FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY AND RISK MANAGEMENT AND ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEES

Tuesday, May 3, 2016

8:01 a.m. to 5:06 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

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)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:01 a.m.)

Call to Order

Introduction of Committees

DR. WINTERSTEIN: Well, good morning. I would like to remind everyone to please silence your cell phones, smart phones, and any other devices, if you have not already done so.

I would also like to identify the FDA press contact, Sarah Petticord. If you're present, please stand. There she is, waving. Good morning.

My name is Almut Winterstein. I'm the chairperson of the Drug Safety and Risk Management Advisory Committee, and I will be chairing this meeting. I will now call the joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Product Advisory Committee to order.

We'll start by going around the table and introduce ourselves. Let's start down on my right.

DR. HERRING: Hello, I'm William Herring from Merck.

DR. KRASNOW: I'm Steve Krasnow, medical oncologist from the VA Medical Center in D.C.

DR. BOHNERT: I'm Amy Bohnert from the University of Michigan.

DR. RAGHUNATHAN: Hello. I'm Trivellore Raghunathan from University of Michigan.

DR. MCCANN: Hello. I'm Mary Ellen McCann from Boston Children's Hospital.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist from Rutgers University

DR. HIGGINS: Jennifer Higgins, consumer representative.

MR. O'BRIEN: Joe O'Brien, patient representative.

DR. BILKER: Warren Bilker from the University of Pennsylvania.

DR. FLOYD: James Floyd from University of Washington.

DR. CRAIG: David Craig from Moffitt Cancer Center, Tampa, Florida.

DR. KAYE: Alan Kaye from Louisiana State University Med School in New Orleans.

DR. ISRAEL: Heidi Israel from St. Louis University Medical School.

DR. EMALA: Charles Emala from Columbia University.

DR. PERRONE: Jeanmarie Perrone from the University of Pennsylvania.

DR. WINTERSTEIN: I'm Almut Winterstein, professor and chair for pharmaceutical outcomes and policy at the University of Florida.

LCDR BEGANSKY: Stephanie Begansky, designated federal officer for today's meeting.

DR. BROWN: I'm Rae Brown from the University of Kentucky.

DR. SHOBEN: Abby Shoben from the Ohio State University.

DR. MORRATO: Elaine Morrato from the Colorado School of Public Health at the University of Colorado.

DR. GALINKIN: Jeff Galinkin from the University of Colorado.

DR. BATEMAN: Brian Bateman from Massachusetts General Hospital and Brigham and

Women's Hospital.

DR. FRY: Michael Fry, Providence Health Services of Oregon.

DR. STANDER: Paul Stander, internist from the VA Medical Center and University of Arizona in Phoenix.

DR. TYLER: Linda Tyler, University of Utah hospitals and clinics.

DR. CHOUDHRY: Niteesh Choudhry, Brigham and Women's and Harvard Medical School.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips, Augusta University Medical Center and University of Georgia College of Pharmacy.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the acting associate director for public health initiatives in the Office of Surveillance and Epidemiology, Center for Drugs at FDA.

DR. MANZO: Good morning. I'm Claudia Manzo. I'm the director of the Office of Medication Error Prevention and Risk Management in OSE-VIII.

DR. LaCIVITA: Good morning. I'm Cynthia

LaCivita. I'm the division director for the Division of Risk Management in OSE and CDER.

DR. THROCKMORTON: And I'm Doug Throckmorton, deputy director for regulatory programs, Center for Drug Evaluation and Research, FDA.

DR. WINTERSTEIN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for a 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 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 topics during breaks or lunch.

Thank you.

Now I'll pass it to Lieutenant-Commander Stephanie Begansky who will read the conflict of interest statement.

Conflict of Interest Statement

LCDR BEGANSKY: Thank you.

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 representatives, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with the 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 his or her 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, member and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves discussion of the results from assessments of the extended-release and long-acting opioid analgesics risk evaluation mitigation strategy, REMS. The agency will seek the committees' comments as to whether this REMS with elements to assure safe use assures safe use, is not unduly burdensome to patient access to the

drugs and to the extent practicable, minimizes the burden to the healthcare delivery system.

The ER/LA opioid analgesics REMS requires that prescriber training will be made available to healthcare providers who prescribe ER/LA opioid analgesics. Training is considered REMS-compliant if: 1, it, for training provided by continuing education providers, is offered by an accredited provider to licensed prescribers; 2, it includes all elements of the FDA Blueprint for Prescriber Education for ER/LA opioid analgesics, the blueprint; 3, it includes a knowledge assessment of all the sections of the blueprint; and 4, it is subject to independent audit to confirm that conditions of the REMS training have been met.

The agency will seek the committees' input on possible modifications to the ER/LA opioid analgesics REMS, including expansion of the scope and content of prescriber training and expansion of the REMS program to include immediate-release opioids.

This is a particular matters meeting during

which general issues 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 topic at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Joseph Herring and Linda Scarazzini are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry.

Drs. Herring and Scarazzini's roles at this meeting are to represent industry in general and not any particular company. Dr. Herring is employed by Merck, and Dr. Scarazzini is employed by Abbvie.

We would like to remind members and

temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants will need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committees' discussions. Thank you.

DR. WINTERSTEIN: We will now proceed with the FDA's opening remarks from Dr. Woodcock.

FDA Introductory Remarks

DR. WOODCOCK: Thank you.

Good morning, everyone. I'm Janet Woodcock. I'm director of the Center for Drug Evaluation and Research, and I welcome the committee members and our distinguished guests to this important meeting to discuss the REMS program.

(Pause.)

DR. WOODCOCK: As I said, we're here to

discuss the opioid REMS, which are one of the steps FDA has taken to deal with what we're currently experiencing in the United States, which is a devastating epidemic of prescription opioid misuse and abuse, including a large number of overdose deaths from opioids.

At the same time, expert opinion finds that the treatment of pain in the U.S., particularly chronic pain, is not satisfactory. And one of the problems that have been found is an over-reliance on prescription opioids. And this is a report from the Institute of Medicine fairly recently.

Unfortunately, the science and the data needed to inform policy implementation in this area is often lacking, and we will be discussing that at some length today.

Now, in the U.S., this is not our first opioid epidemic, and of course, the history of mankind is punctuated with episodes of abuse of various opioids, some exceedingly devastating. In the 1860s, there was an addiction epidemic due to over-prescribing of morphine by the physicians and

laudanum in patent medicines that were available freely to consumers. That was controlled by various restrictions that were put in place.

In the 1960s, there was a heroin epidemic that led to the federal War on Drugs, and around that time, there was conservatism on prescribing, based on that recent experience of the heroin epidemic and fear of addiction.

But in the '90s, there was a resurgence of focus on the treatment of pain, very appropriately. And this is just an example here, but JCAHO issued guidelines that pain would be considered the fifth vital sign. But there were many other efforts to try to urge people to adequately treat people with pain in the United States.

At the same time, additional opioid molecules and formulations were developed and marketed, including higher potency, extended-release or long-acting formulations. And practitioners responded with ever increasing prescribing of these drugs.

In the 2000s, FDA began to receive reports

of abuse and addiction, excessive amounts of that, and modified the label of OxyContin, based on this, and also reports of diversion, and we included box warnings. FDA initiated a risk management plan in 2001.

However, in that decade from 2000 to 2010, opioid prescribing continued to escalate, and there was the development of what are called "pill mills" where people could simply stand in line, get a prescription basically without an adequate physical examination for often high potency opioids. And this led in certain regions to tremendous amounts of abuse, misuse, and addiction.

Here is the actual numbers of prescriptions for opioid analgesics from the early '90s through 2013, just what is dispensed by U.S. retail pharmacies. So this doesn't count different opioids used in hospitals and so forth. And you can see this peaked around 2011 or so with over 200 -- this is in thousands -- millions, hundreds of millions of prescriptions of these drugs were provided, much of it hydrocodone and oxycodone.

And you'll see later, much of this was the immediate-release formulations of these drugs.

Now, it does somewhat challenge the imagination that we would need that many opioids in circulation in the United States.

This is the split, an estimated split between the immediate release and the extended release and long acting. And you can see the vast number of prescriptions are the immediate-release opioids peaking at around 184 million prescriptions in 2011. And most of these are your combination with acetaminophen products.

From the U.S. retail pharmacies, a dispensing of extended release or long acting has remained relatively flat over this time at around 20 million. I think part of my point here is that it is well known with various substances that people abuse, that the prevalence of abuse and addiction and so forth rises with availability. Also, the sequelae, the consequences, for example, alcoholism, cirrhosis of the liver, can be correlated with the availability in the society of

alcohol and the extent of its use.

To look further into this, FDA analyzed a large sample. More than half of all the outpatient retail prescriptions in the U.S., including over 176 million patients -- and much of this question is about chronic use of these and the appropriateness of chronic use.

When we defined chronic use as over 90 days, about 12 million patients had a chronic episode of using the immediate release for that amount of time, whereas about 3 million patients had a chronic episode of using only the extended release.

So for the chronic use, the proportion is less obviously than the proportion of total prescriptions dispensed from the IR to the extended release or long acting. However, still, the majority of these are immediate release.

So we hear from some people why use opioids or why has FDA approved opioids? Well, if you are in the medical field, you realize how important and integral these are to much of medical care. They are used in the outpatient setting for things like

trauma, after surgery, and severe pain, say, from ruptured disks and so forth. The alternative armamentarium is limited, especially for outpatients, things like NSAIDs or acetaminophen. Now, the NSAIDs have well-known serious side effects and may not be appropriate where bleeding is a concerned.

Amongst the opioids, the combinations, as I said, are the most popular to be dispensed. And really, the major issue in the outpatient setting is the volume of dispensing, the number of tablets, the duration of therapy.

Now, I look at the people in the audience and on the committee, I'll say most people actually -- despite these being drugs that are abused widely, most people can't take or can't tolerate opioids very well.

So many of you have gotten prescriptions for opioids after, say, a procedure in the hospital or outpatient clinic or emergency room. You've taken that bottle home. You've found that the drug gives you either dysphoria, bad feelings of some sort,

dizziness or whatever, or it just gives you constipation. You stopped taking it, and you left it in your medicine cabinet, and it's still there. And when I've asked audiences around the country about this, many, many people raise their hands; yes, I have these drugs in my medicine cabinet.

We know that much of the abuse of these drugs are from drugs that have been gotten from a friend or relative for free, or have been stolen from a friend or relative, or diverted in other ways. But when we have this availability, this widespread availability, this helps lead to the problem.

So the disposal practices, we at FDA just had another medicine take-back day, where huge bags of medications were collected and turned in. Disposal hadn't been -- we haven't as a society paid enough attention to this. Those are important, but it's also important for prescribers not to dispense so many tablets, especially when many of them are going to go unused.

Now, one of the main issues of contention is

management of chronic pain, non-cancer pain. As I said, physicians have been urged, really appropriately, for 20 years to more aggressively respond to a patient who is having pain. But chronic pain is different than acute pain, and it's really not a single simple entity.

The current approach to treating chronic pain is a multimodal approach, where you use multiple modalities and try a variety of things, including a lot of non-pharmacologic interventions. However, in much of the country, resources for this approach to chronic pain may not be available; in other words, the therapist, the physical therapist and what have you.

In addition, insurance coverage is often not available or not available widely enough. Educating patients about these other modalities is time consuming in the short visits that physicians have, and prescription drug products are widely available, as I just showed, and they're often covered by health insurance. So they have become a default position of management for people with

chronic pain, even though we know, in fact, that a multimodal approach would generally be more successful.

What about inside healthcare settings? This is where opioid medications right now are really widely utilized for anesthesia, surgery, and post-surgical care; trauma and burn care; palliative care; cancer and terminal illness, inside outpatient clinics where they're doing surgical and dental procedures use opioids; nursing homes; terminal illnesses, the hospice, for example, at rehab hospitals widely used to assist in rehabilitation and get patients over that pain; outpatient acute pain; emergency departments and so forth; outpatient cancer pain.

Then, as I said, outpatient chronic non-cancer pain, which is the most controversial area, but I would stress that each of the above has legitimate uses for opioids. So opioids are a legitimate modality. It's just they shouldn't be the default position for treating chronic pain.

Here is a list, which I will not go through,

of pharmacologic and non-pharmacologic interventions that can be used in pain. Here is some of the safety concerns that pertain to each of these modalities. So you can see that treating pain, especially chronic pain, is not a simple procedure, and we don't have really good alternatives that physicians can turn to.

We have in the past decade approved a number of drugs for specific chronic pain conditions, for example, for post-herpetic neuralgia or neuropathic pain or fibromyalgia and so forth. And these modalities, although they have their own liabilities, are becoming more widely used for those specific pain conditions.

However, it's not surprising that some of those treatments are less used by primary care physicians because of lack of familiarity where the opioids are very familiar, been with us for hundreds of years.

So what we're talking about today and what we wish to consult the advisory committee about is how to best reduce overall population exposure to

opioids while retaining appropriate pain management in the various care settings. That's our challenge.

We've had more or less a four-prong approach. First of all, we have tried to prevent the onset of abuse and addiction by, first of all, prescriber education, and that is the REMS that we'll be talking about today.

We've also updated the labels of the opioid drugs to more strongly stress the risks. We have also required studies from the manufacturers for ER/LA opioids for better data on the long-term use of opioids for pain, including a randomized withdrawal study that's being conducted.

We've also developed standards for abuse-deterrent formulations. These are formulations that hopefully will not be as easy to abuse and therefore will be less desirable and lead to fewer deaths and addiction.

Development of alternative pain therapies, as I said, that's an extremely important prong, is to give physicians alternatives. And then to

improve disposal practices with federal and state agencies, we need to coordinate on this. We also are working on prevention of overdose deaths, naloxone both auto injector and nasal spray.

Treatment of addiction, medication-assisted therapy, this is an area that isn't as robust as it needs to be nor is it well utilized in the community, but treatment of addiction is extremely important. And these steps are summarized in an action plan that we have recently published. So today, we're talking about the prescriber education portion of this.

As was already stated, we'd like to obtain the committees' view on the progress so far of the current opioid analgesics REMS, discuss the current REMS program, consider whether it's achieving its goals and whether any modification should be made to the program, whether it should remain the same or should it be eliminated.

Should the REMS be modified? That's a question you will be asked. Should the content of the current blueprint be expanded?

Now, I hope from everything I've presented to you, it should be clear that what we really need is for physicians at every level -- primary care physicians, other prescribers, nurse practitioners, and so forth -- to understand pain management and to understand the various modalities available for pain management. And we also need to have better data on what modalities work best in which situations.

But in this case, we're talking about the current blueprint and should it be expanded or not. That blueprint really is devoted to those extended-release or long-acting opioids, their pharmacologic properties, and how to use them in which settings.

Are the current medication guide and patient counseling document appropriate? Is the REMS for the IR opioid analgesics necessary to ensure the benefits outweigh the risks of these drugs? That is the statutory standard that we have for imposing a REMS.

Should prescribers be required to complete

training in order to prescribe opioid analgesics through a closed, restricted distribution REMS or through other mechanisms?

Now, FDA has long supported the administration's proposal that this training be part of getting your certification for being able to prescribe opioids. There's a program administered by the DEA that actually you must enter and receive a number in order to be able to prescribe scheduled drugs of all kinds, including opioids. So that is already a system that is in place.

We will describe today the challenges that would be inherent in trying to put a closed distribution system around opioids, given, as I have described earlier, how ubquitous their use is in medical practice in healthcare today. Then, of course, we would welcome other suggestions from the committee.

Thank you very much for your attention, and I look forward your deliberations. Thank you.

DR. WINTERSTEIN: Thank you, Dr. Woodcock.

We will start now with Terry Toigo who will begin the presentations from the FDA.

FDA Presentation - Terry Toigo

MS. TOIGO: Good morning, everyone. I'm Terry Toigo, the associate director for drug safety operations in the Center for Drug Evaluation and Research. I will be providing some background today on the development of the extended-release and long-acting opioid analgesic REMS that FDA approved in 2012.

For today, I'm going to highlight some of the activities over the past 10 years or over the 10 years that preceded FDA's determination that a REMS was necessary to assure the safe use of opioid analgesics. And then I'll discuss some of the activities related to the development and approval of the REMS. Then, as you can see on this slide, you'll hear the REMS referred to in a variety of ways over the next few days.

It will be the extended-release and long-acting opioid analgesic REMS, the opioid REMS, the ER/LA opioid REMS, the ER-LA REMS, or the ER/LA

REMS. They all mean the same thing.

In 2000, FDA first received reports of significant problems with prescription opioid abuse, especially involving OxyContin. The problems included crushing of the tablet to defeat the extended-release properties, misuse by several different routes, and addiction, overdose, and death.

The first risk management plan for an oral extended-release opioid was developed in 2001 for OxyContin. Labeling changes were made to warn that the extended-release opioids were not to be used when immediate-release opioids were adequate. Boxed warnings were added to call attention to the potential for abuse, misuse, and diversion of a product.

Safe-use conditions highlighting the importance of not cutting, breaking, chewing, or dissolving the ER products were standardized in the label for extended-release products. The risk management plan focused on education, surveillance, and intervention when a signal of misuse or abuse

became apparent.

As FDA worked to address the problems of prescription opioid abuse and misuse, several advisory committee meetings were held to discuss the extended-release opioids. The first was a 2002 meeting of the anesthetic and life support drugs advisory committee. There were four more public discussions at advisory committee meetings, one in 2003, two in 2008, and one in 2009.

The committee recognized the growing public health problems of abuse. At the same time, the committee members expressed concern that any risk management measures that would restrict opioid treatment could prevent appropriate use of these products and reduce access to the important analgesics by patients who needed them.

Despite FDA's risk management activities over almost 10 years -- these included, as I mentioned, adding warnings to product labeling and developing risk management plans to prevent inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics -- as this slide shows,

unintentional death resulting from these products continued to increase.

During the time FDA was working to address the growing problems with ER/LA opioid analgesics, Title 9 of the FDA Amendments Act of 2007 gave FDA three new safety authorities: the authority to require the REMS, the authority to require safety labeling changes, and the authority to require PMRs.

We considered the new safety authorities and specifically how can our authority to require sponsors to implement a REMS influence some of these behaviors while other behaviors may be influenced more directly through actions that were outside of FDA's purview.

In February 2009, FDA informed sponsors of ER/LA opioids that their products would require a REMS to ensure that the benefits of those products continued to outweigh the risks. Although each individual sponsor was required to submit a REMS, FDA asked the sponsors to work together to develop a classwide REMS for ER/LA opioids.

At that time, there were 22 companies involved. FDA recognized that putting together a workable REMS for these widely prescribed opioid products would present challenges. Therefore, we invited all affected sponsors to a meeting to discuss how such a program could best be designed to manage the risks while also considering reasonable burdens on the healthcare system. This meeting was held on March 3, 2009.

Following the meeting with industry, FDA opened a public docket on April 20, 2009 to obtain information about the proposed REMS. We asked questions such as how restrictive a system should be designed? How would such a program be implemented given the number of patients, prescribers and other healthcare providers involved in their use? What systems, for example, in pharmacies already exist that could be used to implement a REMS? What metrics could be used to assess the success of the REMS?

FDA received more than 2,000 comments on the proposed REMS. Later in my presentation, I'll

highlight some of the themes that we heard from stakeholders.

In February 2009, at the same time we notified sponsors of the need for a REMS, FDA held a stakeholder meeting to discuss the regulatory process and standards for review of opioid analgesics. Over the next several months, FDA met with many stakeholders about the REMS.

In early May, we held four separate stakeholder meetings to obtain comments and opinions regarding the development of REMS for opioids. Later in May, we held a public meeting during which more than 100 people provided comments on their experiences with opioid drugs along with suggestions for a REMS for the ER/LA opioid products.

Beginning in the summer of 2009, there was a lot of internal work ongoing at FDA. More than 70 people from FDA were part of eight working groups. They examined data from the public docket, gathered additional information, analyzed issues, and then made some recommendations.

In December 2009, FDA held another public meeting to hear from the industry work group about their views on the specific features of the REMS.

In July 2010, FDA held another two-day advisory committee meeting to present their proposal for a classwide opioid REMS and to solicit feedback from advisory committee members and the public on the components of the REMS. At that time, many of the committee members said they wanted to see a REMS for both the ER and the IR products, and a few suggested that a REMS for ER products should at least be implemented as a first step followed by a REMS for their IR products.

In October 2010, the committees discussed the design of postmarketing studies for OxyContin and Embeda to assess the known serious risks of these products and whether product-specific properties intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse and their consequences: addiction, overdose, and death.

As you can imagine, with multiple public

meetings, more than 2700 comments to the docket, and about 100 FDA staff involved, there were many things FDA needed to consider when developing the REMS. What is the scope of the REMS in terms of drugs and healthcare providers to include? How will the REMS impact the healthcare system? How will the REMS impact patient access to drugs?

Comments highlighted that the opioid REMS will be the largest and most complex program of its kind and that we needed to consider size in identifying potential hurdles to effective REMS development. Many comments suggested that if the REMS applies only to long-acting opioids, there will be shifts in prescribing to immediate-release products or other pain relievers, even if they are less effective for the patient.

Some commented that methadone should have a separate REMS. Many comments supported prescriber education. But comments were divided as to whether such education should be mandatory. Comments from a wide variety of stakeholders highlighted potential benefits to educating patients and their

caregivers regarding safe use, storage, and disposal of opioid medications, in addition to the broader education on pain management and the benefits and risks of opioid treatment.

Many comments focused on education-based elements and said that if education is mandated, REMS certification should be linked to DEA registration to maximize participation, minimize cost, and streamline the prescription process.

FDA considered proposing that the REMS require individual prescribers to enroll in a REMS program and real-time verification of prescriber training at the pharmacy level. FDA heard from commenters that a requirement like this could cause some prescribers and pharmacies to opt out of the program with potential adverse consequences to access to pain medications.

FDA also heard that we should link certification, as I mentioned, to DEA registration or to state requirements such as state medical board licensure. FDA also considered whether the proposed REMS should include enrollment of patients

in a registration system.

Numerous comments at the public meeting and in the docket stated that a REMS that employs a patient registration system would be overly burdensome and create a stigma for pain patients that could adversely affect patient access to necessary medications.

All REMS are required to contain a time table for assessments, and for a REMS of this size to address the problem of this complexity, assessing the effectiveness of the program as well as its impact on appropriate access to pain medications is critical.

Finally, we heard from some that less restrictive elements should be implemented first to determine if they are effective in mitigating risk while preserving access.

FDA considered the statutory requirements related to risk, burden, and patient access, so we tried to strike the right balance between reducing abuse of opioids and assuring appropriate access to pain medications for patients in need.

As the last few slides have shown, there were many varied opinions, but one thing about which all stakeholders were unanimous was the need for prescriber education. That was a clear and consistent message, and it is the reason we focused the REMS on prescriber education.

REMS notification letters were sent to sponsors of ER/LA opioids on April 19, 2011 specifying the required elements as listed on this slide. We also focused on ER/LA opioids rather than ER and IR opioids because the FDA concluded that ER/LA products were determined to have an increased risk on a per tablet basis compared to other opioid products.

Accidental or purposeful misuse of ER/LA opioids is more likely to result in adverse events, including respiratory depression or death, and thus the focus of the REMS was the ER/LA products.

The key element of the REMS program is prescriber education, the content of which is described in the REMS notification letter. The prescriber education program includes general

information about the use of long-acting and extended-release opioids to aid in patient selection and counseling and specific information about the individual drugs in this class. It was intended to inform prescribers about how to recognize the potential for and evidence of addiction, dependence, and tolerance.

FDA expected that the training would be conducted by accredited independent CME providers, and rather than require a mandatory training as part of the REMS, FDA supported mandatory training program linked to DEA registration as proposed in the administration's comprehensive plan to address the epidemic of prescription opioid abuse in 2011.

We worked in collaboration with the ACCME and other accrediting bodies and CE providers to ensure that the programs developed under the REMS would be in compliance with ACCME accreditation criteria and the standards for commercial support; that is, that the programs would meet ACCME standards of independence and that the content and format of the activity would be free from

commercial bias.

We thought having the training provided by CME organizations would be an incentive and not create new burdens on prescribers because most healthcare professionals are routinely engaged in continuing education activity. We expected the CME training to be provided through unrestricted education grants by the companies.

As with any new project, there will always be lessons to be learned. This slide highlights some of the communication challenges in developing the blueprint.

We learned in July of 2011 that FDA and the CME community had different expectations for the blueprint for prescriber education. The CME community wanted to be sure that FDA controlled the content of professional education. FDA believed that the model we proposed did result in FDA control of the content.

Given the time constraints around this project, FDA decided at that time to develop the content for the blueprint and to seek public

comment.

The blueprint was published in the Federal Register in November 2011. We received comments from about 65 individuals or organizations. Most of the comments were favorable. Some offered specific edits. Some comments were negative. The negative comments focused primarily on the REMS being ineffective in addressing the problem because it's voluntary, industry is involved, and the ER/LA focus is too narrow.

FDA approved the REMS in July of 2012. The approved REMS included a patient counseling document for the prescriber to give to the patient, including a blank space to write specific drug information; a one-page medication guide to be given to the patient when the drug is dispensed, and the final FDA blueprint that was posted on the FDA website to be used by accredited CE providers to develop training supported by independent educational grants from the ER/LA opioid analgesic manufacturers.

The content of the FDA blueprint focused on

the safe prescribing of ER/LA opioid analgesics. It was directed to prescribers of ER/LA opioids, but it was certainly relevant for other healthcare professionals.

So in summary, the overarching goal of the ER/LA opioid analgesics REMS, as you'll hear many times over the next two days, is to reduce serious adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics, while maintaining patient access to pain medications.

When developing the REMS, FDA considered stakeholder input about the scope and the impact of the REMS on the healthcare system and patient access. As you think about whether and how to modify the REMS, please consider how we can best minimize the burden of implementing any of your suggested changes on the REMS, on practitioners, on patients, and on various others in the healthcare setting.

Thank you. And I'll now turn it over to

Cynthia LaCivita.

FDA Presentation – Cynthia LaCivita

DR. LaCIVITA: Good morning and welcome. My name is Cynthia LaCivita. I'm the director for the Division of Risk Management and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research.

My presentation today will include an overview of the risk evaluation and mitigation strategies authorities. And as Terry had mentioned, you may hear the REMS mentioned throughout the day as the ER/LA REMS, the extended-release and long-acting opioid analgesic REMS, as well as a summary of the ER/LA REMS assessment plan.

The Food and Drug Administration Amendments Act of 2007 provided FDA the legal authority to require REMS, risk evaluation and mitigation strategies or REMS. REMS are risk management plans that use risk minimization strategies beyond professional labeling. They can be required pre- or post-approval to ensure the benefits of the drug

outweigh the risk.

The components or elements of a REMS may include a medication guide or patient package insert, a communication plan for healthcare providers, elements to assure safe use, and an implementation system. It must also include a time table for submission of assessments of the REMS. As per the statute, communication plans, and time table for the submission of the assessment only applies to NDAs and BLAs.

The elements to assure safe use includes certification or specialized training of healthcare providers and also certification of pharmacies or other dispensers of the drug. The drug can be dispensed or administered only with evidence of safe-use conditions such as a pregnancy testing prior to receiving a drug with a risk of teratogenicity. It could be dispensed or administered in certain healthcare settings such as hospitals. It could require that a patient using the drug is subject to certain monitoring, and it could include the enrollment of a patient that

would receive treatment in a registry.

You can see that educational materials are important components of these elements to assure safe use, and they're not mutually exclusive. In fact, there is considerable overlap. Some elements may or may not be limited to the ability to prescribe or dispense the drug.

REMS can be restrictive or non-restrictive. REMS that are restrictive programs will include certification of healthcare professionals, certification of pharmacies or other dispensers of the drug. It can also limit where the drug is dispensed or administered. In addition, it may require patients to enroll in the program or require documentation of a safe-use condition. Non-restrictive REMS mix training or education available to likely prescribers or other healthcare professionals.

There are two possible scenarios when training is a requirement of a REMS. If training is required in order to prescribe or dispense the drug, it is considered a restrictive or closed

distribution program. Training is mandatory for those who decide to participate in the program. The second scenario is training is not required in order to prescribe or dispense the drug. This is considered a non-restrictive program.

Sponsors are required to make training available, and participation is voluntary for prescribers. Because it is voluntary, participation may be lower than desired.

I'm going to provide a couple examples and kind of illustrate how these programs may work. This is an example of when REMS training requirements are not required in order to dispense. The sponsor provides or makes training available. And as you can see by the dotted line around the arrow, this is voluntary for the prescriber to complete training.

The next example is a REMS with a restrictive program or a REMS that requires training, and it also illustrates the infrastructure to support such a program. Note that the FDA may require specific elements in a

REMS, but the sponsor is responsible for implementing the REMS.

So the sponsor provides training to the prescriber. The prescriber would complete the training. That information would be stored in a sponsor database. The prescriber would see the patient and prescribe that drug. The patient would take it to the pharmacy. In order for the pharmacy to participate in this REMS program, they would need to complete certification.

The pharmacy would verify that the prescriber is part of this program. The distributor would verify the pharmacy is part of this program before they ship the drug to the pharmacy and before the drug can be dispensed.

Next, I'll provide an overview of the ER/LA opioid REMS program. The ER/LA REMS includes nine active ingredients. The program is mandated for sponsors but voluntary for prescribers. The approved REMS comprises 24 sponsors and approximately 60 applications.

The goal of the ER/LA REMS is to reduce

serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release or long-acting opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

The elements of the ER/LA REMS include the medication guide. It also includes prescriber training via continuing education or CE, which is supported by a grant by the sponsors and guided by the FDA blueprint. Education of prescribers was one risk strategy that was emphasized and supported by all stakeholders at public meetings. Training is not linked to the ability to prescribe or dispense. The REMS leverages the existing infrastructure of the CE system used by prescribers, and sponsors do not drive the content of the FDA blueprint.

This REMS also includes a patient counseling document, letters to healthcare professionals, a REMS website, as well as a time table for submission of assessments.

The ER/LA REMS medication guide is a one-page format, and it includes information application to products and product-specific information needed for safe use. It aids the patient in the use of the medication at home, and it's intended to be an adjunct to patient counseling, not a replacement.

The patient counseling document is another tool in the REMS. It facilitates discussions at the point of prescribing with patients and/or caregivers. It facilitates discussion at the time of prescribing, and it's also a one-page document that provides important safety information about all the ER/LA opioid analgesics.

There is space available for the prescriber to write information down about either drug-specific information of maybe specific information for the patient to ensuring safe use.

The prescriber education in the REMS is done via continuing education or CE. It is supported by independent educational grant from the ER/LA sponsors and is provided through accredited CE

providers. Prescriber training is not a mandatory precondition for prescribing or dispensing. The content is not exhaustive, and it's not a substitute for a more comprehensive pain management course.

The FDA blueprint for prescriber education of the ER/LA products was developed to provide the core messages to be communicated to prescribers through CE.

The FDA blueprint covers the following topics: assessing patients for treatment of the ER/LA opioid analgesic therapy; initiating therapy; modifying dose and discontinuing use of an ER/LA product; managing therapy with the ER/LA opioid analgesics; counseling patients and caregivers about the safe use of these products. It also includes general drug information about the products as well as specific drug information for the ER/LA opioid analgesic products.

What is REMS-compliant training? The CE programs must provide REMS-compliant training, and to meet that bar, training is provided and offered

by an accredited CE provider. It should include all the elements of the FDA blueprint for prescriber education for the extended-release and long-acting opioid analgesics, a knowledge assessment of all the sections of the blueprint, and is subject to an independent audit to confirm that the conditions of the REMS training have been met.

The agency has estimated there was approximately 320,000 ER/LA prescribers. The REMS was approved in July of 2012 with the FDA blueprint.

The first REMS-compliant training became available in February of 2013. The agency believed because the concern for public health that the REMS should include targets for training. However, the training of this magnitude under a REMS was unprecedented for the agency, and we had no prior experience with a training program that used CE to attain these targets.

Based on discussions with industry and internal discussions within the FDA, it was

determined that the targets would be 25 percent, 50 percent and 60 percent of the estimated total of the prescribers of the ER/LA products at years 2, 3 and 4 after REMS-compliant training became available.

The presentations today will really focus on the 36-month REMS assessment report that was received by the agency of July of 2015. The elements of this assessment report includes the number of ER/LA prescribers who have completed training, an independent audit of the quality and the content of these educational programs.

It includes prescriber surveys that looks at the awareness and understanding of the risks, as well as long-term evaluation of the retention of knowledge and changes in behavior. It includes a prescriber survey that looks at their understanding of the serious risks and safe use. It includes surveillance studies, drug utilization patterns, changes of prescribing patterns, and it also looks at any changes in patient access to the ER/LA products.

After the presentations have concluded and we have heard from the individuals in the open public hearing, we will ask the committee to consider the following: What are the expectations for a voluntary educational program?

Are the data sources and the methodologies used to evaluate the REMS appropriate?

Has the REMS had an impact on patient access? Is the REMS meeting its goals?

Does the REMS ensure safe use?

Is the REMS unduly burdensome? And to the extent possible, does the REMS minimize the burden on the healthcare delivery system?

In addition, are the FDA blueprint, the medication guide, and patient counseling documents sufficient or are changes needed?

Should a REMS be required for the immediate-release opioid analgesics to ensure the benefits outweigh the risk?

Should prescriber training be mandatory in order to prescribe the opioid analgesics? And lastly, consider if the ER/LA REMS should continue

without modifications, be eliminated, or be modified, and if so, how?

This ends my presentation, but I want to thank you for your participation and attendance at this important meeting. Thank you.

DR. WINTERSTEIN: Thank you, Dr. LaCivita.

We'll now continue now with the NIH presentation. Dr. Compton.

NIH Presentation - Wilson Compton

DR. COMPTON: Good morning, everyone. It's a pleasure to be here on behalf of the National Institute on Drug Abuse and the National Institutes of Health, with so many esteemed colleagues from the FDA and from across -- now, I've gotten my training on how to use the device. We'll see if it works.

In preparing for this talk, I was thinking about what a complex challenge you all have, which is to understand the impact of a broad system designed to shape and provide a behavior. But we aren't holding all the other elements constant. All of us in science like to hold everything

constant, except for one variable and modify that, and then we can determine whether it's had the impact that we expect.

