million people with no misuse -- that means they're taking their opioids as prescribed -- but who meet minimal criteria for prescription opioid use disorder using DSM-5 criteria.

Note that the criteria most met are unsuccessful efforts to cut down, spending a great deal of time obtaining opioids, and craving. I would submit that they are the patients that are dependent but not addicted.

There are two components to any drug's effect, which are direct effects and reaction, seen here as A and B. In the case of opioids, the reaction is a brain adaptation since the important drug effect is in the brain. The brain's reaction is opposite to the drug's effect, meaning it attempts to cancel the drug's effects in order to achieve homeostasis, seen here in the top line; whereas with few dosing, seen here as panel A and

panel B, the adaptation stays above the line, so remains positive, but the adaptation recovers after drug discontinuation.

After many doses, however, the combined effect is not positive, it moves out of positive territory, and also does not recover when the drug is discontinued. This is what produces the state of dependence seen in the next slide.

This is the classic picture of the three stages of addiction, the first stage being the binge intoxication stage or the stage of erratic use; the second stage being called the withdrawal or negative effect, stage 2, and the third stage being loss of executive function. Patients who receive prescribed opioids, we have submitted, can enter the addiction cycle at stage 2, and in fact don't necessarily ever leave stage 2. Stage 2 persists with all its adverse symptoms, which are listed here on the right; and this stage may be called dependence. It's important to note that as a conditioned or learned state, it should be thought of as continuously emergent, not limited to

drug withdrawal.

"Stuck on opioids" means that the opioid is not helping pain and may actually be making the pain worse since part of stage 2 is withdrawal hyperalgesia. It means that getting off the opioid is difficult, sometimes impossible. It is a dependence and not an addiction, although in this state, there's an increased risk of moving into stage 3, completing the cycle, and developing addiction. This state is pathological. It's not benign. It's a miserable state to be in because of all the adverse effects shown in the last slide.

Because ER/LA opioids are given round the clock, the adaptations leading to dependence are much more likely to arise. This is logical and validated by existing animal research but does need further validation in humans. A big research question would be, are limited-dose, pain-contingent, short-acting opioids less likely to produce this dependence? Thank you for your attention.

DR. BATEMAN: Thank you.

Speaker number 9, please state your name and any organization you are representing for the record. You have five minutes.

DR. FRANKLIN: Thank you. I'm Gary Franklin. I'm the Medical Director at the Department of Labor and Industries in Washington State, which is the state workers compensation system. Dr. Jaymie Mai and myself in 2005 reported the first opioid deaths, unintentional deaths, from prescription opioids in the country in a peer-reviewed journal. We started to notice these deaths in 2000 and 2001. Soon after, the state, along with twenty other states or more, made much more permissive the prescribing of opioids. And in the absence of more clear direction from the FDA, things just remained chaotic and got worse.

The CDC has backed off of its 2016 recommendations to be careful at 50 and 90 milligrams, and also backed off of the recommended day supply of the first opioid prescription. But as you've heard already today, the data on effectiveness for opioids is very

limited.

This is the Krebs study, the SPACE randomized trial, which followed people with the kinds of conditions that we see in worker's compensation: chronic low back pain and chronic hip and knee pain. And in this, really, high-quality study, treatment with opioids was not found to be superior to treatment with non-opioid medications, so things just became more and more confusing.

This was a study that was published in MMWR that shows the likelihood of being on opioids at 1 year and 3 years. According to the number of days of opioids taken in the very first prescription, the risk of use at 1 year increases by 1 percent per day, starting with day 3 of the first prescription. This has to do with what you've already heard, which is tolerance and dependence setting in within days to weeks, and the risk going up tremendously and very likely dependent setting in.

We published a study in 2008. This was

almost 2,000 patients with acute low back injury who came into the workers comp system. It was at least four days of lost work time, and we found that getting opioids for just seven days, or two prescriptions, was associated with a doubling of the risk of being on disability at one year.

More than 10 studies have been published at this point to demonstrate that just a little bit of opioid use in the injured worker population is very likely contributing to the initiation and perpetuation of disability in workers compensation. The study that you are looking at included 4 percent mortality and overdose rate in the Tennessee Medicaid population. It's probably highly related to this disability problem since many of the patients on high doses in Medicaid are on the dual eligible system, on SSDI and SSI, because they have become disabled and they're on high-dose opioids.

We have also recently published a study that looked at by linking a state prescription drug monitoring program data with our state billing data

for opioids, that there is a very strong association between pre-injury opioid use and opioid use patterns after a work-related injury.

And my last point here is that for patients that were not on opioids prior to their injury, there's very little chance that they're going to be on opioids in the workers comp system after their injury. But for patients in the yellow bars that were on chronic opioids prior to their injury, they're very likely to be on opioids for a long time in the workers comp system. And again, this is very likely relating, in my opinion, to the development of tolerance and dependence after only days to weeks of the initial opioid use.

Thank you very much. I think that it would be extremely helpful for the FDA to clarify some of these things and to deal with the extensive harm coming from the association between opioids dependence and disability in injured workers. Thank you.

DR. BATEMAN: Thank you.

Speaker number 10, please state your name

and any organization you are representing for the record. You have 3 minutes, speaker number 10.

MR. HENNESSY: Hi. My name is Paul Hennessy; no financial conflicts of interest. I appreciate the work that this committee is doing and for the opportunity for public comment. AADP and AAC must remain transparent for the public, as much of the FDA and HHS is now shrouded in mystery. For example, since the recent staffing changes at HHS, VRBPAC has operated in secrecy with no public input. This has led to a delay in the Novavax BLA approval for the COVID vaccine, so I represent millions of Americans turning to any committee such as this out of desperation.

Novavax's BLA is being held up by Marty Makary and Tracy Beth Hoeg, who want to push anti-vaxxers 06:38:11 [indiscernible] and restrict access. The safe and effective non-mRNA alternative is what myself and many others rely on for protection, and yet the FDA has delayed BLA approval for no reason.

While I understand this committee is not

VRBPAC, I'm asking this committee to reach out to CBER and other FDA officials, and ask them to expedite approvals on Novavax's BLA. It's time for extraordinary measures, and for everyone, including you all, to do your part to make sure we get access to the vaccines we pay for.

This is relevant to you all because the opioid crisis worsened during the early days of the pandemic, and studies have shown those with opioid use disorders suffer disproportionately from COVID-19. Opioid use disorder contributes to immunosuppression and respiratory compromise. So why on earth does FDA want to limit COVID vaccine access? Without Novavax protection, people suffering from addiction are vastly more vulnerable to SARS-CoV-2. Your lack of action could indirectly cause more harm.

RFK Jr. has lied about single-antigen vaccines not working, lied about COVID being mild in children, and wants to do unethical placebo trials and attempt to delay approvals. It's a pathetic attempt to restrict vaccine under the

guise of scrutiny, and we need this committee and others to speak out.

Novavax's saponin-based adjuvant provides a broad range of immunity against many variants. It's the best COVID vaccine we have, and we cannot lose access to it. Please, this is an extraordinary time and requires unorthodox action. Do whatever you can in your power to pressure the FDA to approve Novavax's BLA. Thank you.

Clarifying Questions (continued)

DR. BATEMAN: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. We're going to take about 15 or 20 minutes and circle back for any remaining questions for OPC or the FDA. When you ask your question, please remember to state your name for the record before you speak, and direct questions to a specific presenter, if you can.

Let's go back to the OPC questions first, and a question from Dr. Gordon.

DR. GORDON: Adam Gordon. I just was going

to clarify earlier this morning -- and it should be a yes or no answer probably -- on both the 3033-1 and 3033-2 studies, that the only morphine equivalent dose that was considered was at baseline. There was no follow-up in regards to changing of that morphine equivalent dose over time or whether it be up or down; but it was only at the baseline condition that that was the risk factor.

DR. WALKER: Alec Walker. 3O33-2, the study was of the effect of a decision to put somebody on chronic opioid therapy, and then following out the long-term consequences of that in terms of the outcomes. There was no following of tracking of dose in terms of looking at an effect on outcomes.

Dr. Yarborough, would you like to answer to Study 1?

DR. YARBOROUGH: This is Dr. Yarborough. Yes, you're correct; only baseline.

DR. BATEMAN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Hi. Elizabeth Joniak-Grant. I had a question about the -2 study. Given that the mental health and SUD diagnoses were

basically ascertained by checking the electronic health record or claims, do we have any information about how they were diagnosed? And why I asked these questions is do we know that they were administered any appropriate testing for it?

We've seen instances where patients have questioned their doctors about opioid prescriptions, and they're marked as drug seeking. We've had instances where a patient is upset or had a diagnosis -- for example, me. I was diagnosed with PTSD at 18, and to this day -- I'm going to be 50 -- they still are like, "Oh. You have PTSD." And I said, "No. I've dealt with that many, many years ago. I'm doing all right now."

So I was wondering was anything problematized or looked at with them, or was it just there's an earmark in here for this at any time, and it goes into our data set as being a diagnosis.

DR. WALKER: The diagnoses that appeared in 3033-2 were based on insurance claims diagnoses as submitted by the caregivers. There was no further

assessment of how a person arrived at the diagnosis. However, for the outcome of OOD, there were medical record reviews that confirmed that the specified level of sensitivity and specificity that the caregiver supplied, insurance diagnosis did correlate very well with what was in the medical record. Again, that was not standardized.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I had a question related to study number 2. If I understood the explanation correctly, I thought it was mentioned that there was a slightly higher risk in those that were entered in the later era. Those are also the patients with shorter follow-up. So I was wondering, if my understanding's correct, maybe they could talk a little bit to the extent of whether you think that affected the estimates of the outcome or not.

