FOOD AND DRUG ADMINISTRATION

Evaluating the Effect of the Opioid Analgesics Risk Evaluation and Mitigation Strategy Education Program on Prescribing Behaviors and Patient Outcomes

Exploring the Path Forward for Assessment

Virtual Public Workshop

Friday, December 11, 2020

9:00 a.m. to 4:20p.m.

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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

(9:00 a.m.)

Welcome and Introduction – Judy Staffa

DR. STAFFA: It's 9 a.m., so given that we have a lot to pack into today's meeting, I'd like to get us started. I want to thank all of you for joining us this morning and taking the time. We look at this as a very important scientific workshop, and we're holding it virtually, which I'm sure will have its challenges. But I appreciate your patience and bearing with us, and I'm hoping we're going to have a good discussion despite that.

We will be talking today about rigorous scientific approaches for evaluating the impact of the Opioid Analgesic REMS Educational Program on Prescriber Behavior and Patient Outcomes. As we start this meeting, I would like to point out that unlike many of FDA's public meetings, this meeting is not an advisory committee meeting. I'm sure many of you may have dialed into the advisory committee meeting on the new vaccine yesterday, and this is a very different type of meeting.

So we will not be asking any direct questions, or voting questions, or asking for this panel's advice or recommendations on regulatory aspects of the Opioid Analgesic REMS program. Rather, we've invited you all to join us today and to put on your scientist hat because what we'd like to talk about are study designs, outcomes, and methods that might be feasible to use to evaluate these programs despite some of the considerable challenges, which we've tried to lay out somewhat in our Federal Register notice, as well as our issues paper we attached to that.

Again, this has been a challenging area, and we'll be recapping some of those issues in our presentations this morning just to make sure everyone's on the same page as we begin our discussion this afternoon.

On a practical note -- and I mentioned this earlier for those who dialed on earlier -- we would like to alert you that we're not going to be generally using our webcameras for today's meeting, and the reason for that is just to avoid any kind

of bandwidth or technical difficulty. However, our presenters this morning, those who are going to be presenting slides, do have the option of turning on their camera during their presentation if that makes them feel more comfortable, but then we ask that you turn it off when you're done.

When we get to the discussion sessions this afternoon, we're going to go over the procedures of how we use the hand-raising functions in Adobe Connect, but we will not be using the webcams for the discussion period at the time.

So I'd like to start out today by going around our virtual table and having each of our panelists and our FDA participants to just briefly introduce themselves, and that way we can also do just, I guess, one more sound check to make sure we hear everybody before we start. I'm going to start with the panelists. When I call your name, if you could unmute yourself, and introduce yourself, and then go back on mute, that would be great.

Let's start with Dr. Alexander.

DR. ALEXANDER: Hi. Good morning. My name

is Caleb Alexander. I'm a practicing internist and professor of epidemiology and medicine at Johns Hopkins.

DR. STAFFA: Thank you.

Dr. Anderson?

(No response.)

DR. STAFFA: Dr. Anderson, we can't hear you. I'm not sure if you're trying to speak.

(No response.)

DR. STAFFA: Okay. We'll come back to Dr. Anderson.

Dr. Becker?

DR. BECKER: Good morning. Will Becker, associate professor at Yale School of Medicine, general internist, and core investigator at the PRIME Center of VA Connecticut. Good to be here.

DR. STAFFA: Thank you.

Dr. Cervero?

DR. CERVERO: Good morning. This is Ron Cervero. I'm a professor and deputy director of the Center for Health Professions Education at the Uniformed Services University of the Health

Sciences. Thank you.

DR. STAFFA: Thank you.

Ms. Cruz?

MS. CRUZ: Hello. My name is Kari Cruz, and I'm a lead health scientist at the Center for Disease Control and Prevention's Division of Overdose Prevention. Thank you.

DR. STAFFA: Thank you.

Dr. Floyd?

DR. FLOYD: Good morning. This is James Floyd. I'm an associate professor of medicine and epidemiology at the University of Washington, and I'm a practicing internist.

DR. STAFFA: Thank you.

Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: Good morning, everybody. Martin Garcia-Bunuel. I'm a primary care physician and also the deputy chief of staff of the VA Maryland Health Care System.

DR. STAFFA: Thank you.

Dr. Goldmann?

DR. GOLDMANN: Hi. It's Don Goldmann. I'm

an infectious disease consultant and epidemiologist at Boston Children's Hospital, and professor of epidemiology at Harvard TH Chan School of Public Health, and also chief scientific officer emeritus at the Institute for Healthcare Improvement.

DR. STAFFA: Thank you.

Dr. Howley?

(No response.)

FEMALE VOICE: I believe Dr. Howley will be joining late.

DR. STAFFA: Oh, okay. I see her name listed, so I thought perhaps she had joined. We'll circle back to Dr. Howley.

Dr. Katzman?

(No response.)

DR. STAFFA: Dr. Katzman?

(No response.)

DR. STAFFA: Okay. We'll circle back to Dr. Katzman.

Dr. Larochelle?

DR. LAROCHELLE: Hi. I'm Marc Larochelle. I'm a primary care physician and Health services

researcher with a focus on chronic pain and addiction at the Grayken Center for Addiction at Boston Medical Center.