Well, my challenge and my job is to let you know about not all but at least some of the federal, state, and local efforts that are being conducted right now and have been conducted over the last few years, that can influence your ability to understand the impact of the REMS program and put it into the context of all of the efforts that we are engaged in to respond to the opioid morbidity and mortality crisis across the United States.

I'm particularly pleased that the National Institute on Drug Abuse has been able to partner with the FDA on these efforts. The FDA commissioner, Bob Califf, and the director of NIDA, Nora Volkow, are the leads for a subcommittee within the Department of Health and Human Services that over the last several years has been working to bring together the efforts of all the different agencies and operating divisions of Health and

Human Services to address these complex issues.

I'd like to say that we are completely successful, but that would not be true. As anyone who has been following the data on the opioid mortality can understand, we are actually not ahead of this crisis. So we need your help and everyone's help in figuring out how best we can address this public health urgent need.

Now, what I don't have for you are the data to show the number of deaths, and you'll see that later in the presentations. But all of you-all are familiar that we have an epidemic of overdose deaths in our country.

What I've highlighted for you, though, with this slide from the CDC is a reminder that it is not universal. While there have been deaths everywhere in every part of the country, they vary considerably by geographic region.

So as you're considering implementing a federal program and federal regulations, we need to think about how will they impact the hot spots, the areas that are particularly concerning when it

comes to the overdose deaths, of course, the most serious consequence of the opioid issues here.

So will they have an impact in the Appalachian region? Will they have a particular impact in the Southwest? How about parts of Alaska that look like they've been particularly hard hit? These are some of the questions that I think will be influenced by your deliberations in the next day and a half.

Is it just opioids? The answer would be no. There are some very important information reminding us that it is the combination of opioids with other substances.

For instance, when we look at the deaths or the emergency department visits associated with opioids, we see an increased rate of benzodiazepines also being identified in those cases.

When we look at it the other way, when we look at the benzodiazepines, it turns out that opioids are almost always involved in the overdose deaths that are associated with the

benzodiazepines. But this association has been increasing in recent years, so we see that there's a complexity in terms of the opioids that it involves other prescription medications.

I haven't mentioned that it also includes illicit substances and alcohol, but all of these add to the difficulty in caring for these patients and in determining the best public health strategies to address the issues.

Now, while this panel or these panels are convened to address the issues around prescription opioids, we've learned that opioids are not distinctly separated into the prescription opioids on the one hand and illicit opioids on the other, that there's a relationship between the increasing availability of prescription opioids and what we've seen as an increasing use of heroin all across the country.

So what you see on the left are data from the surveillance system out of SAMSHA, the National Survey on Drug Use and Health, reminding us that heroin rates have been increasing just in the last

few years. So while the data on prescription opioids suggests trends starting in the 1990s and early 2000s, for heroin, the epidemic has really taken off in about the last five or six years.

Now, there may be regions of the country where it started before that, but it's been this last few years that have really drawn remarkable attention because of the problems associated with heroin.

When you look on the right, you see that the number of deaths associated with heroin have more than quadrupled in the last five or six years so that there are now more than 10,000 deaths in the most recent data from 2014.

Now, it's been well documented that there's been a shift in the heroin epidemic that when we look -- when we talk to patients that are entering treatment for treatment of heroin addiction and we ask them what was your first opioid that you used, those that started their opioids in the '60s or '70s, their first opioid exposure would have been heroin. It doesn't mean that was their first drug,

of course.

In a drug-using trajectory, we think of marijuana, alcohol, tobacco, other illicit substances being first, but their first opioid would have been heroin. It would have been very typical that those individuals would have used prescription opioids when they weren't able to obtain their drug of choice.

But what's been a shift, starting in the 1990s and the 2000s, was that the prescription opioids were their first opioid exposure and that heroin was secondary, was down the road, was after there was an extensive record of use of the prescription opioids, often abuse or dependence; so an addiction-like syndrome related to those prescription drugs and then a transition to heroin over time.

Some of the transition perhaps has been due to shifts in the availability of the prescription opioids. This is suggested by Ted Cicero and colleagues, and I think you'll be hearing from Dr. Dart later on, who is one of the co-authors of

this publication that showed that as OxyContin formulation changed and there was decreased liking and decrease in use of OxyContin among heroin user -- or among those being admitted to drug treatment -- there was a corresponding increase in heroin use.

But I would point out that as the rates of OxyContin misuse continued to decline, we didn't see a corresponding increase in heroin use. So there's a complexity of this relationship of the policies and regulations related to prescription opioids and the transition to heroin. In fact, right now, the CDC has a funding announcement to try to provide support for better understanding of this complex relationship of the prescription opioids to heroin.

It's well known that most heroin users -- I've mentioned to you -- report the previous non-medical use of prescription opioids, but it's a little bit counterintuitive that most of the non-medical users of the prescription opioids don't transition to heroin.

From the large national data, we see that it's something like 3 to 4 percent make that transition. In a local study out of Ohio that was a nicely designed prospective cohort study, they found about 7 and a half percent progressed to heroin after three years.

But again, that suggests that it is still a minority of those who would look like they're at risk for the transition make that important change from the non-medical prescription-type opioid users to heroin.

We have seen heroin increasing in all regions of the country. The increases have been particularly significant in the Northeast and Midwest. We've seen increases for all patient subgroups, for all population subgroups, but particularly, the increases have been for non-Hispanic whites of young and middle-aged populations. So that's drawn a great deal of public attention because of the changing demographics of opioid use and misuse in our country.

Most recently, we've seen a serious outbreak of fentanyl, and this adds both in terms of the devastation because of the high rate of overdose deaths associated with fentanyl, it being such a potent opioid agent. It also adds a complexity to our public health surveillance system.

Most of the fentanyl that's implicated in these overdose deaths is from illicit origin. It comes from clandestine labs often in East Asia or in Latin America, but yet on the medical examiner reports, we can't always tell that.

So it may be reported as a death associated with fentanyl, and so that adds to the complexity of how we interpret the number of deaths during the last few years, that are associated with what I think of as prescription opioids, when they may be mixed in with what is much more typical of the illicit opioid situation.

So I just encourage you to take careful look at the overdose death rates. If you're trying to disentangle those that are due to the prescription-type drugs versus illicit, it's not an easy puzzle

to disentangle.

That's a very rapid fire version of some of what's been drawing our attention to this, why it's such a complex area to study. What are we doing about this? Secretary Burwell, shortly after she was sworn in, convened a small group across the department to ask what were we doing and to challenge us to come up with major priority areas that the department could get around as our priorities to address the opioid crisis in our country.

We've identified three major areas as part of the Secretary's initiative, the first one focusing on the prevention activities relating to prescribing practices. Believing and understanding that the prescription and excess availability of prescriptions for diversion are a key driver of this public health crisis, then, we need to change those prescribing practices.

In addition, we're focusing on immediate life-saving techniques related to wider distribution of naloxone, and we'll talk about that

a little bit. Then, if the people who are overdosing are addicted to opioids, what about expanding the availability of treatment so that we can help them turn their lives around and improve their outcomes?

So those are three major areas: prevention, immediate life-saving and long-term addressing the addiction issues in terms of expanded access to medication-assisted treatment.

In order to implement these priorities, we've engaged in a number of activities at a federal level. I highlight for you the most recent of two annual meetings that brought together state officials so that we could help the states share their best practices, learn from one another, and really teach us at a federal level what might be most helpful to all the states who are much closer to the frontlines in addressing these issues.

We focused both on those three priority areas in terms of medication-assisted treatment, greater access to naloxone and prescribing practices, but we also focused in particular on the

infectious diseases associated with injection drug use exemplified by the hepatitis C and HIV outbreak in Indiana.

When we think about addressing the prescribing practices, a key element has been the prescription drug monitoring programs. What I want to highlight for you is that these vary in important ways.

So even as we think about their potential impact and there is evidence for their impact on prescribing practices and outcomes, they are authorized in nearly every state with a little gap in the middle. And Dr. Israel can perhaps speak to Missouri for us, and we'll ask her to see what she can do about it.

In addition to just whether they're implemented across all 50 states, we also need to pay attention to how well -- not just are they authorized but how well are they implemented across the state. So a key issue is are the states allowed to share data across their borders.

Just think about where we are geographically

here. Just within a few miles, you can be in three jurisdictions. So if we keep the data just within Maryland but we don't have data from the District of Columbia or Virginia, thinking locally, that would be a big gap in the ability to understand what prescriptions our patients are getting.

Are prescribers required to check these? That varies. That's even fewer of the states that require that. I would also point out that only a certain number of the states have really implemented a fully function PDMP so that this is an ongoing system that's changing.

So as you are evaluating, considering the REMS program, think about how effective this tool might be in being coordinated with the REMS, and it certainly varies across the country.

When we think about other actions that have been designed to change prescribing practices, one of the most important was a changing of the rescheduling hydrocodone. And following the rescheduling in October of 2014, we saw a marked reduction in hydrocodone prescriptions.

One of the questions with this reduction in hydrocodone is, well, would they just be made up for in other opioids? And the answer was no, that overall, there were reductions in the number of total opioid retain prescriptions. This translates, according to the authors, to some 750 million -- I had to think about it for a minute -- a million fewer tablets.

So that tells us about the extraordinary number of tablets that are potentially available for diversion, and so a reduction by some 10 to 15 percent can translate into a huge number of fewer tablets that are dispensed.

Now, it's not all good news that comes from the data. There was an important publication that came out in January that reminded us that even in the highest risk patients, prescribing practices may continue to be quite problematic. So this was a cohort of some 2800 overdose patients seen in an emergency department or seen in a hospital setting, and they were followed long term with administrative data.

Now, what happened to them? What was remarkable is that some 90 percent continued to be prescribed opioids even after experiencing an overdose event.

Among those who were prescribed a high dose of opioids prior to their overdose event, again, about 90 percent remained on opioids, and about two-thirds of them remained on the high-dose opioids. About 17 percent of those high-dose patients had another overdose event during the ensuing two years.

Given the risks with benzodiazepines, it's important to point out that a third or a little more continued to receive benzodiazepines over the ensuing couple of years.

Now, I will point out that this cohort was collected over a long period of time from 2000 to 2012, so there may have been important changes in practice. And certainly, after 2012, with all of the attention to opioid prescribing, there certainly could be changes.

But this reminds us of the serious nature

and the difficulty in medical practice even when faced with something as serious as an overdose event. We still see continued high-risk prescribing practices.

The Centers for Disease Control have been addressing this issue with multiple efforts, but in particular, I'll highlight their three major domains of improving the data quality. We rely on them for the overdose death data, so our understanding of how the fentanyl outbreak has influenced our interpretation of that overdose death is a challenge for the CDC and all of us.

They've been working assiduously to provide healthcare providers with resources to improve patient safety, and of course, to strengthen state efforts through grant programs and educational outreach to the state public health officials.

What's garnered a lot of attention has been the desire to provide guidelines to help educate and provide support for clinicians that want to do the best they can with taking care of our patients. So an issue when we reviewed the guidelines with

the CDC was that there weren't very many of them. Some of them were outdated, and they were not without potential conflicts of interest in their development.

So one solution has been for the CDC to support the development of new guidelines. These were released just about a month ago and are intended for primary care providers. While they focus on prescribing opioids for chronic pain, I would point out that there's at least one recommendation that focuses on short-term acute, the immediate-release opioids.

So it does try to touch on the broad range of opioid prescribing. And after all, even the use of opioids for chronic pain starts out with a single first prescription. So it often starts out with treatment of acute pain before we transition to chronic pain treatment.

Are practices required as part of education of clinicians? One way to think about this would be the medical education requirements for licensure. As a clinician, I renew my license

every year, so I know what my state requires.

I was pretty surprised when I reviewed this to see how much variation there is across the states in what's required. So when we think about using the states as lever for changing prescriber education, of course, that's a very promising approach, but it means you have at least 50 different jurisdictions that can be considered and will vary in how they implement these practices.

So for instance, a few states have no continuing medical education requirements. But even those that are shaded in the lighter blue that have some, it varies considerably from rather minimal in certain states, perhaps just focusing on a single target area for education to those that require a more typical 25 or 50 hours of some type of continuing medical education each year.

There are a few states that require pain or controlled substances medical education specifically for certain specialties and a handful that require it for really all their prescribers for all their specialties. But I point this out

just to remind you as you're thinking about how the REMS is having an impact, that this is the environment, that it varies considerably across the country.

So that's a little bit about what we're doing in terms of prescriber issues. I haven't pointed out educational issues that are going on in both the federal and state and local level, but those are continuing as well.

Let's turn a little bit to the direct overdose intervention. In this very room, we had a meeting in 2012, which was designed to draw attention to the potential for naloxone as a life-saving tool and to look at what the barriers and opportunities were for wider access to naloxone.

This led, within just about two years for the Evzio product and then three years for the Narcan nasal spray, to the development of an auto-injector and now a nasal spray that's been approved by the FDA for use for treatment of overdose.

Now, one of the issues again is the variation in how this can be implemented across the states. One of the big pushes has been for wider distribution through easy access in pharmacies. For instance, there may be standing orders authorized in certain states. Can non-medical personnel issue naloxone and use it? So this requires getting naloxone into the hands of those who may be able to use it to reverse an overdose.

One of the issues is the patient to whom I write or to whom naloxone is dispensed may not be the person that it's used on. So what are the liability issues if it's used on somebody else? What happens when a prescription I'm writing for one patient is then used by someone else?

That's a complex ethical and safety and legal issue, and so there's been a push to change the liabilities laws. So I point out that these vary across the states.

Again, there are some issues around drug users in particular being willing to both use these life-saving medications and then also to follow up

with calls to first responders. Are they willing to call 911? Well, that will depend to a certain extent on whether they're going to be arrested when the police show up who are often the first responders.

So there's been a push to change what are either Good Samaritan or other laws that may inadvertently disincentivize calling for emergency response and trying to prevent unnecessary not calling for extra help. So those are some of the laws that are being looked at across the country to influence the naloxone distribution.

We have seen a marked increase in naloxone prescriptions recently. If we went back just a few years, most naloxone would have been distributed for community use through non-governmental organizations, through other groups, mostly in major urban areas. But we've seen in the last few years a marked increase in retail distribution of naloxone, and we think this represents a new route that may markedly increase the availability and potentially the use of this overdose intervention

tool.

Now, the final area that I'm going to highlight for you relates to medical treatment, medication-assisted treatment. An important public health study coming out of Baltimore reminded us that when they increased the availability of first methadone, and then as buprenorphine became available and was in widespread use in Baltimore, they saw a reduction in their overdoses in the city of Baltimore.

So this was reasonably strong ecological evidence for an association of medication-assisted treatment with reduced overdose deaths in a population setting.

But one of the issues is how do we provide this care when there isn't enough treatment available? There's a mismatch between the need for treatment and the availability of clinicians, whether that's methadone clinics or buprenorphine providers, buprenorphine certified providers.

Just think about some of the large rural areas where we showed you where the hot spots for

the opioid epidemic, and you can imagine the difficulty of providing clinicians in areas like Scott County, Indiana, where there was the hepatitis and HIV outbreak and has almost nonexistent medical infrastructure to provide these life-saving interventions. That's a real challenge for all of us.

There are some examples across the states of approaches to improve treatment capacity. These are collaborative care models, the famous ECHO model in New Mexico, which is a way to use telemedicine and use professional support at a distance that I think shows great promise.

We might also consider looking at other countries that have much greater use of telemedicine and long distance prescribing as an example that we might consider in the United States as well.

Now, there are a few success stories to point to. We've seen some improvements. Particularly, Florida is one of the most positive examples where the regulations around pain clinics

and the regulations that prevented healthcare providers from directly dispensing painkillers from their offices were associated with a marked reduction in overdose deaths in the ensuing few years.

So as Florida implemented a series of new regulations, we saw improvements in the public health measures in that state.

We see some improvements in some of these other states that are highlighted for you as well. And I highlight for you a single example coming out of Staten Island that combined guidelines, public service announcements, their increased use of the PDMP, town halls and a lot of public information sharing, and did see some reduction in the overdose deaths in that particularly devastated part of New York City compared to the other boroughs.

Now, we are implementing new approaches at the federal level. For instance, we've just implemented our priority goals. These are goals that each federal department sets for itself and that are highlighted through the White House, and

we've identified three major priority goals that will be tracked through administrative data related to opioid morbidity and mortality that we think will help improve the distal outcomes.

Of course, overdose deaths and the morbidity associated with the opioids is our distal outcome, but we think these targets in terms of the amount of opioids being prescribed, reducing those and increasing the naloxone availability through increased prescriptions for naloxone and increasing medication-assisted treatment availability are key ways that we can measure. And we think these are, of course, logical steps in addressing the overdose crisis in our country.

It's been remarkably gratifying and exciting to see President Obama drawing attention to this issue with a town hall meeting in Charleston, West Virginia a few months ago, and then in early April with his participation in the opioid meeting in Atlanta. And this includes a major focus on developing partnerships to improve prescriber training.

So I would certainly think as you're trying to evaluate the REMS, this might be a big jump start to how to get more providers interested and more of the medical associations and other participating in the wider availability of prescriber training, among other efforts to impact the opioid crisis in our country.

In a pretty rapid-fire way, I hope I've illustrated for you how much these are serious public health issues for our country; that they are complex issues with interrelated causes; that when we think about the prescription of opioids -- and that of course, is your major goal and challenge here -- don't forget that these are related to the other aspect of the opioid epidemic, whether that's heroin or more recently, fentanyl; that our approach is to address the upstream drivers, what you're focusing on.

I'll be very excited to hear your answers to those key questions so that we can implement your best advice and do a better job of curbing this serious public health crisis. But it's not just

you-all operating in a vacuum. There are clearly multiple other drivers of this epidemic that state, local, and federal officials are trying to implement.

So as you look at the outcome of the REMS program, you'll need to be thinking about this broad social, medical, and health context to understand the implications. Thank you very much for your attention.

Clarifying Questions

DR. WINTERSTEIN: We have now time for clarifying questions. Most of you have been at ACs before. The way this works is you raise your hand. Stephanie and I are trying to create a list of all who have raised their hands, and we will go on to Dr. Higgins.

DR. HIGGINS: My question is for Dr. Compton. You mentioned that naloxone has some safety concerns. My understanding is that self-administration or administration of others is essentially harm free. But could you respond to that comment?

DR. COMPTON: Could you repeat the question? I'm sorry. I was standing up and --

DR. HIGGINS: You mentioned in your presentation that nasal naloxone administration has some risk associated with it. My understanding is that it's essentially harm free for self or others to administer it, and I'm wondering what your thoughts are that.

DR. COMPTON: Well, thank you for that question. I actually didn't mean to imply that it has significant risks. One of the benefits of naloxone, one of the reasons so many of us are enthusiastic about its wider distribution is the remarkably minimal side effect profile.

Some of the concerns in terms of wider availability might be are people reaching out for help once they are dose with naloxone. That may not be enough, particularly with the fentanyl epidemic and the fentanyl issues.

We're concerned that the high opioid dose that overdose patients have may require more than just the single or double dose of naloxone. So are

we making sure that they're reaching out for additional help that may be necessary?

There also can be some concern with mild or moderate withdrawal symptoms with resuscitation, but certainly as a clinician, that seems rather minimal compared to somebody who's not breathing.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: I just wanted to clarify a little bit the comment about the side effects of naloxone. For a person that is chronically administering narcotics, the issues related to naloxone can be deadly. Now, that doesn't mean that we shouldn't discuss the more widespread availability, but there's cardiac ischemia associated with the administration of naloxone in people that are addicted or chronically use opioids. Pulmonary hypertension is associated with it, and we're correct in presuming that those are issues that have to be taken in the context of someone that's not ventilating themselves.

But I would disagree with any thought that there are minimum risk to supplying naloxone.

DR. WINTERSTEIN: Thank you.

Before we proceed, we had a few people who joined, and we need to have introductions. I think starting on the right, Dr. Scarazzini, you came in late. Would you like to introduce yourself real quick?

DR. SCARAZZINI: Sure. Good morning. I'm Dr. Scarazzini. I'm the vice president and head of pharmacovigilance and patient safety at Abbvie.

DR. WINTERSTEIN: Then we have Dr. Hoffman.

DR. HOFFMAN: My name is Erica Hoffman. I work at the VA in Pittsburgh. I'm a primary care provider.

DR. WINTERSTEIN: And we have Dr. Garcia-Bunuel.

DR. GARCIA-BUNUEL: Hello. I'm Martin Garcia-Bunuel. I'm a primary care physician and worked in both rural and urban areas. I'm also the associate chief of staff for the VA mental healthcare system for ambulatory and emergency care and the acting deputy chief of staff. Thanks for having me.

DR. WINTERSTEIN: Thanks for being here.

Dr. Gupta?

DR. GUPTA: My name is Dr. Anita Gupta. I am an anesthesiologist, a pharmacist, and I'm also a pain specialist. I am vice chair of the Division of Pain Medicine at Drexel University College of Medicine in Philadelphia.

DR. WINTERSTEIN: And Dr. Buckenmaier.

DR. BUCKENMAIER: Dr. Buckenmaier. I'm the director of the Defense of Veterans Center for Integrated Pain Management out of the Uniformed Services University. I was enjoying a nice drive this morning on 495.

(Laughter.)

DR. WINTERSTEIN: Glad you made it.

Okay. Let's proceed with questions. Dr. Emala.

DR. EMALA: I have a question for the second FDA presentation, Dr. Toigo. I think it's slide number 5. The data on the slide shows the death rate from opioids, and I'm curious if it's known, which of the -- if the death rates can be

attributed to ER versus IR formulations of the opioids.

MS. TOIGO: I don't have the answer to that question, but I think Judy Staffa does. So I'm going to turn it over to her and let her answer it so I don't give you the wrong answer.

DR. STAFFA: Sure. Judy Staffa. No, actually. In death data, the opioid information is coming from a tox screen. So you may be able to differentiate which drug it is, but you can't differentiate the formulation.

DR. WINTERSTEIN: Dr. Morrato.

DR. MORRATO: Yes. I also had a question for Dr. Toigo, so she has to go back up, I guess. I wanted to clarify a little bit. I know it was in the briefing documents as well as you mentioned it. The original goal of the FDA was to link the continuing education with the DEA licensure process. I know that was the recommendation of one of the advisory committees, and I'm just wondering what led to challenges in not having that happen.

So was it a question of political will in

trying to work across agencies that became difficult? Are there technical challenges with the systems? Are there other things that we should be considering, whether or not that's a viable option?

MS. TOIGO: Doug might want to provide more detail on that in current, but I think at that point, it was an administration proposal. It would have required legislative challenges or legislative changes, and they didn't happen at that point in time.

Doug, do you want to add any more?

DR. THROCKMORTON: Yes. I want to just clarify something. So there were two goals, I would say, with regards to education. The first goal was to implement the extended-release long-acting REMS. We believed it would -- we concluded it was an important component of providing educational materials to prescribers.

In addition, we believed this broader mandatory providing of education was also important but separate.

So those are two separate goals. That

second goal, as Terry said, would require a legislative change, and that was something that has not yet been accomplished but continues to be a goal that's stated for the government and HHS.

DR. MORRATO: So as a follow-up, I know that the commissioner's appointment was held up in Senate because of issues in part related to opioid as part of the discussion.

Would you say today's legislative environment has changed from a few years ago, or is it not? And I know you can't predict, but is that something we should be seriously considering now especially with the President having an opioid initiative?

DR. THROCKMORTON: I wouldn't want to comment on the legislative environment. We could probably all do that, but I would say from the highest levels of government, from the President on down, there's now a clear acknowledgement that we need to do all we possibly can to improve the state of pain management in the U.S. and the management of the opioids crisis.

I think there's also widespread agreement that the best possible prescribing practices need to be supported. So I think there's continued interest in using all of the levels of government to accomplish that in a variety of ways.

DR. WINTERSTEIN: I have a quick follow-up question to this. Is there information on the prescribers who actually took one of those accredited CE programs available? So is there anywhere, some type of registry or identification by name who did the CE program?

MS. TOIGO: Do you mean can FDA identify which prescribers have taken the training?

DR. WINTERSTEIN: Exactly.

MS. TOIGO: FDA can't, and I don't believe -- you'll hear from the industry, but I don't think the industry can, either. So there isn't a national registry of everybody who's taken a REMS-compliant training.

DR. WINTERSTEIN: It wasn't completely clear from the briefing document. It sounded like there is interest in finding out who actually took the

program and who not, and that would -- of course, those types of analysis would be facilitated by knowing who took it.

MS. TOIGO: Well, and I think that the presentation that you heard Dr. LaCivita give explained in that type of -- that was one way in which you have that information, but the current program does not provide that.

DR. WINTERSTEIN: Dr. Bateman.

DR. BATEMAN: This question is also for Dr. Toigo. Can you say a bit more about the decision not to include immediate-release opioids in the REMS program? As it was developed, how did the FDA weigh the risks and benefits of including immediate-release formulations?

MS. TOIGO: So I think the time those discussions were ongoing was 2009. The new legislation for the REMS was passed in 2007. So we were getting familiar with REMS and the requirements, but the main reason we chose it was because we thought the risk from the extended release was greater and we heard different things

from the committee.

We did hear a lot about including IRs, but we also heard that if you're going -- that you need to at least start with the ERs. So we looked at it by risk, and we looked at it by burden. And the burden associated with doing it for every IR prescriber at that point in time was significant, and so it was kind of a staged approach.

DR. WINTERSTEIN: Ms. Shaw-Phillips.

MS. SHAW-PHILLIPS: Thank you.

I have a question also about the federal response, perhaps for Dr. Compton, and I know the DEA, certainly when we're talking about rescheduling hydrocodone, was talking about eventually going to e-prescribing for Schedule IIs.

Where is that in the federal approach? Because certainly having electronic prescribing will allow closer tracking and a more integrated tracking process, but also may decrease the need for some of the large single prescriptions that are going out on paper right now.

DR. COMPTON: I can't comment on the

specific status of the e-prescribing across the country other than to say that this certainly is a promising approach in terms of how can we use newer techniques or alternative techniques for prescribing themselves. Much like years ago, the triplicate prescriptions were a way to address forgery and diversion and represented state of the art a number of years ago.

So can this be an approach? It's certainly something under discussion, and you might reach out to the DEA to get an update specifically on that.

Also, while I'm responding, there was an earlier question about can we disentangle the subtypes of medications that are involved in the overdose deaths. While you can't do that from the national data, there are case series coming out of a number of states.

I think it's important to point out that most of the decedents who die from prescription drug overdose deaths, at least from the case series that I've read, don't necessarily have their own prescription. So that it is not always the direct

prescribing that's relating to this overdose situation, but it may be the indirect availability through diversion and use by other people.

So it's an added complexity as you're thinking about prescriber education. It's not just for the patient in front of them, but it's also for the wider community that's around that patient and may be harmed by the availability of these medications.

DR. WINTERSTEIN: Dr. Gupta.

DR. GUPTA: Thank you.

These questions are for Dr. Compton, slide number 13. I just wanted to clarify. When you listed total opioid prescriptions, are you including C3s and C2s, or what are you including on that slide?

DR. COMPTON: I think you might want to ask one of the co-authors, Dr. Throckmorton, who is sitting right here, who can make sure that we understand what's --

DR. THROCKMORTON: So total opioid prescription do you mean there, that top line? Is

that what you're asking about?

DR. GUPTA: Correct.

DR. THROCKMORTON: I'd have to look back. Honestly, I don't recall.

As you are no doubt alluding to, the specific definitions of what you include there can matter a great deal. The focus of this paper was obviously on the bottom line and on the impact of changing hydrocodone prescription through the up-scheduling, but I can get you that information.

DR. GUPTA: I have two more quick questions. The slide after that, 14, you stated that 17 percent of high-dose patients overdosed again after two years. Do you know how many -- what percentage of those patients actually died?

DR. COMPTON: I don't know offhand. You certainly have the reference at the bottom of the slide and can check the original publication. It was not most -- it was a small number.

DR. GUPTA: Okay. And then the last question was looking at, is there any data maybe from your agency on looking at how patient

satisfaction scores may have been related to the escalation of opioid use?

DR. COMPTON: We certainly are hearing concerns of what I would term a perverse incentive for patient satisfaction around their treatment of pain leading to excess prescribing of opioids, but actual data on that question is scant. I'm not aware of actually any data that really brings to bear on that question, but there may be some that some of you-all may know about. And I'd be certainly interested to learn about it if you have sources.

DR. WINTERSTEIN: Dr. Galinkin.

DR. GALINKIN: I applaud the FDA and industry in pursuing this issue, but I guess this is for either the FDA presenters. Since prescribing habits are often set during training, are the REMS intended to be for people in residency or medical school, or have you worked with the ACCME at all in making this training part of that program, a mandatory part of medical school or residency?

DR. LaCIVITA: Hi. This is Cynthia LaCivita. We haven't -- the REMS requires that sponsors make this training available to likely prescribers. That doesn't restrict who can take the program. We haven't worked directly with medical schools at this point in time. So it's really open to any prescriber.

DR. WINTERSTEIN: Dr. Floyd.

DR. FLOYD: I have two questions. The first I think is for the FDA. Is there any requirement that the educational component be administered by private CE organizations, or could it be administered by a federal agency such as CDC or NIDA?

DR. LaCIVITA: It can be any accredited CE provider.

DR. FLOYD: And the second question, I think is for Dr. Compton. Is there any interest or possibility for NIDA or another agency to create a broader opiate prescribing educational component that could replace the kind of private CE elements?

DR. COMPTON: Well, I'm not sure that it

would replace, but there's certainly an opportunity for additional educational elements. There are others available at a federal level. There have been NIDA-sponsored CME programs. Those are currently not in as widespread distribution. They're also a little bit dated and need to be updated.

That's one of the issues with developing CME. As we learn new information, they have to be constantly updated and maintained. So looking for the opportunities, whether these are federal or through private partnerships, is a key element of how we can address this educational need.

DR. WINTERSTEIN: Dr. Choudhry.

DR. CHOUDHRY: Niteesh Choudhry. So I was hoping to hear a little more from the FDA about the multi-stakeholder problem or what opportunities are possible, and I think this is a recurring theme likely for us over the course of the next couple of days.

We heard a little bit about boards of registration of medicine and the regulatory

requirements that would be possible, but there's numerous other bodies, for example, specialty boards of medical practice, which may not be regulated in quite the same way.

So as we think about REMS or its expansion, contraction, whatever, can you give us any more information about what would be necessary to actually foster greater collaboration other than sort of a unified desire to all solve the same problem?

DR. THROCKMORTON: This is Doug Throckmorton. I'll take a start at that, and then we'll see if others have other comments. But let me step back and talk about the REMS, which I think is obviously the central focus for us or the two days.

The REMS authority for us extends over the manufacturers, and so under the authorities that the previous speakers talked about, we could require certain activities of the manufacturers, in this case, to make monies available for the dissemination of this continuing education

material.

We have less direct ways to partner with other groups. As you said, we're all very interested in this. The state boards and things, we had extensive conversations at the time in 2009 and 2012 when the REMS was put into place to find opportunities to partner there.

Obviously, very interested in that, but the REMS for us began with that authority, began with our ability to require the conduct by the manufacturers. Additional partners sort of would come out of that, and obviously something we're very interested in.

DR. AUTH: I'd like to add to that. I'm Doris Auth from the Division of Risk Management. Excellent response to that, but I would also like to add that we do have a presentation this afternoon from the Conjoint Committee for Continuing Education where they will describe the activities that they've undertaken. And this is an organization separate from the FDA.

It's a multi-partner academic, industry

collaboration that has attempted to increase the uptake of the REMS CE. So that presentation will be later this afternoon, so you can hear a little bit more about those efforts.

DR. HERTZ: Hi. This is Sharon Hertz. I'm the division director for the Division of Anesthesia, Analgesia and Addiction Products here at FDA. And I will say that there are a number of other bodies working on this as well. There's a number of professional societies that are involved in educational programs, not just for their own members, but for general practitioners as well.

So there are a lot of other stakeholders. We've been in touch with them, working with them in a variety of different ways.

Also, when we developed the blueprint, we worked on that in the context of also working with some of the other agencies. So there is already quite a bit of collaboration.

DR. AUTH: One more thing. I did fail to mention that that collaboration, the Conjoint Committee, also does include a lot of associations.

DR. WINTERSTEIN: Dr. Brown.

DR. BROWN: I was wondering specifically about the information relating to pediatric prescribing practices, if that was considered in the development of REMS. And as I was looking through some of the material, the American Academy of Pediatrics wasn't specifically mentioned.

So I wondered if that organization was given an opportunity to comment on the development of REMS.

DR. MANZO: This is Claudia Manzo with OSE. The FR notice, which included the blueprint, was posted on the Federal Register, and so any organization or individual would have had the opportunity. Perhaps Terry has more information specifically about pediatric organizations.

MS. TOIGO: I'm trying to think back to the 65 comments that we went through, and I think there were comments from AAP in there. The blueprint does not have any specific comments related to pediatrics, though, and I can't -- I'd have to go back and look for you to recall to get specifics,

but I do believe they submitted some comments.

DR. BROWN: Do you think that since OxyContin has been developed as a drug, which can be administered to adolescents and younger children that -- did that occur before REMS were being developed or after? I'm not clear on that.

But the question is, if that occurred before, would that have changed anything about the management of the development of REMS?

MS. TOIGO: So I think Sharon's going to answer that, but one thing, the REMS, in addition to including the prescriber training, included a medication guide and a patient counseling document.

The patient counseling document, although it was general for all opioids, it was intended to allow the physician that was prescribing it to use it as a counseling tool for an individual patient, which is why there was room to write specific directions for an individual patient.

So I think Sharon's going to address timing of -- I don't remember when the timing for pediatric indications came in.

DR. HERTZ: So you used some terms in there, and I'm not entirely sure how to jibe them with some of our process. But the long history of pediatric development for OxyContin began well before we had REMS authority and was taking place independent of the REMS activity. The company had initiated studies based on a variety of things.

We're going to be discussing pediatric opioids in great depth in a meeting in September. So I don't think -- well, I won't get into the details now. If you have additional questions, I'll try and answer them.

The REMS, when we were working on the REMS, we weren't focused on adults only in the sense that the problem was across the board. We were getting data as we were looking at it from a variety of programs, and some of them did include pediatric ages down to -- I think some of the databases and survey information typically goes down to age 12. I'm thinking of the National Survey for Drug Use and Health and some other data.