DR. WALKER: I'll ask Dr. Seeger to comment on the people who entered study too late in the study.

DR. SEEGER: John Seeger. We'd like to

bring up the slide illustrating the point from the core presentation and draw your attention to the last row here on this table and the figure. There's an indication that patients entering in the last cohort era had about a 25 percent increased risk of OOD. And some of this goes away with multi-variable adjustment, so this is just adjusted for nothing at this stage.

If you remember the earlier slide about the changing landscape of opioid overdoses, this could correlate to increased illicit use of fentanyl and some increased mortality associated with that. But that's not directly addressed by this, but that's one possible explanation.

DR. HUYBRECHTS: Thank you.

DR. BATEMAN: Any additional questions for OPC? Dr. Reich?

DR. REICH: Yes. There's been so much debate now and discussion on the pain adjustment. I just wonder, just to be really clear from the OPC, how that was determined, how that adjustment was made, and how was it adjudicated. Maybe you

can just give a little more detail around that. Was it ascertained at the interview? Was it patient's information that determined it? Just give me some more details on that, please.

DR. WALKER: I'd like to ask Dr. Hasin to talk about the pain adjustment, how it was done, and the reasons to believe it.

DR. HASIN: Thank you. Deborah Hasin, Columbia University, Lead Investigator of Study 5. There were actually three measures that were generated by the PRISM-5-OP for OUD diagnoses concerning prescription opioids, and we were interested in taking all perspectives on this into account in design and testing of the instrument.

So we had what we called a fully unadjusted measure, which actually corresponds to the perspective that's been expressed this afternoon in some of the comments. There are 11 criteria for OUD from DSM-5, as there are for other substance use disorders. And for the fully unadjusted measure, if the criterion occurred, it was rated as positive without regard to any situation like

whether they were taking as prescribed or not, or whether they were using only for pain relief, or for other reasons, too; for example, to get high.

The DSM-5 measure did correspond to the DSM-5 OUD criteria. So for the DSM-5 measure of those 11 criteria, withdrawal and tolerance were not rated as positive -- and that is to say adjusted -- if they occurred among participants who used their opioids as prescribed as defined in DSM-5.

The pain-adjusted measure that many people have commented on incorporated the DSM-5 adjustment and further considered the behavioral criteria positive only if additional patient information from the interview, which was administered in a semi-structured format by well-trained clinical interviewers, indicated that the criteria represented addiction indicators, meaning non-therapeutic intent rather than treatment of pain. The point was that if patients were using the opioids only for pain relief, that we didn't want to count this criterion towards a diagnosis of

addiction.

The study that we did to validate it showed that indeed the rates differed across these three measures, with the highest rates in the unadjusted measure, the intermediate rates for DSM-5, which you've commented on and seen, and lower rates for the pain-adjusted measures. But we validated the three using external validators representing common characteristics of addiction; for example, a family history of substance use disorders or a previous history of substance use disorders involving substances other than opioids. The strongest associations with those variables was found for the pain-adjusted measure, intermediate for DSM-5 and weakest for unadjusted measures.

DR. REICH: And just to be clear, every interviewer had a standardized script and elicited this response when prompted, or was it kind of up to the interviewer to determine whether they needed to probe that next step?

DR. HASIN: Every time a criterion was endorsed, the interviewer systematically probed all

the potential reasons.

DR. BATEMAN: Dr. Blanco?

DR. BLANCO: Yes. I think the main thing we have to decide today is the balance between risks and benefits of using these medications long term. We've heard a lot of risks. Did the studies find any benefit to the patients in using these medications, either per se or in comparison with alternatives, treating the pain with other medications or with other interventions, non-medication alternatives?

DR. WALKER: Alec Walker. Both studies 1 and 2 were designed as studies of adverse effects. They did not investigate benefit.

DR. BATEMAN: Mr. Phillips?

MR. PHILLIPS: Rick Phillips, patient. I'm confused about this idea about using opioids for pain versus addiction. I question if somebody actually would say I'm not using opioids for pain. I mean, if I were interviewing 10 people who are using opioids, and perhaps using them for a greater amount than prescribed, I would think that all

10 people would say I'm using it for pain, and I don't get how an interviewer could separate between the two.

Can somebody clarify that, please?

DR. WALKER: I'll ask Dr. Hasin to comment on whether the responses are credible.

DR. HASIN: Deborah Hasin, Columbia University. You may remember from what Dr. Yarborough said this morning that there were two types of patients in the validity study. One of them was patients from pain clinics and one of them was patients from substance abuse rehabilitation settings who had received prescriptions for opioids for chronic pain.

So in response to the question of wouldn't they always say they had used them for pain, the patients in the pain clinics did say very often that they used them for pain. The patients in the drug treatment settings, even though they'd received the prescription supposedly for pain, quite often told us that they used the opioids for other reasons, for example, to get high or for

non-indications of opioid use.

MR. PHILLIPS: Thank you for clarifying it.

DR. BATEMAN: Dr. Dejos?

DR. DEJOS: Mike Dejos, Methodist Le Bonheur Healthcare. I do want to ask a further clarifying question as it relates towards the pain-adjusted DSM-5. I recognize the language here is it's positive only if repeated unsuccessful attempts were made to quit or cut down. During this time of Study 1, I recognize across the country, some folks were trying to implement gradual dose reduction. And when providers initiated gradual dose reduction to make some types of attempts to wean patients off of opioid medications, how would that be classified here? I recognize also that this is primarily completed by patients, but how did those outcomes make an impact for this overall metric?

DR. WALKER: If I understand your question, it is, if the attempts to reduce dose are provider initiated rather than patient initiated, how is that counted in the pain-adjusted measures?

DR. DEJOS: That is correct. Sorry. I

should have clarified.

DR. WALKER: Right.

Dr. Hasin?

DR. HASIN: They were patient initiated.

DR. BATEMAN: Dr. Rebo?

DR. REBO: I don't have a question [indiscernible - off mic.].

DR. BATEMAN: Any final questions for OPC?

(No response.)

DR. BATEMAN: Okay. Then we'll take any final questions for the FDA presenters.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I had a question related to the interpretation of slide 59, and it's also a little bit broader because it sort of relates to interpretation of heterogeneity.

When that slide was presented, concern was raised about, I think, the estimate for KPNW, indicating that that is the estimate that stood out. But looking at those estimates, the KPNW estimate seems very similar to the HealthCore estimate, and it just seems to be a matter of

precision rather than through heterogeneity, whereas maybe the estimate for Optum stands out a little bit.

So I was wondering whether FDA could clarify a little bit in the context of this particular example, but also more broadly how they interpreted heterogeneity and when it was a concern in terms of interpretation of the results.

DR. LEE: Hana Lee, FDA. So there are multiple sources that could cause increased heterogeneity. One is differences in effect estimates and the other is differences in uncertainties of those estimates. So here in this example, there are multiple sources that could cause increased heterogeneity across sites, but one of the key sources is the higher uncertainty in KPNW estimate. Optum also has higher uncertainty in its effect estimate, but also its magnitude of the risk of OOD is higher. So considering all those factors together, direction of the risk of OOD is consistent.

There are other examples provided in the

backup slide. Can you pull up page 135?

For other factors, sources of heterogeneity could be different. For example, for QMME, the source of large heterogeneity is uncertainty in KPNW and also insignificant result, as well as somewhat of a higher uncertainty in Optum. But also considering the direction and strength of association, we could reasonably conclude that there's a strong association. And for antidepressant example, the heterogeneity index is 0.52, also indicating large heterogeneity, but you can see that the direction is pretty consistent.

DR. HUYBRECHTS: Thank you.

DR. BATEMAN: Okay. Any other final questions for the FDA?

(No response.)

DR. BATEMAN: Okay. If not, we'll proceed with the charge to the committee from Dr. McAninch.

Charge to the Committee - Jana McAninch

DR. McANINCH: Hi. Jana McAninch, OSE. First, as always, we greatly appreciate the open public hearing comments and all of the thoughtful

questions from the committee.

We will now turn our attention to the committee discussion. There are no voting questions, so we're relying on committee members to draw on your own expertise and to discuss your interpretation of the study findings in light of what you've heard today, what was provided in the briefing materials, and other evidence of which you may be aware.

The first two questions focus on the quantitative outcome estimates generated by each study, and the third question is on the risk factor analysis. For each of these questions, we've also provided some considerations or prompts on topics about which we're especially interested in hearing discussion. But the questions were designed deliberately to be quite open-ended, so please don't feel constrained by those those prompts, those sub-bullets.

The last question asks the committees to discuss whether there are any important novel findings from these PMR studies that FDA should

communicate. Although we have provided some information about current FDA-approved opioid analgesic labeling, and you've heard some more about that in the the open public hearing, labeling is a primary vehicle for FDA to communicate drug information, but we are not specifically or only asking the committees to opine on changes in opioid labels.

What we really want to know is if you believe that there is compelling new evidence from these studies that would benefit providers, patients, or other interested parties, and if so, what you believe that is. If you have recommendations about the best way to convey that information, you are, of course, welcome to share that as well.

Questions to the Committee and Discussion

DR. BATEMAN: Thank you.

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 will proceed with the

questions to the committee and panel discussions. I'd like to remind public observers while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we'll pause for any questions or comments concerning its wording.

This is our first question. Discuss your interpretation of the estimates of the incidence and prevalence of misuse, abuse, and OUD in patients using opioid analgesics long term, PMR 3033-1, and then a number of subquestions about factors influencing interpretation.

Any questions about the way the question is worded or the issues presented?

(No response.)

DR. BATEMAN: Okay. If not, I'd suggest we take each of these four bullet points in turn, so I'd invite people to start by offering your comments on the study strengths and limitations and how that impacts on interpretation.