DR. STAFFA: Thank you.

Dr. Losby?

DR. LOSBY: Yes. Good morning. My name is Jan Losby, and I'm from the CDC. I'm a branch chief for the Health Systems and Research Branch in the Division of Overdose Prevention, and my background is as a program evaluator.

DR. STAFFA: Thank you.

Dr. McMahon?

DR. McMAHON: Good morning, everyone from Chicago. I'm Graham McMahon. I'm an endocrinologist and internist and an adjunct professor of medicine and medical education at the Northwestern University, and CEO at the Accreditation Council for Continuing Medical Education.

DR. STAFFA: Thank you.

Dr. Morrato?

DR. MORRATO: Good morning. This is Elaine

Morrato. I'm an epidemiologist as well as a dissemination and implementation scientist. I'm professor and founding dean at the Parkinson School of Health Sciences and Public Health at Loyola University in Chicago.

DR. STAFFA: Thank you.

Dr. Roach, have you joined us?

(No response.)

DR. STAFFA: Dr. Roach?

(No response.)

DR. STAFFA: Okay. We'll circle back to Dr. Roach.

Dr. Sandbrink?

DR. SANDBRINK: Yes. Good morning. I'm a neurologist and pain physician at the Washington DC VA Medical Center. I'm a clinical associate professor of neurology at Uniformed Services University, and I'm the national program director for Pain Management and Opioid Safety and PDMP for the Veterans Health Administration.

DR. STAFFA: Thank you.

Dr. Thomas?

DR. THOMAS: Yes. Hi. Good morning. It's Dave Thomas. I'm in the NIH OD. I'm a senior advisor to the director of the Office of Research on Women's Health, and I'm also a founding member of the NIH Pain Consortium.

DR. STAFFA: Thank you.

Dr. Walker?

DR. WALKER: Good morning. This is Alec Walker. I'm a pharmacoepidemiologist. I'm a principal at World Health Information Science Consultants. It's WHISCON.

DR. STAFFA: Thank you.

Ms. White?

MS. WHITE: Good morning. My name is Julie White, and I'm the director of Continuing Medical Education at Boston University School of Medicine.

DR. STAFFA: Thank you.

Dr. Winterstein?

DR. WINTERSTEIN: Good morning. I'm a pharmacoepidemiologist. I'm professor and chair of Pharmaceutical Outcomes and Policy and director of the Center for Drug Evaluation and Safety, both at

the University of Florida.

DR. STAFFA: Thank you.

Now, I'm going to circle back.

Dr. Anderson, could you introduce yourself?

DR. ANDERSON: Good morning. Sorry. I got dropped off, and I'm back. Daren Anderson. I'm a general internist health services researcher and the director of the Weitzman Institute in Middletown, Connecticut.

DR. STAFFA: Great. Thank you.

Dr. Howley, have you joined us?

DR. HOWLEY: Yes. Hello. This is Lisa Howley. Good morning from North Carolina. I am senior director at the Association of American Medical Colleges and delighted to be here.

DR. STAFFA: Thank you.

Dr. Katzman?

DR. KATZMAN: Can you hear me now?

DR. STAFFA: Yes, we can.

DR. KATZMAN: Oh, great. I'm a professor of neurology and psychiatry at University of New Mexico, and I direct the public health initiatives

at Project ECHO. Thank you.

DR. STAFFA: Thank you.

And Dr. Roach? Has Dr. Roach joined us yet?

(No response.)

DR. STAFFA: Okay.

Rich and Paul, if you could let us know when Dr. Roach joins us, we'll have him introduce himself at that point.

MR. TRAN: Will do, Judy.

DR. STAFFA: Thank you.

Okay. Well, thank you all for being here. You can tell we've assembled a very broad group of folks from all different disciplines to have this discussion. We think that all these different disciplines will inform our thinking in this area.

I now have the great pleasure to introduce Dr. Patrizia Cavazzoni, who is the acting director of the Center for Drug Evaluation and Research at FDA, who will provide some opening remarks.

Dr. Cavazzoni, are you on the line and able to hear us?

(Pause.)

DR. CAVAZZONI: Good morning.

DR. STAFFA: Good morning. Dr. Cavazzoni, we can hear you. Can you hear us?

DR. CAVAZZONI: Yes. Can you hear me? Can you tell me that you're hearing me?

DR. STAFFA: Yes, we can.

DR. CAVAZZONI: Alright. Thank you.

DR. STAFFA: Thank you. Please go ahead.

DR. CAVAZZONI: Very good. There was silence.

Opening Remarks - Patrizia Cavazzoni

DR. CAVAZZONI: Good morning, and I'm sorry for the technical glitches, which are of unknown origin.

Good morning. I'm really pleased to be here and to provide some introductory remarks. I would like to start by welcoming all the attendees and thanking you for the time that you're taking to join this important meeting.

We have convened this scientific workshop to discuss ways to evaluate the impact of the Opioid Analgesics Risk Evaluation and Mitigation Strategy,

or OA REMS, on prescriber behavior and patient outcomes. The Opioid Analgesic REMS, required by the FDA and implemented by the manufacturers of opioid analgesics intended for use in an outpatient setting, is one strategy among multiple national and state efforts to reduce the risk of abuse, misuse, addiction, overdose, and death caused by prescription opioid analgesics.