So we did have data on a fair spectrum of

the population as we were working on trying to improve education.

DR. WINTERSTEIN: Let's stop here.

We have more time for questions as we have a large number. We have noted you, Dr. Galinkin.

We have more opportunity to ask questions later. I'd like to remind the committee, this is a very large committee, to try to focus your questions on the presentations that happened because there's more to come later on. This way, we can try to make this as efficient as possible, but we'll break now for 15 minutes until 10:15, and reconvene here for the next part of the presentations. Thank you.

(Whereupon, at 10:01, a recess was taken.)

DR. WINTERSTEIN: Okay. Let's get started. 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 relationships that they may have with industry such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you don't 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 industry presentations.

Industry Presentation - Paul Coplan

DR. COPLAN: Good morning, chairperson and members of the advisory committees. I'm Paul Coplan, and I represent the 24 REMS program

companies known as the RPC. I'm the chair of the metric subteam of the RPC, responsible for the assessment studies of the REMS, and then the head of medical affairs strategic research at Purdue Pharma.

I'm an adjunct assistant professor of epidemiology at the University of Pennsylvania School of Medicine. I've been conducting postmarketing studies of vaccines and pharmaceutical products for the past 20 years.

The RPC thanks the FDA for including us in this important discussion of the ongoing efforts to lessen opioid abuse and misuse. RPC has worked for the last three years to educate patients and prescribers on the safe use of extended-release and long-acting opioids and to reduce inappropriate prescribing, misuse and abuse of ER/LA opioids and their consequences.

The RPC is a consortium of all 24 companies that hold FDA approval to market extended-release and long-acting opioid analgesics known as ER/LA opioid analgesics. The FDA approved REMS for ER/LA

opioids requires all companies that hold NDAs and ANDAs for ER/LA opioid products to implement the REMS.

The REMS results that we present to you today were built on the REMS framework we presented to this joint advisory committee in July 2010 that Terry referred to earlier. The advice of this committee was carefully considered in the design and implementation of the REMS as was that of the FDA task force that designed and finalized the approved REMS.

We look forward to this committee's advice in ways to improve the impact of the REMS.

Let me provide the agenda for our presentation. Each presenter will review a topic, provide key accomplishments or findings and offer recommendations for enhancements. I will present the design of the REMS. Dr. Marsha Stanton, the Chair of the RPC continuing education subcommittee, will present on the REMS-compliant continuing education activities.

Next, Professor Charles Argoff, a practicing

pain medicine physician, a professor of neurology and a pain management educator who provides REMS CE training, will discuss his experiencing providing REMS-compliant CE training and the public health impact.

Dr. Soledad Cepeda, from Janssen Research & Development, will present results from six of the REMS assessments studies. Then Professor Richard Dart, an emergency medicine physician and toxicologist and director of the Rocky Mountain Poison & Drug Center will review the surveillance data.

Next, Laura Wallace, who is a director of risk management at Purdue Pharma, will provide the consortium's perspective on lessons learned and our suggestions to improve the REMS. Finally, I will return to make closing remarks and answer your questions.

We also have a number of additional experts with us today from partner organizations that helped implement the REMS to answer your questions. With the exceptions of Dr. Dan Alford and Valerie

Smothers, all have been compensated for their time.

I'll now describe the design of the REMS. Opioid abuse is a complex problem requiring a comprehensive solution as reflected in the President's national drug control plans from 2011 and 2014. Although opioid abuse is often discussed as a single problem, it is important to differentiate the types of opioid abuse, as Dr. Compton, said in his presentation.

The first broad category involves the abuse, misuse, addiction and overdose of prescription opioids, which includes immediate-release opioids and ER/LA opioids. It is the ER/LA opioids that are the focus of the ER/LA opioids REMS. The second broad category is illegal drugs such as heroin and illicitly manufactured fentanyl.

Focusing on prescription opioid analgesics only, here you see the trends in opioid prescriptions using an FDA slide presented by Dr. Gerald Dal Pan and others at the science advisory board recently. The blue bars indicate total prescriptions in millions. The green line

indicates prescriptions for ER/LA opioids, and the red line indicates immediate-release opioids.

ER/LA opioids are generally higher dosage strength forms than IR opioids, but ER/LA opioids prescriptions are approximately 10 percent of the prescriptions of all opioids.

A serious concern is the increased drug overdose deaths involving opioids. In 2013, there were 16,000 deaths involving prescription opioids in the U.S., more than associated with traffic accidents. National mortality data show increasing drug overdose deaths involving all opioids, including both prescription opioid analgesics and illegal drugs like heroin, shown in red in this figure.

Drug overdose involving natural and semi-synthetic opioids, the category, which captures the majority of the opioids included in the REMS but includes both immediate-release and ER formulations of those opioids, did not increase between 2011 and 2014, as shown in the green line. However, heroin deaths shown in the orange line

increased sharply between 2011 and 2014.

The approved goal of the REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release and long-acting opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose and death.

To fulfill this goal, the primary focus of the REMS is to educate prescribers to select and manage patients appropriately and to educate patients to understand and prevent the risks associated with ER/LA opioids. The FDA-approved REMS did not include specific actions targeted at substance abusers.

The approach FDA took with the ER/LA opioids REMS in novel in both its scope and the tools that it employs. It is the first involving such a large consortium of companies ranging from large brand and generic companies to very small grand and generic companies.

It is also the first to use accredited

continuing education as its primary tool. This introduced a number of complexities. The rules governing how industry can support continuing education courses needed to be followed as well as following FDA's rules for REMS implementation and principles of good pharmacoepidemiology studies even though these were sometimes conflicting. We also had to develop processes for decision-making and contracting with vendors on behalf of 24 companies.

The REMS establishes communication components, educational and training components and assessments. Let's look at these components.

First, the medication guide, it is a concise one-page document designed for patients. It is distributed by pharmacists and is part of the package insert for each ER/LA opioid. It addresses proper storage, directions for safe use, how to avoid abuse and overdose and how to recognize the signs of overdose. It is tailored for three types of ER/LA opioids: methadone, transdermal patches and oral formulations.

Another element of the REMS is a one-page patient counseling document. Prescribers can use it to counsel patients on the dos and don'ts of safe and appropriate opioid use and disposal.

The REMS includes a Dear Prescriber Letter that was used to inform prescribers about the REMS, the need to take a compliant REMS CE course, the availability of the medication guide and patient counseling document and where to find CE courses. The letter was distributed twice to all 1.3 million prescribers registered with the Drug Enforcement Agency to prescribe Schedule II and III narcotics as well as state licensing boards and professional societies.

The first letter informed prescribers about the REMS, and the second informed them that the CE courses were available and a way to find them. The letter is now sent annually to prescribers who are newly registered with the DEA, and this is how we get physicians emerging from medical school, to address Dr. Galinkin's question. As they get a DEA registered prescriber number, they would then be

sent the letter.

The ER/LA REMS uses accredited continuing education to train prescribers on appropriate and safe use of ER/LA opioids. During the development of the REMS, FDA solicited input on potential topics from a broad group of stakeholders, including ER/LA opioid manufacturers, the medical community, other federal agencies and the CE community.

The FDA then developed the core messages and organized them into a six-section, 16-page blueprint with bullet points of the content required to be covered in the REMS CE. CE providers used this blueprint to develop course content consistent with the CE standards. The RPC can have no input or influence in the course content.

FDA also designed the REMS to allow for CE courses and activities not funded by RPC to count towards the targets for the number of prescribers who complete REMS-compliance CE courses as long as the course covers all the content in the FDA

blueprint.

The FDA requested data on completers of CE courses that met FDA's blueprint but were not supported by RPC.

FDA established target numbers for training of ER/LA opioid prescribers. There was little historical precedent to use for establishing and benchmarking such targets. The target for March 2015 was 80,000 and for March 2016 was 160,000 ER/LA opioid prescriber completers reaching a final target of 192,000 next year.

Completers were defined as people who completed a REMS-compliant CE training, including both those funded and not funded by RPC, took a post training test and who reported having written an ER/LA opioid prescription in the last year.

The number of prescribers who completed a REMS-compliant CE training was 37,500 by March 2015, which is the data covered in the FDA briefing book for this advisory committee. Data by March 2016 shows 66,200 completers.

These numbers do not meet the goals in spite

of the over 800 CE training courses being made available. There 91,200 people who completed a REMS-compliant CE course but did not officially count because they did not report prescribing an ER/LA opioid in the past year.

We conducted focus groups with ER/LA opioid prescribers to better understand how they respond to REMS-related education. Several prescribers mentioned their reluctance to report that that they had written an ER/LA opioid to an industry sponsored educational course because of marketing concerns or legal liability risk.

Some of the 91,200 completers may have been ER/LA opioid prescribers who chose not to report the ER/LA opioid prescribing or maybe new ER/LA opioid prescribers about to start prescribing.

The REMS also includes a toll free call center that RPC maintains. Its purpose is to provide information and to respond to questions about the REMS. It was active within two weeks of FDA approval of the REMS.

The RPC maintains a website,

er-laopioidREMS.com. The website provides comprehensive information on the REMS and links to download all of the current REMS materials, including the REMS approval letter, the FDA blueprint, Dear Prescriber Letters and answers to frequently asked questions. In addition, anyone who wants to take a CE training can go to that website and find all the courses that are available.

To standardize the timing of all the assessments conducted for the REMS, we established time periods relative to the approval of the REMS in July 2012. The assessments for the REMS considered the two years preceding the approval of the REMS as the baseline pre-REMS period. The year following approval of the REMS was the REMS implementation period.

During this period, the Dear Prescriber Letters and the patient counseling document was sent. The REMS website was active, the medication guide available on the website, and the call center was active all within 60 days after the REMS

approval.

By March 1, 2013, the first CE course was available. The period starting in July 2013 was considered the period when the REMS was active. The RPC established metrics to track the progress of the REMS and to assess its effectiveness.

Measurements include whether the communication components of the REMS were implemented such as the Dear Prescriber Letter being sent; number of CE activities, participants and completers; an independent audit of CE trainings to ensure they cover the content of the FDA blueprint and were not subject to industry influence; survey results from samples of patients and prescribers; surveillance data from existing databases on rates of abuse, overdose, addiction and death; ER/LA opioid utilization patterns; trends in prescribing of opioids by prescriber type; and changes in patient access to opioids assessed by changing prescribing patterns after the REMS.

Following the time table established in the

REMS, RPC has provided reports on these metrics to the FDA at six months and one year after the REMS implementation and annually thereafter.

There were several limitations of the REMS, which we were aware of before the REMS started. These include assessing behavior change in prescribers who completed REMS-compliant CE training was limited because RPC did not have access to which prescribers had completed REMS training. This was due to firewalls that prevent industry influence on CE.

The survey samples were not fully generalizable to the population of ER/LA opioid patients and prescribers. Because the REMS was part of a multifaceted national plan to prevent opioid abuse with education as one of the four components of the White House's plan, it was interwoven with other interventions, and therefore, its individual contribution is difficult to assess.

I would now like to turn the presentation over to Dr. Marsha Stanton, executive director of medical affairs for Pernix Therapeutics and Chair

of the continuing education subteam of RPC.

Industry Presentation – Marsha Stanton

DR. STANTON: Good morning. I'm Marsha Stanton, current Chair of the RPC CE subteam, and I have over 30 years of pain management experience both as a practicing clinician and in medical affairs functions for the pharmaceutical industry. I'm pleased to present what we have already accomplished of terms of CE activity totals and audits for this ER/LA opioid REMS and to offer consideration for future improvements.

The REMS is all about education. It is the first time that accredited CE activities have been an integral component of a REMS and a first time that they have been used to address a major public health issue. They accomplish two important things: They offer in-depth learning, and they also fulfill the general requirement to complete some CE activities mandated by the various state licensure boards.

FDA's blueprint is the roadmap. Each CE provider uses it to independently create customized

educational activities. They include both accredited continuing medical education and continuing education. We will refer to all of the activities as continuing education or CE throughout the presentation.

The content is delivered using a combination of print, live lecture, interactive discussions or internet-based media. The accredited CE courses may last more than three hours and include a pretest and periodic assessments throughout the educational activities to establish adequate mastery of content.

REMS CE content must include all six knowledge areas or sections of the FDA blueprint, including assessing patients for treatment, initiating therapy, modifying dosing and discontinuing use, managing therapy, counseling patients and caregivers on safe use, general drug information and specific drug information. Each section builds upon the previous one.

The ER/LA opioid REMS requires that a sample of 10 percent of the total CE activities be audited

for compliance with the CE accreditation standards. The RPC has met this goal.

A total of 29 audits were performed for the 36-month reporting period. Additional audits are now in process. One hundred percent of those completed met all content requirements for accuracy and assessment. Nine audits, however, included observations that did not impact CE content but did involve how the disclosure of financial support was represented. Subsequently, all nine have been remediated.

The way the program works is that CE providers submit proposals to RPC's external grant management system. Based on a review of the timing, credentials, audience, reach and various other elements of the provider's submission, the RPC evaluates the proposals for approval. The medication manufacturers cannot participate in any phase of content development due to the accreditation standards.

Over the last three years, 151 CE proposals have been received for review, and 31 have been

approved. We fund grants based on whether they meet the FDA and RPC requirements such as being blueprint compliant and not based on cost.

A total of 839 CE activities have been conducted as of February 29, 2016.

The REMS includes course completer goals. FDA based its goals off estimates of the number of prescribers who had written at least one ER/LA opioid prescription in the previous 12 months. In 2012 when the REMS was approved, that number was 320,000.

FDA really had no precedent on which to base completer targets so the following were established: By March of 2015, the FDA wanted 25 percent of prescribers who had written at least ER/LA opioid prescription in the previous 12 months to have completed a REMS-compliant CE for a total of 80,000 prescriber completers. A year later, the goal was 160,000 prescriber completers, and by March of 2017, the goal is to be 192,000 prescriber completers.

On this slide, you can see the upward trend

in CE training completers over time. On the Y axis are cumulative completer totals. Yearly time points are along the X axis. Prescribers who satisfy the requirement of having written a recent ER/LA opioid prescription are shown in dark blue. The light blue bars represent the prescriber completers as well as those who don't satisfy the requirement. The dark blue represents these prescriber completers who can be technically counted as the REMS assessment, although we know the CE has reached far more healthcare professionals.

Those who have participated are predominantly primary care prescribers at 67 percent, non-pain specialists at 20 percent followed by pain specialists at 12.8 percent. This suggests that REMS-compliant CE training is reaching the appropriate audiences.

REMS-compliant education is offered nationwide in cities across the country to ensure the education reaches appropriate audiences of healthcare professionals who are involved in

managing people with pain. REMS-compliant education activities are offered at national conferences, primary care conferences, specialty conferences. In addition, some medical schools, residency programs and health systems are adding pain management training to their curricula and ongoing training. And in addition to live activities, there are always multiple online courses.

Some CE grants have activities that extend through 2018. Additionally, CE providers submit proposals on a non-annual basis, and updated reports on activities and audits are provided to the FDA on an ongoing basis.

This sort of a program is a first of its kind, and our completer targets were developed without any precedent to base them on. We are proud of what we have accomplished to date and believe that we have an impact on outcomes even though we fell short of the prespecified completer targets.

There are a great number of requirements

under the REMS that guide what we can and cannot do. For example, industry is only allowed to create general awareness of the availability of REMS-compliant programs and may not advertise. In addition, CE programs must include all blueprint sections, resulting in lengthy courses that are not tailored to individual learner needs and do not take into account or consideration prior learning or proficiency.

Additionally, only recent ER/LA opioid prescribers count towards the REMS goals. Of note, other healthcare professionals that have a vital role in patient care do not count towards the targets.

Finally, the RPC is not the only source for education on safe and appropriate use of opioids. We have found many additional CE programs or activities closely related to but not strictly compliant with the FDA REMS.

As this slide shows, non-REMS-compliant programs are numerous, varied and could potentially account for a large number of participants that are

not counted as part of the RPC's data collection or towards the FDA goals.

With these challenges, innovation and creativity are important. We encourage CE providers to develop new ways to presenting REMS-compliant CE. These include exploring adaptive approaches to count towards REMS goals; increased online activities, including development of several mobile apps; webcasts; i-books; and blended learning such as combining digital and face-to-face formats. Case-based studies and clinical discussions may also enhance participation.

There have been notable accomplishments associated with this inaugural use of accredited CE to fulfill a REMS training requirement. Systems and processes for REMS CE data collection, reporting, aggregation and auditing were developed and operationalized. Some communications have been established with REMS stakeholders, including CE providers, the ACCME and the CCCE.

We have assured the availability of diverse, comprehensive courses and successfully navigated a

path that met both the REMS requirements and the CE standards for having no involvement with content development, advertising or data collection on the CE participants. We have educated a significant number of target prescribers and even more healthcare professionals.

I would now like to invite Dr. Charles Argoff to the lectern to discuss his experience as an ER/LA REMS educator with direct patient care. Dr. Argoff is professor of neurology at Albany Medical College and the director of the Comprehensive Pain Center at Albany Medical Center. He has published in numerous peer-reviewed journals, serves on multiple journal editorial boards and has authored pain management textbooks, including a pain management book for the lay public.

Dr. Argoff.

Industry Presentation - Charles Argoff

DR. ARGOFF: Good morning. I'm Dr. Charles Argoff. I'm in the trenches both as a medical doctor caring for people with pain and in teaching

physicians. On a typical day, I see patients with various types of chronic pain conditions. I teach residents and medical students at our pain center. I participate in research studies. I also develop and deliver educational programs for the ER/LA opioid REMS.

For my clinical experience, the ER/LA opioid CE program has been successful. It targets growing audiences of healthcare providers that need information to maximize benefit and minimize harm of ER/LA opioid prescribing. I have noticed in doing these programs over the last three plus years that there is more acceptance and willingness to participate in education around opioids. Prescribers are changing their clinical behavior and prescribing habits after taking REMS-compliant CE.

I firmly believe that education is the cornerstone of changing behavior. Consider this: Clinicians do the best they can but most have limited exposure to pain management education. Only five medical schools currently offer pain

management training. Thankfully, 60 more have pledged to have programs in the future, but that means physicians today have been playing catch up on this important topic. That's why I often look at and see large numbers of people in one of my REMS CE trainings who know they need additional education on these critical issues.

Providers need information on how to care for people in pain, including opioids and other pharmacotherapy as well as other treatment modalities. These include interventional approaches such as injection and neurostimulation, psychological support, lifestyle changes, complementary and alternative medicine, physical medicine and rehabilitation. Pain management is much more than just opioid therapy.

As a physician and pain educator, I am confident that REMS-compliant CE has had a positive impact on the medical community who have participated. Prescribers report increased confidence after completing REMS-compliant CE. That increased confidence has resulted in changes

to practice, including increased urine drug testing, increased patient counseling and improved awareness of how to identify potential patients who are diverting, misusing and abusing prescription opioids.

I strongly believe that this REMS and REMS-compliant CE have played a role and have contributed to a decrease in opioid prescriptions since 2013.

One of the challenges in interpreting the impact of the REMS is linking training with prescription behavior and patient outcomes. A recent retrospective observational study does exactly this. The preliminary results were only made available a few weeks ago and have not been provided to the FDA. They come from Amazing Charts, a division of CE provider Pri-Med.

I have been given permission by Pri-Med to share these initial study results today. The study uses electronic health record data. It looked at all users of these EHRs, stratified by whether or not they had taken REMS-compliant education. It

compared prescribing patterns for ER and IR opioids as well as patient outcomes such as abuse and dependence for the time period before the training was offered and three years after the training implementation.

Those prescribers who received REMS-compliant continuing education saw an overall decrease of 10 percent in their ER/LA prescribing compared to a 4 percent increase in the untrained group. Changes in IR opioid prescribing were the same for both groups.

There were improvements in the outcomes of abuse, dependence and overdose among patients of trained prescribers. There was a 50 percent decrease in abuse and dependence diagnoses among these patients compared to a 29 percent increase in these events among patients cared for by members of the control group. A similar pattern was seen for overdose.

These prescribing behavior and patient outcome data suggest the positive impact of the ER/LA REMS. These results provide evidence of the

effect within the trained group, particularly compared to the control group who did not improve in any category over time.

Other studies, including one published in Pain Medicine by Dr. Dan Alford and colleagues of Boston University, show similar results. And these were based on self-reported data.

In conclusion, ER/LA REMS education is making an impact. Appropriate use of ER/LA opioids can be facilitated by greater knowledge of how and when to prescribe them along with knowing how to mitigate risks to prevent dependence, abuse, overdose and death.

Thank you for your time today.

I will now turn the lectern over to the RPC.

Industry Presentation - Soledad Cepeda

DR. CEPEDA: Good morning. I'm Soledad Cepeda. I'm an anesthesiologist and a pain specialist with a PhD in epidemiology with Janssen. I have been working with the RPC metric subteam on measuring the impact of the REMS for the last three years.

I'm going to talk about what we measured just as the impact of the REMS. These assessments include evaluation of patients' perspectives, prescribers' knowledge, knowledge retention and opioid prescribing behaviors. And we also have analyzed outcomes.

I will show some of our key findings for each REMS assessment, and then I will provide an overview of some of the limitations of our assessments and ways we are already addressing those shortcomings.

Let's look at patient knowledge first. We surveyed the impact of the REMS on patient knowledge annually, and I will show you last year's results. This was a 20-minute survey with 80 items with 22 knowledge questions. It was administered by HealthCore who commercially insured the patients. It was completed by telephone or online.

The survey includes questions to determine patient understanding of the risks associated with the ER/LA opioids, if they got and understood the medication guide and if the patient counseling

document was used. The survey also asked patients about their satisfaction with access to ER/LA opioids.

We included commercially insured adults who filled at least one ER/LA opioid prescription from September 2013 to August 2014. The target sample size was 400 patients; 423 patients completed the survey of the 2,400 we were able to contact.

Looking at the 423 completers and comparing their characteristics with any users of ER/LA opioids in the commercially insured database, our responders were more of female and an average of 5 years younger. The geographic regions were similar. In addition, 94 percent were white, which is similar to the source population, and 23 percent had not achieved greater than a high school degree.

We assessed knowledge in two ways in all of our surveys. First, we calculated overall scores like when you grade an exam, and second, we calculated the number of questions answered correctly by 80 percent or more of the responders.

Let's look at how patients did first. The

overall scores ranged from 40 to 100 percent correct. Seventy-three percent of the responders met or exceeded FDA recommendation target of a score of 80 percent correct or higher as highlighted in yellow.

Now, let's move from the overdose score to knowledge on key risk areas. The following are the areas with the highest knowledge scores: not sharing or selling ER/LA opioids with others, seeking help for side effects like trouble breathing, talking to a healthcare provider if a dose doesn't control pain and not drinking alcohol while taking an ER/LA opioid.

They were five questions that were answered correctly by fewer than 80 percent of the responders. Seventy-seven percent of patients knew not to go into a hot tub or sauna while using a patch. Seventy-six percent recognized that pills should not be split. Seventy percent knew to inform their healthcare provider of fever. And just 55 percent knew that they had to read the medication guide every time an ER/LA opioid is

filled.

However, 98 percent of patients reported reading the guide at least once. They achieved an average knowledge score of 86 percent. Two percent of the responders who reported not reading the medication guide had an average knowledge score of 72 percent.

Looking at the patient counseling document, fewer than half of the responders reported receiving this document, and only a quarter reported that the providers referenced the document during counseling.

In terms of satisfaction with access to opioids, 71 percent of the patients reported they were able to obtain a prescription for an ER/LA opioids when needed. Seventy-eight percent of participants were satisfied with their overall access to ER/LA opioids. These findings, however, only represent the experience of patients already on ER/LA opioids.

Now, let's move to prescriber data. We assigned three different prescriber surveys. The

first was conducted in 2013 before CE activities begun. We are not sharing data on this survey today because FDA asked us to focus on the most recent survey data. The results show lower knowledge scores than trained prescribers.

So let's review the most recent surveys. The first compared knowledge of subjects with and without training. We also asked about general awareness of the REMS materials. The second survey looked at longer term retention of knowledge.

The first survey was a 25-minute survey. There were 124 items with 68 knowledge questions. Prescribers were identified in two ways: the first through RPC sponsored CE providers in order to recruit the trained prescribers and the second through a national prescription database in order to recruit prescribers who were not expected to have CE training.

All participants must have written at least one ER/LA opioid prescription over the last year. The target sample size was 600, half with training, half without. For the sample with training, all CE

providers were asked to recruit all their eligible participants via email. Responders without training were randomly selected from an IMS list of all ER/LA opioids prescribers.

We mailed a large number of invitations because the expected response rate was 5 percent or less. The survey was conducted from February to April 2015. In total, 612 prescribers completed the survey, 301 with training, 311 from the IMS database.

It is important to note, however, that 54 percent of the IMS responders reported that they had actually participated in a REMS-compliant program, which by the way was a surprise. Because of this, we split the prescribers recruited from the IMS database based on whether they self-reported having received training.

We looked at baseline characteristics among responders with and without training. Although they have similar gender, there are some differences. Subjects with training are more likely to be physicians, to have pain management

training and have fewer years in practice.

Now let's go to the results. In terms of REMS material awareness, the responses showed limited awareness of materials such as the medication guide, patient counseling document, ER/LA website, and Dear Prescriber Letters.

These results highlight that more work should be done. However, trained responders showed higher awareness of REMS materials compared to the sample with no training.

We also compared the behavior between those who had and those who had not received CE training. Trained participants more often used the patient and counseling document for discussion with patients. They also used more screening tools, patient prescriber agreements and urine drug tests.

In addition to measuring awareness of the REMS materials, the specific aim of the survey was to assess understanding of the six knowledge areas outlined in the FDA's blueprint. Those with training had higher knowledge scores. Overall, 72 percent of questions were answered correctly by at

least 80 percent of prescribers.

Moving to the long-term evaluation, its purpose was to determine knowledge retention and practice changes. We surveyed prescribers six months to a year after they took REMS-compliant training.

The survey was a 30-minute evaluation. There were 102 survey items with 65 knowledge questions, including case scenarios. Prescribers were identified through RPC supported CE providers to ensure they had previously received training.

We targeted 600 subjects between February and April 2015. Only 328 prescribers completed the survey. The majority of participants were male, 66 percent were medical doctors, 28 percent of whom were pain specialists. Nearly 60 percent of prescribers had been in practice for more than 15 years. Forty-six percent had prescribed ER/LA opioids more than 10 times in the past month.

Let's look at the results. Of the six risk messages, only two had average scores less than 80 percent: initiating therapy and product-specific

information. The mean score was 83 percent, and 70 percent of the questions were answered correctly by at least 80 percent of participants.

A key insight from this survey is that product-specific knowledge is limited.

Has prescriber behavior started to change after the REMS? To measure inappropriate prescribing, we started opioid use from before the REMS implementation, 2010 to 2012, to after, 2013 to 2014. We measured prescription volume using two U.S. retail prescription databases.

Compared with the pre-REMS period, opioid prescription volume decreased by 4.3 percent. The largest decrease, 20.7 percent, was observed in patients between 19 and 40 years of age. As a comparator, we looked at immediate-release opioids. The data show a decrease in immediate-release opioid prescription volume of 7.6 percent.

In addition, we studied prescriber behavior from a number of different angles, from volume of opioid prescriptions by medical specialty to changes in areas of inappropriate prescribing.

There were decreases in the number of prescriptions in medical specialties that often care for patients with acute pain where ER/LA opioids are not the first line of treatment. For example, the largest decrease was observed in dentists at 49 percent and in emergency medicine specialists at 26 percent. We saw decreases for many other specialties as well.

On the other hand, we saw a significant increase in ER/LA opioids prescriptions among nurse practitioners and physician assistants. This intrigued us. We looked further. We learned that the number of physician assistants and nurse practitioners prescribing opioids increased after the REMS, 12 percent for nurse practitioners and 16 percent for physician assistants.

These professionals, in fact, wrote more prescriptions for every class of drugs we examined, benzodiazepines, cholesterol lowering drugs, ulcer medications, anticonvulsants, and antidepressants.

There has been some decreases in inappropriate prescribing since the implementation

of the REMS. We looked at four areas of problematic prescribing that could increase the risk of overdose: first, the use of benzodiazepines, which are not recommended for concomitant prescribing with ER/LA opioids. There was a decrease of 3.7 percent in concomitant prescribing after the REMS.

Next, the use of extended-release hydromorphone and fentanyl patches, which should not be given to opioid naive patients. Here, we saw a decrease of nearly 9 percent for extended-release hydromorphone and a numerical decrease of 2 percent for fentanyl patches.

Last, the use of high-dose extended-release morphine, which should not be prescribed to opiate-naive patients. The numerical decrease here was nearly 3 percent.

All this data taken together suggest that inappropriate prescribing began to improve after the REMS became active.

The next step is to see if changes in behaviors are starting to improve outcomes. We

looked at these through emergency department visits and hospitalizations due to opioid overdose. So we conducted a retrospective cohort study of commercially insured patients in the U.S. We also included Medicaid data from one state since it was the only Medicaid data available at that time.

The study included patients who received at least one dispensing of ER/LA opioids during one or more of the REMS study periods. Data was run from before the REMS through August 2014. Opioid overdose was defined using diagnosis claims for poisoning by opioids.

We studied more than 80,000 commercially insured patients in the pre-REMS period compared to nearly 44,000 patients in the post-REMS period. The cohorts were smaller in the Medicaid population.

The baseline characteristics of patients after the REMS changed, commercially insured and Medicaid patients had more risk factors for opioid overdose. They had more psychiatric comorbidities and more history of benzodiazepine use. However,

this is not unique to opioid exposed subjects. We also saw increases in the prevalence of these conditions in all commercially and Medicaid insured patients.

We calculated incidence rates by dividing the number of overdoses during each REMS period by the total person time at risk within that same period. We found that the incidence of opioid overdose in the commercially insured patients was lower than the Medicaid population, 85 versus 245 per 10,000 person years.

The incidence rates for emergency visits and hospitalizations due to opioid overdose appeared to go up in both commercially insured and Medicaid databases after the REMS. But this is not surprising. We saw changes in patient characteristics I just described.

After prespecified adjustments for demographic characteristics, pain conditions, psychiatric comorbidities and baseline medication use, the risk ratio was 0.8 for both commercially insured and Medicaid patients.

A sensitivity analysis was performed excluding abuse-deterrent formulations, which yielded similar results. The risk ratio remained at 0.8. The decrease in overdoses after the REMS persisted after accounting for changes associated with abuse-deterrent formulations.

I want to show you some of the limitations of the risk assessments and the steps we have taken to solve them. Looking at the patient survey first, it only included commercially insured patients so the generalization of findings could be limited. We have already expanded to include Medicaid and Medicare patients and are now surveying patient caregivers as well.

Next, the long-term evaluation survey, we did not recruit the targeted number of participants. This year, however, with closer communications among the survey vendor, the CE providers and IT support, we already have recruited two-thirds of the sample size.

In both surveys, prescribers show limited knowledge in some areas of the blueprint. We have

communicated these results to CE providers so that they might address those knowledge gaps.

Regarding emergency department visits and hospitalizations due to opioid overdose, the study predominantly included commercially insured patients. We now have access to two additional states with Medicaid data.

We did not assess death. We now are linking the HIRD database to the National Death Index. We couldn't do that at least before because the National Death Index did not have data for the post-REMS period because of the lack in the data availability, but now it does. So we are going to use it.

The data show good reach of the medication guide but poor awareness of other REMS materials. It shows that knowledge of product-specific information is limited. We have seen some decreases in inappropriate prescribing and numerical reductions in emergency department visits and hospitalizations due to opioid overdose after the REMS became active. These benefits, however,

cannot be attributed solely to the REMS because the REMS is only one part, an important part of a multifaceted approach in the fight against opioid abuse.

Now, Dr. Dart will continue this discussion about surveillance data and health outcomes.

Industry Presentation - Richard Dart

DR. DART: Good morning. My name is Rick Dart, and I'm the executive director of the RADARS system. I'm also director of the Rocky Mountain Poison & Drug Center and a professor at the University of Colorado.

This morning, I'm going to cover the surveillance monitoring. I'll highlight some key findings and limitations and areas for improvement by augmenting and improving our data sources and analyses.

Overall, there is general agreement between the assessments of the RPC and the FDA briefing books. That's always good news. The studies suggest significant decreases in many but not all safety outcomes. However, these decreases

generally began before the REMS and were not always limited to the ER/LA products covered by the REMS.

On the other hand, we did observe that the ER/LA REMS products decreased more than immediate-release products in general. This observation is promising, although its interpretation is unclear since both extended- and immediate-release products could benefit from the ER/LA REMS training.

Since the REMS is one of many interventions that have occurred in the U.S., we can't tell from this data whether it contributed to this decline. In addition, all surveillance studies, of course, have limitations.

Also, everyone agrees that assessing abuse is extremely challenging. For example, the ER/LA REMS drugs in this case account for a small part of total opioid sales. So it's likely that refinement of the analyses and longer monitoring in particular are needed to assess the effect of the ER/LA REMS program.

Table 15 in the sponsors' briefing book

shows the data sources used for evaluating the ER/LA REMS. You have already seen data regarding the emergency department visits. I'll provide data from the RADARS system, NAVIPRO and the Washington State Medical Examiner.

RADARS has been an independent entity under the Denver Health and Hospital Authority since 2006. Our surveillance activities are financed primarily by subscriptions from the pharmaceutical industry.

We maintain a strict arm's length relationship with subscribers. For example, no organization has access to the raw data nor do they participate in the design or guide the analyses performed. However, we do provide our datasets to FDA for analysis when requested.

As we all know, there is an enormous challenge inherent in performing surveillance of substance abuse. The people abusing try to hide their behavior. Thus we can only measure abuse when they choose or sometimes are forced to reveal themselves. This occurs when they have an event

that stimulates them to call a poison center, when they are caught during a drug transaction, when they enter treatment for substance abuse or when they voluntarily decide to offer confidential information such as an online survey.

Therefore, the strategy of RADARS has always been what we call mosaic surveillance. We measure abuse behaviors from multiple different angles to provide a more complete picture of abuse.

From these various sources, we build large databases that allow us to trend data over many years with hundreds of thousands of cases across multiple programs. These results have been disseminated in over 60 peer-review publications.