We'll go to Dr. Gordon first.

DR. GORDON: Adam Gordon. I just want to first say thank you to the FDA and the other agencies in order to conduct the study. I thought 3033-1 was a nice study to look at the incident outcome, especially regarding OUD outcome.

One of the study limitations that I found that was confirmed in my question earlier was it really was a static risk assessment. Many patients have various waxing and waning of pain, waxing and waning of potential harms associated with opioid use. This could also be secondary to the doses that I mentioned earlier. They change over time that may cause people to be unstable, and it's not a static or stable risk assessment over time. So my limitation of the study was that it used a one cross-sectional time point for that risk assessment, and in clinical care, that's generally not done. It's done at the time the patient is being seen. Thank you.

DR. BATEMAN: Dr. Dejos?

DR. DEJOS: Mike Dejos, Methodist Le Bonheur Healthcare. Overall, I do think the study reminds

me that sometimes our greatest strengths can sometimes be a limitation. I recognize that Study 1, the utilized HCSRN -- which is comprised of a large number of huge large academic medical centers, organizations, primarily along the West Coast and East Coast -- I think it was noted by our presenter earlier that parts of the Southeast were not represented, probably to the greatest extent as we had hoped. We recognize that Alabama, Arkansas, Tennessee, which is where I practice, and then also Kentucky, may have not been fully represented within the outcome. So I do think that might be a limitation in terms of generalizability.

Tennessee, for example, created in 2019 a whole initiative where organizations across the state, not only are they utilizing their controlled substance monitoring databases, but we're taking a more judicious approach in terms of opioid use. For example, opioid prescriptions are now limited to 180 morphine milliequivalents unless there are other conditions that are being made. So that's something I'd take into consideration.

Then the other aspect that also I believe is potential limitation is that I believe for folks to be assessed in this analysis, they had to be consistent in their health care over the past year. And we know in general practice, especially in areas where there are very social determinants of health that impact accessibility towards health care, some of our patients are not always able to make their appointments, and they get lost through different pathways. Thank you.

DR. BATEMAN: Dr. Rebo?

DR. REBO: Thank you. Elizabeth Rebo, Kaiser Permanente. I agree with a lot of what Dr. Dejos just said. Another piece that struck me as interesting was that the population was limited to English-speaking folks only, which living in California, we have a lot of people that English is not their primary language. There's a large language barrier. So that, I do think, is a limitation of the study, as well as predominantly white folks were studied.

But what I really think is that this

probably underrepresented what the true risk is, based on these limitations in this study. So I think if we were able to look at a broader patient population, we would see even more significant and concerning results.

DR. BATEMAN: Do you want to say a bit more about the factors that might have led to an under-ascertainment? You said you'd expect these estimates to be lower.

DR. REBO: I think if you were able to make it a little bit more generalizable to the population as it exists in the United States, I think that the incidence would be higher than what we saw in this study.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: I have some comments on the first study, but they don't nicely fit into the bullet points. Is it ok if I just kind of summarize my comments?

(Dr. Bateman nods yes.)

DR. FLOYD: Thank you.

I'll say first, I think there's a lot of

rigor in the work that was done. These are carefully thought-out study designs and recruitment of highly selected samples. So those of you who do epidemiologic studies, you know that people who enroll in these studies, these surveys, are fundamentally different from the majority of people who don't. The goal is to create validity and rigor so that in this kind of well-defined patient population, you can try to say something that's valid. But the estimates are highly unlikely to generalize to all opiate users in general, and probably maybe even any other population of opiate users.

So I think the FDA is asking, what is it in these new studies we've done that maybe should go in the label? And I would argue none of it. I think it reinforces what we already know. There are some methodologic advances. I think it adds to the field, and it's valuable, but in terms of should any of those specific findings go in a label, I would say no. One reason, that has been brought up by a lot of the public comment speakers,

is that there's a real risk of reporting underestimates of some of these adverse effects and giving the wrong message.

The second point I want to make is this idea of the pain-adjusted outcome measure for OUD, it took me most of the day to realize this is just a problem of cause-specific outcome. This is a common problem in clinical trials and epidemiology, where if you look at a composite like mortality, you're not going to have any power to detect an effect of a therapeutic on it. So you might look at something like cardiovascular mortality or sudden cardiac death, so attributing the cause to the outcome, which increases specificity, but in other ways reduces your power to find an effect, and often reduces in underestimates of harms.

So I think of it like this. I don't think it's a better or worse measure. It's simply a complementary measure. It has high specificity, but I would never take that 1 or 2 percent and say that's a transportable finding that should ever go in a label. I'm almost certain the real risk,

absolute risk, is much higher. But the issue isn't what is the number and should that go on the label? I think it is an issue, it's interesting, but I don't think it's that big of an issue, and I don't think we're going to go putting these numbers in the label.

The third thing is, you asked us not to comment on the label. You're interested in, really, a nice scientific discourse on these studies, and should anything from these studies go on the label? I think not. But I agree with many of the public hearing commentators that already based on the large body of evidence we have, the label is too weak, and it doesn't effectively communicate the current knowledge about the benefits and risks of opiates.

Right now, it's written as if, okay, if you're thinking about taking an opiate, you've never taken one, know that these drugs can cause misuse, addiction, and very soft language about death. But we're talking really about long-term use with an ER/LA product or long-term use with a

short-acting product. So I do think there's room to include some nuance and some more information in the label about that, but again, it's a little bit irrespective of the findings from these two nicely done studies, which are really just one piece of the puzzle and the totality of evidence about harms from long-term effects.

And I think the most important thing is we actually have no compelling robust evidence that long-term therapy with opiates has any efficacy on outcomes that matter to patients. That is the most important thing, and that actually does not show up in the label. And it changes the equation entirely about how we think about these harms, the potential harms, trying to estimate the quantity of them.

So those are all my comments about the first question. Thank you.

DR. BATEMAN: Dr. Becker?

DR. BECKER: Will Becker. I'd also like to comment about the ascertainment, or the outcome of pain-adjusted DSM-5 OUD. I understand the rationale for trying to achieve greater specificity

by pulling in patients' attribution for their use, but I think it's also important to recognize opioids work -- as was mentioned by one of the public commenters, opioids can take over the endogenous opioid system, and they can also worsen pain and create hyperalgesia.

So patients' attributed motivation for use might not fully represent what's actually going on physiologically, and we would not -- I think it could be a mistake to make a carve-out for patients who attribute their use to pain only when in fact they're suffering from some of the most dire adverse consequences of opioids.

So I think the science behind the validation of the pain-adjusted DSM-5 OUD was rigorous, but I'm worried about some of the underlying assumptions in its creation. I think it deserves further study, but I would really not want to see those numbers promulgated as a true incidence rate for OUD. Thanks.

DR. BATEMAN: Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I

wanted to go back to some of the strengths and limitations in a comment that was made earlier. I echo what was mentioned earlier. I think these are very rigorously done studies that have a lot of strengths. In terms of how generalizable and does it really reflect the risk, I think one of the challenges has to do with the specific population of interest for these two studies, and that was long-term users of opioids, and I think that restricts the generalizability in a way that you're conditioning on long-term use. So in order for patients to make it into the study, they had to survive the short-term use, and those could be the patients that are most at risk initially.

So in that sense, whereas it was the goal of the study itself to focus on the long-term use, I think that could have resulted in an underestimate of the potential harms of treatment overall. Thank you.

DR. BATEMAN: And maybe I'd just add to that. Particularly in the the long-term opioid therapy, they selected for people that were opioid

naive when they started using them for extended periods, which is a pretty unique and selective population.

Mr. Phillips?

MR. PHILLIPS: In terms of the strengths and limitations of the study, I thought that all the data presented here today was remarkably good, and I really applaud the FDA and those who conducted the study on their rigor. Having said that, I think that adding misuse and overuse in one category paints a very difficult picture, in particular for people who are over 50 because I suspect that people over 50 have more misuse in terms of underuse than those over [sic] 50.

I know that most of the people I know who use opioids will get a prescription for 7 days, or 10 days, or whatever, and it will say take every X number of hours. I don't know anybody who does that simply because they dislike the effects so much, and they would be counted in this study. They would be counted if they were surveyed as a misuse because they did not comply with the

prescription as written. I think that's unfair, and I think they are two separate categories.

The second thing is I really do question the addition or the lumping together of age categories as a singular idea. We saw the 18 to 25 or 18 to 30 as being a high-use category. I think that that's a separate bullet in these findings. And I think that saying, broadly, this contributes to our knowledge about the opioid epidemic is a miscategorization of what the findings really are. I think that if we looked at it in terms of age categories, we would have a better view.

One final thing about the label, I got to tell you, I don't know anybody that reads the label. The doctor tells me to take this. I start taking it. And unless the label is very explicit, and unless the pharmacist or doctor implies to us you have got to be careful with this medication, writing more stuff on the label really just doesn't help. That's my opinion. I don't have anything to back that up. It's just my opinion.

DR. BATEMAN: Thank you.

We'll move on to the other panelists' comments. But I do think it'd be useful for the panel to provide additional input on this pain-adjusted OUD measure. We heard in the open public hearing some concern around the validity of that, or the way that might color interpretation of the study, so panelists can think a bit more about feedback to provide to the FDA on that question.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant, a few different comments. I think to echo some of what was said, some of the limits, the sample majority of white of 78 to 83 percent impacts negatively the generalizability. Also, many of the individuals were 60 or older. I think it was 45 to 48 percent. Also, the history of SUD being in the 29 and 34 percent ranges seems pretty high for this group, so I wonder if that would result in actually elevated numbers of people who would have misuse and abuse, and OUD.