The primary component of this risk evaluation and mitigation strategy is a voluntary education program for prescribers, nurses, pharmacists, and other healthcare providers involved in the treatment or monitoring of patients with pain.

A consortium of manufacturers, known as the REMS Program Companies, provide grants to accredited continuing education providers, who then developCE activities for healthcare providers. This RPC is also required to conduct annual assessments of the REMS and provide summaries of data to FDA that are used to determine whether the REMS is meeting its risk mitigation goals.

Although the REMS assessments examine many aspects of the process and outcomes of the REMS CE program, the focus of our discussion today would be evaluation of the effects of REMS CE on prescriber behaviors and patient outcomes.

Despite efforts in recent years to improve the assessment of the opioid analgesic REMS, many scientific challenges remain. Foremost among these is the wide variety of CE venues, formats, and targeted healthcare provider types for the currently funded REMS CE activities, as well as expectations of effect from a one-time completion of the CE. In addition, multiple concurrent education activities from non-REMS sources may make the effect of REMS-compliant CE more difficult to detect.

Our panelists today include individuals with expertise in dissemination and implementationscience; public health; health services research; pharmacoepidemiology; program evaluation; and CE program implementation and assessment.

The workshop has three main objectives.The first objective is to discuss what specific measurable outcomes might demonstrate that training -- based on the opioid analgesics REMS education blueprint for health care providers involved in the treatment and monitoring of patients with pain, the FDA blueprint -- is effective in educating prescribers and other healthcare providers, including pharmacists and nurses, involving the treatment and monitoring of patients in pain and about recommended pain management practices and the appropriate use of opioid analgesics.

The second objective is to discuss the feasibility and value of various approaches to studying the specific effects of the opioid analgesics REMS continuing education, CE, on prescriber behavior and patient outcomes amidst the numerous concomitant strategies to combat the opioid crisis at the federal, state, and local levels.

The third objective is to discuss whether

there might be suitable alternative study approaches to better understand the influence of CE more broadly on pain management practices and patient outcomes.

FDA's regulatory decisions relating to opioids are guided by our goal to protect and advance public health. Achieving this goal involves ensuring that safe and effective therapies are available to meet the medical needs of people living with pain, maximizing the safety of those products, and conveying accurate information that can enable the public, patients, healthcare providers, insurance, and others to make informed evidence-based decisions about the use of these products.

FDA also has an imperative to make positive contributions to addressing the public health crisis in addiction and overdose involving opioids. This broader public health lens is reflected in our recent draft guidance on Considerations for Benefit-Risk Assessment of Opioid Analgesic Drugs. Effectively addressing this continuing crisis will

require multiple interventions and many stakeholders working together in a coordinated way.

FDA continues to support this critical effort to further educate healthcare professionals on pain management and safe opioid prescribing practices, as well as developing effective non-addictive products for the treatment of pain, expanding therapeutic options for the treatment of substance-use disorders, and encouraging the availability and use of overdose reversal medications. We appreciate your joining us for this important workshop and look forward to a fruitful day of scientific discussion.

DR. STAFFA: Thank you so much, Dr. Cavazzoni. We very much appreciate your setting this up and framing the discussion we're going to be having today.

Before we get started, we're going to have a series this morning of background talks to get everyone kind of up to the same speed on the history and where we have been so that we can frame our discussions for moving forward this afternoon.

Before I begin, I just wanted to make sure I introduced all of the FDA folks who have been involved with this meeting planning, the small core group.

I'm Judy Staffa. I should have introduced myself at the beginning. I am the associate director for Public Health Initiatives in the Office of Surveillance and Epidemiology. I will call on my co-conspirators on this meeting as well and ask them to introduce themselves.

Dr. Manzo?

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

DR. STAFFA: Thank you.

Dr. McAninch?

DR. McANINCH: Hi. Good morning. I'm Jana McAninch. I'm a senior medical epidemiologist in the Division of Epidemiology in the Office of Surveillance and Epidemiology here in CDER.

DR. STAFFA: Thank you.

Dr. Auth?

DR. AUTH: Good morning. This is Doris Auth. I'm a pharmacist by training and currently the acting deputy division director in the Division of Risk Management in the Office of Surveillance and Epidemiology.

DR. STAFFA: Thank you.

Dr. LaCivita?

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

DR. STAFFA: And Dr. Liberatore?

LCDR LIBERATORE: Hi. Good morning, everybody. My name is Lieutenant Commander Mark Liberatore. I'm a pharmacist officer in the U.S. Public Health Service, and I serve as deputy director for safety here at FDA's Division of Anesthesiology, Addiction Medicine, and Pain Medicine, also known as DAAP, and that's in the Office of New Drugs in CDER.

DR. STAFFA: Great. Thanks, team. As you

can imagine, there are a lot of other folks behind the scenes making this meeting happen, so thanks to all of them for all of their hard work.

Now I'm going to turn things over to Dr. Manzo, who's going to give us some background on this opioid analgesic program to make sure everybody's up to speed.

Claudia, can I turn it over to you?

Presentation - Claudia Manzo

DR. MANZO: Yes. Thanks, Judy.