Like all postmarketing surveillance programs, the RADARS system has limitations. Some are listed here, and these are presented in the FDA briefing book. We address these limitations by using the same technique that policymakers have used for decades: by studying trends and comparing and contrasting those trends between our different groups and other data sources. In other words, we

triangulate the real answer.

We also perform sensitivity analyses to assess the effect of various factors on the results.

Let's start with the RADARS poison center program. One nice feature of poison centers is that we receive cases regarding poison exposures from various populations and all age groups and have a long track record to compare to.

Poison center participation was very consistent through the analysis period for the REMS, covering 85 to 93 percent of the U.S. population. It's important to remember, though, that poison centers do represent spontaneous reports of acute health events. Currently, the database has a total of over 565,000 cases.

Now, poison centers have always received a large number of cases involving prescription opioids. RADARS participating poison centers are certified by the national association and have been in operation for 20 to 50 years.

Each call at a poison center is received by

a specially trained nurse or pharmacist who performs initial triage and provides care advice to the caller. Each case is followed to its conclusion whether that be treatment at home or through hospitalization.

After the care is complete, each case involving a prescription opioid for RADARS is sent to the central database. All poison centers collect case data using the same electronic record, which includes mandatory fields. In other words, crucial fields like the identity of the drug substance, medical outcome and others must be completed before the case can be closed.

In our surveillance for the ER/LA REMS, we track the trends of poison center rates of intentional exposures and intentional abuse exposures. These categories provide similar results, but intentional abuse is more specific to our analysis for the REMS.

This is defined as an exposure resulting from the intentional improper or incorrect use of a substance where the person was likely attempting to

gain a high, euphoric effort or some other psychotropic effect. This definition is similar to that used by FDA.

So how do these abuse trends look in poison center data? This slide compares the poison center intentional abuse cases for the ER/LA opioid group, IR opioids and stimulants. It shows three different adjustments for population, for prescriptions dispensed and for dosing units. Dosing units refers to the number of pills or tablets dispensed.

The ER/LA opioid population adjusted rate decreased 44 percent from the baseline period to the active period. This decrease was significantly greater than the 31 percent increase for the IR opioid group. Adjustment for either the number of prescriptions dispensed or for the number of dosing units showed the same results.

The ER/LA REMS drugs generated significantly fewer cases to poison centers during the active period than pre-implementation period, and in each case, the decrease was greater for the ER/LA

opioids than for IR opioids.

Now, let me switch to a forest plot to show you other categories that we investigated. This slide is from the FDA's briefing book. This slide also shows intentional abuse cases, as I showed on the previous slide, but this time, it's broken out by individual ER/LA REMS drug.

The decrease in abuse events was spread across multiple products with the greatest reduction for extended-release products, as you can see.

This figure from the FDA briefing book shows that similar to the poison center program, most ER/LA REMS products decreased in our substance abuse treatment programs as well.

Poison centers have many different call categories. The yellow portion of this slide shows that abuse specifically for adolescents, misuse for all ages, adults and child unintentional exposures, so those would be accidental for many people, and major medical outcomes, including death, all these outcomes decreased from the pre-REMS period as did

deaths from ER/LA opioids recorded by the Washington Medical Examiner.

Like RADARS, the ER/LA REMS opioids decreased in the NAVIPRO ASIMV program as well, which is notable because NAVIPRO uses a different sample of substance abuse treatment centers.

The one outlier was our college survey, which showed an increase in abuse endorsements. This may be a product of very low abuse rates in general in this program for the opioids.

Overall, the pattern observed is that almost all analyses indicated a significant decrease in abuse and overdose with the ER/LA REMS opioids. In many but not all cases, the decrease in outcomes was greater for the ER/LA opioid group than the IR opioid group.

Now, most of the data I presented are from RADARS programs, which creates the question of how RADARS compares to other data sources. We compared population-adjusted rates of abuse from the RADARS poison center program to the Drug Abuse Warning Network, DAWN, from 2004 to 2011 when DAWN ended.

The correlation of RADARS poison center data and DAWN emergency department visits regarding all opioids in aggregate was strong, 0.95. We also analyzed each drug class individually and all showed good to strong correlation.

Similarly, we calculated the correlation between deaths captured by RADARS poison center and the national mortality data from the National Vital Statistics System or NVSS. Poison center deaths comprise about 5 to 10 percent of the opioid deaths reported to NVSS.

So the question is whether poison center mortality rates are a reasonable sample of the total number of opioid deaths in the United States. The correlation for the NVSS category of natural and semi-synthetic opioids, which is the category containing the vast majority of ER/LA REMS drugs, and the poison center data was good with a correlation coefficient of 0.67.

One challenge is that NVSS, as was previously mentioned, does not report the specific product involved. Therefore, it can't analyze the

ER/LA REMS drugs alone. Poison center data, while only a sample of total deaths, allows us to identify specific products, and therefore, we can identify the ER/LA REMS group of drugs.

The same two sources, NVSS and poison centers, show that heroin deaths are unfortunately increasing as was previously noted. The correlation of these two programs was strong at 0.9.

We also compared population adjusted rates of abuse from the RADARS treatment centers to the treatment episode dataset for 2005 to 2013, a program run by SAMSHA. The correlation of these two programs was also strong at 0.94.

As we have noted several times, total opioid deaths in the National Mortality Database, the blackline on this slide, have increased progressively over the past decade. Nearly all of the ER/LA REMS drugs fall into the category of the natural and semi-synthetic opioids, which is represented by the red line. This category peaked in 2011 and has been relatively flat since that

time.

Here, I've added several of the data sources we discussed today. Each line represents the percent change or relative change for that program since 2011. Whether the program be the National Mortality Database, the National Survey of Drug Use and Health, the Washington Medical Examiner or the RADARS programs, abuse and misuse of the prescription opioids in general and the ER/LA REMS drugs specifically have decreased in recent years.

So why are all these measures improving? I've inserted just a few of the interventions that have developed in recent years. These include the remarkable rise of prescription monitoring plans, which now exist in all states except Missouri.

National drug take back programs have grown nationwide. Abuse deterrence formulations were introduced in 2010. In 2011 and '12, radical changes to pain treatment in law enforcement were implemented in Florida. And in 2012, the ER/LA REMS first became active.

Because of the complexities of evaluating

opioid abuse, multiple interventions, rise of cheap heroin and illicit fentanyl and surely other confounders that we're not aware of, it's impossible to ascribe these improvements to a single source.

In conclusion, the ER/LA REMS surveillance plan detected changes in trends specifically to the ER/LA drug class and individual drug products. These changes were remarkably consistent across multiple independent sources. In many cases, the decrease for the ER/LA REMS group was greater than IR, although we have to realize that REMS education could affect IR formulations as well.

These changes coincided with a plateau in the NVSS deaths for natural and semi-synthetic opioids and a decrease in poison center mortality for the ER/LA REMS. However, as I mentioned, multiple factors could potentially contribute to these changes. It just isn't currently possible to determine the contribution of individual interventions.

That being said, education like that

provided by the ER/LA REMS is a logical and important component to produce lasting change.

Thank you for your time.

Industry Presentation – Laura Wallace

MS. WALLACE: Thank you.

I'm Laura Wallace. I'm a member of the RPC metric subteam and an epidemiologist by training with nearly a decade of experience working on REMS programs, including the ER/LA opioid class REMS.

Today we've discussed how this REMS in unique. It is the first to use accredited continuing education courses as its primary approach. Its scope also is unprecedented, 24 companies of widely ranging sizes with both branded and generic medications, 19 CE providers, 839 accredited education programs and a broad range of assessment tools and data sources.

We have learned a lot since implementing the REMS. We have learned how to collaborate, how to educate and how to assess the program. But there is still work to do, and we are committed to using what we have learned as part of a process

evaluation to improve upon the REMS and to inform the design of other REMS programs in the future with the help of FDA, this committee and other stakeholders.

So what have we learned? First, the importance of collaboration and project management. Since the REMS was instituted, over 800 REMS-compliant continuing education courses with consistent messaging have been offered.

These have been rated positively by completers with generally good results on assessments. This could not have happened without dedicated project management and collaboration between the 24 companies of the RPC, the agency, the CE community, accreditors, data providers for assessments, medical writers and many more.

We also have learned to systematically look at the REMS communications activity such as the Dear Prescriber Letters to see where improvements can be made. For example, only 47 percent of prescribers acknowledged receiving a letter about the REMS despite multiple mailings of large numbers

of letters, resulting in lower awareness of the REMS than hoped.

Another area in which we have learned a great deal is the REMS assessments. We have reviewed all surveys, surveillance studies and other assessments included in the REMS to determine aspects that function well and those that can be improved. We have also discussed areas where changing out comes of interest and data availability suggests new studies could be useful.

Even as we consider improvements, it's important to note barriers. A clear challenge is that the ER/LA REMS represent only a small proportion of opioid prescribing compared to IR opioids. So prescribers may opt for a more general pain management CE course that includes coverage of IR opioids and other treatment strategies rather than one specific to ER/LA opioids.

While it's reasonable to consider IR opioids in discussions about the public health impacts of this class of drugs and the educational needs of providers, today I will focus on data-driven

recommendations for changes to the ER/LA opioid class REMS program based on what the RPC has learned from its experience with this REMS since its implementation.

We have five recommendations. These actions will help to ensure the balance between further reducing abuse, misuse and addiction, avoiding undue burden to the healthcare system and allowing access for appropriate patients with severe pain.

First, the RPC proposes to enhance REMS communication activities. One improvement will be to make the REMS CE website more user friendly. Also, to supplement existing communication activities, the RPC is planning to launch an awareness campaign featuring a website that will help interested healthcare professionals to better identify the most appropriate REMS-compliant training for their needs.

This campaign also includes additional activities such as a plan to promote REMS awareness on appropriate healthcare professional-focused websites, in journals and at conferences.

Second, we propose to expand the REMS to include the extended healthcare team. The current REMS focuses on educating recent ER/LA opioid prescribers. However, in practice, clinicians report that many other members of the healthcare team, including nurses and pharmacists, are actively involved in counseling their ER/LA opioid patients. Therefore, education of all team members involved with patient care is critical of implementation of REMS learning and ensuring the public health impact of the REMS.

Professional associations and accrediting bodies for pharmacists, nurses, physician assistants, nurse practitioners and other members of the healthcare team involved in counseling and caring for patients will be critical partners in implementing this change.

We also recommend REMS-compliant education to be targeted to new healthcare providers and to those caring for patients in communities where patients may not have access to pain medicine specialists.

Third, the RPC suggests revising the FDA blueprint to reflect evolving stakeholder input and feedback and to take into consideration the needs of adult learners.

Specifically, the RPC proposes to include tools to manage opioid risks such as co-prescribing of naloxone;

Condense the content to be shorter, more in line with the length of non-REMS-compliant trainings; utilize case studies more frequently in the trainings;

Use adaptive approaches to ensure prescribers who already have knowledge and competence on specific sections of the blueprint can focus their efforts on the sections where they need additional training; emphasize general principles of safe ER/LA opioids prescribing rather than the details of specific drugs since most prescribers only regularly use one or two from within the class;

Address other topics in pain management such as how to deal with patients suspected of abuse,

misuse or diversion and establish standard assessments across CE activities to allow the effectiveness of different activity types and delivery formats to be compared over time to aid in course improvement.

Fourth, while the RPC does not believe that it's necessary for training to be made mandatory, if it is, the majority of the RPC supports tying schedule II and III narcotic DEA registration to completion of REMS-compliant opioid education or other recognized attestation of knowledge such as board certification in pain medicine.

This approach would ensure all prescribers have appropriate training in pain management with opioids so that patients can continue to access treatment options without imposing undue burden on prescribers or pharmacists.

Recognizing that this would likely require congressional approval, the RPC welcomes the opportunity to work with FDA, DEA, legislators and other key stakeholders to develop an actionable plan for linking education with registration.

Finally, we suggest harmonizing the safety topics covered by federal opioid educations, including the FDA, NIDA and SAMSHA, as recommended in the national pain strategy. This graph shows the overlap between the popular course offered by NIDA and the REMS blueprint. Thirty-nine percent of the REMS messages are covered in full or partially by the NIDA course.

Utilizing the principles of this REMS and the lessons that we have learned could be helpful in the development of consistent, practical and effective educational programs. The process to do this could be fairly streamlined, especially considering many of the agencies and experts needed for this are participating in today's meeting.

We believe we should modify the REMS in these evidence-driven ways. The approaches I've outlined are based on our experience and the lessons that we have learned. They will help to improve provider knowledge and contribute to safer use of opioids by appropriate patients who need them.

Now, Dr. Coplan will offer concluding remarks.

Industry Presentation – Paul Coplan

DR. COPLAN: Thank you, Ms. Wallace.

I'd like to provide a brief summary of the salient results. We've sent 3 million Dear Prescriber Letters to inform ER/LA opioid prescribers about the REMS. Thirty-three percent of prescribers included in the prescriber survey reported that they had read the letter.

RPC funded over 800 REMS-compliant CE courses that were conducted. There have been 438,000 participants in these courses, 157,400 completers in these courses of which 66,200 ER/LA opioids prescribers met the definition of a completer for the goals.

In survey results, patients using ER/LA opioids had a score of 86 percent, and prescribers had a score of 83 percent of questions answered correctly.

The impact of these components was assessed in surveillance studies. There were consistent

decreases in the outcomes that the REMS was designed to decrease. Rates of abuse of ER/LA opioids decreased by 44 percent after the REMS became active in a poison center study.

In two studies of ER/LA opioids abuse in drug treatment center surveillance systems, ER/LA opioid abuse decreased by 21 percent and 46 percent.

Rates of misuse of ER/LA opioids decreased by 23 percent in a poison study. Rates of opioid overdose, of poisoning, emergency department visits showed a numerical decrease after adjusting for changing patient profiles and risk factors for opioid overdose.

The rate of death involving opioids decreased by 39 percent in the state of Washington. In most cases, these decreases for ER/LA opioids were larger than those for immediate-release opioids and other controlled substances that were not targeted by the ER/LA REMS.

However, these decreases cannot be attributed only to the REMS since the REMS was

interwoven with other opioid abuse interventions in the White House's national drug abuse prevention plan.

In several cases, abuse and death rates started to decrease just before the introduction of the REMS such as the state of Washington mortality database.

In addition to these findings, there have also been some changes in inappropriate prescribing such as decreases in concomitant prescribing in benzodiazepines and ER/LA opioids and decreases in prescribing of opioids indicated for use only in opioid-tolerant patients to opiate-naive patients.

We have also learned the letter used to communicate about the REMS to prescribers was not sufficient in doing this.

It would be helpful for competing CE courses to align on their content so that federal and state CE courses for safe opioid use complement each other to achieve a national educational goal. Consistent post-training measures for CE courses would allow identifying which offerings work best

and for which prescribers. And concise medication guides can have good reach.

The activities of the companies to reduce ER/LA opioids abuse and misuse are not limited to the REMS and include a program of 11 postmarketing studies of ER/LA opioids to better characterize their long-term efficacy, their incidence and risk factors of abuse, addiction, overdose and death among patients with chronic pain who use ER/LA opioids and developing validated measures of those risks.

Unused medication take back programs, developing abuse-deterrent formulations of opioids and new molecular entities to treat pain with fewer serious risks.

The ER/LA REMS can be considered of consisting of two phases. The first phase started in 2010 with the advice provided by DSaRM and AADP members at the first FDA advisory committee. This first phase covers the development and implementation of the REMS through today and was guided by the White House's prescription drug abuse

prevention plan of 2011, which identified four pillars of action by the federal government: education, monitoring, policing and medication take back.

The REMS results we present today are the first four years of work in continuing education support. The second phase of the REMS will include evaluation, revisions and implementation of the new program.

This phase will be informed by the FDA's approach to opioid analgesics as articulated by Drs. Califf, Woodcock and Ostroff in the New England Journal of Medicine recently; the new CDC guidelines for opioid treatment; the national pain strategy; and evaluation of the lessons we have learned from the REMS thus far.

In addition, your advice from today and tomorrow's meeting will be important for steering the next phase.

I'd like to acknowledge the broader RPC team, both employees of RPC member companies and partner organizations who contributed extensive

time, effort, skill and insight to implementing the REMS.

The ER/LA REMS is novel in its scope in the use of continuing education activities. The REMS has contributed towards increased awareness and knowledge of both patients and prescribers and reductions in serious risks of ER/LA opioid abuse, misuse, addiction, overdose and death.

The RPC takes our responsibilities in the REMS seriously and are committed to continuing to be part of the solution. We propose a number of additional enhancements to the REMS to ensure that these medicines are prescribed to the right patients at the right time.

Thank you for your attention. We welcome your feedback on the REMS and its outcomes and on our recommendations for further work together.

DR. WINTERSTEIN: Thank you very much.

We have Dr. Parker who joined, so if you would like to introduce yourself. Finally made it.

DR. PARKER: Thank you. Ruth Parker, Emory University School of Medicine. Thanks.

Clarifying Questions

DR. WINTERSTEIN: Thank you.

Okay. We have now time for questions for the industry. Well, let's start with the questions for the industry, and then if we have time, we take the one from before the break. Please try to direct your questions to a particular speaker, if possible, and try to direct your questions to the content that was presented so that we can keep this efficient.

We have tomorrow a lot of time for discussion, so today, right now we're really in the clarifying questions type of mode. Thank you. We'll start with Dr. Higgins.

DR. HIGGINS: I have two methodological questions that I believe it would be Dr. Cepeda who could answer this most clearly. The first is with your prescriber survey, was that an online survey, and had there been consideration of the fact that it seems that apparently a younger cohort of physicians was responding?

I'm wondering if that method had been

considered and whether there was an opportunity for people to send in paper survey questionnaires.

The second question is regarding the Medicaid data. Which state was being used, and is that state representative of Medicaid data generally?

DR. COPLAN: Dr. Stemhagen, could you please address that first question? And then, Daina, could you address the second question about the state?

DR. STEMHAGEN: I'm Annette Stemhagen from United BioSource Corporation, and we developed and are conducting the prescriber surveys.

So yes, the answer to your question, the predominant mode was internet. Prescribers were offered the option of either internet or paper so that most of them were internet with very few paper. We're now in the process of fielding the survey again, and we have three options. We have internet. We have phone for those who choose not to use the internet and continuing the paper.

DR. COPLAN: And with regards to the

Medicaid, the state Medicaid, which state was involved?

MS. ESPOSITO: Daina Esposito, HealthCore. For the state that provided the Medicaid data, the nature of our agreement with that state is that they provided their data on a de-identified basis and don't allow us to disclose which it was. We are looking forward in the second year of the study, which is currently ongoing, expanding to include two additional states, which will give us a little bit better idea about that.

DR. WINTERSTEIN: I have a quick follow-up on the Medicaid study, actually. There was mentioning of an adjustment that was done for prior characteristics, and on slide 88, there were a number of prior characteristics or patient characteristics listed.

Are these the ones that you adjusted for?

MS. ESPOSITO: The analysis per protocol was that we adjusted for characteristics based on a backwards stepwise regression. So we included this list of characteristics as well as other pain

conditions, demographic characteristics and, for example, the number of prescribers that were used, the specialty of the prescriber and so on.

We did also look to see if the backwards stepwise regression model gave different results than an analysis that used all data. We had some issues with convergence when we tried to use all variables. However, the results were basically the same.

DR. WINTERSTEIN: I'm curious about the selection of those variables. So we see that there is an increase of substance use disorder in the post-REMS period, yet you adjust for this, which, in fact, is actually a cause for the outcome that you see later on. Wouldn't that be a precursor for the outcome?

MS. ESPOSITO: Sure.

DR. WINTERSTEIN: I'm curious why you adjusted for that because actually, if we see that substance use disorder goes up, wouldn't that cause ER visits and so on?

MS. ESPOSITO: Sure. So something that we

did see was that this was actually not limited to the population of patients that used extended-release and long-acting opioids. There were many changes that occurred over the study period, including, for example, implementation of the Affordable Care Act.

Our Medicaid state and also the Anthem data in the main study expanded coverage to individuals who weren't previously insured, and in fact, when we look at rates before and after the REMS of some of these psychiatric comorbidities abuse behaviors and so on. In terms of the prevalence, again, comparing after the REMS to before, we actually do see that there are increases in the general population that are in some cases larger than the increases in the ER/LA population.

DR. WINTERSTEIN: But that still doesn't reduce the issue that your causal inference at the end, you don't know what that increase means. You're adjusting for something that is a precursor. Whether this is real and there's really more patients with substance abuse disorder or a

measurement issue, but it's still there.

I'm just curious what you make out of the adjusted analysis in this because you're --

MS. ESPOSITO: Sure.

DR. COPLAN: Well, since prior history of substance use disorder is a risk factor for overdose, we thought it would be important to stratify on that to make sure that -- since that was changing in prevalence pre to post, we thought it would be important to stratify or adjust for that so that we can compare rate changes within people in that strata.

DR. WINTERSTEIN: I get that, but I mean, you have two time components. So you have a population pre-REMS, and you have a population post-REMS. The population pre-REMS has less substance use disorder than the population post-REMS. So there is a logical conclusion that that increase in substance use disorder may have occurred in this particular population and we don't know why.

So if we're thinking that there's an

increase in substance use disorder, then to adjust for it would essentially mean that I'm removing patients moving toward an overdose.

DR. COPLAN: Too much removing but more just comparing patients without -- looking at pre, post changes for people without prior history of substance use disorders and then with people with substance use disorders, at least that's how we looked at it.

DR. WINTERSTEIN: Dr. Gupta.

DR. GUPTA: This question is for Laura. Regarding the RPC recommendation number 4, it says, "If training is required, tie it to DEA registration."

My question is: For academic institutions, when there are residents and interns who are prescribing opioids, many of them often will use institutional DEA licenses. They may not get their own individual until many years later.

How will you address that issue and that gap?

DR. COPLAN: Yes. I think there are

different ways in which we communicate about the REMS to prescribers. One is through the Dear Healthcare Provider Letter. The other way is through the advertising budget of the CE providers. Each CE course that we fund has a budget in which they make prescribers aware of the training and about the REMS. So there are two different ways.

DR. WINTERSTEIN: Dr. Choudhry.

DR. CHOUDHRY: I have a question for Ms. Wallace about slide 131, which is -- we talked about harmonizing content, and I think again, this has come up several times.

I'm curious if you could provide a little bit more detail first about what's in the "no" section. So what's NIDA covering that's not being covered in the FDA blueprint for this REMS?

Secondarily, there's another Venn here as in another circle. Is there content that's in the FDA blueprint that's not covered by the NIDA content?

MS. WALLACE: The very brief answer is yes to both. The slide that I'm putting up here is a bar chart showing how the two continuing education

programs relate to each other.

In terms of things that are covered by NIDA but not by the REMS group blueprint, the NIDA course that was previously offered had two different components that covered different aspects. There's more focus on broad pain education, and there's also more on medication-assisted therapy, co-prescribing of naloxone for rescue for overdose, et cetera.

In terms of the REMS, you can see that specific drug information, for example, is not covered at all by the NIDA course. The general information that is included in the REMS is mostly not covered, and then it varies throughout the other categories.

DR. WINTERSTEIN: Dr. Bateman.

DR. BATEMAN: This question is for Dr. Argoff and relates to slide 49. So these are potentially really important data because they look at the impact of training in a direct way and show a rather dramatic impact of training on important clinical endpoints.

I think it would be useful for us to know more about how this study was conducted so that we can understand how robust these findings are because I think it speaks to how effective the REMS training is.

Can you talk about the size of the cohort, whether the analyses were restricted to ER/LA patients, and then whether there was any adjustment for patient or provider characteristics in the trained and untrained groups?

DR. ARGOFF: So the numbers of people who participated in terms of number of prescriptions?

DR. BATEMAN: Just what the population under study was, I guess you show --

DR. ARGOFF: Right. So these were users of Amazing Charts. Amazing Charts is an electronic health record that's used in various places across the country and is owned by Pri-Med. And the data that I presented today are just in the process of really being worked out, but I will tell you what I know and what's available to date.

The same providers were studied continuously

during the three-year period, both those who had participated in REMS training and those who had not. So these data regarding the reduction in overdose and other -- and abuse are based upon evaluating the same people who are prescribing to their patients different opioids -- the breakdown has been discussed already -- and the changes pre- and post-training for those who participated and the control group are those who did not participate.

Did that answer your question?

DR. BATEMAN: I think so. I guess --

DR. ARGOFF: That's what we know this far.

DR. BATEMAN: -- you worry a little bit that the people that receive the training are different from those that didn't receive the training and might be subject to the other secular trends that are going on across the study period. So I think it's useful to understand whether the characteristics were roughly the same or adjusted for analysis in some way.

DR. ARGOFF: So if I understand your

question, you're asking were the two different cohorts similar in prescribing, did they prescribe a similar number of opioid?

DR. BATEMAN: Similar kinds of patients, similar regions, similar characteristics that again might make them subject to secular trends in a similar way.

DR. COPLAN: So essentially, the design there was 441 -- it was a retrospective. So there was 441 trained prescribers, and then about 2,000, 3,000 other opioid prescribers in the electronic health record database who hadn't taken the training. And then looked within -- so like within prescriber pre-, post-change in terms of their prescribers' practices and then the patients of those prescribers.

So this number here, the 444,000, represents the number of patients covered by the trained prescribers. So these were the 444,000 patients who had seen the 441 trained prescribers. So the control for the differences in prescriber characteristics was addressed by looking at pre,

post for that -- for trained prescribers versus pre, post for non-trained prescribers.

DR. WINTERSTEIN: Do you have any statistical significance testing on this, just as a -- I was trying to calculate what the raw numbers were, but there's so many zeroes.

Okay. Several people have that question.

DR. CHOUDHRY: It was 3.5 versus 1.5. The absent numbers, it looks like.

DR. WINTERSTEIN: Oh, thank you.

Please go ahead if you want to comment on it.

DR. COPLAN: Dr. Argoff, did you want to comment?

DR. ARGOFF: Could you please repeat the question?

DR. WINTERSTEIN: The question was the statistical significance. We were trying to calculate the raw numbers of patients who actually were identified with no overdoses, and it seems our colleagues calculated this. We are in the single-digit numbers in comparisons; is that

correct?

DR. ARGOFF: Correct.

DR. WINTERSTEIN: So we have no significant p-values, I would deduce?

DR. COPLAN: We could try to get back to you with p-values on that.

DR. ARGOFF: That was going to be my response.

DR. WINTERSTEIN: Great. Thank you.

Dr. Gerhard.

DR. GERHARD: My question also would be for Dr. Argoff, although at this point, maybe it's more a comment. It's basically just kind of a follow-up to the discussion that we just had and Dr. Bateman's comments.

I would think obviously, we have very, very little information about this study. The details weren't provided. The study, if I understand correctly, is still ongoing.

So I would just, from my perspective, urge that we take this with quite of a grain of salt here because we don't have a lot of information,

just the general set-up comparing volunteers for a continuing education program with non-volunteers opens a lot of questions.

I would go a little further than saying this makes us a little bit worried. This would make me very worried, and even with adjustments, it's questionable of whether you can tease out the true effect of the intervention from the fact that these physicians volunteered.

Just looking at the outcomes so we talk about the overdose numbers, which are in the single digits, if I read this correctly from slide 49, the other outcome that was looked at, abuse/dependence, assessed from ICD-9 codes in the electronic health records, probably not the most sensitive way to get that abuse and dependence as a measure.

So I would just take this with a lot of -- we basically saw a lot of approaches to evaluate and look at the effects. They were described as a mosaic approach, looking at a lot of different things.

At the same time, I would probably not put

this in the same pool of points of evidence here. I don't think we know enough from this study to take it really into consideration. These numbers as presented on slide 49 look very impressive, but I don't think at this point there is enough there to allow us to really take those as a true finding here.

DR. COPLAN: Just as a point of clarification, this study was not part of the formal REMS assessment. So that's why it wasn't a part of the briefing document, but it was a study that became available relatively recently. And we thought it be helpful to show because it gives a sense of the type of study you could do and the kind of measures you could get at to look at this.

That's more -- I agree with you that this should not be put on the same level of evidence as some of the other studies, but it provides a sense of what kind of protocol you could do.

DR. WINTERSTEIN: Dr. Staffa, you had a comment?

DR. STAFFA: Actually, yes. I wanted to

follow up on this same study. I share some of Dr. Gerhard's concerns of just not understanding the details because as was stated very clearly, we've not seen this and frankly weren't aware of the existence of the study at all.

But my main question is, these are electronic health records. I'm assuming they might be from primary care, but it's not really clear what kind of practice they're from.

But I'm wondering whether or not they're linked to death data because what we've seen in the past is if you don't include people who have died, it can often distort what you're seeing because you're focusing on only those folks who remain alive. And I'm wondering if anyone can address whether this was linked to any kind of death data at all.

DR. COPLAN: Dr. Argoff, could you address it? So the question is whether the -- could you just describe the electronic health record database environment in terms of practice setting and also whether it would -- if a person was prescribed a

prescription opioid and had an overdose death, would that be captured in the electronic health record?

DR. ARGOFF: The principal investigator behind this study is here today, and I would like to be able to answer your question as clearly as possible. So with your permission, I will get back to you with that information so that I might be 100 percent sure with my response to you because we're not analyzing these data right now, if that's acceptable to you.

(Dr. Staff nods yes.)

DR. WINTERSTEIN: We can revisit after the break.

Dr. Krasnow was next.

DR. KRASNOW: Thank you.

I'll direct this to Dr. Cepeda. It involves several slides. It seems that decreased prescribing is a metric that shows a positive effect of the REMS program, but it seems that increased knowledge could also lead to more appropriate prescribing of narcotics.

In that context, I was wondering if the data shown on the nurses and PAs whose prescribing increased might have reflected a baseline under-prescribing and whether the knowledge gained from the program might have led to more appropriate prescribing or whatever.

DR. CEPEDA: In the prescriber data, we asked the prescribers about if you had a change in behaviors. And we have some data that we can show you.

Usually, what they told us is that subjects with training more often changed their practices and that tend to prescribe more immediate-release opioids and other options instead of extended-release opioids.

DR. WINTERSTEIN: Dr. Morrato.

DR. MORRATO: Thank you.

My question extends, I think, from where we were just talking, and it has to do specifically with slides 83. And this is one of -- I would agree it's not only a REMS with tremendous magnitude and unprecedented, but the evaluation

data is also tremendous. And I know the companies and FDA have been working really hard on this.

I'm wondering if there might be a way to look at some of this that helps us to address the question of the continuing education program impact on a population basis. So I know the REMS had targets of numbers of doctors or numbers of prescribers, and we have this data. We look at impact of prescriber on their own individual.

I'm wondering if there's a way to kind of combine these. So in figure 4 of the briefing document, you see a nice pie chart that is similar to this in which we start to see prescriber type, has physicians as a large pool. I don't know if you can break it out into some of these other classifications.

But what I'm thinking is not just looking here where this is looking at prescription -- I'm sorry. I'm trying to combine this information into one so we get a sense of who are we reaching with the training and then who are the ones where we're seeing the effect of prescriptions, not just in

change within that group but getting a sense of the relative market share or population attributable component that those particular groups represent.

So, for instance, if here we're reaching 21 percent of our sample that's getting educated, I think is the -- if I got my colors right -- the advanced practice nurse, what proportion of patient prescribing is attributed to that particular profession? Of this number 8,344, what proportion that we estimate right now are nurse practitioners are we reaching?

So we're trying to get a sense of the proportion that we're reaching, and then we're looking at the effects of prescribing on an individual level. Well, what proportion of patients is that affecting?

We could have had tremendous impact on dentists, but if they only are prescribing less than 1 percent of prescriptions, it's not giving us a sense. Likewise, nurse practitioners may have a big increase and represent a big proportion of patients that are getting seen.

So I would imagine you have these N's and numbers and could do that calculation, and that might give us a way of looking at where are we really doing well in reaching the education impact on prescriptions and where might there be holes. I hope that's clear.

DR. COPLAN: So the proportion of different medical specialties trained, the attributable fraction of the opioids that they prescribe --

DR. MORRATO: Right.

DR. COPLAN: -- and therefore, the expected outcome in terms of that.

DR. MORRATO: So it's sort of if you look at implementation science, they'll have a thing called "adoption," which is how many people have voluntarily adopted and take the voluntary training. And then there's component called "reach" where you're trying to say of those that have adopted, what is the reach of the impact of that?

So this might be a way to sort of serve as that proxy. How many are training and what

proportion of patients. Because if your training -- if the continuing education is hitting the high prescribers, you may have a smaller proportion of prescribers but hitting a lot of the patients or affecting a lot of the patients that they're seeing. Likewise, it could be the opposite. It's hard to say until you see the information.

DR. COPLAN: Yes. One of the data limitations that we face that we kind of alluded to in the core presentation is that the CE providers are the ones who know which prescribers have completed their course. And they don't share it with other CE providers, and they won't share it with us.

We obviously would like to create that aggregated database and then look at who's taken the training and who are they in terms of high prescribers, low prescribers, do they -- underserved communities, et cetera.

But we're not at that point where we can get that aggregated database because of the firewalls

between CE and industry, and that's one of our recommendations, that we try and solve that going forward.

DR. MORRATO: But you have this -- you at least have the pie chart --

DR. COPLAN: We do have this, yes.

DR. MORRATO: -- where you could at least be looking at the nurse practitioners and physician assistants is where in the other data you're seeing a big change.

DR. COPLAN: We could, yes.

DR. MORRATO: And clearly, with slide 83, right, you do have the N's for that to be able to look for those different prescriber types what are the number of patients that they're uniquely seeing or prescriptions being written to be able to do that analysis at least with that data.

DR. COPLAN: We could do that, yes.

DR. WINTERSTEIN: Ms. Shaw Phillips.

MS. SHAW PHILLIPS: This is for Dr. Cepeda as well. Going back to your information about the post-test results showing lack of product-specific

knowledge, was there any analysis done with that? So did you have information to be able to determine if the lack of product-specific knowledge was related to lack of relevance for that individual practitioner?

Since none of the answers were over 80 percent, was it more targeted again where the practitioners had the knowledge they needed for the products they used but very little in the other, or was there not enough detail provided in your analysis to make that determination?

DR. COPLAN: Ms. Wallace, could you please address it?