To speak to the question asked about having the pain adjusted, I think having adjusted

definitions and pain-adjusted definitions are really important. I am here as a patient representative, but I'm also a qualitative sociologist. And as everyone knows, associations and correlations, correlations do not equal causation. We can say that again, and again, and again, and then when people casually start talking about things, all of a sudden these correlations start turning into causes more, and more, and more. I think we have to be really mindful that the reasons why could really help us get closer to understanding is this a cause or is this just an association, and are there other factors at play?

So to consider a misuse, one thing looking at misuse, I wonder if this is really clinically helpful. I'm glad that they've separated it out to say that it could be taken for therapeutic reasons, for pain reasons. But is this really telling us how much at risk someone is or someone's having negative consequences of opioid use, or is it saying their pain isn't being managed effectively at all; therefore they're having to do things

somewhat differently?

To speak to Mr. Phillips' comment, there were questions where they separated out in the POMAQ, where they asked were you taking less or were you taking more? And most of the questions that we're talking about, misuse and abuse were actually for reasons signaled under taking more, so that kind of addresses some of his questions.

But to have some of these things that were flagged -- sorry, give me a moment here -- that it wasn't strong enough to treat my pain; to sleep better; I had more pain; I misunderstood how much to take, these are all flagged as misuse. And there are people, especially if you're on immediate-release, that, okay, you take it 4 to 5 hours. Well, if I need to wait 4 hours, I have to wait another 30 minutes. I want to go to bed. I feel terrible. I feel like my pain's kind of controlled. Do some people take it earlier so they can go to bed? Certainly they do.

So I think we have to be really mindful of what we're talking about in the real world because

sometimes we really jump ahead and we say, "Oh, misuse is terrible." Or is misuse just my pain is not controlled? I'm having a terrible time, and I'm just trying to manage until I can get into my pain management specialist 6 months from now. And I don't have a lot of other choice. And no one will talk to me over telehealth. And no one will respond to my MyChart because it's an opioid. Therefore, all I can do is try and manage the best that I can before I get there.

I think that is an experience of lots and lots of chronic pain patients over time that we need to be really mindful about when we're talking about these things.

DR. BATEMAN: Thank you.

Dr. Shoben?

DR. SHOBEN: Abby Shoben. I don't have an answer to your question about the pain adjusted versus DSM-5, but two quick comments about the study strengths and limitations.

One, just echoing that I think these were really nicely done studies, one of the things that

I liked about them was the impressive retention rate at 12 months, which I hadn't heard as one of the study strengths. Then the other one is about the generalizability in terms of it's an observational study. The landscape has changed fairly dramatically and pretty quickly, so these are in addition to opioid, quasi-naive patients starting on long-acting drugs. This was from 5-6 years ago, so this may limit the generalizability going forward. Thanks.

DR. BATEMAN: Thank you.

Dr. McCann?

DR. McCANN: Hello. Dr. Mary Ellen McCann. I think I have an echo.

(Pause.)

DR. McCANN: I just have a couple of comments. One is to echo what other people have said about the consistent healthcare inclusion criteria. As I go over my own life and my cohort of people that are over age 50, consistent health care is something that you developed or got when you were in your 40s somewhere.

So I think that inclusion criteria shifted it to an older population. The consistent health care also shifted it towards people who were more responsible and were able to hold down a job, and therefore not losing their health care. So I think that limits the generalizability.

As to the pain-adjusted DSM-OUD score, I don't know what that really means. I think if I were prescribing these drugs, and I were to explain what the risks are to my patient, I would want to know the number of the chance that they have opioid use disorder, not whether it's pain adjusted or not, so I don't think it's particularly helpful. Those are my comments. Thank you.

DR. BATEMAN: Okay. Thank you.

I'll call on the other folks who've raised their hand, but two other issues I'd just like to put on the table for us to give input to the FDA on. The first, the length of follow-up of this study of one year and some of the limitations associated with that, and whether those were addressed in the cross-sectional study. And then

second, the point that Dr. Shoben raised about the evolving landscape and how both the landscape around prescription opioids and illicit opioids have changed since the study was conducted, and how that might inform interpretation.

So we'll go next to Dr. Reich.

DR. REICH: Jeff Reich, Sparian Biosciences. Thanks for letting me weigh in. First, just acknowledgement that some folks have made but worth reiterating; a tremendous effort to get this study done, and great coordination I think between FDA and industry to do these postmarketing studies. It's not easy, and you can see how productive it can be to generate this kind of vigorous debate. So that should be acknowledged.

Two things I'll say just in comments. In my mind, the pain-adjusted OUD seems to underestimate the level of OUD, and by the same token, the misuse seems to overstate the case, so I think the two need to be examined. To me, it doesn't matter how you get to the state of OUD, just that you're there. So qualifying it based on the use of pain

medications seems to distort it.

In terms of the misuse, I counted, and of the 27 bullets, 13 of them have to do more, what we've talked about already. But I would classify more as mistreatment or misdoctoring, for that matter. I had more pain, I needed more pain medications, to me, is arguing for problems managing the pain patient. It's adding to the stigma, and it's a bit pejorative to label that as a patient misuse.

I think this zooming out gets to a bigger issue about how the pendulum swings in pain management with opiates. We went through an era where they were very liberalized, and we saw what happened with that. And I fear as the pendulum swings too far the other way, we get to the point where they're so vilified that pain management becomes undermanagement, and that affects the whole spectrum of pain patients, from the cancer and palliative care, to patients who can be responsibly managed with chronic opiates to manage chronic pain.

DR. BATEMAN: Thank you.

Dr. Bicket?

DR. BICKET: This is Mark Bicket. Just some general comments, and I'll try to hit the laundry list of everything that's been mentioned. When I think about the study strengths, in particular, this inclusion of this patient interview and the patient-reported measures certainly stand out. These are clinical diagnoses that require some interaction with the patients, and the reason these studies really stand out to me is because of the thought that went into that.

We've heard some recent comments about the conception of misuse and some of the criticisms that may be present. I do think once you dig into the details of how -- for example, if you took less prescription opioids because you have less pain, that's not getting categorized as misuse. Once you dig into the details in the appendix, it kind of separates out some of these distinctions about what truly is categorized as misuse versus not; and that reinforces to me the thought of ascertaining this

notion of misuse that went into study number 1 that we're discussing here.

In terms of the changes with prescribing over time, we've clearly recognized that the overall landscape of opioid prescribing has shifted significantly, for many reasons. And because of that, it's likely that the LtOT cohort probably is a bit more relevant than the ER/LA cohort in terms of informing what may be closer to our conception of today's practice. But we're still separated by several years, and the doses that people are initiating now are lower, to a degree, that make having some inference there somewhat limited, even though the LtOT cohort is probably a bit more relevant.

When it comes to OUD definition, I would say, both for myself and perhaps others in the clinical community, that the OUD definition of just the DSM-5 OUD is how most people are going to define OUD given that's the definition of OUD, so that is helpful to know.

I also did find that the composite outcome

as a secondary measure was helpful to see. While it may not be accurate, I do think there is a group of clinicians who think about harms saying, "Well, the composite outcome of misuse OUD, or other harmful outcomes, when you lump them together like that, it is something that gets thought about, meaning this is a bit of a binary outcome of, is someone going to have a harm that I don't want them to have?" And all of those are harms that I don't want to have. So I do appreciate the ability to understand better that composite outcome and do think it has utility in that regard. Thank you.

DR. BATEMAN: Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. It seems that a lot of the discussion we're having and a lot of comments relate to generalizability and how generalizable are these estimates. I think no matter how hard we try, there's never going to be a single study that we can do that is going to give the estimate for the entire population of opioid users.

The inclusion criteria are going to be

different in terms of their geographic area, whether they're publicly insured or privately insured, their history of uses and so forth, and the outcome measures, which we've already discussed at length. Is it pain adjusted? Is it more the traditional OUD diagnosis? But what stands out to me is that regardless of that heterogeneity, the results are quite consistent, like the risk is high. It increases with higher dose and it increases with longer duration.

So rather than maybe just focusing so much on what is the specific estimate, to me, that's a main finding of this study, especially in the context of the studies that are already available in the literature.

And related to that in terms of the changing landscape, I think one of the comments that was also made during the public hearing is that even though the landscape is changing, there are still patients with chronic pain that require the treatments. So in that sense, for that population I think it remains very relevant in these studies,

remains relevant in the discussion, and remains important. Thank you.

DR. BATEMAN: Dr. Rebo?

DR. REBO: Elizabeth Rebo, Kaiser Permanente. I wanted to circle back around to something Mr. Phillips said in regards to your comments around patient education, lack thereof, in that you don't believe that changing the label would help with that, and I want to look at that and talk about it from a safety science perspective.

So again, being a med safety leader, safety science is what I'm grounded in. And when you think about something like a label change, I kind of look at that as education, which is a low leverage risk reduction strategy.

So I agree completely with you; I don't think that just changing the label is going to get us the desired output that we need. There would absolutely need to be, if there were label changes made, that part around the education, the physician, the provider education to the patient,

the pharmacy education. And we even heard during the public comments that still is not happening, just as recently as in the past week.

So do I think that just changing the labeling alone is going to get us where we need to be? No, I don't. So I think we need to think about this also from the safety science perspective of how could we create potentially higher leverage reductions, error reduction strategies that could help in this realm as well.

DR. BATEMAN: So building on that comment and some of the comments we heard in the open public hearing, we know that the risks assessed in this study -- misuse, abuse, opioid use disorder, addiction -- are all represented in the label in a qualitative fashion. But with this study, we now have quantitative estimates.

So I think an important question to the committee is, is it appropriate for the FDA to consider adding quantitative estimates drawn from this study to the label? And if so, what would be the key quantitative estimates to include?

Dr. Floyd?