This morning I'm going to provide some background on the Opioid Analgesic REMS, both the components and how we got there, as well as the REMS assessments more generally and for the Opioid Analgesic REMS, and then also to follow up with walking through the agenda, and then conclude.

For those that may not be aware, a risk evaluation and mitigation strategy is a drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the drug outweigh its risks. It can include a number of interventions that

really would be designed to help reduce the occurrence or the severity of those serious risks.

FDA has the authority to require a REMS before approval or post-approval if we become aware of new safety information. In making those determinations as to whether a REMS is required, FDA must consider a number of factors which I won't go into detail about. Some additional key points about REMS, the first is really more process related. FDA notifies the company when a REMS is required and the elements of that REMS.

The sponsors actually design and develop those programs and FDA reviews and approves the REMS. The sponsors are also required to conduct an assessment and submit the assessment of the REMS to FDA, and FDA reviews it to determine whether the REMS is meeting its goals. REMS programs can be designed for a single product, an innovator product with its associated generics or potentially biosimilars, or a class of products.

Because of the variations in requirements and possible restrictions, REMS can add

administrative burdens to the healthcare delivery system and may unintentionally create barriers to patient access. That's something we very much have to consider as we're working with sponsors to develop these.

The REMS for the extended-release and long-acting analgesic program really started around 2009. This was right after, or closely after, we had our REMS authority. At that time, because of increasing overdose deaths, FDA notified the application holders of all of the extended-release and opioid analgesic products that a REMS was going to be required for these products to ensure the benefits outweigh the risks.

Because of the size and scope of this program, FDA sought quite a bit of stakeholder feedback before making a determination of what the elements would be, and then in 2011, FDA officially notified the sponsors of the required components and asked them to submit the proposal. In July of 2012, FDA approved the extended-release Opioid Analgesic REMS, which is a shared-system REMS.

As mentioned before, the primary component is a voluntary educational program that was targeted to prescribers of these products and the education was focused primarily on the risks and safe use of those products. The education was developed by accredited independent CME providers based upon the blueprint that was developed by FDA.

The REMS also includes patient materials, including a patient counseling document and a product-specific medication guide, as well as a requirement for the RPC. That's the actual industry group that was formed to develop, implement, and assess the REMS. The requirement is also for that group to assess the impact of the REMS.

In 2016, after FDA received the first full assessment of the REMS, FDA convened a joint meeting of the Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees to obtain input on whether the REMS was meeting its goals; whether there were alternative methods to evaluate the program; whether the FDA

educational blueprint should be revised or expanded; whether the program should be expanded to include the immediate-release opioid analgesics; and whether there were any additional modifications that should be made to the REMS.

The advisory committees gave us quite a few recommendations in modifying the REMS, including that the REMS should be expanded to include the immediate-release opioid analgesics. They recommended that the focus of the education should be expanded to include general pain management principles and the risks and benefits of various pain treatments.

They recommended that the training be mandatory for prescribers, though they recognized the difficulties and the feasibility of doing so under the REMS authority was difficult, and it was preferred that this be implemented either through DEA registration or state licensure. Finally, they recommended that the training should be expanded to the entire healthcare team, not only to prescribers.

They also recommended a number of improvements to REMS assessments. Regarding surveys, they thought there should be a better sampling approach and that surveys that are conducted for evaluation purposes, should be shortened, and that the sample sizes should be larger and more generalizable.

They also pointed out that monitoring the level of opioid analgesic prescribing is not helpful without some evaluation of whether the prescribing is appropriate, though they struggled with how to define appropriate prescribing.

The committees suggested that drug utilization and patient outcomes data can be tied to the educational program to see how the REMS directly affects physician and patient behavior, including the pre- and post-comparison of those changes in behavior.

The modified REMS was approved in September 2018. It is now referred to as the Opioid Analgesic REMS, and the requirements were expanded to include the manufacturers of all

immediate-release, extended-release, and long-acting opioid analgesics that are intended for outpatient use and not covered under another REMS.

As with the previous program, the primary component is an education program. The target audience has expanded to include other members of the healthcare team, including pharmacists and nurses. The manufacturers again are required to make this education available and are doing this by providing unrestricted grants to CE providers to develop content based on an expanded blueprint.

That training was first made available in March of 2019. I want to point out that the education under the program remains voluntary and is not required in order to prescribe or dispense the drugs. Again, there are patient materials. We've made some changes, fairly extensive changes, to the patient counseling document, and that did undergo user testing.

This is the goal of the opioid analgesics REMS. I'm not going to read it. It was revised to align with the components of the program. While

the objectives are really more tied to the imparting knowledge to healthcare providers and patients, the aspirational goal is that that knowledge would assist healthcare providers in reducing adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing.

I'm now going to turn to REMS assessments. When the REMS authorities were put into place, this was really the first time that FDA could require sponsors to conduct an assessment of their risk mitigation strategy. We really are still fairly early in that, kind of in our adolescence years of understanding how to do this, and we are gaining experience.

What the statute specified was that the REMS shall include an assessment of the extent to which the REMS is meeting the goals or whether one or more goals or elements should be modified. The statute does not specifically describe how a sponsor would conduct an assessment.