MS. WALLACE: No, I'm not Dr. Cepeda. I'm another member of the metric subteam, and I've looked at this issue specifically. One of the things that we evaluated looking at this was how many different types of ER/LA opioids a given prescriber on average across all of the prescribers is usually prescribing. And 62 percent of prescribers only use one or two of the drugs within the class. Seventy-six percent only use three

drugs within the class.

So what we've heard from some of our CE providers and others is that practitioners are really only interested in the drugs that they specifically are prescribing, which may be one of the reasons for that knowledge gap.

MS. SHAW PHILLIPS: But none of the analysis correlated those numbers?

MS. WALLACE: That's not a question that we could get at because of the design of the CE programs and the CE knowledge assessments.

DR. COPLAN: Dr. Argoff, would you like to add to that response from the perspective of a CE course provider?

DR. ARGOFF: I'd like to also add, too, I'm a practicing physician. I direct a clinical pain center. I direct a fellowship, ACGME-accredited fellowship. I'm not doing today, obviously.

But if you wanted me to, I could list all of the different products that are currently in the ER/LA class. And to the point that's been made by a survey and to your question, which is an

excellent question, most people are not familiar with all even with the morphine category. There's once a day, twice a day, three times a day. In fact, the original was three times a day. And now even with the oxycodone category, there are approvals that are different.

The average clinician is not exposed in their clinical practice to the customary use of each of these products. So it's really new information. Having done so many of these programs to thousands of people, it's really new information. So I'm not surprised by that result as a clinician and provider of these educational activities.

DR. WINTERSTEIN: Dr. Galinkin.

DR. GALINKIN: I have two questions. The first is for Dr. Cepeda, and my question for her is: What percentage of reading and I mean non-English and non-percent patients were actually looked at in the patient survey data? And from that data, additionally, is the REMS data available such as the patient information sheet in non-

English forms?

The second question for Dr. Dart is that I noticed -- I thought it was striking that the college survey data seemed very different than the outcome data, and my question is: Is the outcome data skewed by the fact that naloxone potentially become more available and there's less deaths now, have you looked at that?

DR. COPLAN: So for the first question, Daina, could you please address it?

MS. ESPOSITO: Daina Esposito, HealthCore. In the patient survey, it was actually exclusively English-speaking patients who were surveyed. I believe that in terms of documentation, the patient counseling document is available in Spanish.

DR. GALINKIN: So is there an intention to eventually look at non-English-speaking patients? Because they're a huge population in the United States.

MS. ESPOSITO: It's a great recommendation. I know in this year, we've expanded out to Medicaid, and it's certainly something that we can

look at.

DR. COPLAN: Dr. Dart, could you please address the question around the college survey and whether that's related to the availability of naloxone?

DR. DART: The college survey data are interesting because opioid endorsement by college students in our survey is very small. So stimulants and a lot of other drugs, especially marijuana, are much, much, much higher.

The other thing is that we put those dates up there because of the study period, but actually, it's gone back down in the college students. So just so you know that trend hasn't continued.

In regards to relation to naloxone, though, I don't think we actually know the answer to that. We don't have that information generally. Now that you bring it up, I think I can go look at that in the poison center data at least, but I don't have that right now to offer.

DR. GALINKIN: I guess my question around that is: Do you get less -- do the naloxone people

tend not to call poison control centers, I guess? And that's --

DR. DART: That's one of the limitations of poison center, right, is it's hard to know who's calling. So I don't think we can answer that, either. I can give you anecdotes on both sides of that because we're hearing a lot of people saying that naloxone is their parachute and they actually have parties where one person is the designated naloxone person for the group and the rest do what they want and there's someone there to save them.

So that's such a morass. I mean, I'm in favor of naloxone in general, but we have to understand that there's going to be some counterproductive behaviors that go with it probably.

DR. WINTERSTEIN: Dr. Raghunathan.

DR. RAGHUNATHAN: Thank you.

I have a question to Argoff. I don't know whether given all the comments, these HBCs that you used in your observational study, do they include the people who have not prescribed ER/LA in the

past 12 months? If so, then what happens with those people who report zero and zero in both periods? Do they consider them as a decrease or increase or exclude?

DR. COPLAN: And this is with regards to which study?

DR. RAGHUNATHAN: The slide 48.

DR. COPLAN: Dr. Argoff, could you please address it?

DR. ARGOFF: Let me answer your question here. The test group, just to remind us, used the Amazing Chart system. They attended and completed a Pri-Med REMS-compliant CE course, and they had prescribed at least one opioid or more to patients. The control group used the same system but did not attend a Pri-Med REMS-compliant CE course.

DR. RAGHUNATHAN: So they also prescribed more than one opioid?

DR. ARGOFF: That exact data, I will come back with you after lunch if that's acceptable to you.

DR. RAGHUNATHAN: And also, the second

question is: When you have so much -- on slide 88, you have so much difference between the pre and active period, differences in the covariates, and when you do a regression analysis, you can get very spurious results.

Did you try to do any alternative methods like propensity score method in order to see whether or not the pre and active periods are comparable?

DR. COPLAN: I'll ask Daina Esposito from HealthCore who did the analyses to comment on this.

MS. ESPOSITO: Daina Esposito, HealthCore. For the second year of the study, we actually have modified the protocol upfront to include a propensity score analysis.

We did not conduct a propensity score analysis in the first year of the study. However, model results when we used a selection approach versus all available covariates as well as in the sensitivity analysis were virtually the same.

DR. WINTERSTEIN: Last question before the break, Dr. Stander.

DR. STANDER: Yes. Thanks.

I don't know exactly to whom I should address this, perhaps Dr. Coplan. It's kind of a simple question. I'm just wondering about the logistics of these REMS courses in terms of are they traditional didactic lecture location, hours, and am I understanding that they're paid for by your consortium so there's no cost to the actual prescribers?

DR. COPLAN: I'll ask Dr. Stanton from the continuing education team to address that question.

DR. STANTON: All of the education is obviously done by the CE providers. Each of the audiences is fairly broad in its capacity. So if you look at these, as I mentioned in my core presentation this morning, we have a variety of different activities that are incorporated into the education.

Obviously, they're listed here, but there are many more. And as time goes on, the CE providers are really trying to encourage different ways of thinking, being more creative, doing the

kinds of things that typically aren't just a didactic presentation to encourage people to participate.

DR. STANDER: And the participants, is there a cost to them, or is the consortium covering the cost for the attendance?

DR. STANTON: We are covering the cost for the educational grants. There may be a slight cost actually by the individual CE provider.

DR. COPLAN: So we can't control the CE provider, whether or not they charge, but there's no -- we provide a grant that covers all the cost to the CE provider.

DR. STANDER: Thank you.

DR. WINTERSTEIN: We still have a few additional questions. They are noted, and we will get back to those who have indicated they have questions after the break.

We will now break for lunch. We will reconvene again in this room in one hour from now, which would be 1:20. Please take any personal belongings you may want with you at this time.

Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press or with any other member of the audience. Thank you.

(Whereupon, at 12:20 p.m., a lunch recess was taken.)

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

(1:20 p.m.)

DR. WINTERSTEIN: All right. Let's get started in a minute. So we will continue with presentations by the FDA.

FDA Presentation - Igor Cerny

DR. CERNY: Good afternoon. I'm Igor Cerny. I'm a REMS assessment analyst with the Division of Risk Management. I've often said I would hate to be the guy who's the last person presenting before lunch and the first one after lunch, so now I'm that guy.

So I'll be providing a brief introduction to the FDA presentations that you'll be hearing this afternoon regarding the RPC REMS assessment data. So you've seen this goal many times now, but the point of the REMS is obviously to reduce serious adverse outcomes. And the outcomes we're most worried about are addiction, unintentional overdose, and death, and we want to do this while maintaining access to pain medications for patients.

You've seen this assessment plan before. We're looking at the number of ER/LA prescribers who've completed training. There's an independent audit of the quality and content of the educational programs. Obviously, there's prescriber surveys, a patient survey; surveillance studies looking at key safety outcomes, drug utilization patterns, changes in prescribing behavior and then an evaluation of patient access.

So these presentations will follow me. We'll be having a FDA review of the patient and prescriber surveys, then a review of the epidemiologic and drug utilization data. And then lastly, I'll be back to provide some overall FDA conclusions and considerations.

You've seen this figure as well. Back in 2011, FDA estimated, using various databases, there are about 320,000 ER/LA prescribers. Then in July of '12, the REMS was approved with the blueprint, and then on February 28, 2013, the first REMS-compliant training became available.

The assessment plan stated then, two years

after that date would be the first training target, which is the 80,000 prescribers, which is a quarter of the total. And these are the data that we're viewing in this current 36-month assessment report that was submitted July '15.

The next milestone was February 26, 2016, a few months back where the training target would be 160,000 prescribers, which is half of the total, and we'll be getting a formal report of that in July of '16. And lastly, February 28th of next year will be the third training target of 192,000 or 60 percent of the total.

So you've seen various versions of this chart, but as you've heard, there have been about 839 or so RPC-supported REMS-compliant CE activities. And between February and May of '13, there were only nine, but since then, they've been coming out at a fairly high rate. And typically, these trainings have generally been live and more of those than internet based and more of those than print.

Now, you've had some of these terms defined

for you as well, REMS-compliant training. What is that? Well, it's offered by an accredited CE provider. It contains all elements of the FDA blueprint, and then it also assesses, tests for all of the blueprint sections. And the training is subject to independent audit.

A participant is considered a partial completer of CE activity. A completer is one who's completed all components of a CE activity and then met the criteria for passing, and then ER/LA prescriber completer is a completer who happens to be registered with DEA to prescribe Schedule II and III controlled substances and has written one ER/LA prescription, at least one in the past year, and this is all self-identified.

So the reason I go through those definitions again is to show you this chart, which you've seen. As of 2-28-15, you can see there are 143,000 participants, 82,000 completers, 37,000 ER/LA opioid prescriber completers. That's compared to a goal of 80,000, and that's 47 percent of the target.

Now, for 2016, you see a great jump in the number of participants. We've heard often about the large, vast scale of this program and the intended audience, 157,000 or so completers, 66,000 prescriber completers. The goal, I remind you, is 160,000, and that represents 41 percent of the target.

Lastly, the independent audit findings, the RPC is to conduct an audit of at least 10 percent of their funded REMS-compliant training to evaluate whether the training covers all elements of the blueprint. The post-course knowledge assessment measures all sections of the blueprint and whether the training was conducted in accordance with ACCME or appropriate accreditation standards.

The results were indeed 10 percent of the RPC-funded CE programs were audited, and 69 percent met all the criteria of REMS-compliant CE. And the primary reason these 31 percent didn't meet the criteria were issues of disclosure of financial relationships.

So with that, I will turn the podium over to

Ms. Harris and Dr. Hsueh who will be presenting the survey data.

FDA Presentation - Shelly Harris

MS. HARRIS: Hello. My name is Shelly Harris, and I'm a REMS assessment analyst in the Division of Risk Management in CDER. Today, I along with my colleague Dr. Hsueh in the Division of Biometrics will be discussing our review of the prescriber and patient surveys for the ER/LA REMS.

So first, I'm going to provide a brief overview of the REMS survey review process. Then I will go through the two prescriber surveys and the patient surveys providing results and comments for each. And some of this you've already heard previously, so it will be some duplication.

Next, Dr. Hsueh will go over her statistical evaluation, which includes future considerations of surveys. And finally, I will provide overall conclusions from the survey reviews.

Now, I'm going to provide some details on the REMS survey review process. When a REMS is established, if the assessment plan includes

surveys, the FDA encourages the sponsor to submit a survey methodology protocol to FDA for review. The methodology often includes proposed recruitment methods, sample size, data analysis methods, and a draft survey.

This methodology is reviewed by social scientists in the Division of Risk Management along with other FDA divisions as needed by consult. FDA provides recommendations for additions or changes to the sponsor, which the sponsor is not obligated to follow but usually does.

When the survey results come back with the REMS assessment report, they are included as one component of whether or not the REMS is meeting the overall program goals.

To date, most REMS assessment surveys have been cross-sectional surveys of prescribers and patients. In addition, many use convenience samples to recruit patients and prescribers.

We recommend that all sponsors conduct pre-testing or qualitative testing of their surveys before implementation. We also ask sponsors to set

target knowledge rates, which is the minimum knowledge rate that if achieved, determines whether or not the REMS met its goal of communicating the key messages of the REMS. There's no standard for this rate, and it's usually provided on a case-by-case basis, but in a majority of instances, 80 percent is considered acceptable.

We currently have an FDA guidance in development that addresses some of these survey design considerations.

This is the timeline of all the ER/LA REMS surveys that have launched to date. First, the ER/LA REMS was approved in July 2012. Then the year 1 patient survey was launched later that year. Next, the pre-REMS prescriber survey was launched in February of 2013, and this was a cross-sectional survey with prescribers who had not yet completed the REMS-compliant training.

The REMS-compliant training became available shortly after at the end of February. The year 2 patient survey was launched in September 2013, and the follow-up and the long-term evaluation

prescriber surveys that you just heard about were both launched in February of 2015.

Today, I'm going to be discussing the follow-up and long-term evaluation surveys and the year 2 patient survey from the 36-month assessment report. First, the follow-up prescriber survey.

The purpose of the follow-up prescriber survey was to assess prescribers' awareness and understanding of the risk associated with using ER/LAs and appropriate prescribing behaviors.

The survey compared prescribers who had completed a REMS-compliant CE activity, and these were recruited directly from CE providers, with those who had not completed a REMS-compliant CE activity, and those were recruited from IMS health data. It was assumed if the respondent was identified through IMS data that they had not completed a CE activity.

The results were also compared to the results of the pre-REMS knowledge survey conducted before implementation of the REMS. And again, this was a cross-sectional survey with prescribers who

had not completed the REMS-compliant training, and it was used to compare general differences in knowledge from pre- to post-implementation. But they were not the same prescribers that were included in the follow-up survey.

So for this survey, over 11,000 prescribers were invited from IMS data, and no information was provided on how many prescribers were invited from the CE providers. In total, there were 993 respondents from both of these recruitment sources.

Prescribers were eligible if they prescribed an ER/LA at least once in the previous 12 months. Of those 993, 682 were eligible, and 311 were ineligible. Seventy did not complete the survey, while 612 did complete the survey, leaving 311 from IMS and 301 from the CE providers.

The main health profession was MDs or DOs. And the main specialty was general practice, internal medicine. The most commonly prescribed ER/LAs were oxycodone, fentanyl, and morphine. Most respondents were from the West, but there was representation from all regions. Over half of

respondents have prescribed ER/LAs 10 or fewer times in the past month, and 34 percent practiced medicine for more than 10 years.

The key risk messages in this survey followed the domains of the FDA blueprint. The survey also included questions on prescriber awareness of REMS material, prescribers' perceptions of patients' access to opioids, and self-reported prescriber behaviors.

So the target knowledge rate for this survey was 80 percent. Overall, responses met this target for both respondent groups, those recruited from CE providers and those recruited from IMS data. CE providers had slightly higher knowledge scores than those from IMS. The lowest scoring key risk message for both groups was product-specific information.

In terms of self-reported prescriber behaviors, the majority of respondents self-reported always or regularly counseling patients about important risk and using a patient prescriber agreement when first prescribing an

ER/LA. A little under half of respondents self-reported using the patient counseling document. A high percentage of those were recruited CE providers versus the IMS sample.

Overall awareness of REMS materials was low such as the medication guide, patient counseling document, DEA REMS letter, and the REMS website. In general, CE respondents had higher awareness of REMS materials than those from the IMS sample.

In terms of the impact of the REMS on patient access, while 38 percent thought the REMS added difficulty to patient access, 37 percent reported no impact. Other respondents reported that the REMS either made it easier for patient access or didn't know the impact of the REMS.

The main obstacles reported for patient access to opioids were insurance coverage, insurance authorizations and approvals, and the patients' ability to pay for the opioids.

Prescribers were also asked how their prescribing behaviors had changed since the implementation of the REMS. While almost half

reported no changes in prescribing, 23 percent reported limiting, which ER/LAs they prescribed. And 18 percent reported prescribing fewer ER/LAs. Other prescribed more ER/LAs, and 9 percent prescribed more immediate-release opioid medications.

CE respondents were more likely to report that they prescribed more non-opioid medications and more immediate-release opioids now versus IMS respondents.

Across all key risk messages, respondents who completed a CE activity were more likely to answer questions correctly. In addition, high volume prescribers were more likely to have higher knowledge rates.

Knowledge rates and appropriate prescribing behaviors recommended in the blueprint improved from the pre-REMS survey to the follow-up survey, but there was some concerns about the sample. While respondents recruited from IMS data were assumed to have not taken a REMS-compliant CE, over half of them self-reported that they did complete

one. In addition, limited data was provided about respondents recruited from the CE providers such as the number of invitations sent, so no response rate could be calculated.

In addition, we're not certain of prescribers' level of awareness of the REMS. Prescribers had a low awareness of the REMS materials, and in addition with all the different training efforts that are coming from various sources, we're not sure if prescribers know which trainings are considered REMS compliant. And actually, 12 percent of respondents that were confirmed CE completers self-reported that they did not complete a REMS-compliant CE activity.

Next, I will discuss the long-term prescriber evaluation survey. The purpose of this survey was to assess prescribers' knowledge, retention, and practice changes after completing a REMS-compliant CE activity. It included a subset of questions from the follow-up prescriber survey along with case-based scenarios used to determine if prescribers were able to apply knowledge learned

from the CE training.

A subset of CE providers sent 5,449 invitations to all prescribers who completed a CE activity. From those, 4,900 didn't respond, and there were 546 respondents. Sixty-one respondents declined to participate, and respondents were eligible if they completed a REMS-compliant CE activity in the past 6 to 12 months.

From those, 361 were eligible. They met this criteria, 124 were ineligible, and 33 did not complete the survey, leaving a total of 328 respondents that completed the survey.

The majority of respondents were MDs and DOs, and the most common specialty was pain management followed by others, which was a catch-all category of all remaining specialties that aren't listed there. The most commonly prescribed ER/LAs were the same as in the follow-up survey with oxycodone, morphine, and fentanyl.

Most respondents were from the West. Over half have prescribed ER/LAs 10 or fewer times in the past month, and 60 percent have practiced

medicine for more than 15 years.

The key risk messages for this survey were the same as the ones in the follow-up survey, but they also included case-based scenarios with questions across each domain. And the case-based scenario topics included starting treatment, a typical office visit, how to recognize potential diversion, handling early refill requests, patient counseling topics, what to do if changes in clinical presentation occur, and product-specific questions.

The target knowledge rate for this survey was 80 percent as well, and 4 out of the 6 key risk messages did not reach this target, including key risk message 1, assessing patients for treatment; key risk message 2, initiating, modifying, and discontinuing therapy; key risk message 5, general drug information; and key risk message 6, product-specific information.

Thirty-two percent of respondents self-reported that since they completed a REMS-compliant CE activity, that they did not

change their prescribing behaviors; 38 percent reported prescribing more non-opioid products, and 23 percent reported limiting which opioids they did prescribe. Respondents also reported prescribing more or fewer ER/LAs and prescribing more immediate-release opioids similar to the follow-up prescriber survey.

In addition, respondents reported that they more often checked their state's prescription monitoring program, completed a patient-prescriber agreement, and used the patient counseling document with patients since they participated in the training.

Respondents reported that the main barriers to applying information that they learned at the CE training to practice was not enough time, patient noncompliance, and patients finding new ways to obtain drugs that they did not learn about in the training.

So overall, knowledge rates did not reach the target of 80 percent for 4 out of the 6 key risk messages. Most low-scoring items were case-

based scenarios, questions. This suggests that although respondents may know the information, they were not able to apply it to a real patient scenario. And particularly for the product-specific questions, prescribers may not have prescribed those products, so they weren't aware of product-specific information for that particular ER/LA.

In addition, this survey had sample concerns as well. There was limited data provided from the CE providers, so we're unable to determine if some CE programs were over- or under-represented with survey respondents or if respondents from a certain type or specific type of CE program had higher knowledge scores. In addition, the proposed sample size was 600 respondents, and this target was not reached.

Finally, I will discuss the patient survey. Respondents were eligible if they were ages 18 or older and had received at least one ER/LA prescription in the past 12 months. All respondents were identified from a database that

was limited to commercially insured patients.

There were 11,500 respondents that were identified as eligible from that database. Of those, approximately 9,000 were not contacted, and 2,441 were contacted. From those, 1,746 refused, and 272 did not meet the screening criteria when asked screening questions. And that left 423 respondents who completed the survey.

Most respondents were Caucasian with over 56 percent reporting annual incomes of 50,000 or more. Over half were between the ages of 50 to 64. Seventy-five percent of respondents had some college or more. There was geographic representation from all regions. Most respondents were female, and 83 percent had used an ER/LA before the most recent prescription, and 16 percent were new users.

The patient survey included four domains. The first domain was related to patients' understanding of the risk. The additional domains include questions about patients' receipt of REMS materials, patients' access to and satisfaction

with access to opioids, and patients reported prescriber behaviors. The target knowledge rate for this survey was 80 percent as well, and knowledge rates exceeded this target across all key risk messages.

Patients reported a lower frequency of appropriate prescriber behaviors. For example, only a little half reported that their healthcare provider always or regularly cautioned them about the risk associated with ER/LAs, and 50 percent reported that they were cautioned about side effects. In addition, only 26 percent reported that their healthcare provider used the patient counseling document with them during discussions.

In terms of receipt of REMS materials, most patients reported receiving the medication guide with their last fill, but only 38 percent reported receiving the patient counseling document when they were first prescribed an ER/LA.

Patients were also asked about their perceptions of access to ER/LAs. Most respondents were satisfied with their ability to get an ER/LA

prescription if they felt they needed one and were satisfied with access to treatment with ER/LAs. However, almost half thought they needed to see their healthcare provider too often when they needed an ER/LA prescription.

Knowledge was high across all of the key risk messages. The two lowest scoring items were how to safely store opioids and the need to read the medication guide with each prescription. In addition, most respondents or patients reported being satisfied with their access to opioids and their ability to obtain an opioid if needed for pain. But as was mentioned before, all patients were prescribed an ER/LA in the past 12 months so therefore, already had access to ER/LAs.

Similar to the other surveys, there were sample concerns. The respondents were not representative of all ER/LA patients. All the survey respondents were commercially insured, and no patients on Medicaid or Medicare were included. In addition, most respondents were Caucasian with some college or higher, and over half had incomes

of 50,000 or more a year.

Finally, no patient caregivers were included as survey respondents when we would expect that there are caregivers that may be managing these medications for patients that need to be aware of these risks as well.

Next, Dr. Hsueh will present her statistical evaluation.

FDA Presentation - Caterhine Hsueh

DR. HSUEH: Good afternoon. I'm Ya-Hui Hsueh from the Office of Biostatistics. In the next few slides, I will address three main study design issues, which may impact the interpretation of the survey results. I will then present consideration for future survey design and additional analysis.

My colleague Ms. Harris has just summarized the different survey designs and the results for the two prescriber surveys and the patient survey. I'm going to discuss some overarching issues for this survey, namely, the comparability, validity, and the generalizability.

First, I will address the comparability issue in the follow-up prescriber survey. In the follow-up prescriber survey, about half of the prescribers were recruited from the CE providers, and the other half of the prescribers were recruited from the IMS data.

A pre-REMS prescriber survey was conducted to assess knowledge and the prescribing behaviors before the implementation of the REMS program. Note that this was three different samples of prescribers.

The RPC report presents two comparisons to assess the impact of REMS-compliant CE training on prescribers' knowledge. In the first comparison, knowledge rates were compared between the CE providers sampled and the IMS sample. In the second comparison, knowledge rates were compared between the pre-REMS survey sample and the follow-up survey sample.

So why is the comparability important? Comparability is important for assessing the impact of REMS intervention because if groups in a

pairwise comparison are not similar, the differences of knowledge rates between groups might be explained by the difference in characteristics rather than the REMS CE training intervention.

For example, those who self-selected or volunteered to take the optional REMS CE training may be different from the general ER/LA prescriber population. The next two slides will illustrate that in each of these two pairwise comparisons, the samples are indeed different.

This slide shows the prescriber characteristics for the first comparison of CE providers sample versus IMS sample. The RPC collected very limited prescriber characteristics. In almost all of them, we observed notable differences between the two samples in terms of health professional, primary medical specialty, region, prescription volume in the past months, and the practicing years after postgraduate education. Therefore, these two samples are not similar. Furthermore, the characteristics where they differed may impact knowledge.

Let's look at the characteristic of practicing years after postgraduate education for prescribers who had MD or DO degree. The CE providers sample in orange had higher proportion of physicians who practiced less than five years than the IMS sample in blue. Conversely, the IMS sample had a higher percentage of physician who practiced more than 15 years than the CE providers sample.

For the characteristic of health professional, we see that 61 percent of the CE providers sample had MD or DO degree compared to 47 percent of the IMS sample. Conversely, the IMS sample had more physician assistants than the CE providers sample. Therefore, differences in knowledge between the CE providers sample and the IMS sample could be due to the differences in these characteristics rather than the REMS CE intervention.

The story is similar for the second comparison of pre-REMS versus follow-up prescriber surveys. The RPC report fewer prescriber characteristics. In almost all of them, there were

notable differences between the two survey samples in terms of gender, primary medical specialty, region, prescription volume in the past months, and the practicing years after postgraduate education. Furthermore, the characteristics where they differed may impact knowledge.

For example, for the characteristics of primary medical specialty, the pre-REMS survey, which is in orange, had more general practitioners, internal medicine than the follow-up survey in blue, while the follow-up survey had more pain management specialists than the pre-REMS survey.

Another example is the characteristics of practicing years after postgraduate education for prescribers who had MD or DO degrees. Pre-REMS survey sample had higher proportion of a physician who practiced more than 15 years than the follow-up survey sample. Therefore, these sample differences could explain the differences in knowledge that might not be attributable to the REMS CE intervention.

The second issue is the validity. Behavior

was self-reported in the survey and were not independently validated. Therefore, these self-reported behaviors may not accurately reflect what happens in practice.

Examples of self-reported behaviors that could be independently validated are number of prescriptions in the past months or whether urine drug screen test were performed more often, less often, or about the same since REMS CE training. I will come back to this point and present more details about the use of other data sources for validity in the end of my talk.

The third issue is generalizability. More specifically, are knowledge rates observed in the sample generalizable to the population of prescribers or patients? There are multiple issues threatening generalizability. I already presented the comparability issue in the follow-up prescriber survey.

Other threats to generalizability are use of convenience, non-random sample and high non-response rate. As my colleague Ms. Harris

presented earlier, the survey samples were convenience samples, not probability samples, so survey participants may not represent the prescribers or patients as a whole. In addition, non-response rate was high or unclear for each survey.

Keep in mind that probability sampling is the gold standard for surveys because they can ensure the sample is representative of the population for measurable and unmeasurable characteristics.

In the next four slides, we evaluate whether convenience sampling and the non-response impact the characteristics of the sample compared to their target population. We start with comparison of the CE providers sample in the follow-up survey with all ER/LA prescribers CE completers.

Next, we will compare the IMS sample in the follow-up survey to all ER/LA prescribers. Then we compare the long-term evaluation survey sample to all ER/LA prescriber CE completers. Lastly, we compare the patient survey sample to drug use data.

The first evaluation of generalizability is whether the CE providers sample of the follow-up survey is similar to the general population of ER/LA prescriber CE completers. For all ER/LA prescriber CE completers, the RPC reported only two characteristics, which were health profession and a primary medical specialty. Both of them had notable differences between the CE providers sample and all ER/LA prescriber CE completers. Therefore, the survey sample is different from the target population.

More specifically, the first box plot shows that all ER/LA prescriber CE completers, in purple, had a higher percentage of MD or DO than the CE providers, in green, while the CE providers sample had a higher percentage of physician assistant than all ER/LA prescriber CE completers.

The second box plot shows that all ER/LA prescriber CE completers had a higher percentage of general practitioners or internal medicine than the CE providers sample, while the CE providers sample had more pain specialists and non-pain specialists

than all ER/LA prescriber CE completers.

Next, is the evaluation of whether the IMS sample of the follow-up survey is similar to the general population of ER/LA prescribers. The RPC report fewer prescriber characteristics. In all of them, there were notable differences between the IMS sample and all ER/LA prescribers in terms of prescription volume in the past months, primary medical specialty, health profession, and the region. Therefore, the survey sample is different from the target population.

For example, the first box plot shows that for prescription volume ranging from zero to 5 prescriptions, all ER/LA prescribers in purple had a higher percentage than the IMS sample in green. For prescription volume ranging from 6 to 50 prescriptions, it is the opposite. The IMS sample had a higher percentage.

Another example in the second box plot shows that the IMS sample had a higher percentage of pain management specialists than all ER/LA prescribers.

In this slide, I present an evaluation of

whether the long-term evaluation survey sample is similar to the general population of ER/LA prescriber CE completers. Only two characteristics were reported for all ER/LA prescriber CE completers. They were health profession and primary medical specialty.

Both of them had notable differences between the long-term evaluation survey sample and all ER/LA prescriber CE completers. Therefore, the survey sample is different from the target population.

More specifically, all ER/LA prescriber CE completers in purple had a higher percentage of general family practice or internal medicine than the LTE survey, in green, while the LTE survey had a higher percentage of pain specialists than all ER/LA prescriber CE completers.

Finally, this slide evaluates the generalizability of the patient survey sample. There were notable differences between the patient survey sample and the drug use data in terms of age, prescription payment type, and the prescribe

specialty. Therefore, the survey sample is not representative of the target population. Please note that the unit of analysis of drug use data is the prescription volume.

By design, all patients surveyed participants had a commercial insurance, as shown in green, while near half of the drug users in purple had government-sponsored insurance and other prescription payment type.

We also suspect that the sample is not representative of general population for race, income, and the education level. In the patient survey, 94 percent of the patient survey sample were Caucasian. Over half of them had a total household annual income of at least $50,000, and 75 percent of them had at least some college education.

Finally, I present some considerations for future survey design. Here, we propose some considerations for future survey design to assess impact of REMS-compliant CE training on the prescribers' knowledge.

This diagram illustrates a self-controlled design. In this design, each person serves as his or her own control. Their knowledge will be tested twice, once before CE training and once after CE training. One can then compare the results to assess the impact of CE training.

Another design to consider is the randomized experiment. One can randomize a sample of prescribers to either receive or do not receive a CE training. And one can compare the knowledge between these two groups. In both self-control design and this randomized design, using a probability sample will further ensure the that results are generalizable to the population of interest.

To validate the self-reported behavior, one can explore using a longitudinal database such as electronic medical records or claims data, link it to the CE training information. This database would have prescribers' behavior in the periods before and after the REMS CE training.

To generalize results from survey sample to

nationally representative target population, surveys on probability random samples should be used. Probability random samples are the gold standard for generalizing survey results because they are representative of the target population not only on the measurable characteristics but also on the unmeasurable characteristics.

In summary, the survey results may have limitations of comparability, validity and the generalizability. Prior FDA recommendations to address these issues were the following: survey design and the results should account for differences in baseline characteristics; when appropriate, survey results could be standardized to be more representative to the target population; additional data source could be recruited for patient survey such as Medicare and Medicaid.

Although this analysis can add to understanding of the results, they do not account for major differences among the survey populations, which good design approaches could address. Therefore, we propose the following considerations

for future survey designs: probability random samples, self-control, randomized experiment, and linkage to longitudinal database of behavior.

Now, Ms. Harris will give an overall conclusion for survey.

MS. HARRIS: In conclusion, generally we saw high knowledge rates for most of the six areas of the FDA blueprint for both prescribers and patients, and taking a CE activity seems to be associated with higher knowledge rates.

Lower scoring items were most often in the domain of product-specific information or were case-based scenario questions. FDA has provided the RPC with recommendations to revise some questions that may be unclear and to re-categorize some questions in different domains of the blueprint, recognizing that there is overlap between some of the different areas that the questions could fall.

Most prescribers self-reported that they always or regularly conduct appropriate behaviors as recommended in the REMS training such as

counseling on risk, but patients reported a lower frequency of these same behaviors being conducted by their healthcare providers.

In addition, while some prescribers reported changes in prescribing behaviors since the implementation of the REMS, we don't have any additional information on if these changes were due to the REMS training. We have recommended the addition of follow-up questions to assess why prescribing behaviors may have changed.

Lastly, because the surveys have limitations, we're not sure if high knowledge rates can be attributed to the REMS. The surveys take a cross-sectional look at different prescribers and patients at different time periods instead of following the same prescribers and patients over time.

We have concerns about how representative the survey respondents are of the general population of ER/LA patients prescribers and CE completers, and we have asked the RPC to provide additional comparison data for us to look into this

further.

The patient survey in particular may overestimate the effects of the REMS materials since respondents were not representative.

For the next survey, we recommended the inclusion of patients on Medicare and the Medicaid, and the RPC has already proposed the use of additional recruitment sources for these patients. We also recommended the inclusion of patient caregivers, and we heard a little earlier that this was something that was being considered for the next survey.

Finally, alternative survey designs should be considered, including the designs that were presented today, to better determine if increases in knowledge can be attributed to the REMS.

Thank you-all for your time today.

FDA Presentation - Jana McAninch

DR. McANINCH: Good afternoon. I'm Jana McAninch. I'm from the Division of Epidemiology, and I will be discussing the epidemiologic outcome studies and drug utilization surveillance studies

that were submitted as part of the 36-month REMS assessment.

The RPC submitted more than 5,000 pages of surveillance study results as part of this assessment reflecting an enormous amount of work and coordination. Some of these findings were presented earlier today.

In this presentation, I will focus on some key points in FDA's interpretation of the epidemiologic outcome studies and drug utilization data with regard to what they can and cannot tell us about changes in opioid-related safety outcomes and prescribing patterns and how these findings relate to evaluating the effectiveness of the REMS. I will then offer the committee some considerations for future assessment of this REMS.

The first observation I would like to make is that several studies indeed did suggest reductions in adverse outcomes related to ER/LA opioids. However, most of the observed decrease occurred prior to the launch of the REMS and in particular, to the launch of the continuing

education offerings.

This pattern was clearest in the RADARS poison center and treatment center studies. The left panel shows trends in intentional abuse exposure call rates, but a similar pattern was seen for other types of calls as well, including misuse, abuse in adolescents, pediatric unintentional exposures, and exposures resulting in a major medical outcome or death.