DR. FLOYD: Sorry. I said I was done, but I just wanted to reinforce something I said earlier about why I'm arguing against including quantitative estimates.

Now, in the context of most of the safety or efficacy issues, which come from a large registrational phase 3 trial, it's clear that you're talking about the context of the large phase 3 trials. You might say, "Oh, 10 percent of people had a heart attack in this clinical trial." Because this is not a clinical trial, and these are observational studies with complex sampling designs that have big implications on the interpretation, I think that the risks outweigh any benefits of including a number because, again, it's likely not transportable to any identifiable patient population external to the study. And that's not really the point, I think, of the studies.

DR. BATEMAN: Are there other perspectives?

With the risks, just in a qualitative way, it doesn't really give the physicians, the

prescribers, a point of reference to think about the magnitude of the risks, perhaps. So that might be an argument to include some data, even if they are limited.

Dr. Gordon?

DR. GORDON: Adam Gordon. With regards to that question, I would be very concerned about putting exact numbers into the label. There are two reasons. Number one is that even among this committee and some of the concerns we had today with regards to the definitions that we have for issues, abuse, and even OUD within this cohort of these studies, putting the quantitative values in there would probably confuse providers than it would in terms of clarifying what the actual risks are.

Then secondarily, going to the bullet at the very below, many of the risks and estimates with regards to those risks are very consistent with what we've seen in the ranges in the published literature already. I don't think it's going to add too much by specifying a specific number.

There are ranges of all this stuff, and I think we have to recognize that going forward.

DR. BATEMAN: Okay. Dr. Shoben?

DR. SHOBEN: Sure. Just a quick comment as to the speculation on what the benefits and risks of putting the quantitative data into the label are could be studied. And it probably has been, but you could look at how seriously providers take the warnings with and without the quantitative information.

DR. BATEMAN: Mr. Phillips?

MR. PHILLIPS: The key point of education is the pharmacist, and it's at the point of dispensing. It's a conversation, not a label. But that is the key way to communicate the finding, whatever finding it is.

DR. BATEMAN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. On one hand, I would say that quantitative information would be useful because in research that I've done with general laypeople and also with clinicians, everybody's definition of a

high risk or a low risk is exceedingly different. I mean, I talk to regular people all the time in my work, and they think your risk of opioid addiction if you take a prescription is 50 percent. You flip a coin, and look out. You could be in trouble. And I've met clinicians that are right there, too.

That being said, I don't think this study by itself is sufficient to warrant giving those numbers. I think that would really need to be something that is looking across literature, looking at meta-analyses, and really drawing in, and being very clear with any type of terms because we know that even with the best intentions, even when things are written to only impact certain groups in certain ways, there tends to be a great deal of fallout, often on the backs of chronic pain patients when it comes to opioids.

Then speaking to the opioid pharmacovigilance, that's where we are. Chronic pain patients -- and I think it's really important to bring it back to them because this is who we're talking about here -- tons have been forced to

taper, and the panel knows this, or stop opioid pain meds. People can't get back on them. People can't find doctors to prescribe them. People can't get pharmacies to fill them. Professional associations have come out with limits. State legislatures have come out with their limits. Hospital administration has come out with their limits. Patients have been forced to get invasive procedures they don't want to get as a stepwise practice, so to speak, in order to perhaps have access to opioids.

We see this again and again, and this has been discussed for a long time in the chronic pain community. The chronic pain community that needs opioids, their goals aren't to climb a mountain. Their goals are to get out of bed, to take care of their kids, to work, even potentially part-time, and cook. They're just trying to do basic activities of daily living.

And it's clear that chronic pain patients are suffering, so I think we have to be very mindful that even the best laid plans, when it

comes to labels, when it comes to guidelines, when it comes to anything, it gets out in the wild and people run with it. And there generally are tons of -- everyone likes to say unintended consequences, but when people keep raising alarm bells saying these are likely consequences, we can no longer keep hiding behind, well, they were unintended. We didn't mean for that to happen.

So I think we have to really keep that in the forefront of our mind and really consider what are the benefits of opioids. There hasn't been a lot of funding to study some of that. There hasn't been a lot of looking at what's happened with forced tapering, other than people are suffering, people are suicidal. But in the public comments, which I read through them, there are people that say that opioids save their life.

So I recognize the risks of OUD. I recognize the troubles that can come with all of that. But we also have to remember that there can be just as much damage, if not more, on the other side of things.

And one final thing I just wanted to point out, because I think it's really important, is that a lot of the patient comments, they're really upset that they feel what they see as PROP's role are impacting guidelines, and impacting comments, and impacting the narratives. I would just like to point out that there were actually four people of the 9 comments related to opioids today that are either on the executive council or the advisory board of PROP that gave comments today, and three of them did not identify any association as such. And I just want to put that out there because that is something that has surprised me in the past when I've sat on these committees before. Thanks.

DR. BATEMAN: The points about the generalizability of the estimates I think are well taken, but I wonder if the panelists can comment on whether these studies shift our knowledge or our sense of the magnitude of the risks of misuse, addiction, abuse, or whether these are really consistent with where clinicians, pharmacists, patients are thinking these risks are. So folks

can think about that.

Dr. Becker?

DR. BECKER: Will Becker. Yes. Just echoing the point Dr. Gordon made, I do think these estimates are in line with a lot of what we've seen in the published literature. Settling on what numbers to put on a label seems like a challenge, given that there's going to be a range in studies, the empirical data that we have.

I would also like to point to the elephant in the room that many in the public comments refer to, which is the lack of long-term data on effectiveness. If we're talking about the impact a label may have on guiding practice, I think we would have to acknowledge that the label, as it currently stands, is sort of an implication that there is known effectiveness data, but there truly is not. I don't have a sound bite solution to that, but I did just want to acknowledge that.

The undertaking, if I were in 2025, to start a patient on long-term opioid therapy for chronic back pain, let's say, well, if I were considering

starting it, I would really, really be concerned about what's the likelihood that this is actually going to meaningfully benefit my patient. And that's what keeps me up at night, starting a patient on a therapy that six months down the road, a year down the road, they're going to say, "I feel kind of stuck." If we increase the dose, then now they're undergoing some of the harms related to the physiologic dependence, and I couldn't have said I didn't know those risks going into it. So I just did want to bring up this issue about effectiveness. Thank you.

DR. BATEMAN: Thank you.

We'll go to Dr. Bicket next.

DR. BICKET: Thank you. This is Mark Bicket. On the topic of communication about information in the study and/or potential label changes, I generally believe that both the patient community and the prescriber community would benefit from having information about these studies available to them. One option to consider would be updating the section on postmarketing experience in

the label to at least describe this study.

It does seem consistent with other studies out there for the reasons I mentioned before about the strengths with the measurement of the outcomes for misuse, abuse, and opiate use disorder. Using the patient interviews, it does stand out to me as helping to refine the estimates of the risk in these two populations, the ER/LA and the LtOT. I think that information in that context would be helpful, and that's one option for where someone who would be interested could go to look at it, in the label, which seems very appropriate. Thank you.

DR. BATEMAN: Thank you.

Dr. Huybrechts?

DR. HUYBRECHTS: So with respect to what information potentially might be useful to put in the label, in the context of the literature that is out there, the range is huge. But if I remember correctly from the materials, the mean is actually quite consistent with the estimate from these studies. And I'm wondering if we're going to put

some information in the label, where it would make sense is to say this is the range, depending on all of these factors -- the way outcomes are being measured and so forth -- but the mean sort of is around here, and that these studies would be consistent with that. So I wonder whether that would be something to consider.

DR. BATEMAN: Okay. Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant, and a quick comment in reference to what Dr. Bicket was saying.

I get a little bit concerned because I think when people look at the labels and look at the information, a lot of times misuse gets conflated with abuse. It's kind of seen as something that's inappropriate or negative. It has negative connotations. So what I would be concerned with is if we were talking about including information, should misuse be included? Because there are so many caveats to that, that would have to be understood to really understand what information is being provided, and I think a lot of the caveats

would get lost in translation.

Also, how would we handle it in terms of cherry picking when we do have these confidence intervals, when we do have these things? People have to spend a good amount of time to look through and really think through what this means. And is the clinician that's having patient, after patient, after patient going to sit there and figure it out, and really have a nuanced understanding? Some certainly would, but I get concerned about what pieces would come with it. And they wouldn't have the benefit of having read all the data that we did to really understand what each outcome means.

DR. BATEMAN: Okay. Thank you.

One last comment before we take a break.

DR. FLOYD: Sorry. It's on this same comment. I just want to push back a little. I don't think the issue is, is misuse nuanced enough? I think the elephant in the room, the big issue is the complete lack of evidence of efficacy with long-term use.

It's hard when you're talking to a patient.

I practiced that in my county hospital in Seattle for 20 years. Someone's in pain. They know that if they take hydromorphone or oxycodone, in that moment, their pain is likely to go down that day, maybe the next day. So of course people feel like they need it. They feel certain it's better, except we don't have scientific evidence that starting these patients on opiates, continuing them for 6 months, 12 months, produces any tangible benefit whatsoever, and that needs to be stated front and center. That is the most important issue here. And it's because of that, that harms are much more important.

If you have a life-saving cancer that cures half of the people who would otherwise die, it's a non-issue. This is a treatment that, literally, from long-term use, we do not have rigorous evidence that there are marginal effects in any population that's ever been studied. Our approach comes from probably Sir William Osler's time, and we almost never do it. We're supposed to say, "Okay. You're bed bound because you have chronic

pain. I'm going to start opiates. I'm going to measure your functional status. Can you get up? Can you comb your hair?"

We never do this. I think of all the patients that I've treated who are on chronic opiate therapy. Probably less than 5 percent ever had a kind of assessment like that. So I just really want to push back on some of the fringe issues that I think we're talking about and focus on the cat's out of the bag. The failure to act 10-15 years ago is really what got us here.