I want to acknowledge that there has been

recent criticism of FDA's oversight of REMS assessments. For example, REMS assessments do not always include the information needed or high-quality data necessary to determine if REMS is meeting its goals. FDA's review of REMS assessments and actions on REMS assessment findings are not timely. And with respect to the Opioid Analgesic REMS, the FDA has abandoned its effort to require evaluation of the Opioid Analgesic REMS continuing education impact on prescribing behaviors and patient outcomes.

To address that criticism, we are focusing greater now on assessment planning by developing and incorporating assessment planning into the design of a REMS and by directing sponsors to link the design with the assessment and ensuring sufficient and appropriate data collection.

We're also working to identify key metrics and threshholds for program success, and ensuring timely REMS methodology submissions that include sufficient and appropriate data collection and analysis.

This is a model that was created by Elaine Morrato, one of our panelists, as well as Gita Toyserkani and Linda Huynh from the Division of Risk Management. It really provides a holistic view of an evaluation of a mitigation strategy that links input to performance outcomes and health impact.

We are just beginning to pilot this within the Division of Risk Management, and while we didn't apply the opioid analgesics REMS assessment plan to this model, as you can see, we would follow directly under the knowledge skills category for its intervention. If you follow along that same row, you can see how that intervention might impact performance outcomes and health impact.

I'm going to now turn to the Opioid Analgesic REMS assessment and describe what the elements of the assessment plan are. The RPC or the sponsors were required to provide metrics on the program implementation, including information on the distribution of REMS letters, which were sent to healthcare providers and professional

societies informing them about the availability of the continuing education. They provide information on the status of grants that are awarded, the availability of CE activities, and the composition of the grant review committee. There's also information on REMS CE learner metrics, as well as results of independent audits of continuing education.

We do have some preliminary data from our 24-month REMS assessment that was submitted by the RPC. During this grant review period, they awarded 12 grants that included nearly 100 continuing education activities with a variety of formats, including didactic; case-based; multimedia; interactive; and adaptive design.

These are some numbers of the learners that completed the REMS CE activity. This really covers the period of about two months after it was first made available for an entire year, so up to May of 2020. As you can see, approximately a little over 100,000 healthcare providers have completed the REMS CE with about 70 percent of these describing

themselves as opioid prescribers and about 60,000 having a license to prescribe a controlled substance. Most of these learners are physicians and advanced practice nurses, so we have a variety of other disciplines, which is exactly who the REMS education was targeted to.

The RPC is also required to conduct an evaluation of healthcare provider knowledge, including pre- and post-continuing education activity testing, as well as a long-term evaluation of the retention of the knowledge. Both of these will inform the first objective of ensuring that the training based upon the blueprint is effective in educating prescribers and other healthcare providers.

The assessment plan also includes an evaluation of patient knowledge and experiences, including a survey of patient understanding, as well as an evaluation of patient experiences around pain management, which will be conducted using focus groups. These will inform objective 2, which is informing patients about their roles and

responsibilities regarding their pain management plan, risks, and safe use of opioid analgesics.

The RPC was also asked to provide an evaluation of concurrent educational interventions because we wanted to understand how REMS CE fits into the larger scope of other educational interventions that are being implemented. They also provided a summary of major legislative and policy changes between 2016 and 2018 that may impact prescriber behavior.

The RPC continues to monitor national data on opioid misuse, abuse, overdose, addiction, and death, and national drug utilization trends of opioid analgesics. While these evaluations do not directly inform the goal or objectives, they do provide contextual information and could give us information at a population level.

Finally, and of course the subject of this particular meeting, the RPC was directed to evaluate prescriber and patient outcomes that are impacted specifically by the REMS CE. The approval letter specifies that the RPC should use an

appropriate control group to control for confounding and to allow for an assessment of whether any of those changes in prescriber behaviors or patient outcomes can be attributed to the CE.

The RPC was directed to develop and use metrics that assess prescriber behaviors and patient outcomes relating to the key messages in the FDA blueprint and that this evaluation should also include an evaluation of unintended adverse patient outcomes resulting from changes in prescribing practices. These metrics would inform the aspirational goals and intent of the education and will be the focus of our discussion today.

This morning you're going to be hearing a number of presentations, so we ask you to bear with us. We will hear shortly about the REMS blueprint, the FDA blueprint that is, as well as how the CE community has actually implemented and developed content based upon that blueprint.

You'll then hear a number of presentations about what's been done by the RPC so far and others

to evaluate the REMS education, as well as some experience that the CDC has in evaluating the opioid guidelines. Then you'll hear more about possible other complementary evaluations and about how the CE community generally evaluates continuing education.

Following lunch, we'll begin our panel discussion, the first being a discussion of the measurable outcomes to evaluate the effectiveness of the training. The second will really be a discussion of the feasibility of studying the impact, particularly amongst the concurrent interventions. Then lastly, there will be a discussion of alternative or complementary approaches to broadly evaluate the impact.

This will be followed by a public participation session for individuals that pre-registered. If attendees have comments, they won't be able to speak today, but they'll have the opportunity to submit their comments to the docket until February 11, 2021, and we hope to adjourn somewhere between 4:30 or 5:00, and I will now turn

it back to Judy.