This pattern was perhaps even more clear in the RADARS treatment center study shown on the right. This study suggested sharp downward trends during the pre-REMS period in self-reported ER/LA opioid abuse among individuals entering treatment for opioid addiction. These early decreases accounted for most of the overall reduction seen when comparing abuse rates in the pre-REMS to the active REMS periods.

The second observation is that in most analyses, decreases seen across the REMS periods were not limited to ER/LA opioids, although in some analyses, decreases were larger for ER/LA opioids

than for comparator drug classes.

For example, the figure on the top shows the relative percent change in population-adjusted rates for intentional abuse-related exposure calls to U.S. poison centers, comparing the pre- to active REMS periods for ER/LA opioids and for the comparator drugs, IR opioids and prescription stimulants.

The figure on the bottom shows changes in rates of overdose death in Washington state involving opioids with an available ER/LA formulation compared to the changes in rates of death involving IR hydrocodone and benzodiazepines.

Comparator drug classes are potentially useful to assess to what degree observed changes were specific to drugs that were the subject of an intervention, in this case, the REMS, but I'll talk a little later about why these comparisons may be of limited use in this case.

Another observation was that studies examining similar outcomes sometimes had differing results. As shown in the two previous slides,

several measures of opioid misuse and abuse were seen to decrease across the study periods, and this was true for both adolescent and adult populations.

However, the RADARS survey of college students indicated increases in non-medical use of both ER/LA and IR opioids as shown here. It's unclear whether these discordant results were due to true differences in these behaviors in the underlying populations or were more the result of differences in study methodologies.

All of the surveillance studies have limitations related to data sources and methods. One overarching limitation is that in many of the studies, we don't know how comparable the study samples were to each other over time. This was particularly true for this study sampling individuals entering or being assessed for substance abuse treatment.

The RADARS treatment center study and the NAVIPRO ASIMV and CHAT studies use convenient samples that change over time as sites drop in and out of the surveillance networks. These changes

can result in shifts in geographic distribution as well as client mix, and then overlaid upon these shifts are potential changes in program capacity and treatment access relative to need; for example, due to changes in reimbursement policies or availability of office-based treatment for opioid use disorders.

With regard to the poison center data, there is some evidence, as Dr. Dart pointed out this morning, suggesting that poison center call data may correlate with trends in emergency department visits for opioid misuse and abuse. However, there have also been decreases in overall poison call center use as well as changes in patterns of use since 2010, potentially affecting the fraction of actual cases that are captured in this data system over time.

In both examples, these factors can result in selection bias over time where trends seen in the study sample may not reflect what is actually happening in the underlying population.

The studies also had limitations related to

data quality, particularly in the definition, ascertainment, and validation of study outcomes. This was true for the HIRD and Medicaid studies, which relied on coded administrative claims that have not yet been adequately validated and that failed to capture most fatal overdoses. If the claims codes used in a study do not accurately measure the outcomes of interest, the study may be unable to detect true associations or changes over time.

The Washington State Medical Examiner study was limited by the fact that for many opioid-related deaths, the investigators could not determine whether an extended- or immediate-release formulation caused the death. For example, this would be the case for deaths where the medical examiner documented simply oxycodone or morphine as an implicated drug.

Finally, a concern in the RADARS treatment center and NAVIPRO ASIMV and CHAT studies is that the introduction of new products and efforts to improve data quality have necessitated revisions to

the survey instruments over the study period. Unfortunately, these revisions can include changes in question order and wording that can potentially lead to bias when examining changes in abuse rates over time.

Finally, most of the studies had relatively limited generalizability, meaning that the findings even if valid with their own study population, may tell us little about the wider population. Just one example of this was the study of Washington state overdose deaths.

We know that efforts to combat opioid overdose vary across states, and Washington state has been one of the leaders in overdose mitigation efforts. In 2007 and 2010, the state issued opioid prescribing guidelines followed by legislation restricting high-dose opioid prescribing, which became fully effective in early 2012. It's very possible that these state-specific factors played a role in the decreases in opioid overdose death rates that were seen in this study.

Next, I'll briefly discuss some of the drug

utilization analyses. As shown in this FDA-generated analysis, from 2010 to 2015, the estimated number of dispensed prescriptions for ER/LA opioids declined from 22.4 million to 21.1 million.

During the same time period, the estimated number of dispensed prescriptions for IR opioids also decreased from approximately 178 million to 150 million when oxycodone-acetaminophen prescriptions are added to the IR opioid category used in the submitted RPC analysis, which is shown in red in this figure.

Although these decreases may seem modest, they should be interpreted within the context of more than a decade of continuous increases in opioid prescription volume.

Also notable is that changes in prescription volume varied considerably across individual ER/LA opioids. For example, prescriptions dispensed for morphine ER increased by approximately 20 percent while oxycodone ER decreased by 39 percent, and methadone decreased by 28 percent from 2010 to

2015.

The 36-month assessment included analyses to try to understand how prescribing behavior and patient access might have changed following implementation of the REMS. There were a number of limitations in these analyses that made them difficult to interpret.

Perhaps most importantly is that prescription dispensing data do not provide information on clinical context, and therefore, tell us little about the appropriateness of prescribing or about access to these medications for patients who may truly be benefiting from them.

This table describes changes in the proportion of ER/LA opioid products and doses indicated only for opioid-tolerant patients that were prescribed to patients who did not meet criteria for opioid tolerance based on longitudinal prescription dispensing data. These proportions decreased slightly across the study periods but remained quite high during the active REMS period.

It is unknown, however, how completely

patients' medication history was captured as it was possible for them to have received additional opioids in settings of care or pharmacies not captured in the database. This is just one example of the challenges in interpreting the prescribing behavior analyses.

In summary, what do these surveillance studies tell us about changes in prescribing and safety outcomes since 2010? First, it does appear that, overall, both ER/LA and IR opioid prescription volume have begun to decline after more than a decade of increases.

This is encouraging in that fewer opioids being prescribed may mean fewer opioids available for potential misuse, abuse and overdose. However, because of the lack of clinical context, the utilization data tell us very little about whether prescribing is appropriate or whether patients who are benefiting from opioids are able to access them.

The epidemiologic studies suggest decreases in some but not other safety outcomes, although the

observed decreases generally began before the REMS was launched and were not limited to ER/LA opioids. In addition, the studies all had methodological issues that limit our ability to draw definitive conclusions from their findings.

Finally, we need to think about what the decreases in some of these outcomes mean in light of the recent CDC data mentioned earlier today showing continued increases in prescription opioid overdose death rates nationally.

So is the REMS making progress toward its goal of reducing adverse outcomes associated with inappropriate prescribing, misuse, and abuse, including the outcomes of addiction, unintentional overdose and death?

Well, as you've heard today from other speakers as well, this is a very difficult question to answer. Evaluating the effects of an intervention using observational data is inherently challenging, and there are several notable factors that contribute to this challenge here.

First, we must consider the reach of this

intervention. As you've heard, the absolute number of healthcare professionals who have participated in a REMS-compliant continuing education activity is quite large. However, a relatively small proportion of ER/LA opioids prescribers have completed a REMS training to date.

Therefore, simply examining overall changes in prescribing or adverse outcomes at the population level across time periods, as was done in all of these studies, would be expected to underestimate any actual effect on these outcomes among prescribers who completed a REMS training.

We also don't know whether the REMS is reaching the prescribers who most need additional education or what proportion of prescribers and other healthcare professionals would need to be trained to broadly impact practice and population outcomes or how long it might take to see these changes. Together these factors raise the question of whether it is reasonable to expect to see measurable changes in these population outcomes yet as a result of the REMS.

Second, even desirable changes in prescriber and patient behaviors could have mixed effects on the population outcome measures used in these studies. For example, safer opioid storage and disposal could result in fewer tablets available for abuse leading to decreased reported abuse of these drugs among people entering treatment. However, improving provider skills in recognizing abuse or addiction in their patients could theoretically result in more referrals to treatment, leading to increases in rates of reported recent prescription opioid abuse in these populations.

Safer opioid dosing and use might be expected to result in decreased emergency department visit and poison center call rates for opioid overdose. However, earlier recognition of overdose symptoms could also lead to more people accessing care in these situations.

These are just a few examples of the complexity of the path from the REMS intervention to measurable population outcomes.

Finally, and perhaps most importantly, again, as you have heard from other speakers today, it's exceedingly difficult to isolate the impact of the REMS from the many other interventions and secular trends occurring since 2010, some of which Dr. Compton and others have discussed already.

It is theoretically useful to examine comparator drug classes to look for changes that were specific to ER/LA opioids. However, many of the key messages in the REMS trainings apply to these drugs as well, limiting their usefulness as director comparators.

In conclusion, some of the surveillance study findings are encouraging. However, trying to draw conclusions about the impact of an intervention from observational data is difficult, perhaps even more so given that the path from prescriber training to the various population outcomes of interest is not straightforward and also recognizing that the REMS is just one piece of a large, multifaceted response to the complex opioid crisis. Therefore, the surveillance data

are not able to tell us what impact this REMS might be having or whether it's making progress toward its goal.

Before I close, I would like to offer for the committees' consideration a few thoughts on future direction for the surveillance component of this REMS assessment. We feel that further scientific discussion is needed to determine the best way to move forward with evaluation of this REMS within a landscape of concurrent efforts, secular trends, and imperfect data.

First, while there is no ideal data source, we believe that there are other data that might be useful to monitor overall trends in opioid-related safety outcomes and provide contextual data to inform REMS-related regulatory decisions.

For example, nationally representative surveys such as the National Survey on Drug Use and Health and Monitoring the Future use well-established sampling methodologies and validated survey instruments to assess the prevalence of non-medical use of opioids and opioid use disorder in

the United States. In addition, CDC's National Vital Statistics system compiles coded death certificate data from the entire United States.

These data sources, of course, come with their own limitations. For example, they currently have limited information on specific drug products and formulations, as well as relatively long lag times for data to become available. However, these disadvantages may be offset by the ability to more reliably assess trends over time and the greater generalizability of the data to the U.S. population.

As new data sources and methodologies develop, they will need to be evaluated as to their potential value in informing opioid- and REMS-related regulatory decisions.

Finally, the studies in this assessment make comparisons across time periods. However, to directly evaluate the effect of the REMS on prescribing or patient outcomes, one could consider a different design that compares changes in selected outcome measures for prescribers who have

completed REMS training to prescribers who have not.

Such a study would require innovative methods. First, prescriber level data linkages between training completion, prescribing and patient outcomes are not readily available and would likely require prospective data collection. Outcomes of interest would need to be selected, operationalized, and validated; and it would need to be determined whether confounding factors could be adequately addressed using an observational design or whether only randomization would be likely to yield valid results.

So we recommend further discussion to explore whether such a study would be feasible and also whether it would be likely to provide valuable information to guide future decisions related to this REMS. Thank you.

FDA Presentation - Igor Cerny

DR. CERNY: Panel members, I just want to thank you. It's approaching 2:30, and you've been saturated with data. So I'm going to try to

provide some high-level FDA overall conclusions regarding the assessment report data, as well as present some considerations going forward as we move towards the discussion and the eventual questions we'll be asking the panel.

You've seen this goal. I'm not going to go over it again, reducing serious adverse outcomes, maintaining access. You've seen this before about the training numbers and how we have not achieved the target for the prescribers, but there's been a lot of participants and a fair number of completers.

So overall, what we see is a large number of health professionals have participated in or completed the training, but the targets for the prescriber training have not been met. And some factors that likely limit the uptake of this training include that fact that it's voluntary in nature; the length of the training, 2 to 3 hours, may explain why some people start a training and don't manage to finish the training.

There's no test-out option. And as we've

discussed, there may be sub-optimal REMS awareness, and this may be confounded by the fact there's numerous competing trainings, so it may be difficult for a prescriber to tell the difference between a REMS-compliant training and one that is offered by another body or entity.

The definition of a prescriber misses new prescribers, and we had discussed, misses institutional prescribers. And the health professional non-prescriber completers shouldn't be dismissed because they may very well be individuals involved in communicating important safe-use information to patients.

So some considerations for REMS-compliant training to think about is how much do we allow for a voluntary educational intervention to impact prescriber behavior, and how many prescribers will we need to have trained, and how much of a change in clinical practice would be needed for us to see measurable effects on outcomes?

The training goals and targets that we've discussed, are these reasonable for a voluntary

educational program? How can we encourage not only more training uptake but the completion of training? Do individuals who take a voluntary training, who choose to do so, differ from individuals who choose not to take such a training? Is it time to consider some form of a mandatory training?

Should training be tailored to specific prescriber types? For example, a pain specialist may need a different training than a primary care provider, and high-volume prescribers may need a different training than low-volume prescribers.

Regarding the surveys, we note that overall knowledge rates for most of the six areas of the FDA blueprint were high for prescribers and patients. For the follow-up prescriber survey, CE completers more frequently answered questions correctly. Regarding long-term evaluation for prescribers, CE completers were more often reported appropriate prescribing behaviors such as risk counseling or screening patients for misuse and abuse.

Patients had a very good understanding of the ER/LA opioids risks, but as we've discussed, survey respondents are not optimally representative of the general population of either ER/LA prescribers or patients.

There's potential issues with comparability amongst the study groups, and also these are convenience samples. They're self-selected. There's a high non-response rate. There's some issues with generalizability of these data.

Regarding the surveillance data, much of the provider surveillance data indicate decreases in some of the adverse events of interest. However, these data also indicate decreases began to occur or had occurred before full REMS implementation.

Decreases have occurred in agents not subject to a REMS, for example, immediate-release opioids, benzodiazepines. And as we've heard, numerous federal, state, local, health-system-related efforts to try address opioid issues just help to confound the issue. And the surveillance sources have significant limitations. For example,

the convenience sampling, questions of generalizability there as well.

So overall, it's very challenging to assess if and to what extent the REMS has contributed to the overall decreases.

You've seen this slide before. This just sets the tone for the utilization data. On the Y-axis is the number of prescriptions in the millions, and on the bottom is the years going from '91 to 2013.

Now, you've seen this great escalation in all opioids, and you know that 90 percent of these are the IR opioids. Then, around 2011, you start to see a slight bend in this curve.

You've seen this data as well presented by Dr. McAninch just a few moments ago, where you see a decrease in the ER/LA prescriptions written over time from 2010 to 2015, and you see the same decreases for the IR opioid data, whether it's the adjusted numbers in green that FDA ran that included the oxycodone-acetaminophen combinations or the RPC-selected opioids. But for all three

lines, the bend in the curve began prior to REMS approval and certainly prior to the first REMS-compliant CE.

So overall conclusions, there have been fewer prescriptions dispensed for ER/LA opioids, but you've also had fewer prescriptions dispensed for the immediate-release opioids and other comparators. This modest decrease should be viewed in light of the escalation in opioid prescribing over the past 20 or 25 years.

The ER/LA decreases appear to have started prior to full REMS implementation and driven mostly by decreases in oxycodone, somewhat with methadone. Decreases were also noted in ER/LA prescriptions written by most of the medical specialties in the pre-REMS through the post-REMS period. But also, many of these decreases began prior to full REMS implementation.

The ER/LA to IR opioid switch data and ER/LA prescription data are difficult to determine without knowing the why. One can switch from an ER/LA to IR opioid. The concern with that is that

someone will take the training and be turned off from prescribing a ER/LA agent, but indeed, a patient's medical situation may change. You may see insurance coverage changes that may explain the change for an ER/LA to IR opioid.

Similarly, with early prescription fill data, that was considered a potential signal of abuse, but also it could also indicate a patient's pain condition is worsening.

So without knowing the why, it's difficult to assess these data. Prescription of opioids intended for use only in opioid-tolerant patients continues to many opioid non-tolerant patients.

Regarding the patient access data, the RPC has provided utilization data as well as responses to patient and prescriber survey questions. But utilization data don't directly inform this issue. Responses to survey questions regarding access are somewhat reassuring, but as we talked about, questions remain about the appropriateness of the survey populations and their generalizability.

So overall, we can't tell whether the REMS

has impacted patient access to ER/LAs based on these data. And in general, when you're looking at utilization data and survey data, you're interviewing or you're looking at patients who have received the ER/LA. So those who could not get a ER/LA are not assessed in any way, so that's a limitation of these data.

So overall, summary of relevant findings, survey results generally lean towards the good, good overall knowledge and behaviors. Prescribers who often took the REMS-compliant training often did better, and the surveillance data do indicate decreases in some adverse event.

However, it is challenging to determine whether the REMS is meeting its goals due to several reasons: Has there been sufficient time allowed for the educational intervention to have had an impact? Do we have adequate data to inform burden in access? Limitations in surveillance, utilization, and patient access data as have been discussed; the changes in the surveillance and utilization data findings that predate the REMS and

are seen in drug classes not subject to a REMS; and also, unknown reasons for decreases in surveillance outcomes and utilization metrics.

We've often talked about is this is all due to more judicious prescribing? Have people been scared off? We don't really know why we're seeing these decreases. As has been discussed, difficulties in differentiating between the effects of the REMS among the absolute multitude of related efforts.

So as we consider next steps, when FDA assesses any REMS, it looks to see whether or not the goals have been met but also looks to see has this REMS assured safe use, is it unduly burdensome, and does it restrict patient access.

As we consider the responses to those questions and look at the assessment data, we have a range of options that go from being less restrictive to more restrictive. Certainly, less restrictive would be just to eliminate the REMS, or we could keep the REMS as is, or certainly, we could modify the REMS scope and elements.

This would encompass a number of potential options. We could revise the patient materials, the MedGuide, the patient counseling document. We could expand the blueprint, and this would include information on the management of pain as well as the recognition and management of overdose and addiction.

We could institute a closed, restricted program. You've heard a little bit about that and will hear more about that. And that would include mandatory training and some sort of a system where prescribers, pharmacists, and patients enroll or are certified in the program. It also could include the immediate-release opioids, and certainly we're open to suggested modifications from the panel.

Regarding the REMS assessment elements, we could look at different data sources to assess surveillance and utilization, or we could look outside entirely and look at alternative methodologies, studies of outcomes and behaviors and those trained versus non-trained. As has been

discussed, this would often be very challenging studies to do, a number of confounders. We could modify the survey design and analyses and other suggested approaches by the panel.

That concludes my presentation. I'd like to thank you for your time and attention.

DR. WINTERSTEIN: Thank you.

We can now move on with more questions, but before that, I believe Dr. Coplan had some data to share with us in respect to those questions prior to the break.

DR. COPLAN: Yes, thank you.

There were a number of questions before the break about the Pri-Med study, and we wanted to come back to those.

We wanted to reiterate that I think when we read FDA's briefing document about the studies and the limitations that Dr. Cerny and others pointed out, we realized that this Pri-Med study would provide relevant information as to a new study design, given that ideally what we're looking for to reiterate is that we'd be able to look at who's

taken the training, what the prescribing changes were in the people who'd taken the training or not taken the training and then what their patient outcomes were.

That's difficult to do currently because the standards for commercial support prohibit the CE providers to share the list of the people who've taken the training with us

Then we have the HealthCore and Medicaid data that looks at prescriber changes, and then we have patient changes. We have prescription changes in IMS, and then patient changes in the claims data. So we're not able to triangulate those data.

The Pri-Med data provides an opportunity to do that. So we apologize to FDA about that you didn't have time to review it prior. We did send an email to FDA just to report that we would be presenting this. We will submit a full study report once we've analyzed the data and carefully reviewed it.

But Dr. Argoff would like to provide some more details on some of the design questions that

were asked before the break.

DR. ARGOFF: Thank you for this opportunity to follow up.

So there are several questions, and in the next couple slides, I want to summarize to the best of my ability, answers to those questions. But please, understand that we don't have all the answers at this time, as Paul just mentioned.

First, Amazing Charts is a national electronic health records vendor. It's owned by Pri-Med. There is 7200 healthcare providers who are participating nationwide who are physicians, 11.5 million patient charts and the user license agreement for Amazing Charts allows the analysis of de-identified patient data.

This gives you a representation on the bottom right, this 2015 population of the states so you get an idea of the population of the states to give you an idea. And the shaded areas are the number of Amazing -- or the presence in the different states throughout the country essentially where Amazing Charts users exist.

So just to summarize more about the Pri-Med study details, only providers who prescribed opioids were included. So that's an important point. The trained cohort were 441 providers who had received REMS-compliant CE training. The control cohort were 4669 providers who were not trained, and the cohorts matched on specialty. Eighty-five percent of both cohorts were primary care physicians and 15 percent specialists.

The last slide I'd like to present is just details regarding what we plan to do in terms of future analyses. So we have future analyses for publication, including the comparison of patient and provider characteristics, statistical significance.

That was a question that was asked. Adjustment for covariates with propensity score matching, and then the death outcomes, as mentioned, were not captured in the database. But perhaps in the future, they can be linked to the National Death Index. And I'll turn to the podium back to Paul.

DR. COPLAN: Yes. Thank you.

So could we have the slide A-5. So some of the metrics that could be obtained in such electronic health record study would be to compare trained and untrained prescribers, and that comparison could either do propensity score matching to ensure that prescriber characteristics were comparable or potentially through randomization.

What we could look at is changing prescribing volume, high prescriber versus low prescriber outcomes; look at partial training versus completer training versus no training, whether we see differences in that; durability of REMS-compliant CE in terms of whether the outcomes are maintained over what period of time; repeat CE effect on prescribing and outcomes; and change in average number of prescriptions per patient and change in the average ER/LA opioid dose per patient and change in average outcomes per patient.

So I think this reflects some of the learnings that we've learned from this last three

to four years of implementing this.

The other thing, too, I should mention is that the abuse and dependence diagnoses, the 304 and 305 ICD-9 codes, are not validated, as was pointed out.

We do have a study, study 3-B I think we call it, that's being done by Michael von Korff and his colleagues at Group Health Cooperative in collaboration with Upton and Vanderbilt and Kaiser Permanente to develop a diagnostic algorithm for abuse and addiction using diagnostic coded terms and then to validate it in a study as well as opioid overdose.

So we could apply those definitions to the electronic health record environment so that we would have outcomes that would have better positive predictive value and better sensitivity to pick up the outcomes.

So this, I think, reflects some of the recommendations that we have going forward in terms of enhancing communications so there's better awareness amongst prescribers about the REMS,

expanding the REMS to extended healthcare team, revising the blueprint to make it more flexible to include some of the newer learnings about safe opioid prescribing.

If training is required, tie to DEA registration. And harmonize the federal courses so we don't have these conflicts in terms of prescribers doing different courses and then not counting for one versus the other. Thank you.

Clarifying Questions

DR. WINTERSTEIN: Thank you.

Moving back to the questions that have been going around since before the break, we had Dr. Raghunathan. Do you still have a question or not right now?

DR. RAGHUNATHAN: Not now.

DR. WINTERSTEIN: Dr. O'Brien.

MR. O'BRIEN: It's Mr. O'Brien, but a lot of my questions were addressed with the FDA. But to that extent, I do have questions for the FDA, if I could, for Dr. Hsueh with slide 28, I believe it is.

I just want to thank you because the difficulty I had -- and I was going to ask Dr. Cepeda with some of her slides, 62, 63, 64 in that area there -- was the comparability. I was struck in the briefing notes to find that the population of the patient survey was, in fact, highly female, Caucasian, between 35 and 60, I believe, was in the briefing data. And I could not find any direct correlation to the adverse outcomes.

So my question to Dr. Hsueh first of all was: You had mentioned that the difficulty was comparability to the target population, and just if you could elaborate. What did you mean? Who was your target population that you're looking for?

DR. HSUEH: The target population for the patient survey should be the all ER/LA patients.

MR. O'BRIEN: All ER/LA patients. So we're not trying to get -- is there any data that can reflect -- and anybody can answer this, I suppose. As I said, I could not find to say, okay, if we go from those ER/LA patients that are prescribed based

on a date and 99 percent of them do not have adverse outcomes, do we have any matching, sex, age matching, to the population for adverse outcomes?

DR. HSUEH: For the comparability here, actually, I just want to point out that since the patient survey -- like the majority of them were Caucasian, and then they are high educated, and only 5 percent of them greater than 65 years old, so they are not representative to the general population.

I mean, in general, you would have patients older than 65 years old, they are taking the ER/LA.

MR. O'BRIEN: Well, to that question, I guess I'll go to the next slide, 20, yes. And this slide here, when we start getting into the knowledge and the high level of knowledge, this slide and the next slide and the questions that were asked that were shown the detail in Dr. Cepeda's as well, there -- particularly, I come out of the device field in spine deformity, and while there's knowledge, there's the difference, the gap between knowledge and doing.

Do the questions address at all that gap in terms of compliance? So do we have compliance? As an opioid user, I knew full well that I should not drink alcohol, but at times when it wasn't reaching my level of pain, then I would have a glass of Crown Royal to go with it. So I would answer the question yes, I knew it, but the question is did I do it?

Was there anything within any of your data retrieval to find whether or not while we had a high knowledge, did they, in fact, do it?

MS. HARRIS: For these questions, most of the questions were about knowledge. Were they aware that there was interaction with alcohol? And there were questions related to patients' perspectives of appropriate prescriber behavior, so did their prescribers do the things that they said they were going to do.

But in this survey, there weren't that many questions that followed up with them to say did you actually drink alcohol even though you knew you weren't supposed to or did you dispose of the ER/LA

properly even if you knew that about it, the correct way to do it.

MR. O'BRIEN: Well, as an elderly patient, did I give it to my son because he needed it for whatever? So we don't really know that transition of medication that's there. So that's it.

Just the other question, which I think was addressed by several already, that the other limitations, that it is self-reported, that we're asking people that got the drug particularly with access. There doesn't appear to be any attempt to see for those that didn't get it.

So it's one thing to see the number of prescriptions go down and decrease and to ask the questions about knowledge, but I didn't see any data that said, well, what's the quality of life for other people and who are the ones that aren't getting it that we're not asking for, and what's happening with their lifestyle as they're going forward.

We see a spike in heroin. Are they going to heroin? Are we getting a transition that in the

end, we're really not accomplishing -- we think we're accomplishing something, but we're not really accomplishing.

MS. HARRIS: And we're interested in that information, too, trying to reach -- especially with the patients, trying to reach patients on Medicaid or Medicare to get a different aspect. Then we're interested in the thoughts of the panel about different studies to learn more about patient access, especially for patients who don't currently have access to drugs.

MR. O'BRIEN: Thank you.

DR. WINTERSTEIN: Dr. Perrone.

DR. PERRONE: Thank you.

Jeanmarie Perrone. This question is for Dr. Dart. Thank you for all your surveillance. This is slide CO-105 from earlier. I didn't get to ask this.

The ER/LA abuse that has been reported that was declining in this period, I know that concurrently -- and you've published some material about the concurrent emergence of abuse-deterrent

formulations during that period. And we've mentioned them in the background of a lot of the secular trends that were going on.

What do you think and maybe what is the answer in terms of penetrance of the market of ER/LAs are now represented by abuse-deterrent formulations?

DR. DART: Great question. Certainly, the abuse-deterrent formulations have become popular, and I think we may have an analysis without the abuse-deterrent formulations that I can show you.

Generally speaking, what it does is it weakens the association, but the trends are in the same direction. But you lose power because you've lost a fair amount of drug from the ER/LA group because if you take the ADFs out, then they're not as many ER/LA products left, of course.

So this slide, a little hard to see, but the first line there says, "Treatment center abuse and population denominator." And the ER/LA is actually the second confidence interval. The IR is the first, which shows the same frankly, that is, the

association -- the direction of the change remains the same, but the power is reduced, and they're marginally or not statistically significant after that.

So I was encouraged because I was concerned that the removing the abuse-deterrent formulations would actually completely reverse the effect, which it did not. Now, that doesn't say it is the ER/LA REMS that caused that. It just says there's something else there contributing, and perhaps the ER/LA REMS contributes to part of that.

DR. PERRONE: I guess my observation that both opioids were going down in that reporting period, maybe the greater increase in the ER/LA opioids could be accounted for by the abuse-deterrent formulations.

Then two other related questions. One is, what is the current -- and this isn't really for you, but what is the current number of ER/LAs that are represented by abuse-deterrent formulations? So how much of the market now is abuse-deterrent formulations? I don't know who can answer that.

The second question is just for the FDA. Was there anything in the blueprint to prescribers to recommend abuse-deterrent formulations in the REMS program?

DR. COPLAN: The answer to the first question is 22 percent. That has to do with opioids that have section 9.2 of their label that designates them as having abuse-deterrent properties, category 1 through category 3. That's about 22 percent.

DR. PERRONE: Twenty-two percent, so across all of the opioids that your companies --

DR. COPLAN: Across all the ER/LA opioids, right.

The second question about the blueprint, no, it doesn't specifically mention abuse-deterrent formulations. Oh, it does.

Dr. Argoff.

DR. ARGOFF: Technically speaking, it does. So I'm not trying to be -- never argue with my colleague. Section 6 is product-specific information, and that's one of the beauties about

that section that it goes through each available treatment and actually it's an opportunity educationally to highlight which may be abuse-deterrent and which may not be. So it's in section 6 that the product-specific information comes out.

DR. PERRONE: I mean, our observation at our institution was our prescribing of long-acting ER/Las, actually went down and individual opioids or immediate-release went up often by patient request, either for insurance purposes I think is a nice thought or perhaps because there was more value to the immediate release after the abuse-deterrent formulations came to market.

So that might be another opportunity for study.

DR. COPLAN: Agree.

DR. PERRONE: Thank you.

DR. WINTERSTEIN: Dr. Bilker.

DR. BILKER: I have a question. I'll address it to Dr. Coplan. Most of what was presented in terms of the surveys is looking at

high prescribers versus low prescribers, but it's similarly important to consider appropriate versus inappropriate. It may be the case that many of the prescribers that aren't high prescribers are prescribing inappropriately and causing many of the deaths.

DR. COPLAN: Dr. Cepeda, would you like to address it?

DR. CEPEDA: We know that subject, that prescribers with high volume of prescriptions have higher knowledge, and they reported they used more REMS tools. So they used more the patient guideline, and also, they used more patient agreements.

DR. WINTERSTEIN: Dr. Brown.

DR. BROWN: This is for Dr. McAninch, and it relates to her slides 9 and 10, where she was describing the declining prescribing of opioids prior to the time that the REMS was even approved.

I'm wondering, to your best judgment, is there any information that can be available that is going to help us define whether there's any impact

of REMS on the decrement in opioid prescribing, or is it a part of it, or what's going to happen if we make the REMS more inclusive of other medications?

DR. McANINCH: I'm just trying to refer to the slides that you're speaking of. Are you talking about the changes in prescription volume?

DR. BROWN: Yes.

DR. McANINCH: Okay. I think -- can you put up slide 11, please?

Is this what you're referring to, sir?

DR. BROWN: Well, I was mostly referring to whether or not you thought that there was anything else that we could know. We've gotten a lot of information about issues. Some relate to the success of REMS programs. And I'm wondering if there's any other information data source that could be made available to us to help us to find what part REMS played in the reduction in opioid prescribing behaviors.

DR. McANINCH: Yes. Well, I think a part of is a question of data source, but part of it is a question of design and how you design those

studies.

We tried to bring that up a little bit, and then there was some discussion earlier today about a study that compared participants or completers of the REMS training to prescribers that have not completed training, and looking at changes in prescribing behavior, prescription volume, other aspects of prescribing behavior from before to after training in people that were trained, and then comparing that change to the change that you see in a control group across that same time period that didn't participate in the training.

It would require somehow controlling for baseline differences between those two groups, both in the prescribers and in their patient panels. And whether that could be done through the methods that we typically use to control for confounders in observational studies is a question that I sort of put back to the committee, or whether really a randomized design would be needed to control for both measurable and unmeasurable confounders to try to isolate what the impact of the intervention

itself was as opposed to all of these other things at the institutional level, at the state and federal level, as well as secular trends in drug abuse that are all coming into play.

DR. BROWN: I just want to make sure that we've gotten all the information that there is to get in order to make a decision about this prior to invoking randomization and going through that whole process.

DR. McANINCH: We're not aware of any wonderful data source out there that's going to answer that question. But I think continuing to explore that, and new data sources are evolving and being developed, and we'll have to be evaluating those as to what their value might be in a REMS assessment.

DR. WINTERSTEIN: I just have a brief comment, which goes back to how we started. I'm wondering -- I mean, I understand the CE credit and the issues with sponsor involvement in CE credit, but I'm wondering whether the FDA would not be able to get the CE information for those physicians who

were participating.

The AMA and NPI, there's a lot of information on prescriber characteristics that could be pulled together to really look at, number one, over-prescribers on one end, similar to what Dr. Morrato described, just to see who are actually the people we think should be targeted in CE and to what extent do they participate and so on.

It might be really an interesting concerted effort to try to assemble that database to get some idea.

The other idea that just came to mind was I thought there are some states now that require mandatory pain management CE. And that could lend itself to some interesting quasi-experiment right there because there is no physician choice involved anymore; just as an idea. I don't know. I haven't really looked into this real closely.

Dr. Parker was next.

DR. PARKER: I just had to put a footnote to what you just said. Payers, who's being reimbursed for it, in addition to that. I mean, that's

another data source just for consideration; somebody pays. So that was not my question.

I wanted to look at -- and I think, Ms. Harris, maybe you can help me here -- again, at the prescriber survey comments and what we know and don't know based on what's available. Because I keep hearing -- it keeps hitting me on the head; I think I'm supposed to hear it -- this thing about the goal of REMS in reducing the serious adverse outcomes and those being addiction, unintentional overdose, and death.

So I'm going back to the prescriber survey and your comments as you looked through it. And first, I wanted to -- so there were two sources of that, the prescriber survey and then the long-term evaluation of the prescriber survey.

One of the things that really struck me -- and I don't know if you have any other information, but I find it striking that 12 percent of the completers of the CE didn't know that they had completed it. So I just wanted to say that. I find that striking. That to me says something.

And it's part of the softer part of the data, but I think it's worth underscoring.

I wanted to go more specifically to a couple questions about the prescriber survey. Number one, when I see the description of the health professionals and the specialties, I see no mention of dentists or oral surgeons. And I wonder if they're included in those categories or they're specifically excluded from the prescribers and whether or not when I hear reference to prescribers, am I supposed to be including them in -- what category do I put them in and how do you think about that? So that's one question.

The other one relates very specifically to a finding on -- and I can't read what slide number it is.

Can you read that for me, the number?

DR. CHOUDHRY: Twenty-two.