I really am not convinced that any labeling is going to have any impact whatsoever. It probably is not. But if you're going to do something, make it count. And I think the thing that would count is putting front and center, we do not have rigorous evidence that long-term use of opiates has any tangible benefits to patients. And I'll probably repeat that a few more times during this meeting because I think it is, by far, the most important issue, and we're kind of dancing around it.

DR. BATEMAN: Alright. I think it's a good moment for a break, so we'll now take a quick 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. We will resume at 3:40.

(Whereupon, at 3:20 p.m., a recess was taken, and meeting resumed at 3:40 p.m.)

DR. BATEMAN: We'll now move on to question 2, also a discussion. Question 2 is discuss your interpretation of the estimates of the incidence of fatal and non-fatal overdose in patients using opioid agonists long-term, PMR 3033-2.

Please also comment on factors influencing your interpretation, including study strengths and limitations; ascertainment of opioid overdose and any potential for bias; heterogeneity of results across study populations, particularly those with Medicaid versus commercial insurance; generalizability of the findings and relevance to patients currently using opioid agonists given the

evolving opioid landscape; and consistency of findings with other available evidence or clinical experience.

I guess, first, any clarifying questions on the way the question is worded?

(No response.)

DR. BATEMAN: Okay. If not, we'll go to Dr. Becker.

DR. BECKER: Thank you. Will Becker. Yes. I would just say, overall, it was a very well-done study, and I think provided some important insights; but did just want to highlight one of the issues that was raised regarding loss to follow-up and how that might bias the estimate.

We know that patients who develop opioid use disorder often have problems with insurability. Life can become chaotic, jobs are lost, insurance is lost; and therefore, probably a disproportionate number of folks with OUD ended up in the lost to follow-up group. And, of course, we know OUD is the most potent risk factor for overdose, except for having a prior overdose.

So, in summary, it seems almost likely that the risk estimate is an underestimate because of this differential ascertainment bias caused by loss to follow-up of a larger proportion of folks with OUD. Thanks.

DR. BATEMAN: So the notion that the cumulative incidence estimates are going to be lower because of informative censoring.

Okay. Other comments?

Dr. Amirshahi?

DR. AMIRSHAHI: Thank you. Maryann Amirshahi. As a medical toxicologist, I really would have liked to have seen more detail with regards to the specifics of the overdose, as I previously alluded to, because what we really want to do here is try to mitigate overdose deaths. So I think that we should really get some more details with regard to were these intentional. Were they suicide attempts? That would inform us for more aggressive screening for patients that we're going to be prescribing high dose or chronic opioids to versus medication adverse events, or, obviously,

abuse for the euphoric effects, for example.

Secondarily, this was something that was going to be a little bit hard to tease out, I recognize. But once again, when we have people that have limited access to the opioids that they're getting via prescription, they often turn to illicit opioids. So how much of that was driving the overdoses that we were seeing in these studies? I think that will help us to inform mitigation strategies moving forward.

DR. BATEMAN: My understanding was there was an attempt to define an algorithm for intentional overdose, but they weren't able to validate that algorithm.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. Just a very quick follow-up comment to what was mentioned earlier. I think it's a really well-done study. What would have been nice is if the focus had not been on just the first event, but there had been follow-up for subsequent events, because I think that, again, could lead to an underestimation of

the event rates.

DR. BATEMAN: Dr. Gordon?

DR. GORDON: Adam Gordon. Similar to 3033-1, looking at the last bullet, this is pretty consistent with regards to many of the studies that are observational regarding the rate of overdose incidence over time. So I just wanted to point out that nothing was really shocking in terms of some of the estimates. Thank you.

DR. BATEMAN: Other comments? Dr. Joniak-Grant?

DR. JONIAK-GRANT: Hi. Elizabeth Joniak-Grant. I agree with what people have brought up so far. I also wanted to mention that I was struck with this one; that there was a really heavy enrollment in the south that made up 58 percent of the sample, and I think it only consisted of two sites for the South. So I was surprised that it was so strong towards those two sites and how would that impact things.

Also, I understand that they tried to get different areas represented, and had reasons for

not covering the middle of the U.S. But that's a big -- I don't want to say a negative; that would be the wrong word. But that's something that's a really big thing to be missing, is where did rural America fit into this and where did other areas fit into this. Kind of, from Detroit to the West Coast, there weren't any institutions represented.

I also wanted to mention I think there was a lot of heterogeneity in the results for this. I was really struck by the fact that the rates were considerably higher for Medicaid patients. But there was a signal -- I would call it a signal -- that regular visits and care could serve a protective function, and I wonder if that could help us understand that with Medicaid patients, it can be a lot harder to access routine care, and have regular appointments, and have consistency. So I wanted to mention that; that there could be these multiple things going on.

Also with Medicaid care, sometimes for alternative treatments to opioids, there can be a lot less options. I know with migraine meds, for

example, Medicaid doesn't allow some of them. You can't get the discount cards, and it can be a lot harder to get these other options on board, so to be mindful of what is going on with all of that. I think the relevance to the current patients is the same as we discussed pretty at length regarding 3033-1.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: Thank you. Mark Bicket. I did want to say I appreciated the ability to look directly at a large proportion of patients with Medicaid and felt that was a nice strength to the analysis. While the cumulative risk for that group was higher than the other groups, it seems like the other groups set a bit of a floor for what an estimate may be for the outcomes of interest.

The other comment I was going to make was about the switch or add analysis. Overall, I appreciated the inclusion of that. It is a little tricky to appreciate, given most use of extended-release and long-acting often comes along with an increase in dose. The changes in dose may

not have been accounted for, which was acknowledged before. But I just bring that up, as it's a little tricky to understand that, well, is it really the switch to an extended-release/long-acting or is it that change in dose that also happens; and would that partially attenuate the observations that we see when that switch to an extended-release/ long-acting happens? I do feel like those are more minor points, overall, to studies that were generally well done. Thank you.

DR. BATEMAN: Does anyone want to comment on the heterogeneity of the results across the study populations, 5-year cumulative incidence of 4 percent in the Medicaid population versus 1 and a half percent in the commercially insured population?

Dr. Gordon?

DR. GORDON: It's a little bit about heterogeneity, but it's a little bit more about something that we haven't factored in, in either Study 1 or Study 2; that there are a lot of external factors with regards to dose and treatment

algorithms in different states.

This is out of Vanderbilt, Nashville, Tennessee. I'm not going to point out any particular state, but there are many states that have Medicaid policies that are very restrictive and/or paternalistic toward patients on chronic opioids. And we've seen in Medicaid populations that the rates of adverse events, including overdoses, are very different from state to state. And I think we have to recognize that this may be a state issue rather than a Medicaid issue when we're dealing with study number 2.

So even though there might be heterogeneity between the results with this particular state and non-Medicaid populations, I do think that there's still heterogeneity between the states and Medicaid, and we have to be very careful --

DR. BATEMAN: So the question was whether it's generalizable to the entire Medicaid population.

DR. GORDON: Yes. There are a lot of external issues associated with opioid-related

treatment that we're not accounting for in either one of the studies, and I think that needs to be recognized. Thanks.

DR. BATEMAN: Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I was also going to comment on the heterogeneity, and maybe a little bit in contradiction. I don't know, but I think it's more or less expected, or in line with expectation, that in the Medicaid population, we see higher levels. I think we see that in different areas as well. It's just a very different population. And if we think about some of the risk factors, the known risk factors for misuse and abuse, they're just known to have a higher prevalence in this population.

So in that sense, it didn't really surprise me that there was such a much higher risk in the Medicaid population, whether it is just because it's a Medicaid population or compounded by the fact that maybe they're from a particular area. To me, it was in line with expectation and gave face validity to the study to me.

DR. BATEMAN: Other comments?

(No response.)

DR. BATEMAN: I guess for my part, I agree that it's expected the Medicaid population would have a higher risk, but I think 4 percent across 5 years is really quite high when you think that 17 percent of these are fatal overdoses, and probably many overdoses don't come to medical attention. So I did think that was notable.

Comments on the consistency of findings with other available evidence or clinical experience; anyone want to comment on that?

DR. AMIRSHAHI: Maryann Amirshahi. One of the things that one of my colleagues had alluded to was the fact that we cut things off at the first overdose. And when you look at trends in overdoses and mortality, when people overdose, they're really likely to have a second overdose and die from that within days, or a month, or a year. And I think that that's something that was really missed in this particular study because it really does truly underestimate the burden of illness.

DR. BATEMAN: Okay. Thank you.

Any other comments on discussion question 2 before we move on?

(No response.)

DR. BATEMAN: Okay. Discussion question 3, discuss your interpretation of the risk factor analyses in PMRs 3033-1 and 3033-2 and what you see as the most important findings. Please consider the designs and analytic approaches; consistency of findings with other available evidence or clinical experience. In particular, please comment on study results related to dose and formulation, ER/LA versus immediate-release/short-acting.

Any clarifying questions on the the wording of this discussion question?

(No response.)

DR. BATEMAN: Okay. If not, Dr. Floyd?

DR. FLOYD: Sure. I'll kick it off. I actually didn't make too much of the risk estimates, and I want to give a little background.

A lot of the work I do is looking at millions of genetic variants or thousands of

proteins, and trying to say, can we predict some outcome, or are each of these proteins, or SNPs, variants, causally related to the outcome? And there are different approaches to both sets of questions, and I think the approach that was used is a little bit outdated.

So, in particular, if you use hypothesis testing -- things like p-values -- to select variables that then go into a multi variable model, none of the variance estimates or p-values that come out of it later are valid at all. So it's become very outdated as an approach to building a model or prediction models.