DR. STAFFA: Thank you very much, Dr. Manzo.

I wanted to just make a note that if folks have questions about anything they're hearing in the presentation, we're hoping to just fold those in to this afternoon's session. So we won't be stopping for clarifying questions because we think that a lot of those questions will actually be very pertinent to the discussion anyway. So just take your notes, and we'll be folding those in this afternoon.

Before we go ahead with Lieutenant Commander Liberatore's presentation, I've noticed that Dr. Roach from CMS has joined us.

Dr. Roach, could you introduce yourself since we missed you this morning?

DR. ROACH: Sure, and I apologize for being late. I had a last minute emergency that came up meeting-wise. I'm Jesse Roach. I currently work at CMS. I'm a nephrologist. I'm also the acting chief medical officer for quality measurement at CMS, so I help oversee and work with all of our

quality measurement programs throughout the agency. Before I was there, I was in CDER, and actually in generic drugs at the FDA. So I'd like to thank you guys for having me, and I'm looking forward to participating.

DR. STAFFA: Great. Thank you. So glad you could join us.

Now I'm going to turn it over to Lieutenant Commander Liberatore, who's going to walk us through some of the high points of the FDA blueprint.

Presentation - Mark Liberatore

LCDR LIBERATORE: Great. Thanks, Dr. Staffa.

Good morning, everybody. My name is Lieutenant Commander Mark Liberatore, and as I said, I'm a pharmacist officer in the U.S. Public Health Service. I serve as deputy director for safety here at FDA's Division of Anesthesiology, Addiction Medicine, and Pain Medicine, also known as DAAP.

I was asked this morning to provide an

overview of the blueprint that is part of the approved risk evaluation and mitigation strategy, which is required of opioids intended for use in the outpatient setting. I'm going to start by talking about why the blueprint exists.

To start, it's important to state that the FDA regulates drug companies. FDA does not regulate the continuing education community. FDA believes that provider education is an essential tool in the proper treatment of pain and key to driving down the consequences that stem from the opioid crisis. Because of their inherent risks, FDA has required a REMS, or risk evaluation and mitigation strategy, for opioids intended for use in the outpatient setting, and one of these elements FDA is allowed to require is provider training.

Again, FDA doesn't regulate the CE itself, rather, FDA regulates the REMS, and to be clear, the blueprint is part of the REMS. It was established to provide a guide as to what must be covered by the CE program. But because the drug

companies themselves don't develop the CE, the blueprint doubles as kind of a firewall between the drug companies that fund the CE and the CE providers that develop it. To put it a different way, the blueprint is an FDA--approved document that is part of the REMS, and CE providers independently develop CE based on this document.

As a little bit of history here, the blueprint that's currently approved is version 2.0. The original blueprint was approved in 2012 with the original REMS. If you look bullet to bullet, left to right on this slide, you can see the comparison. The 2012 REMS is only required of the ER/LA, or extended--release, long--acting opioid analgesics. The new REMS and blueprint component approved in 2018 is required of all opioid analgesics intended for use in the outpatient setting.

So very quickly, what do I mean by that? In general, the REMS covers products that one might receive from an outpatient pharmacy. Products like intravenous opioids are not included in the REMS,

nor are some of the products used in the treatment of opioid-use disorder like buprenorphine products used in the treatment of opioid dependence. Those products have their own REMS, as do transmucosal fentanyl products. Just to frame this up, when you're thinking about products in this REMS, you should think of opioid analgesics that would typically be prescribed for outpatient use.

So back to the list. In the second bullet, you can see that the 2012 version of the blueprint had a lot of product-specific information. It consisted of what could almost be looked at as many versions of the labeling. When we approved the current blueprint, that product--specific information was removed, and the blueprint turned its focus to the fundamental concepts of pain management, which I'll discuss more in this presentation.

Finally on this slide, note that the older blueprint was heavily focused on targeting prescribers, and while prescribers are the main target audience of the new blueprint, the program

now requires that education be made available for all healthcare providers involved in the treatment and monitoring of patients with pain.

Starting here and for much of the rest of the presentation, I'm using language directly from the blueprint, and I've provided a citation at the bottom of each slide for your reference. I mentioned two slides ago that FDA feels that provider education is important. Why? Well, we're still very much in the middle of a national opioid crisis and, yes, there are certain pools of data that show that progress has been made over the last few years but there are other data that show that we still have a long way to go.

We know that inappropriate prescribing is not the only reason for the crisis but it certainly continues to contribute to the adverse outcomes listed above. Furthermore, it's also important to note here that misuse and abuse that leads to addiction can occur when people take opioids as prescribed.

So it's critical that healthcare providers

understand the risks associated with opioid analgesics in general and not just from a patient perspective, but also from an overall public health perspective.

While I've already laid out the reasons why education is important, what are the data that support the need for this effort? First, a large portion of the population in this country report suffering from chronic pain. Many patients who visit an emergency department for pain still receive an analgesic. This leads to a lot of opioids available in the community and a lot of opportunity for nonmedical use. In fact, most people who use prescription drugs nonmedically report getting it from friends or family.