DR. PARKER: Twenty-two. I'm 61, so I can't read it. But on slide 22, the key message number 2 that is so very low there, and if 6 months later, 12 percent have -- we've got this rate of the

message knowledge being incredibly low compared 6 months out to what it was before.

Am I supposed to take note of that? Because it seems like initiating, modifying, and discontinuation, if those are sort of key take-home points of the CE, and it's that low there.

Should I make note that that in the long-term evaluation tanked?

MS. HARRIS: I'll try to address -- I think your first question was related to dentists. I think if you can see for that, it was a catch-all category of "other." Dentists would be included in that. They included general practitioners in one, and the higher specialties were -- I put those in there. But it was a catch-all category of other that would include just every other specialty that was not included in those that are in there, primary care.

MS. SHAW PHILLIPS: Were they part of the MD/DO group or an exclusion from that? Because there's some overlap since some dentists are not.

DR. HSUEH: I don't have that information.

MS. HARRIS: Yes, we don't have that information. But in terms of just the general specialty, they will be included in "other."

I'm sorry. Your second question?

DR. PARKER: So let me just say I need -- that's not as helpful as what I'd like to know. I mean, I'm actually really interested to know if I should be putting -- if that 54 percent includes dentists or if the practice of dentistry is outside of that. Just sort of broadly as I think about who are we going after with the REMS and where it goes, I just want to make note of that.

Does that make sense to you?

DR. PARKER: Slide 9. So we're talking about the prescriber surveys, and there are two charts that are very similar. There's the follow-up and then the long term. There's 9, and then also slide number maybe 19, but they're -- it's basically characteristics of the survey. And you've got it for both -- there's prescriber survey, and then there's another one of

the LTE survey.

Both of them give demographic characteristics, but I don't know where dentistry falls in here, and I'm just asking -- for me to think about REMS, who they're going after, medical, dental, do I put those together? How do I think about it? That was the question on that one.

I'm not sure still, so that's one thing that would be helpful to understand what I'd do with that.

DR. CEPEDA: If I can add -- respond to that question, dentists are not included in that category.

DR. PARKER: So they're not surveyed at all?

DR. CEPEDA: No, they are surveyed, but they are not considered in the physician part.

DR. PARKER: Where are they?

DR. CEPEDA: In the "other" category, and it's -- for the responders, it's like 0.1 percent of the responders for the prescriber survey.

DR. AUTH: Could I just make one comment? And I don't have the numbers. Maybe if one of our

drug use colleagues would have that. But I understand your concern about the dentists. But just try to remember that we're speaking about extended-release and long-acting opioids, and when we do look at the utilization of those products by dentists, it is extremely, extremely low.

When you look at the IR, immediate-release category, that's much higher. But for these products, it's very small and only typically by some maxillofacial oral surgery specialists.

DR. PARKER: Right. So then --

MS. HARRIS: And the other question related to the low rates that you saw on slide 22, if you could pull that one up, I would like to throw part of this back to the RPC because I know in your slides it was different rates for this. So in the initial report, these rates were calculated differently than were presented today so I wanted to know your thoughts, if you could address that.

DR. COPLAN: The 17 percent is a typo. The correct information is 67 percent. We showed that in our presentation.

DR. CEPEDA: We present the mean scores, and here is a complete response rate. So the interpretation of this one is only 17 percent of the responders got 80 percent or more of the answers correct.

MS. HARRIS: Right. So it's a different -- so it's not a typo. It's just a different interpretation, correct? Okay.

DR. COPLAN: And if we look at the mean score -- what we showed was the mean scores. So there are two ways of looking at it, the mean score correct and the percent greater than 80 percent correct. And here, the mean score for number 2 is 67 percent as opposed to the number who got more than 80 percent correct, which is the 17 percent.

MS. HARRIS: So there are still some areas in that message that need to be addressed where prescribers aren't getting the questions right.

DR. COPLAN: And to Dr. Parker's point about the 12 percent of people who'd taken the CE training who didn't recognize they'd taken the CE training, we think in our root cause analysis of

the problem, we think a big consideration is that it's not clear exactly which courses are REMS-compliant CE course as opposed to which is not. Many people may take the NIDA course. I think the REMS-compliant CE courses constitute about 4 percent of the total or even less of the total CE courses available.

So flagging which ones are REMS-compliant and which ones are not while following the standards for commercial support is something that we've been looking into and something we've been working on.

DR. WINTERSTEIN: We'll take a break now. Then we have one more hour of presentations, and after this, we have a full hour for questions. That will hopefully help us get everything answered. So we'll be back at 3:20.

(Whereupon, at 3:08 p.m., a recess was taken.)

DR. WINTERSTEIN: You're a very cooperative committee. Everybody quiets down, very nice.

So we will now proceed with presentations

from organizations, and Cynthia Kear will begin.

Organization Presentation – Cynthia Kear

MS. KEAR: Good afternoon, everyone. My name is Cynthia Kear. Have you had enough data?

(Laughter.)

MS. KEAR: Okay. So my name is Cynthia Kear, and I'm senior vice president for the California Academy of Family Physicians. And I am kind of chief cook and bottle washer for this collaboration called CO*RE.

I am a member of the executive team along with my colleagues Penny Mills from ASAM, Catherine Underwood from APS and Anne Norman from AANP. And here's our collaboration. We have 13 partners. You can see, you can read for yourself who they are, a combination of both large associations as well as smaller specialty organizations. And we also have in addition to membership learner organizations, we have Medscape as part of our collaboration.

You can see at the top that our numbers are fairly significant. We represent 750,000

prescribing clinicians, MDs, DOs, PAs and NPs.

Key things about our collaboration that I'd like to note: We are interdisciplinary. We're inter-professional. We represent both primary care as well as specialists.

A very important point is that we are education only. I will not be advocating anything about mandated or not mandated education. Our members play in the sandbox because we agreed not to join forces, no advocacy. There are differing positions as to whether or not this education should be mandated, but nonetheless, we are all committed to providing our members with a high quality, effective educational experience.

We've been doing this for a long time. We started actually before the REMS was released knowing that it would be coming down the pike and that it would be an important service to our members who happen to be the clinicians who were targeted by the FDA to receive this education. And we knew we'd need time to prepare for it.

So the issues that I would like to address

on behalf of CO*RE today are some of the current challenges of the opioid environment in which this education is happening, customary and usual CE/CME, and then definition of success.

So right now -- and I've noticed -- I've been involved with this now since before 2010. I know far too much about ER/LA opioid REMS, but there is an amazing difference among our learners everywhere whether it's press, at state level, national level about the emphasis and the visibility of opioids, and that's good.

However, there is persistent confusion. What is a REMS? A lot of people still don't know. Is it rapid eye movement? Does it relate to sleep? Is this sleep education? What's happening here?

Even if it is understood that it is the risk mitigation evaluation strategy, there has not been really a compelling value made to the learner as to why he or she should take this education over other education that relates to pain or to opioids or something like that.

CE/CME is a very, very crowded field.

Medscape, which I mentioned is one of our key partners, informed me that in 2015, they had on their online platform -- and of course, they're probably the largest provider of online education in the galaxy -- they had over 1600 accredited educational activities in 2015 up slightly from over 1500 in 2015 [sic].

So this has to be taken into consideration when you evaluate the success relatively speaking of the metrics. It is a very, very competitive field.

So we note that there's increased visibility of discussion about opioids at the national level. CO*RE has had numerous conversations and meetings with many of these people at the ONDCP, HHS. Cathy Underwood has been involved with the national pain strategy. Of course, we know about the CDC and CDC guidelines. Mention was made of the NIH and NIDA, SAMSHA. Of course, the Surgeon General has recently sent out millions or maybe over a million letters to prescribers.

Of course, a lot is happening at the state

level as well, and I think there was a map earlier to show what some of that activity is and what the variability of it is.

But the thing is that there's a wide range of what the knowledge is as well as what the potential solution is for this both at the national level and at the state level. And I see this -- and the comment or the question was just made in terms of how about what's happening at the state level where they are requiring CE.

Just a very quick example, one of our partners, the Physician Association, wanted to do our REMS course in Maryland right here and use the course to fulfill the state requirement. Well, they only require one hour, and our shortest program is two hours. And they said, well, that's just too long.

So you see some of the challenges that are faced in terms of trying to connect all the many, many dots. But the result of this is that there is really still very low awareness about the ER/LA REMS, that there is this amazing fragmentation of

educational offerings. And it all just winds up making the learner very confused.

In the last period, somebody said they were concerned that a high percentage of people didn't know whether or not they had taken this education. Some of the most prominent named programs for the ER/LA REMS are Cope, Scope, Core. It can all get very, very confusing.

Is it an ER/LA REMS program? Is it from NIDA? I mean, busy people are not going to remember these details. These are not compelling.

So let me talk a little bit about accredited education and why it is our belief that this particular activity, while very successful and appropriate, is not fully customary or usual CE or CME.

This is just a little chart that we pulled together to take a couple of elements to compare and contrast what is typical and usual versus the ER/LA REMS. So you'll see that for a typical live and online activity, usually the duration of the

activity is anywhere from 30 to 60 minutes. Based upon the very demanding content of the FDA blueprint, the minimum amount of time that this can be completed is in at least two hours, and that's just different.

The assessment and the evaluation process that is engaged or associated with typical CE/CME is usually much shorter. And by comparison, the assessment that -- as you can see from the long-term evaluation as well at what we, all of the grantors, do voluntarily on top of the long-term evaluation is quite long and quite challenging.

The assessment that CO*RE uses for our educational activities follows the requirement, which is that it covers the entire all six elements of the FDA blueprint. It was written to very, very vigorous standards, the National Board of Medical Examiners. Most evaluation tools for other types of typical and customary educational activities do go to that level.

Key thing here is that reporting is a big difference with this particular activity. All of

the grantees and CO*RE, all of our partners that are part of CO*RE have to -- first of all, we had to create a database process in order to be able to keep the data straight, but there are numerous sources that we have to -- and numerous times of the year when we have to report data. That is very, very different from most CE/CME. Usually, there's a mid-project report, a final report, and somebody enters it into their accreditation system.

Ditto for tracking data, most activities will track your basic learner demographic and metrics type of factors, but with this ER/LA REMS, there are incredibly complex multifaceted pieces of data that all of the providers are asked to get from the learners.

So rather than just sit down at an event and tell me what your name is and what type of clinician you are, it is your practice type, it is your -- whether or not you're DEA licensed. It's your practice setting, and it is whether or not you have prescribed an ER/LA in the past year. And that's just to get started.

So what we find is that with the REMS, there is an inordinate emphasis on reporting and tracking. As accredited providers, what we're much more interested in is the outcomes piece of this, and what we want to spend more time doing is real outcomes that are meaningful and measurable.

In the world of CME, there are well established paradigms for evaluating that success. CO*RE happens to adhere to a very widely adopted one, which is Moore's level of outcomes, and as you can see, going up the pyramid, we start at the very basic of the most kind of interesting information but not meaningful in terms of actual participation, going up through the levels 3-A and 3-B where we really get to knowledge, and what's really most important is reaching level 5 where we see is this educational intervention having impact on performance.

So somebody had mentioned this earlier as well. We're trying to move up the continuum from how many to do you really know to do you really do. That's how we're evaluating this particular effort

and trying to measure whether or not it is successful. And as I said, this is widely available and adopted within the CE community. And I should just mention that Don Moore is actually one of our national advisors to the CO*RE collaboration.

CO*RE has had a fairly large reach. I think we're probably the largest single grantee among some really wonderful colleagues in the grantee world. As of the end of February, we had implemented 526 activities, and you can see our numbers there, resulting in about 29,000 prescribers.

If we were to throw in learners how we feel are critical to the safe and effective prescribing and management of opioids, we would also include nurses, pharmacists, et cetera. And we do reach them through our program, but we don't count them. That would bring us up to 170,000 learners that we have educated since we started in March of 2013.

So to look at that from the perspective of Moore's seven levels, this would be at the bottom

base of the triangle, of the pyramid, and our numbers, again including everybody who we think is important because they're part of the healthcare and healthcare is delivered in teams, so our total number in three years is 170,000 learners.

To contextualize this for you, the CAFP has been involved in two other very successful collaborations that have been widely respected and externally acknowledged as being very successful collaboration. The first is about smoking cessation, a five-year collaboration where we reached 60,000 learners. Now, admittedly, we did not start off with a goal of 320,000, but nonetheless, we were very busy at work.

With the second collaboration, which is about Afib, which was a four-year collaboration, we've reached a little over 75,000. So by comparison if you just look at this from a pure raw metrics, what CO*RE has done and then if you look at the broader enterprise of all of the grantees, from a pure metrics level 1 perspective, this has been very, very successful.

The problem is that if you take a different paradigm, something that is not part and parcel of customary and usual CE, a number such as 320,000 people who have prescribed an ER/LA in the past year, and you use that definition in order to evaluate whether or not this is successful, the whole thing gets turned on its head. It's kind of like looking at it through a telescope through the wrong end.

So what happens is that what we focus on is the centermost smallest piece of this whether or not we're reaching these prescribers, when for us, we would say the entire circle and all the segments of the circle are equally important. But this is a particularly complex paradigm that we're being asked to engage in, and everything that we do is about narrowing the learner as opposed to really focusing on outcomes.

So back to Moore's level of outcomes. So I've shown you, number one, at the base level that just by virtue of participation by adopted CE standards, this would be considered very

successful. But we care more about the learner experience and the quality of the educational activity than just the number of the people in the seats. So we want to move up the paradigm.

If we move to the next important level which is 3, which is knowledge, this is a sampling of CO*RE's learner scores based upon the assessment. Again, this is a very rigorous assessment. It has been built to National Board of Medical Examiner standards and carefully, carefully vetted. These are very, very good scores, very good scores.

You'll notice a difference in terms of blue and red. It is not unusual that online activities tend to have less impact than live activities.

But more importantly for us as accredited providers and as people who want to provide a meaningful service to our members who are these targeted clinicians, we want to look at level 5, and we want to see are you really making changes in your performance and practice based upon the educational activity that you've engaged in.

This is an aggregation of what we have seen

implemented over the three years that CO*RE has been educating learners. And over all five of the elements of the FDA blueprint, we are seeing incredible changes and uniform changes in terms of better patient assessment, more thoughtful initiation of treatment, more careful management of patients.

Particularly, we have seen just kind of off-the-charts improvements when it comes to better education and counseling of patients about the dangers of these drugs as well as about safe storage and disposal.

We also feel that this endeavor is very successful because we are reaching people who are prescribing opioids. This is from a late 2014 survey where we asked our learners whether or not they were prescribing and what they were prescribing. Forty-two percent of them said, yes, they were prescribing ER/LA opioids and had in the past year, but an overwhelming number of them had said that they had prescribed IRs in the last year, 77 percent.

We are informed by a faculty advisory panel,

interdisciplinary, inter-professional, many experts on that field, both well-respected educators, clinicians and academicians. And one of the things they have persistently said to us from the get-go is knowing how to prescribe opioids is kind of fundamental and uniform. It doesn't really matter which class you're addressing. In fact, to start with ER/LA opioids is almost trying to teach somebody to swim by starting at the deep end of the pool.

So from CO*RE's perspective, we think that this actually has been a very -- for the facet that we are involved with, which is education, and reaching learners, we think that this has been a very significant success when it is evaluated by all the definitions that are used by professional accredited providers.

The metric of 320,000 is kind of an albatross that just persistently hangs around our necks. And we would suggest that there is a tremendous disconnect between what it is that accredited education can do and should do and is

doing versus reaching a pure metric for which very few accredited educational programs have a metric associated with them. None of our partners and very few accredited providers I know track things like of their learners as to whether or not they're prescribing. This is very unusual activities that we've been asked to engage in.

So we do have a few recommendations for your consideration. The first is that you continue to use accredited education. It does have, as I've inferred, paradigms that are widely adopted that can be used uniformly to evaluate educational success.

The second is that I think it really is a good safeguard against any perceived content bias. CO*RE has less than 1 percent of our learners say that they see any kind of content bias, really minimal.

We do think that there should be the inclusion of immediate-release, short-acting opioids, that there should also be the inclusion of all of the members of the healthcare team as

appropriate learners of this education.

We would really recommend that the adult education field is well established with well-established and proven scientifically accurate, evidence-based principles for adult education. And we would humbly recommend that those be considered very strongly in terms of any changes that happen.

We would suggest that somebody who has adult education, particularly with the experience of accredited education, be embedded into any planning and decision-making process. There are very simple things that can be averted, issues and troublesome points that can be averted just by having somebody know a little bit more about this process.

For instance, the fact that this education requires two to three hours and that at most educational venues, that's not what's going to be happening, it's really going to be something more in the range of about half an hour to an hour.

As I tried to indicate with the emphasis on reporting and tracking, we would recommend that there be consideration given to streamlining the

process both for the accredited provider and grantee who's trying to successfully deploy this activity but also for the learner so that he or she is not given incentive to not engage fully in the process.

We would really like to recommend that you streamline opioid efforts, especially at the national level, but when possible in conjunction with state. The phrase here "reduce the number of federal programs" might be a little bit too harsh, but I like the word that the RPC used which to "harmonize."

Certainly, to look at the fact that there's a very broad pool of appropriate education out there that is helping to bolster safe prescribing practices, and can we make some of these activities more uniform? And can we make the tracking and the inclusion of the results of these other activities more uniform?

Not on this slide but two final recommendations that CO*RE would like to consider or have you consider is one, the inclusion of

education on PDMPs. We are seeing that the PDMPs are being turned to more and more by prescribers, that the states are moving more and more to improve and strengthen PDMPs and the CDC grants should certainly help.

But catching a learner at a point when he or she has an immediate need for education is one of the best places you can be if you are an educator. That education is going to really mean something because they need that information now. It would be very easy to put on some appropriate small snippets or to even link in longer access to links on -- segments on Medscape or other online activities to make that happen.

The other thing that we would like you to consider is the development and the use of some sort of a national assessment. There are prescribers who do have prior knowledge and can demonstrate proficiency, and they have no incentive and sit down and take a two- to three-hour course right now. But I'm sure that everybody here would like to know that they do have prior knowledge and

proficiency and having such a testing instrument built to the highest standards possible would indeed allow us to achieve that goal.

Thank you very much.

DR. WINTERSTEIN: We're running a little bit late, so Dr. Zacharoff, if you could hurry to the podium.

(Laughter.)

Organization Presentation - Kevin Zacharoff

DR. ZACHAROFF: Thank you and good afternoon. It's my pleasure to be here today and speak with you from a variety of different perspectives, as a clinician with over 20 years of clinical experience, an educator in a medical school in New York and a pain educator online, a grant recipient for REMS education and as a developer of REMS education and also a deliverer of REMS education.

So my initial thoughts when the grant was received from the RPC to develop the REMS education was that this was basically for me a tee-up for a success. I had been medical director of a website

PainEDU.org that had 80,000 voluntarily registered users with it, and these were all people who were seeking out more knowledge about pain and its management.

The partnership was with Albert Einstein School of Medicine in the Bronx, New York in Montefiore Medical Center, and they were bringing another 2,000 people to the table. So with a pool of about 82,000 people and a skewed population who we thought were interested in pain and pain education, it seemed like a tee for me to hit a hole in one.

In 2013, through PainEDU, we did a preliminary spot survey of 130 healthcare providers. Fifty-eight percent were physicians, 33 percent were nurse practitioners, advance practice nurses, and 5 percent physician assistants. And what we wanted to do was we wanted to ascertain familiarity of the REMS, gauge the likelihood that people were prescribing an ER/LA opioid, assess the likelihood of educational participation when the REMS was developed and also identify some possible

barriers to learners participating in the education.

It's worth mentioning that PainEDU under my leadership was really targeting the non-expert healthcare provider. It wasn't really a place where experts would go to learn more about what experts could do, but more about what non-experts really could learn to do.

What we found was that only 27 percent of these 130 people that we polled were either extremely or very familiar with the ER/LA REMS at all. The rest were either somewhat or not at all familiar.

When we asked about the likelihood of prescribing ER/LA opioids for moderate to severe chronic pain, what we found was that there was only 18 percent of the people we surveyed who said they either were not likely to or don't prescribe ER/LA opioids at all for people with this type of pain.

Then, this made me feel really good. When we asked about the likelihood of participating in a voluntary ER/LA REMS education course, 92 percent

said they would either probably or definitely participate in such a program.

But when we asked about potential barriers in this survey, the two things that bubbled to the surface were the belief that the time commitment would be too burdensome. That was half of the people we polled. And a quarter of the people we polled said there really was a lack of understanding about what the educational content course would actually cover.

I think it's worth mentioning that when we talk about the REMS education blueprint, I think we as providers of REMS education have been intimately involved and aware of what the blueprint contains, but the learners don't really know, and they didn't know.

When we asked about what the preferred method of delivery of such an educational program would be, 88 percent said online followed by 39 percent saying print form. And not a lot of people actually said in live delivery format. I think most of the people we surveyed liked the idea that

they could sort of do it in bites and start, stop, come back and do it at their leisure as opposed to sitting in, in one place for two to three hours.

Now, I received a grant from the National Institutes of Health and was co-investigator on a study back in 2011 where we looked at core competencies of primary care providers and opioid risk management.

What we found and we published in the Journal of Continuing Education of Healthcare Professionals back in 2011 was that experts' opinions about what people in primary care need to learn who prescribe chronic opioid therapy was not what people in primary care thought they needed to learn about when prescribing chronic opioid therapy for people with chronic pain.

I think that that was very telling for me in terms of the fact that we need to consider -- and I think it's been mentioned a couple of times here today -- that tailoring to the learner might be a good way to go. The concerns that probably sit at the top of mind of people in primary care who if

they know when to refer may not be the same as the people who are caring for the people who are at moderate to severe risk of aberrant drug-related behavior.

Certainly, I agree with everyone who has said that there are many other good candidates for education beyond just prescribers of ER/LA opioids in the last 12 months, from nurses to pharmacists to physician's assistants. And I would like to underscore physicians or other clinicians in training.

That brings me to an opinion piece that actually appeared in JAMA two issues ago written by someone in the department of internal medicine at Stanford, and it's entitled The Patient You Least Want to See.

What this person wrote about was their internship in internal medicine, and they wrote that these patients were the cases where I was caught between challenging patients and inconsistent supervising physicians, between the power to prescribe potent medications and learning

to compassionately manage pain and between social mores steeped in prioritizing pain management to one recognizing the dangers of misuse of prescribe opioid drugs.

With the pervasiveness of the prescription opioid problem in this country, the inconsistent practices among even seasoned physicians and policy calls for increased prescriber education and monitoring. We may all be trainees when it comes to these complex cases.

This has been a message that I have personally agreed with from the get-go. I believe that we use sort of a seatbelt phenomenon, and I refer to my daughter of 25 who grew up with the idea of when you get in the car, you put on your seatbelt as opposed to me who at age 40 whatever I was, I had to get into the mindset that I needed to start wearing a seatbelt every time I got into the car.

With respect to challenges and the mode of delivery, live presentations definitely bring home the bacon. I have given live presentations for the

REMS education, but it's a long amount of time for somebody to sit there and get the education. The audience is captive, though.

With respect to an online program, certainly my experience was that while there was reasonably good registration and even initiation of the program, it was tough to get people to cross the finish line and complete that third module -- it was three one-hour modules -- even though we were withholding the credits until they completed the third module. It wasn't enough.

So what we did when we developed the program, in closing, is we incorporated questions to the learner in the body of the educational material. What we really wanted to do was create a sense of interactivity with the learner, but we also wanted to capture from them what their thoughts were.

We have an analysis of 955 participants who responded to these questions, and again, this was in the body of the education. It wasn't at the beginning. It wasn't at the end. It was sort of

when we were talking about certain topics, they were queried about it. And you can see the breakdown is similar to what everybody's mentioned in terms of physician MDs and other healthcare providers.

Interestingly, only 39 percent identified themselves as pain specialists. Twenty-eight percent identified themselves as primary care, and the remainder didn't identify themselves as either one or the other.

But here's what we found. We found that with respect to common challenges with chronic pain, the lion's shares of the learners felt that the psychological complexity, the poor patient level of adherence or satisfaction and time constraints were the most common challenges that they experienced.

With respect to opioid therapy itself, the subjectivity of pain and its severity, the pressure from patients to prescribe opioids for them and the difficulty in predicting aberrant drug-related behaviors, these were the things that were on the

top of the mind.

When we asked them what was the most common influencer of prescribing an opioid for people with chronic pain, 60 percent said clinical practice guidelines, 51 percent patient-specific factors, and 44 percent said state guidelines and regulations. And I think this is really telling.

So from the perspective of the information we've gathered, I would urge and join the other people who have mentioned today the idea that we embellish and incorporate additional leaner groups. Non-prescribers play a critical role in the healthcare team, as Cynthia mentioned.

We could also consider exploring other modalities of delivery. When I was managing PainEDU, I developed a set of slides at learners' requests with speaker notes that were put up on PainEDU, and they were downloaded 77,000 discrete times for people to use as part of in-service training.

In-service training is something that people are always looking for to do, and maybe this could

be divided up into six modules that could make a very nice program over the course of a year for in-service training.

Certainly, clinical relevance is key, and this is actually CO*RE data that Cynthia was kind enough to share with me from the survey on learner behavior that CO*RE did.

As we can see, non-prescribers often play critical roles in counseling patients, discussing and even consulting with the prescriber about whether or not an opioid should be prescribed or not. It may be very rare that the patient's actually talking with the physician for an extended rate of time. This data bears that out.

CO*RE also found, as Cynthia mentioned, that immediate-release short-acting opioids are often as much of a challenge, if not more so, than extended-release long-acting opioids and that the value of educating clinicians who are actively prescribing these formulations is probably a very high value proposition.

So in summary, I would say my

recommendations based on my real-world experience would be to merge the real-world challenges and barriers with the educational content and consider tailoring the education to the type of learner that you have in front of you.

Align or facilitate dissemination of guidelines and recommendations along with the education so there isn't confusion about whether people should follow the CDC guidelines or follow what the REMS education tells them to do.

Certainly, target multiple disciplines. Consider utilizing out-of-the-box educational forums such as in-service training, and lastly, definitely consider expanding the scope of the education to include immediate-release short-acting opioids. Thank you very much.

DR. WINTERSTEIN: Thank you.

I see Dr. Kahn is already lined up.

Organization Presentation - Norman Kahn

DR. KAHN: I didn't wait for your invitation. Thank you, Dr. Winterstein.

Thank you, Committees.

I'm Norman Kahn. I really appreciate the opportunity to talk tonight. I'm the last one, so I had better be clear and concise, and I will do that. I have a handful of slides. I'm going to focus on four or five of them. I'm going to make two points. I'm going to make a point about teams. I'm going to make a point about mandatory versus voluntary education and the quantitative and qualitative differences that that makes, and I'm going to make a couple of suggestions at the end.

So first, a little disclosure, this is who I am. However, it occurred to me that there are probably a couple of other things that I probably ought to disclose to you. And in the spirit of full disclosure, I need to just tell you, and you decide how you're going to listen to me based on what you hear.

I spent 15 years as the head of one of the national CME accreditation systems in family medicine. For those of you who are not in continuing education, there are three national accrediting systems in medicine, the ACCME, which

we'll hear from tomorrow, the osteopaths and the family physicians. So I headed the family physicians for 15 years.

I also spent six years on the board of the ACCME, and I chaired the task force that resulted in the revision of the standards for commercial support for continuing education. Now you know.

So I have three slides on the Conjoint Committee on Continuing Education. These are the 26 organizations that make up the Conjoint Committee. This is medicine, nursing, pharmacy, dentistry, nurse practitioners and physician assistants.

We heard a lot of data today. I learned a lot. The three of us here this afternoon, we're about what's really happening out there in the world of clinicians.

The Conjoint Committee has been around 2002, and it always had this objective, which is to use continuing education of health professionals to improve the performance of the U.S. healthcare system. But since 2012, this is our sole focus.

And that is focusing on the opioid epidemic.

This is the only reason that the Conjoint Committee currently exists. This is the only set of activities that the Conjoint Committee currently does. We're pleased to be in a collaboration. I might use the word "partnership" with the FDA and with the REMS program companies in working on this particular opioid epidemic.

So one slide on strategies, this is the first of the slides I'm going to focus on. I'm going to talk about quality educational activities, and I'm going to talk about quantity of educated. So in quality, we have more live courses than we have online courses, but we have more participants online and more completers in the live courses.

So what does that mean? It means that you can go online easy, any time you want and do as much as you want, but if you go to a live course, you're going to finish it.

All of the courses incorporate the blueprint, and they're tailored to needs. So when I started my practice, I was a rural family

physician in a town of 2900 people. I'm not going to go to a course that's designed for an oncologist. I'm not going to go to a course that's designed for a dentist. I'm going to go to a course that's designed for a rural family physician.

So let's talk about the quantity educated. We have heard an awful lot of numbers today. I'm saying there's 647 activities. That's from the ACCME's PARS data. When the RPC or the FDA identifies 839 activities, that includes RPC-funded programs that are not part of PARS.

So what are those programs? So some of those programs come in nursing. Some of those programs come for physician assistants. Some of those programs come from pharmacists, and a lot of those programs come from osteopathic physicians who have their own separate accreditation system.

We've educated well over 200,000 clinicians, 170,000 or so who are completers under the PARS data, but probably 200,000 who are completers among all of the clinicians. This includes prescribers

and their practice team members.

Now, remember I said I was going to make two points about teams and about mandatory versus voluntary. So I'm headed for my first point about teams.

So do you think when I was in rural practice, the only office in my community, that I was the only one practicing and therefore, I was the only one who needed education on chronic pain and pain management? I happened to work with a physician assistant, three partners and an RN.

So this is the way that practice is in this day and age. This is a slide that's very recent. This is a recent survey of family physicians, the baseline of primary care 25 percent of whom are in communities of fewer than 10,000 people; 71 percent work with a nurse practitioner or a PA just like I did when I was in practice; 25 percent work with a behavioral health specialist; and 21 percent work with a pharmacist and 28 percent with a care coordinator.

So let's go back to this practice where we

have a prescriber in the practice and we have a behavioral health person, we have a care coordinator, we have an NP and we have a PA. Who needs education to manage chronic pain in that practice, just the prescriber? No.

This is a team event. So there are three slides on challenges. So let's ask ourselves the question why don't people take the REMS CE? Why are we not getting as many as we would like? Remember, I'm saying we got 200,000 completers out there. No, they're not all people who have prescribed an opioid in the last year.

I hope I just communicated that that's not all we need to be measuring. Yes, I know the law requires us to measure prescriber completers, but to you, FDA and advisory committees, my communication is we've got to train more than just that, more than just prescriber completers.

So some rarely prescribe and therefore don't recognize such education as a priority. Sometimes the prescriber is the expert and doesn't see a need to take advantage of the education.

We've all talked about a lack of awareness. There was going to be an awareness campaign. I'm not sure what happened to the awareness campaign. I'm looking at some of my friends over here in industry. There's a lack of awareness.

Some people just trust enforcement to manage the problem. There's another point that I didn't think of when I put the slides together, which is that some people are taking other CE. Some people are taking the eight-hour course offered the American Medical Association. That's not an RPC-funded program. It's not a blueprint-compliant program. Some people are taking NIDA's course.

There's a lot of other CE. We just simply don't know how many people are taking those courses, and if they are taking those courses, are they prepared to prescribe opioids just because they didn't take the course that we're focusing on?

We've talked about the fact that two to three hours of education discourages some from participating. We're going to get to mandated CE on the next slide so I think I will comment then.

And some people are overwhelmed by demands on practice.

So I've inserted a slide about what are these demands on practice. So put yourself in the position of a clinician in a practice who prescribes opioids periodically because the clinician does manage patients with chronic pain, is working in a team environment and has an electronic health record, which was mandated under meaningful use. I'm not going to get paid if I don't do it.

I've now got to do alternative payment models or merit-based incentive payment systems under MACRA. I'm being measured. Every payer is measuring me, and they use different measures for the different things that I do.

We're working with the America's health insurance plans right now on core measure sets. The first core measure sets have been released in January of this year, cardiology, orthopedics, pediatrics, a few others, so that we can have clinicians be measured by the same things by all of

the health plans.

I've got maintenance of certification. Don't get me started. Perception of relevance. We've got payment reform. If we didn't pay attention to PQRS and meaningful use, we're going to pay attention to APMs and MIPS. And this is the current threat right now.

Now, you come to me, and you say, instead of the usual lunch hour online one-hour program, I want you to take a three-hour program on opioid preparation. And I'm going, I just -- I don't prescribe very often. I'm not part of the problem. I don't have time or energy for one more thing. I'll pass.

But we have more than 200,000 people who have voluntarily said I assessed my need in my practice, this is what I need. I'm going to go get some CE on this, 200,000 completers.

So one slide on mandatory versus voluntary education, this is my second point. Teams was my first point. Mandatory versus voluntary education, so there are 19 states that mandate specific CE,

yes, 46 states mandate CE in general, a certain number of hours, but 19 mandate specific CE.

In every instance, in every instance, this is the legislature legislating something for political purpose. Somebody had a bad experience, and the next thing you know, all of the clinicians in that state have to do CE on a particular program whether they like it or not. And there's lot of different kinds of CE.

Thirteen states require pain management. I expect there will be more of these. So mandatory CE is perceived as a burden.

So I'm licensed in two states. One of them requires six hours of end-of-life care. That's a lot, so I had to do it, though. So I sat down one evening, and I did my six hours of end-of-life care. And my response was, that's done. I'm going back to practice as usual.

There is a huge difference between mandatory and voluntary CE. So let's see what the message is if it's voluntary. So this is where I look at my practice, and I determine I need something. And I

approach the CE as a sponge. I want to learn as much as I can, and I want to change my behavior and practice. And I will learn as much as I can, and I will change my behavior and practice.

We're seeing that on the one slide I don't have here, but Graham McMahon tomorrow morning from the ACCME will share it that shows that that's really what happening in voluntary CE. If I'm mandated to do it, I'll have to do it, I'll do it, and the quantitative numbers will increase. But the value of the continuing education -- and will the outcomes increase with mandatory CE?

I'm not standing up here saying I'm for or against mandatory CE. I'm trying to share with you out there in the real world what's the consequence of making a decision. So if you make a decision for mandatory CE, understand you can't just turn your back and say, okay, we fixed it because now everybody will be educated.