One suggestion is, since you collected all these great data and you can really do these analyses, you could do a prediction type analysis where you use regularized regressions, things like Lasso, Elastic Net, other machine learning approaches, Super Learner, and come up with a reproducible list of features that are likely to be generalizable. So you combine something like that, a data reduction strategy with cross validation,

and you get unbiased estimates of how well your model would work in a similar outside population.

Another approach is if you actually really care about the relationship of each of these variables, you simply test all of them. You don't do a two-stage sampling, do the hypothesis testing. None of those findings are interpretable except as exploratory. But I think that you can do a lot more with this because this was a very high-quality study that was designed carefully and that a lot of resources were invested in. And, really, the standard approach is to, a priori, decide what features you want to look at, or risk factors, and apply a correction for multiple testing to preserve your type 1 error rate. There's just no way around it.

When you don't do it, you get false positives. We have 20 years of candidate gene studies that have showed us that that approach does not work. You get spurious findings. So I would encourage the Consortium to apply one of those two approaches to get results that are more likely to

be transportable. Again, it doesn't require any new data collection, but I think more sophisticated analytic approaches are called for here.

DR. BATEMAN: Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. My comments were actually going to be quite similar to what was just mentioned. I thought the risk factor analysis was difficult to interpret, given its exploratory nature and without a causal framework. It seemed that not only the inclusion but also the interpretation of the specific factors was very much based on statistical significance alone, which is challenging in the context of what are uncommon outcomes. And some of these risk factors may be very uncommon as well.

So I think it would have been more informative if there was a consistent set of predictors that had been decided on upfront based on some causal framework, and then test those same predictors for all of the different outcomes regardless of whether they reach statistical significance or not, and see whether they

consistently come out in terms of an increased risk, even if they're not necessarily reaching that significance threshold.

I think right now, the very different findings, depending on the outcome, depending on the population, seems really a consequence of the focus on that significance threshold rather than more of a causal and framework. And I think as a result of that, that analysis just leads to some very general conclusions in terms of what are the known risk factors but does not provide a lot of additional new insights. So I think some additional analyses using some other techniques would be very helpful. Thank you.

DR. BATEMAN: Dr. Gordon?

DR. GORDON: I'm going to answer the last part of the discussion section, at least in my view, about dose. So we've heard a lot about dose today. We all know, from many studies, including 3033-1, that a higher dose has higher risk, but I think we haven't really commented about the era that the study was actually completed.

At that point, we had a lot of external factors in order to drive doses down to an arbitrary number or to change people's doses based on that high risk at a higher dose. I think that it's very telling that we're only having one point of reference with regards to that dose. At the study beginning, that was the risk factor, but we have no assessment with regards to dose changes and how that may be unstable for a patient to change, maybe taper down, or maybe even going up. We have no assessment of that change over time due to those external factors during this time frame.

So I have a hard time, at least in the data presented today that indicates that there needs to be some arbitrary dose limit or cap, based on the data that we have. And it would be much more telling, especially maybe in 3033-2, where you have data, retrospective data, to look at dose changes over time, and whether those were instrumental in any of the risk factors of the outcome that were assessed; because you could do it using retrospective data collection in terms of looking

at doses over time. So I don't know if we have anything conclusive to say about dose based on the data today. Thanks.

DR. BATEMAN: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. One of the things in addressing the last part of the discussion question was there was a big focus on the formulation, whether it be sustained release or immediate-release and the dose. But one thing that kind of struck me when we were looking at the results was that misuse and abuse was more common with hydromorphone. And during the study period, the hydromorphone I believe was not available as a long-acting agent. It was primarily short-acting because there was a problem with the long-acting formulation.

But perhaps one of the things that we should look at when we're assessing risk factors is not just the formulation of the dose, but the specific opioid involved, because if you look at the pharmacology and the pharmacodynamics of hydromorphone, it crosses the blood-brain barrier

much quicker than a lot of the other opioids, causing an increase in euphoria; so perhaps not all opioids themselves, regardless of the formulation, are created equal.

If you look in the addiction medicine literature, there are abuse likability studies where patients have rated the likability outside of the analgesic effect. So perhaps that might be an important area of future study. And, obviously, this one, I know it was exploratory and hypothesis generating, but perhaps we could maybe take into account the individual opioid that we're thinking about because they may not be the same, regardless of the formulation. Thank you.

DR. BATEMAN: Yes. I think that's an important comment. In the analysis of factors associated with abuse, hydromorphone versus oxycodone was associated with a 7-fold increase in risk, which was really notable and, I think, probably worthy of more study.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth

Joniak-Grant. I think we can't really make conclusions based on this. As others have said, it raises some interesting avenues for exploration. One thing that I had noticed, along with what would have been mentioned, was that there were some signs that ER/LA users actually had lower odds of misuse than immediate-release and short-acting. And given chronic pain patients' discussion sometimes of being on a roller coaster with short-acting pain meds, where they start to get relief, then they start to feel really bad, and then they start to take more, I wonder if as they go up and down and up and down throughout the day, including some of the side effects, if that would explain some of the issues that they have, and why we see more misuse happening, at least in this study.

Also, I was kind of struck by the fact that FDA had intimated in some of their reports that it looks like it could be more about daily dose than whether or not it's an ER/LA versus an IR/SA. So I think some more study on that would be interesting as well.

DR. BATEMAN: Dr. Reich?

DR. REICH: Jeff Reich. I'll just reiterate what I said before in terms of risk factors and identifying and parsing out some of the subgroups. Again, to me, thinking about how this would roll out to the clinical community, the pain community in particular, knowing the subgroups, the types of pain that may or may not be more at risk for misuse, abuse, OUD, I think is really an essential detail.

DR. BATEMAN: Do the panelists want to comment on the association observed for gabapentinoid use and the increased risk for pain-adjusted OUD? We saw in the OPC presentation a 5-fold increase in the adjusted model. Any thoughts on that? It was slide 35.

Dr. Reich?

DR. REICH: Just to follow up on what I had said before about that, that really jumped out and really begs the question as to what's the underlying pain diagnosis there; because that in and of itself, I think to implicate gabapentin, or

draw too many conclusions about gabapentin, I think is really very superficial. And I think you really have to look at what those patients who are on gabapentin are getting treated for to really probe that.

DR. BATEMAN: Dr. Shoben?

DR. SHOBEN: Abby Shoben. I just wanted to hit some of the comments that were made at the very beginning in relationship to this gabapentinoid issue, too, which is to say that the adjusted models are really hard to interpret. It's to your comment, too, that we don't know who these patients are who are getting gabapentin, and we don't even know, really, how to interpret these adjusted models; so more careful thought about the adjustments really needs to go into these analyses.

DR. BATEMAN: Yes, And it is just gabapentin use at baseline.

Dr. Becker?

DR. BECKER: Will Becker. Yes, just really to add on to what others are saying related to the gabapentin, I think their underlying pain diagnoses

is important but, to me, I also think about underlying anxiety and mood disorder. Gabapentin is a gabaergic molecule. It acts similarly to benzodiazepines, and I think there's a propensity for patients who have underlying anxiety to stay on gabapentin once it's prescribed.

So I think we could ask questions about what is the residual confounding that was seen in our ascertainment of mental health comorbidities; not fully clear. I think there was a clinical interview, but I'm still not certain whether that was a diagnostic clinical interview. But in any case, I wonder if the gabapentin use is a marker of more severe mood disorder. Thanks.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: Just related to that same point, I think there are a lot of interesting questions around gabapentin. Many of us have done research on this drug, but aside from benzodiazepines, which really can potentiate, I think, the sedative effects and the risk of death, I really think of a lot of these other medications as markers of

disease severity rather than representing causal effects.

We're taking time discussing gabapentin in particular, but if you actually corrected for multiple comparisons, I highly suspect this would not even be significant here, and you can get blips like this just from random variation. So it may be that with appropriate statistical methods, this wouldn't even be a signal that we call significant because there are already pre-existing questions about gabapentin potential adverse effects, combination with opiates, but I don't think these data resolve that question at all.

DR. BATEMAN: Mr. Phillips?

MR. PHILLIPS: Gabapentin is prescribed for so many different problems and diseases. It is prevalent, for instance, in the diabetes community for neuropathy. It is prevalent in the mental health community. I just don't see that there is enough of a connection here to draw any conclusion about gabapentin in particular.

DR. BATEMAN: Okay. Just in the interest of

completeness, I'll ask the question, were any of the risk factor analyses, the findings from the risk factor analyses, such that they should inform changes to the label? Most of the risk factors, or factors that were associated with the outcomes of interest, are already contained in the label. But anyone want to comment on that issue?

MR. PHILLIPS: I don't think we should add gabapentin.

DR. DEJOS: Mike Dejos, Methodist Le Bonheur Healthcare. Based on the review of the two different studies and discussing some of the strengths and limitations of both, I actually don't believe we should make any significant changes to the label. I actually think we should keep it as is. We did see that a number of label changes were made a few years ago, and we saw quite a bit of a dip, actually, in the number of OUDs that were reported in some of the other outcomes. So, for me, personally, I don't think we need to make any significant changes.

DR. BATEMAN: Okay. Any final comments on

question 3?

(No response.)

DR. BATEMAN: Okay. So then we'll move on to discussion question 4. We've touched on a lot of these issues in our discussion already, but given the interpretation of the findings from these studies and what is currently in the FDA-approved opioid agonist labeling, are there any novel findings that you believe FDA should communicate to healthcare providers, patients, and other members of the public?

Any clarifications on the the wording of the question? Dr. Bicket?