But while inappropriate prescribing may still be a problem, it's very important to point out that people suffering from pain should not go untreated. Undertreated pain carries with it a lot of adverse consequences, so it is absolutely essential that we as healthcare professionals learn how to treat pain properly, employing the best

practices to ensure patient and public safety. I say public safety here because the risk of prescribing an opioid extends beyond the patient. Having knowledge in the area of pain management, from both a nonpharmacologic and pharmacologic perspective, is vitally important to the national effort to address and reduce misuse and abuse.

I'm not going to spend a lot of time on this slide, as I think I covered it, in general, already, but this is to show you how the blueprint lays out the purpose of the document. I'm going to concentrate on a number of areas within the blueprint, but you can see here that the document covers a lot a ground, starting with the fundamental concepts of pain management, through how to counsel patients, to what's called an addiction medicine primer, which is a really important aspect that I'll touch upon towards the end of the presentation.

I'm, again, not going to go through every line of the blueprint, but I am going to dive into a few of the focus areas. First, Focus Section 1

covers the basics of pain management. The blueprint instructs a CE should cover the need for comprehensive pain education, or in other words if you're taking the CE, upfront the CE should tell you why you're taking it, and the CE should cover definitions and mechanisms of pain as not all pain is the same, and then, 3, how to assess patients in pain. After that, the CE should transition a bit, and if you assess the patient and you decide they need to be treated for pain, then that's where the next section becomes vital.

Focus Section 2 covers the treatment plan. It's divided into five main sections as you can see here, each of them very important. In the interest of time, I'm going to cover the points under Sections 3 and 4, but I'm also going to briefly touch on Section 5 as I mentioned earlier. Sections 1 and 2 are very important sections but, again, just in the interest of time, I'm going to jump right to Section 3. And as I mentioned earlier, the link to the blueprint itself is almost on every slide, and as always, you can access all

of the REMS material at FDA's website by searching rems@fda.

The blueprint tells the CE developer what they should be covering when it comes to the pharmacologic analgesic therapy. First on the left, for non-opioid medications, you can see that the main information that you would find in an approved labeling should be covered. You might recall I told you that product--specific information is no longer in the blueprint, and that's true; however, that doesn't mean that the CE shouldn't cover the main pharmacologic information pertaining to the class.

So that's for non-opioids. What about opioids? Well, obviously the same information that's covered for non-opioids should be covered for the opioid analgesics, but there should also be additional information covered, and as you might expect, that additional information should pertain to opioid-specific risks and their consequences.

There's an important sub-bullet here. The CE program should be explaining to the CE user that

the opioids are to be used only as a component of pain management. Opioids are not a one--stop--shop or cure for pain management, and this consideration needs to factor in the overall pain treatment plan for the patient.

So when talking about opioid analgesics, what does the blueprint suggest that the CE cover? Here you can see the list, which is a little more granular than what was presented on the previous slide. For example, take a look at number 6 and you'll see a very important topic: initiation, titration, and appropriate tapering.

It is very important that a prescriber follow the dosage and administration recommendations of, quote/unquote, "start low and go slow" when initiating and titrating a patient. Also, once a patient is stable on an opioid, it is important to understand that if the patient is to be, quote/unquote, "de-prescribed" or even completely taken off an opioid, he or she must be properly tapered.

I'll also draw your attention to number 10.

Here you might find that a CE program re-emphasizes information on proper storage and disposal of opioids. The importance of storage and disposal was re-emphasized in product labeling in 2019, and you may all be aware that just this past July we required all of these same products, through our safety labeling change authority, to include language and labeling regarding the availability of naloxone. Assessing the complete situation and having the conversation with the patient about naloxone and how to get it is just one part of the overall safety strategy that healthcare providers need to learn about.

Part 4 of focus area 2 of the blueprint is less about the pharmacology and more about the management of the patient. The blueprint outlines for the CE provider what should go in this part of the education; for example, overall concept of appropriate use.

We often hear about prescribing in terms of increase or decrease, but what we're really looking for is appropriate, and appropriate may mean not to

prescribe. Here though, appropriate use is talking about the appropriate use of the product, and with that it's important to know how to manage different patients differently. What's acute versus chronic pain? How should patients be approached differently? The balance of benefits and risks is a key message here. Again, the blueprint is telling the CE provider that both the benefits and the risks should be in the program.

As I mentioned earlier, we don't want someone taking CE for opioids thinking that they should never prescribe or dispense one. There are benefits and risks to weigh with any medication, but the balance for opioids is a key concept that should be covered. And finally, serious outcomes of overdose and death, it goes without saying that this is an important topic that needs to be covered in the CE as well.

So quickly here, this is a granular look at part 4. You can see that the blueprint cover is what I just went over in more detail. There are a few additional ideas I want to point you to.

First looking at letter F as in foxtrot, when to consult a pain specialist. It's not expected that after you take the CE based on this blueprint that you would become a pain specialist, but it is expected that you know when perhaps your patient should be referred to one.

Likewise, I'm going to back up here a bit, and looking at letter E as in echo, what to do if you suspect or identify a patient with opioid-use disorder. What exactly does one do in that situation? And that brings me to the last part of the blueprint, which we call the addiction medicine primer. If you're familiar with the Drug Abuse Treatment Act of 2000, or DATA 2000 as it's known, that is a training that prescribers can take to prescribe buprenorphine in the outpatient setting for the treatment of opioid-use disorder.