They won't all change their practice behavior. They may learn nothing. I'm overstating it a little bit, but not much.

We've got a lot of federal agencies. I'm going to skip this slide. Doris will probably roll her eyes when I said anything about this slide anyway. So we will be working on alignment.

NIDA is doing good things. CDC is doing good things. The Surgeon General is doing good things. But it's just really confusing and complicating the landscape out there.

This is the outcomes slide. This is the outcomes slide, and the one thing I would point out is the last two bars that aren't there. This slide ends in 2014. We started our work in 2013, and we started with nine programs. We didn't get ramped up until 2014.

The outcome, whatever portion of it, is due to the voluntary continuing education in the six health professions that we're doing, it's not measured yet. We don't know the impact on outcomes yet of our education.

This one scares us. This is something we're going to be trying to figure out. Is this something we can address? Can we really address

heroin? I don't know yet, but it's on our agenda for the steering committee of the Conjoint Committee.

This is the last slide, future considerations. I would share with you that all of the continuing education we have been talking about today is the traditional didactic and interactive learning. Intention to change is critical. I need to perceive a need for the continuing education.

But there's two other things that we can think about, and I'll leave you with these two ideas for the future as I'm the last one to speak. The first is in 2005, there was released a new type of continuing education. It's called performance improvement continuing education.

In performance improvement CME, in any topic, let's take diabetes, it starts with performance measures. There are specific measures that we expect any clinician managing diabetes to follow. It has to do with smoking cessation. It has to do with whether they're on a statin. It has to do with the level of their hemoglobin A1c.

I measure my performance against that. Then I see where I'm short. I compare myself to national benchmarks. I compare myself to peers. I get educated, and I re-measure after time.

That's a very important innovation in continuing education, which we ought to consider -- I'm talking to myself. I've convened the Conjoint Committee. We will be considering this.

The last one is the use of clinical data registries. The difference between continuing education and clinical data registry is it starts the same way. I develop expectations of performance. What do I expect of myself to perform in the way of managing chronic pain? How am I going to measure myself?

We embed those into the electronic health record. There is a software program -- there are now 163 clinical data registries out there, not for opioids. There is one for opioids that the medical toxicologists have, very small. We've been in conversations with them.

But take another condition like diabetes as an example. The software crawls through the electronic health record and pulls out every one of my patients that I take care of that's got diabetes and provides me feedback on any of the performance measures that we put in to analyze.

I now have a gap analysis in my performance. I need education. I will get education that's targeted to the gaps that I've identified. I will implement changes, and I will demonstrate improvement over time continually.

I go to a CE course for two to three hours. I walk away with as much as I can learn. I change what I can. But that's the only intervention.

Performance improvement CME at least gives me four to six months to reevaluate. The clinical data registry is all of my practice. It's a culture of performance improvement in practice. We'll be talking about these.

Thank you for your time and good luck.

Clarifying Questions

DR. WINTERSTEIN: Thank you.

So we will continue with questions. I think next on the list was Dr. Floyd.

DR. FLOYD: So this was actually a follow-up on one of your questions, and Dr. Brown, about study design. So I think it's for Dr. McAninch.

So I think I agree with your assessment that these surveillance studies of secular trends and aggregate measures of prescribing and outcomes probably can't tell us much about any potential effect of REMS in the setting of all these other more potent kind of policy changes that have occurred. And you presented an ideal study design where the prescriber is the unit of observation and linking that with prescribing and outcomes for patients over time.

My question was, was this considered at the outset of REMS? Was there a reason that this wasn't done from the beginning? Because I would think that this would be the ideal way of assessing the impact.

There are two parts. So the second part is even if we could do that quickly, given the

evidence presented about the incomparability of people who voluntarily sign up and people who don't -- which was presented and this are important predictors, how far out since your training and what your specialty is, and I worry more about the things that you can't measure -- do you think you could actually do a credible observational comparison that you could make a causal inference from? So two parts.

DR. McANINCH: Those are both very good questions. I'm not sure that I'm the best person to answer the first question about the history of the assessment and how these studies came to be the ones that were done.

Doris or Judy, would you like to take a shot at that?

DR. FLOYD: I guess I'm wondering if there are barriers to doing that that we haven't heard of that I don't understand.

DR. McANINCH: Not that I'm aware of, although we've heard this morning from the RPC that there are some issues with firewalls and not having

access to individual level data on completers. But it would seem to me that there would be ways to get around that through using third parties and de-identifying those data, and having prescriber identification numbers that could be linked to other data potentially.

But do you want to say anything more about the original?

DR. AUTH: Doris Auth, Division of Risk Management. When this REMS was approved back in 2012, it was still fairly early in the development and evaluation of these programs. So I think the science of evaluating REMs programs in particular continues to evolve. And we've noted that for each of our REMS assessments, in many circumstances, we end up revising the evaluation assessment plan with each REMS assessment.

So I think at the time what we were focusing on, because this is a continuing education program, is knowledge. Particularly, we wanted to use long-term evaluation studies because that is what the CE community has typically used.

So we had that bucket of knowledge, and we also had the looking at trends in these events and seeing if these trends were changing over time and whether or not our interventions needed to be more stringent.

So I think that it just suffers from somewhat of lack of experience of doing these things. And certainly, we agree now that especially as we've seen from what Dr. Argoff presented earlier is that this type of data is potentially doable, and we look forward to trying to do some sort of study and get this information moving forward.

DR. McANINCH: Have we answered both of your questions?

DR. FLOYD: Actually, the second part of my question is --

MR. McANINCH: Observational study designs?

DR. FLOYD: Yes, is it useful to invest the time and resources and to delay those decisions to do this type of study? And I think it's a broader question of is that observational comparison

actually credible if you're trying to make a causal inference about if the REMS changes behavior, reduces bad outcomes, if we even need to measure that or if we, a priori, just think it's good to improve education and decide we need to do that.

I don't know the answer, and the question is open to others on the panel who are pharmacoepidemiologists as well. Can you do a credible observational study given that you know the people who volunteer are so different than the people who do not, not only in the ways that you've measured already but in the ways that you cannot measure.

DR. McANINCH: Again, this is a question that we have been struggling with as well. Evaluating intervention using observational data is really challenging. I think that it's something worth exploring. I don't know if it's a question that can be answered today.

Just based on our experiences, developing studies and study designs for the ER/LA opioid PMRs, the postmarketing requirements, this was more

than year-long process to work with the industry group to think about study designs and data sources and generalizability, and trying to think about how to get answers to these difficult questions.

So I'm not going to answer that question, but I think that's it's a question that needs to be answered.

DR. WINTERSTEIN: There were some earlier questions about the types of prescribers who prescribe actually opioids, and I think the FDA has some data for us on this.

DR. CERNY: So I'm going to try to focus people's attention -- I'm going to focus on the middle screen here. These are prescribing specialties. These are data for ER/LAs, data for IR opioids, and they all have the pre-implementation, the active period, and the statistical comparison, and the percent change.

So the green shade is for statistically significant decreases from the pre-REMS through the post-REMS period. The pinkish hue is for the statistically significant increases. So both for

ER/LAs and for IRs, you see an increase statistically significant for anesthesiologists. You see an increase -- nurse practitioners. Couldn't quite read that. I'm not 61 yet, but I'm getting there.

So then you see physician's assistants, increase, and you've heard from the RPC that these specialties, physician's assistants and nurse practitioners, are doing more and more of the writing of the prescriptions.

You do see on the IR side, increase in pain medicine statistically significant. You don't quite see that on the ER/LA side. And what I would point out here is you look at the relative numbers, look at the active periods, you see huge differences between the ER/LA and the IR in terms of numbers. But the question about dentists was brought up recently. About 2,000 versus writing IRs, it's 2 million. So obviously, there's a huge difference there.

Same thing with emergency specialists, you see a huge difference there. I imagine people come

into the ER and they sprain an ankle or something, so they get that. And then for surgeons as well, you see some numbers of ER/LAs, but certainly nothing compared to what you see with the IR opioids.

So that's sort of a general take. You can probably dig into some more sub-analyses, but those are from the RPC data that I've stuck into one table.

Any questions?

DR. WINTERSTEIN: Any questions to the table?

Dr. Morrato, you were actually on the list next anyway.

DR. MORRATO: This is very helpful. So the "all other" category under the ER/LA is what would be sort of your trailing not really -- it's a small group, right?

DR. CERNY: RPC, you guys can comment on this, but mostly about a third of these are not really -- whoever filled out didn't tell you what they were. So one-third are a mystery and then --

DR. MORRATO: Oh, so it's not a summation title for what's coming down --

DR. CERNY: No, no.

DR. MORRATO: Okay.

DR. CERNY: And then you have things like psychiatrists, I think they were near the top. You have cardiologists, hematologists, OB/GYN, specialties like that that are in the "all other" category. For the "all other" category for IRs, I didn't see a breakdown for that, but we didn't ask for that.

DR. MORRATO: So my question had to do with one of the things that we're being asked is whether or not we'd recommend expanding to immediate release or not. The thought I had here in just seeing these numbers, because I'm reflecting also on what the CME providers are saying in terms of excess burden and so forth, but this would -- so my question to myself was maybe the existing program is really targeting a group like they presented in their data in which, I don't know, 77 percent of them are also IR prescribers.

So by expanding the CME, how much are you really gaining? Maybe of the people who are doing immediate release, maybe in the ER/LA target for what we're doing. But this data would suggest that certain specialties are not going to be voluntarily or mandatorily if there's a ER/LA REMS, if they're just an IR opioid. So for instance, the ER/LA REMS is not going to really be getting surgery or emergency room or dentistry, et cetera.

So is that right? Is that how you would read it as well?

DR. CERNY: Yes, I would -- we don't know who takes the training, so I don't know without -- we have a disproportionate number of dentists there or what.

DR. MORRATO: Right. Okay.

DR. CERNY: But certainly, you look at the comparison, and that's I think -- trying to do the math real quick -- that's like 1 percent of this total or so.

DR. MORRATO: Okay. So then the other question, are there any other spillover effects

that we might be thinking of that are already reaching immediate-release prescribers or benefiting patients from a risk management that is a result of the ER/LA?

This is sort of maybe the tip of the spear, but it has a spillover. Is there any evidence that FDA has in that regard, or it's just not known or knowable?

DR. CERNY: I don't think we know. I think we assume that if you read about oxycodone, that you'll apply it to both, but we just assume that. We have no data.

DR. MORRATO: And there's no patient knowledge, anything in terms of how patients are thinking about these drugs? I'll give my own anecdote where my son had to get his wisdom teeth removed. There was no mention as to, oh, this is an opioid that I'm receiving or he had surgery.

You might want to group these in your mind that they're just like those bad things you're hearing in the news, right? So that's my experience.

I didn't know if you had any other -- if anyone has -- or if the companies have any experience in terms of how patients think about what is an opioid beyond just knowing it's a Percocet or a Vicodin. They're not necessarily thinking this is a class.

DR. CERNY: I don't think it's covered in the patient survey, that type of question.

DR. WINTERSTEIN: Dr. Stander.

DR. STANDER: Thank you.

First of all, as regarding this chart, I have two questions. On the nurse practitioners, physician assistants, their volume is going up, but it's also they're becoming a very significant part of the primary care workforce. So I just wonder how much that is really accounted for here.

The other thing is many of them may work in other specialty practices, and we just call them nurse practitioners or physician assistants. And some of them may be as part of an oncology or cardiology practice. So that might require some further breakdown.

The other question I have is the hospice and palliative medicine component seems woefully underreported there. I don't know if that's because people like myself who do part-time work with hospice and palliative medicine maybe don't identify themselves that way, but I know my hospice organization probably prescribes that many in whatever that -- I guess that's -- and I'm not sure what time frame that is, but that's a year.

So I'm not quite sure how to account for that, what appears to be incredibly low numbers for that discipline.

DR. CERNY: These are a three-month average, as I recall, from the utilization data, and I believe -- and I'll look at my utilization colleagues. I believe that there are some areas that are not included. And a lot of that is, if hospice, I think is hospital based. I don't think that's included here.

DR. STANDER: I had another question about Dr. McAninch's, but should I wait for that or?

DR. WINTERSTEIN: I think there's an answer

coming with the hospital data is --

DR. STANDER: Okay.

DR. CHAI: This is Grace Chai. I'm the deputy director for drug utilization. We'd actually prefer for the RPC to speak to this data because they actually generated it, but we believe that these are outpatient retail prescriptions.

DR. STANDER: Some hospices have their own pharmacy that are not typical retail pharmacies, and I don't know if that's lost in this data or not.

DR. COPLAN: Yes, that's correct. So this is what IMS would call different channels. This is retail pharmacies. So presumably, hospice care would be in long-term care or more in hospital or in -- so it would be captured more in other channels rather than going to CVS to buy an opioid.

DR. STANDER: And did you have anything about the NP and PA by primary care versus other worlds that they participate in?

DR. COPLAN: We don't have that, but what we do have is we looked into why the NP and PA

prescribing was increasing. And they increased by about 12 percent and 16 percent in terms of their numbers.

Can I just bring up the slide? So this is looking at -- this is from the Bureau of Labor Statistics for the U.S. Department of Labor, looking at the number of NPs and PAs. And I think, as you pointed out, they're an increasingly important part of the healthcare system. Dr. Cepeda presented data to show that they're prescribing of many different classes of medications, including antidepressants and hypertensive, is increasing more than the prescribing of opioids.

There was another question, I think, that Dr. Morrato had about the breakdown of the ER versus IR and what's the incremental number.

Do we have the pie chart? And it turns out that there's about roughly 1.1 million prescribers, according to IMS data, of opioids of which -- this is data from 2015 -- of which 322,000, roughly, prescribe both ER and IR together, about 3,000

prescribe only ER, and a further 755,000 prescribe IR only.

I'd also like to address Dr. Floyd's question about the randomization and why we didn't think about this kind of study design earlier. And when we were designing this in 2010, 2011, first of all, we weren't aware that there would be so many different interventions that would be occurring to address the problem.

But secondly, the solution to -- we couldn't get the name -- we couldn't get data on who had completed CE training because of the laws for commercial support, as mentioned, but the CE providers can.

So the Pri-Med example is where the CE provider is linked to the electronic health record. So we've seen the emergence of electronic health record system around the country, and the CE provider themselves can link to which of their prescribers have taken the training or not. So they do it internally. They're not passing it to a third party, and then they can do their evaluation

in the electronic health records. So we now have a new system we didn't think of -- it wasn't really available.

In terms of randomization, I think there's a trade-off because, clearly, we'd have to do propensity score matching at a minimum to ensure that comparability. But with randomization, we would have to implement a very intensive program of who gets the training and who doesn't.

So that would require more of a focused locale in which we would do the study, and then you wouldn't have the generalizability nationally, as opposed to using multiple electronic health records in which you do propensity score matching and you could get a much broader scope that way.

So I think there's a trade-off between generalizability and validity.

DR. FLOYD: So I'm actually not advocating for a randomized study design. I'm just raising the question of if you want an answer, if that's the one you need to use.

Just to clear up a misconception, propensity

score matching or adjustment won't make the groups comparable. You can only adjust whether you use propensity scores or individual variables as well as you actually measure the things that matter. And I'm not convinced that you can do that when you're comparing people who voluntarily sign up for a CME and people who don't.

DR. COPLAN: Yes, I think it would be a minimum, but it may not be sufficient.

DR. WINTERSTEIN: Dr. Galinkin.

DR. STANDER: Can I ask my question from Dr. McAninch?

DR. WINTERSTEIN: Oh, sure.

DR. STANDER: Thank you.

So first of all, I thought it was a really excellent presentation and pointing out all the pitfalls. I guess my question -- I have two questions.

One is we've been focusing on the number of prescriptions as a measure of total opioid use and sort of trying to explain if that's trend is going down but the CDC's talking about the increased

number of deaths. And I wondered, do you have the capability or any data around the number of actual pills prescribed and/or dosing, that even if the scrip numbers go down, we're actually prescribing higher morphine equivalents and so forth?

DR. McANINCH: Yes. A number of the IMS databases -- and Grace can speak in more detail about them but -- do have data on individual pills or dosage units, So that is something that could be looked at.

We saw some evidence that in -- there was a published study that looked at hydrocodone prescribing after it was rescheduled in October of 2014, and we saw a fairly large decrease in the number of prescriptions and a somewhat attenuated decrease in the number of pills, the number of tablets, indicating that perhaps since it's more difficult to refill a Schedule II opioid, that people are giving more drug per prescription.

So I think that's a good question and something worth potentially looking into some more.

DR. STANDER: Okay. The other question that

you were talking about appropriateness and how difficult it is to determine that. And to the extent that there would be any benefit of any looking at these prescriptions based on whatever visit code diagnostically was listed for -- and particularly on the ER/LA meds, if you'd be looking at a cancer diagnosis versus fibromyalgia or maybe something that others --

DR. McANINCH: Yes, right, so looking for indication --

DR. STANDER: -- indications for --

DR. McANINCH: -- critical context as we think --

DR. STANDER: Yes.

DR. McANINCH: Mentioned that the data that are based on prescription dispensing from pharmacies don't have any information on indication or clinical context. Potentially, EHR data, to some degree claims data, in that you could look for a claim that was close in time to a prescription. But I'm a physician, also, and I know when you have an office visit, you've got a lot of different

diagnoses and a lot of different prescriptions that you're addressing in one visit. So it's hard to link those up.

Grace can talk for just a moment about prescriber survey database that we use sometimes.

DR. CHAI: So Jana is correct. In terms of dispensed prescriptions that are based on dispensing transactions, the indication is not linked. There are other databases out there that may look at physician survey data, for example, but that's based on survey of sample of physicians.

Like, for example, 3200 prescriptions may fill out a survey every month on one day in their practice, and you can see what drugs they mention in what association with what diagnosis. But there is no linkage to the patient actually filling a prescription in those types of databases.

As Jana mentioned, there may be some data sources out there that may be more of an integrated healthcare approach where you may be look from EHR all the way to dispensed prescription, but that's a very certain type of database.

In regards to what kind of prescription data there are available out there, you can get pretty granular in terms of how many tablets were dispensed, what strength and what formulation, in case you were looking for that kind of information.

DR. STANDER: It just might explain, or at least even if the numbers are going down but the morphine equivalents are going up, it might help explain the CDC trend is all I was trying to get at.

DR. CHAI: So I think Terry Toigo mentioned in her presentation about the DHHS opioid agency priority goals.

Was that your presentation?

Oh, Dr. Woodcock's presentation where they mentioned that as one of the metrics.

DR. STANDER: Okay. Thank you.

DR. McANINCH: Can I make another comment just to follow up on the question about some of these indicators going down, but the CDC -- the overdose deaths don't seem to be going down with those.

I think we heard a little bit earlier about the fentanyl from clandestine labs that seems to be increasing and may be involved in some of those deaths. At that level, those are going to be coded so that they're lumped in with the rest of those opioid deaths that are not heroin or methadone so there's that.

Then there's also been a lot of work in the last couple of years in the medical examiner community to improve documentation in death certificates as far as what drugs were involved. And it varies widely across states, but we may also be seeing some changes as a result of improved documentation of drugs involved in overdose deaths. It's hard to say.

DR. WINTERSTEIN: Dr. Kaye.

DR. KAYE: I had a question for Dr. Kahn. So I wanted to ask your thoughts. I was a little taken aback where you didn't think that making testing be mandatory, that it really wouldn't change anything.

It occurred to me, I was thinking of some of

the people I've known over the years, some with no board certification who practiced and lost their license, some people who had many board certifications who have also their license.

If there was a mandatory testing with a report card on performance, looking at pharmacy prescribing or negative outcomes, just a kind of gestalt, would that be something that would change your view? In other words, would a higher expectation for a prescriber be better than lesser or not even an expectation for a provider with the epidemic that we have?

DR. KAHN: Okay. So a couple of responses. First of all, I didn't use the term "mandatory testing." I used the term "mandatory education." As a matter of fact, if we just separate those two for just a moment, my last comment was about the use of a clinical data registry, which currently doesn't exist for opioids but exists in many other conditions.

Essentially, what happens in a clinical data registry is that we identify performance measures

and then we test ourselves against the national benchmarks and compare ourselves to peers. That's the first thing that happens is we're tested.

We don't use the phrase. We use the phrase "we're measured." And then we get feedback on our performance. We identify a gap in performance. We obtain education to learn what to do differently. We implement the education and make the practice behavior change, see how our performance improves over time, and continually repeat.

That's a very different process than getting a letter from the state medical board that says you're licensed in this state. In order to be relicensed, you must take 3 hours of continuing education in opioids. That is a completely different process.

The former works. We see it. Now, there's 163 clinical data registries in conditions of all different types. The latter doesn't work. We have 19 states where it's all done politically, and we know what happens in mandatory education. That was what I was trying to say.

DR. KAYE: Okay. Thank you very much.

DR. WINTERSTEIN: Dr. Choudhry.

DR. CHOUDHRY: So I have a relatively specific and hopefully minor question. I think it's for Ms. Harris, although I suspect Dr. Coplan or team might be able to answer.

So it's on Ms. Harris slide 8, which is we've sort of heard quite convincingly that the generalizability of the survey data as a whole is somewhat limited. Nevertheless, I find it kind of curious that there's actually a number missing and nicely highlighted in red that should be knowable about the number from CE providers, the number of people that were invited. This should be a data point that should be addressable.

So I suspect, Ms. Harris, you don't have that number.

MS. HARRIS: Yes, I have it as a question mark because we didn't receive that. We didn't receive the number of people who were invited from the CE providers.

DR. CHOUDHRY: Is there someone else who

might be able to give us that number?

MS. HARRIS: Someone from the CE programs maybe.

DR. STEMHAGEN: Annette Stemhagen from United BioSource Corporation. The reason that we don't know that is because the invitations for the surveys -- because we couldn't know the names of those prescribers who took the CE -- were mailed out by the CE providers. Not all of them kept records of how many invitations were sent out.

So we don't have that metric. That has been corrected. And this year when we're right in the process right now of fielding that survey, that information is being provided.

DR. WINTERSTEIN: Ms. Shaw Phillips.

MS. SHAW PHILLIPS: This question is for anybody at the FDA. Are there any opportunities through -- and I realize there's problems with generalizability, but with closed system where you could test some of these hypotheses, say, VA, Department of Defense, where you have the knowledge of what providers completed the education and you

also have a system that will be a little bit more controlled than going out to -- but somewhat similar idea to the HR analysis that we saw here today that's preliminary.

Has any of that been investigated or under discussion?

DR. STAFFA: This is Judy Staffa. I think those are certainly possibilities. I think there's no limitation in terms of when you're trying to understand what's happening at the national level and that's where we've been focusing, I think it's a bad idea at all to be refocusing on where -- it's always the trade-off in epidemiology, is where can I get a lot of data on a few people as opposed to getting a little data on a lot of people.

So you need both of those going on at the same time so that you're understanding what could be happening in a microcosm, but then what could that possibly generalize to nationally.

I don't believe we've had those discussions with the folks we have agreements with because again, as a manpower issues, when we have sponsors

who are required to do these programs, we do our best to guide them, and to work with them, and to make sure any idea that occurs to us, we share with them to be exploring. So I think that's one of the goals of this discussion, is to be as exhaustive as possible with all the different ideas that we could have.

DR. STANDER: Could I comment a little bit on the VA? It maybe doesn't answer your question entirely, but I practice at a VA. I think we have another primary care physician who does.

VA has made it very difficult for primary care doctors actually to prescribe opioids on a chronic basis, which many of the primary care doctors, I think, welcome. A lot of the chronic non-cancer pain, the patients have to be referred, at least in my facility, to a pain management program where they are -- patients are educated and really try to be dissuaded from chronic opioid use.

VA's measuring the number of opioids per veteran per facility in comparative -- there's a little bit of a -- as I think Dr. Kahn was talking

about -- measuring and trying to change performance.

So I think it's a different approach, and it may be something to really look at the competence of people who are going to be using these medications on a chronic basis; or for complex patients, maybe it's not -- that kind of management shouldn't be with every possible doctor who sees these patients because they are very complex and you need a team and it's a comprehensive approach.

So anyway, that's a little -- it doesn't answer the question of can we test this out in the VA, we'll educate primary doctors and see how it affects, but in a closed system, you can sort of restrict some of the privileging, prescribing patterns akin to certain -- only cardiologists can prescribe this anti-rhythmic or only a ID doctor can prescribe this antibiotic.

I don't know if Dr. Hoffman wants to comment because she's a primary care doctor.

DR. HOFFMAN: So yes. The other thing that the VA has is there actually is a registry that's

been built for opioid use, and that registry looks at things like how many morphine equivalents is my patient on; are they on concomitant benzodiazepines; have I checked DAU within the past year; have I given the patient informed consent.

So that registry exists, and you could look to see is education on top of those things beneficial.

DR. WINTERSTEIN: Please go ahead.

DR. GARCIA-BUNUEL: I agree with my colleagues, and I just wanted to add a couple of comments or even ask a question related to that.

We are able in our system, in essence, to utilize a clinical data registry, and we do that with a variety of chronic disease conditions as well as in this case, utilization of a high-risk medication.

We have reframed the experience on same level with that intervention as now we have what's called -- it's an informed consent, part of the EMR/iMED consent for prescription of chronic opioids for non-malignant pain. So we are in the

midst of constantly reevaluating ourselves using real-time data, patient data and outcomes.

Having said that, I know it's getting towards the end of the day and I was starting to fade into more of kind of looking at the historical context of this. We've heard a lot of data, a lot of very interesting data, excellent presentations from all involved.

I go back a little bit to some other questions about the history of this group and where we are now with REMS in this rendition for the ER/LA opioids.

Are we in a position to -- especially given some of I would say the fuzziness and lack of clarity in the data thus far, are we in a position to interpret the FDA's role to say we should be moving towards clinical data registries; we should not be designing programs that are going to hinge on retrospective looks at observational data?

We're probably not in a position to design some of the studies that some people would love to see, and therefore, given the critical nature of

this problem nationally, could we -- knowing that we've got states that are very proactive on a multi-pronged approach, but could we use the leverage of both DEA registration of prescribers, continuing development of these PDMP programs, bit more specifically, move away from a discussion of voluntary versus mandatory continuing education and really look at patient-oriented outcomes related to how the healthcare system is interacting with patients?

I guess that's kind of a big FDA question if anyone wants to take that on.

DR. KAYE: In our hospitals today, we have report cards on -- I fill out over 100 of them a month, on anesthesia providers, looking at all these different outcomes.

The challenge is if you go across the country, the average person is not working within a closed system. They're working within their own clinic, and they're doing whatever they want. And some are well-trained and some are not trained at all. That's really where the big hole is or

breaking point in our national system, in my opinion. Thank you.

DR. WINTERSTEIN: Dr. Hertz.

DR. HERTZ: Just to get to the question, I think it's really more for the discussion tomorrow, but the way you phrase it, is FDA saying we should work toward something given the challenges, no, we're not saying that.

We're asking, as you'll see tomorrow with our very long list of questions because we have a lot of questions -- we're trying to lay out what we've been able to collect, what the RPC has been able to accomplish, what we now understand that wasn't yet known when all of this was started.

So we're at this stage of an assessment. Here's what we know now. And then we're going to ask you where you think we should go on a number of different items, including the assessment itself. But we're not suggesting a path. We're really honestly asking.

DR. WINTERSTEIN: Dr. Raghunathan.

DR. RAGHUNATHAN: Yes. About the table that

FDA presented about the number of prescriptions, it is hard to really judge it without having a proper denominator. Just looking at the numerator alone, although it's a 3-month average, there are a lot of other things that could change if the patient population changes or prescriber changes, shifting a prescription from a PCP to the physician assistant.

So do you have any data on the denominator so that we can normalize comparisons between pre and active periods?

DR. HERTZ: This is Sharon Hertz. This was data from the RPC, so I'm going to redirect your question to them.

MS. PHILIPS: I'm Syd Philips from IMS Health, and for these prescription volume, we did not measure the denominator and switching of the number of PCPs, for example, who are prescribing in the pre-implementation period versus the active period.

DR. WINTERSTEIN: Dr. Buckenmaier.

DR. BUCKENMAIER: I just couldn't let the VA

have all the fun and not have the DoD say one thing.

We decided, quite a while ago after 15 years of conflict, that the fact this society has about 5 percent of the world's population and consumes 80 percent of the opioids, we just didn't believe it was that painful living in this country, the current political situation notwithstanding.

(Laughter.)

DR. BUCKENMAIER: So our focus was on finding not alternatives but adjuncts to a standard pill for every ill, and certainly, if I have pain, I should be leaving with a pill, which was not serving our population. It was certainly not serving our veterans.

So like the VA, which I think provided a lot of leadership in this area, we adopted the Stepped Care model. But to your question, we decided we could not rely on our data systems because, as I've heard today, it was just as difficult to determine whether or not what we were doing was making a difference.

so we're ongoing towards a prospective registry to do exactly what you're describing, but the focus is more on not so much -- and I'm not belittling the REMS; I think it's a very important program -- when we have to use opioids, using them correctly. But our focus has been on why are we using so many opioids. And maybe our focus should be on how do we manage pain in a better way so that this problem begins to take care of itself by taking the emphasis away from that particular approach.

We're going to use this registry we call PASTOR, which leverages NIH PROMIS measures for those patient-reported outcomes data to determine those adjuncts.

Only one time today -- I think it was Dr. Argoff, to his credit -- even mentioned complementary and integrated medicine. So I think personally today for me, that's a hole in this system, understanding what is it about our prescribing practices and our management practices of pain that's driving this opioid system. Thank

you.

DR. WINTERSTEIN: Those were very nice final words.

I think we have two more questions, and let's focus on clarifying questions for today so that I can get you guys home on time today, And then we can go into the discussion tomorrow.

We have Dr. Hoffman.

DR. HOFFMAN: I asked my question.

DR. WINTERSTEIN: Oh, sorry. I cannot read -- next to Dr. Hoffman, somebody down there had a question. You're very far, far away.

DR. BOHNER: It's kind of small. Dr. Bohner from -- so my question is for the last set of presenters. It sounded like that there's support for expanding the training to the IR SA opioids, but it also sounded like one of the major barriers to participation is the length of the training.

I'm curious if you've done any work within your organizations to figure out whether you can incorporate that information while not making it even longer.

MS. KEAR: Cynthia Kear. I'll take a pass at that. I think that this is where considering principles of adult education would be very, very helpful in terms of looking at providing the information. The blueprint, as you probably know, is 8 pages, single spaced. It's very, very dense, demanding content.

It doesn't mean that it can't be delivered, but I think the way the whole tracking mechanisms have been set up is that it has to be a one-time shot. Adult education would certainly allow for serialized modularized education, some of the blended models that RPC talked about earlier today.

But I would recommend we take a step back and really think about some of the design options and make sure that the tracking, reporting systems could align with those because our original ideas were not for how we are implementing it now, but rather, we had to move to that in order to fulfill the reporting and the tracking.

But it can be done within a broader context if we can all take a step back.

DR. KAHN: I would just add that I would need one thing in order to incorporate IR, and that is I have no trouble selling the outcomes of extended-release and long-acting opioids. Just the statistics on deaths are so compelling that we've got 26 national organizations brought in to focus in on this solely.

I need the same data for IR, and I heard somebody earlier talk about the fact that you could do a tox screen and you don't know if it's IR or ER/LA. But I would need that kind of data to be able to convince the 26 organizations that adding IR would be good. It just needs to be linked to the outcomes that we're trying to deal with.

DR. WINTERSTEIN: And finally, Dr. Morrato.

DR. COPLAN: Could Dr. Dan Alford please comment?

DR. WINTERSTEIN: Oh, you were sneaking up there and I didn't see.

DR. ALFORD: I was sneaking up.

DR. WINTERSTEIN: Please go ahead.

DR. ALFORD: I'm Dan Alford. I'm a general

internist, primary care doc, but I'm the director of the Scope of Pain REMS program. And I'll just say that we have already incorporated IR opioids in our curriculum, and we've also incorporated multimodal care.

I think for teaching adults, you need to put opioids in perspective and ER/LA opioids in perspective, and the way we've been able to do that all in 2 hours is to really put a lot of the drug-specific information in reference materials and teaching people when they need to look those things up; because as you saw in all the knowledge-based assessments, people forget that stuff, and I forget that stuff. As long as I know when I need to look it up and where to find it, that's the way we do it.

So some of these REMS programs are not all about ER/LA opioids. We talk about IR opioids. We talk about multimodal care. We talk about the whole spectrum of pain care. You bring adults into a learning environment for 2 hours or 3 hours on a weekend, you really need to put everything into

perspective. You can't just talk about one type of drug.

DR. WINTERSTEIN: Dr. Morrato.

DR. MORRATO: I'll make mine quick. I'm just wondering in the spirit of the clinical registry, there's a series of quality indicators they're now publishing. So I know looking at doctor shopping or high dosage. I know PCQA endorsed three new ones.

So I was wondering if the FDA's surveillance efforts or the companies are also starting to track what are system quality indicators in this area, if they'll go back retrospectively where possible but start looking at trends.

DR. COPLAN: One of the postmarketing study programs is looking at developing a validated measure of doctor shopping because there's been a number that have been looked at in the literature but haven't really been validated. So we're measuring that in three different studies, comparing doctor shopping outcomes against electronic medical records, patient report, and the

diagnostic algorithm that I referred to earlier.

So once we have better validated measures, we could look at those as outcomes.

DR. MORRATO: The opportunity is while you're validating that there's at least going to be standards the health systems are reporting. So they may not be as valid, but some of them relate to high dosage use, et cetera, that might be worth kind of adding into the surveillance portfolio.

DR. COPLAN: We haven't thought of PQA. That's a good idea. Thank you.

DR. WINTERSTEIN: Before we adjourn for the day, are there any last comments from the FDA, or would you like to reserve them for tomorrow?

DR. LaCIVITA: No. We just want to thank you for your attention and participation today, and look forward to tomorrow.

Adjournment

DR. WINTERSTEIN: Thank you.

The meeting for today is now adjourned.

Panel members, please remember that there should be no discussion of the meeting topics, or

politics, amongst yourselves or with any other member of the audience.

Please take all personal belongings with you as the room is cleaned at the end of the meeting today. All materials left on the table will be disposed of, so if you want to keep the slides, take then with you.

We will reconvene tomorrow morning at 8:00 a.m. Have a good night.

(Whereupon, at 5:06 p.m., the meeting was adjourned.)