DR. BICKET: I know the question says "novel findings." I guess I'm just wondering is it just something that would be new or of interest? Is that in there, or does it have to be something that would be -- what's the threshold here, I guess, that the FDA has about novelty when it comes to findings? That would be helpful to answer the question.

DR. BATEMAN: I'd suggest to take a broad

reading of that, so anything that emerged out of the studies we've reviewed that you think should inform changes to the labeling.

DR. BICKET: Thank you.

DR. McANINCH: Jana McAninch, OSE. I would just agree with what you said. I think you could substitute the word "important findings" or something like that.

DR. BATEMAN: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. There isn't a lot that I really felt was completely novel here, but there was a lot that I felt was important. So I think when we're communicating with healthcare providers and patients, I think it's worth reiterating somewhere -- whether or not it's in the label, but I think it should be in the label -- to patients that long-term use of these medications really lacks efficacy data. And I think at any point where we can bring that up as part of the discussion I think is meaningful.

The other thing I think is really helpful is that although with a lot of the data, there's a

range of things depending upon how you correct or adjust for it. But one of the things I think that we have pretty good data on is MMEs and the association with adverse outcomes. I think that's something that could be communicated in a less controversial way than some of the other findings that we have and would also inform that, really, we want to use the lowest dose possible and make it a part of multimodal pain management so that we are using the lowest MMEs.

I think that these are important points, that while not novel, this data gives us another chance to bring it up and raise the discussion with patients.

DR. BATEMAN: I think the current labels state that the opioid should be used at the lowest effective dose for the shortest possible duration. Are you suggesting something more quantitative or more specific?

DR. AMIRSHAHI: I think we have pretty good data on MMEs that have been associated with adverse outcomes, so although there isn't really a ceiling

per se -- and that was one of the criticisms of the drug label, was that there wasn't a true ceiling dose on opioids -- we could perhaps put that in the MMEs that are associated with more adverse effects as a general guidance.

Then also, not to downplay the fact that, really, opioids aren't meant to be used in a vacuum, but they're really supposed to be with multimodal pain medication regimens. Every day in the ER, I treat painful conditions, and I always have to sell patients on adding Tylenol in or putting a Lidoderm patch on. So just having those discussions that they're not meant to be used in a vacuum and some general guidance, because we do know a dose where we have an increased risk of adverse effects.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: I just want to try to tie together the comment you made and that Dr. Gordon made. I think that they're both correct, and you can integrate them in one new bullet point.

MMEs mean something different in 2025 than

they did in 2012. So someone who's on 120 MMEs is a very different patient than the average 120 MMEs from 15 years ago. So it's hard to declare a number. But it was very helpful in the FDA slides where they showed example labels, and it does just say take it at the lowest dose possible for the shortest amount of time. But we can confirm more information. We can say we have very rigorous evidence from multiple sources that the higher the dose, the higher your risk of adverse effects.

There's not a clear threshold because it changes based on society, and regulatory pressures, and things like that. But I do think you can make a strong statement that higher doses result -- like use causal language. I don't think there's any debate about it. Just like smoking causes lung cancer; you don't have to do an RCT to prove that. The higher doses of opiates result in higher rates of overdose and misuse.

DR. BATEMAN: Other comments? Dr. Gordon?

DR. JONIAK-GRANT: Okay. Thanks Dr. Gordon. Elizabeth Joniak-Grant. I think if we're

going to do any changes to the labeling, it really needs to be rock solid and not just intimations or best guesses. I think that we've seen how things can go awry at times. So with putting a maximum MME, I prefer the idea of giving some more information, but not necessarily setting what that amount should be.

The CDC guidelines have already addressed this. I mean, this has been well-covered territory since 2016, with corrections. And also, MME computations can be problematic. There have been some publications on that recently about how do we figure those and what do those look like, so I wouldn't want an actual number for MME.

There's been a decent amount of discussion of the long-term use data for -- sorry; it's been a long day. The data for the effectiveness of long-term use has been lacking. I wanted to ask what people are thinking about would be long term; because we all know, most drugs that come on the market, 3 months is kind of where it's at, and that's where a lot of the research stops for most

new prescriptions. Studies don't usually go for 2 years, 3 years, 5 years, 6 years.

So what would they be looking for to have long-term data? Then how would the studies that have had various problems -- but there are some studies that suggest that long-term use for a certain subset of patients can have effectiveness and can support them. Then, obviously, there's a lot of anecdotal evidence from patients who have been on long term who have tried various things and haven't had success for all types of reasons. And I don't want to just discount that out of hand and say, "Oh. Well, all those people's experience doesn't count."

So I think we need to be mindful of that, too. But what do people mean when they say they want to see effectiveness of long-term use? What is long term?

DR. BATEMAN: So I think this question of efficacy studies is really important, but it's not really within the scope of what we're discussing today. So I want to steer things back to just

focusing on these studies that we're evaluating.

Dr. Gordon?

DR. GORDON: Adam Gordon. I like the current label that we currently have with regards to side effects, and I agree with Dr. Floyd and many in the room, too, that we have to be very careful about ascribing a dichotomous risk above a certain dose is somehow much more serious than a lower dose. We know that higher doses are always going to attribute a higher risk to patient populations, and we learned from the CDC guidelines that these can be weaponized in some ways.

If you have a guide label change that gives a certain dose as a target dose, we'll have regulators, states, lawmakers, insurers trying to drive everybody down to that certain dose that we know that there is some untoward outcomes associated with those actions. So I would be very careful about having a certain dose on the label. I think what we currently have, saying a higher dose, get the lowest dose effective is what the target is, and be at that.

The other thing that I think we also need, and I'll just say this, is as we taper people down, we want to make sure that we're improving their risk profile. There has not been a lot of good conclusive studies that show that if you reduce MME down, that the risk actually goes away or reduces as well. But does the change actually cause potential harm as well? We just don't know this yet. So being very cautious in our labeling is going to be very important. I wouldn't want to weaponize through the label process.

DR. BATEMAN: Just to add to that, I think the available evidence doesn't really support a threshold effect at a certain MME level, and someone who's on benzodiazepines or on gabapentinoids may have a different risk profile than someone who's not. So I agree with those comments.

Dr. Floyd?

DR. FLOYD: Really quick, just because I didn't want the unanswered question left hanging in the air. I think there's a clear answer. The FDA

has known it for many years. It's a randomized-controlled trial of people with well-defined pain conditions randomized to opiates, plus multimodal pain management versus multimodal without opiates. That's the study design for 6 or 12 months. I don't think it's like we don't know how to do it; we just simply don't have it.

For over half a century, the regulatory standard for evidence of efficacy from well-controlled studies is a randomized-controlled trial, and the outcome is important. It's not your pain scale. It's death. It's how people feel, function, and survive. It's a validated PRO on functional status.

So the ideal study, I think we've known for a long time, some have been done. They've been null. So it's not that nobody can do this study. People have done the study. To date, we have no rigorous evidence from a well-designed, well-conducted RCT that long-term opiate therapy is beneficial, and I think that needs to be stated because it's important.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: This is Mark Bicket. Just to get back to the question about communication with healthcare providers, patients, and others, I do find the results from Studies 1 and 2 compelling information. It may have echoed some of our previous discussions, but I do think the top-line summary measures for OUD, whether it's the composite measure or other measures, would be helpful to include. They don't necessarily have to be a black box warning, but within the postmarketing study information would be one option there, and/or incorporation into other educational materials that the FDA has, or helps to produce, to help ensure that that message comes out.

I do agree with the notion of being cautious about any implications about dose ceilings given the risk is continuous. It is interesting to look at the current label and notice -- just going back to this comment about the multimodal, the only time multimodal pain treatments are mentioned is in the setting of an opioid taper right now. And it

actually doesn't come up at all in at least a few of the labels that I can just quickly look at right now, which is somewhat surprising and perhaps off topic. But if there's going to be a refresh, it may be helpful to do that, being mindful of these other topics we've discussed. Thank you.

DR. BATEMAN: Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. Going back to the findings of the study, specifically, they're not particularly novel findings, as a lot of us have mentioned, but they are confirming, a lot of the studies that are out there. And I think one thing that is often on our minds, people focusing on drug safety, is the aspect of risk communication, and to what extent do providers/patients have an appreciation for the actual risk.

So in that sense, I wouldn't necessarily focus on the specific estimates from this study, but maybe putting some quantitative information to put some more specification around the qualitative estimates that are currently in the label, whereas

now it just says there is a risk of misuse/abuse, but it's really hard to know what that means to individual providers and patients.

So I'm wondering whether providing some of the range, maybe providing some of the mean, might help with that risk communication and with that risk-benefit trade-off for providers and patients as they make their decision.

DR. BATEMAN: Dr. Shoben?

DR. SHOBEN: Abby Shoben. I don't know all the studies that have gone into what's in the current label, but I will say that my read of the risk as related to the personal or family history of previous substance abuse or major depression understates to me the risk that we saw in these studies from the past-year; substance abuse, substance use disorder. And perhaps that should be looked at in the context of all the other studies, highlighting the recent current history of substance use, it really elevates the risk.

DR. BATEMAN: Okay. Are there any other comments on discussion question 4?

(No response.)

DR. BATEMAN: Okay. Then before we adjourn, are there any last comments from the FDA?

DR. DAL PAN: This is Gerald Dal Pan from the Office of Surveillance and Epidemiology. I'd like to thank everyone for, really, the robust discussion we had today. This has been a very important meeting for us. You've heard the long history of these studies, and it was really important for us to bring them to a public discussion.

So we really want to thank each and every one of you for the time you took to look at these studies before you came here, for traveling here, and for the robust discussion today. So thank you.

Adjournment

DR. BATEMAN: Thank you to the panel. We will now adjourn the meeting. Thank you very much.

(Whereupon, at 4:25 p.m., the meeting was adjourned.)