So let me be clear. The CE from this blueprint is not that, and that's not the intention of this section. Instead, this section of the blueprint tells the CE developer that they need to cover enough about addiction medicine so that the

person taking the training can gain knowledge about the basic elements. Importantly, it covers reasons not to use stigmatizing language and it covers the need to be familiar with a few main points about addiction medicine.

The use of screening tools you see here, that's second from the bottom, is especially important. It's not necessary that every prescriber that takes the training be able to treat someone for OUD, but it is necessary for someone taking the training to know how to use existing screening tools should they suspect someone is suffering from opioid-use disorder.

That brings me to my last slide. In sum, the blueprint is an FDA--approved document designed to facilitate development of CE, but remember that the document itself is not a CE. As the name implies, it's a blueprint. The blueprint was updated in 2018 with the expansion of the REMS, and the CE as the design, based on the blueprint, can target all healthcare providers. It no longer contains any product--specific information. It's a

high-level outline of core messages that must be included in the continuing education programs.

One other point here that I didn't squarely cover before, the CE can be customized depending on the audience or method of delivery. It can be online, live, et cetera. It may also utilize adaptive learning or test-out format so that prescribers that are knowledgeable in some areas are able to skip portions of the CE activity if they demonstrate knowledge. Some programs are also delivered in modules in order to cover all of the content in the blueprint. For all these programs, the blueprint is, again, the outline, and the CE should touch on all points.

Finally, as I mentioned on the previous slide, the blueprint is geared mainly towards the management of patients in pain and patients on pain medicine, but knowledge of addiction medicine goes hand in hand and should be included in the CE programs regardless of the target audience, and that concludes my talk. Thank you.

DR. STAFFA: Thank you, Mark.

Now we're going to move right into a presentation from Julie White, who's going to talk about how the blueprint is actually put into action into the CE program.

Ms. White?

Presentation - Julie White

MS. WHITE: Thank you very much.

Again, my name is Julie White. I'm the director of Continuing Medical Education at Boston University School of Medicine, and I'm going to talk about our program, Safer/Competent Opioid Prescribing Education, or SCOPE of Pain, to try to illustrate what a CE provider does to address a blueprint. I have nothing to disclose, and our program is supported by an independent educational grant from the Opioid Analgesic REMS program companies.

Why accredited CME for REMS? The Accreditation Council for Continuing Medical Education, or the ACCME, is the framework by which to develop and deploy our activities. If you look at pharmacy and nursing, they're very similar

frameworks. The hallmark of accredited CME is independence from promotion or marketing, and we ensure its independence by following strict adherence to the ACCME Standards for Commercial Support. We have to make sure that our content is valid and based on continuously updated scientific best evidence.

The target audience that we identify is according to who's at the front line of the clinical issue and often includes the interprofessional team. Educational needs underlying practice gaps inform content. Educational formats are based on adult learning principles designed to be relevant to practice and result in improvements in clinicians' competence, performance, and patient outcomes. All CE providers are expected to evaluate changes in learners as a result of the education, and emphasis is on patient-centered care, so essentially patients are stakeholders.

SCOPE of Pain was the first program to be funded by a grant from the RPC, and we launched our

initial program on February 28, 2013 in response to the ER/LA Opioids Analgesic REMS that was an online program. We've offered programs continuously since that time. On March 1, 2019, we launched our updated program in response to the September 2018 Opioid Analgesic REMS. As of November 19th of this year, we've had over 200,000 cumulative completions, and 69 percent of that group are controlled substance prescribers, then you can see the remaining participants are allied health personnel.

All of our content is developed under the direction of our course director who is Dr. Daniel Alford. He is an internist and a practicing primary care clinician. He has expertise in pain management and addiction medicine, and he works with our faculty to develop this content independently of the funding and the funder.

The content is continuously updated according to blueprint modifications, guidelines, and peer-reviewed literature, and we ask always of our participants whether they've detected any bias

in the activity, and we're happy to report that close to a hundred percent have detected no bias.

Our target audience, and this will vary depending on the provider, will have a particular expertise in primary care medicine, so we focus on those who are providing continuity of care for managing both acute and chronic pain. In 2019, in response to the 2018 blueprint, we added content for episodic care providers who treat acute pain in the post-operative and emergency department settings.

In our needs assessment, the ACCME expects -- and this is a quote -- "that accredited providers will address problems in practice and/or patient care. As part of that effort, the provider examines those problems and looks for knowledge, strategy, skill, performance, or system deficits that could be contributing to the problems, and by doing so, the accredited provider is able to plan and implement education that will effectively address the problems."

So in addition to the blueprint, we look at

other things that we see in the environment such as guidelines and public health data. Importantly for us, we've been doing this programming on this topic since 2010, so we have a lot of feedback data and analysis of questions that come up during programming that helps inform our planning.

I won't read these practice gaps. Dr. Liberatore already addressed a lot of this actually. But understanding these practice gaps gives us the information we need to create an activity that places the blueprint elements in context for the practitioners. We know that many clinicians struggle with knowing when to prescribe opioids, how to prescribe them safely using assessment monitoring tools, and then how to discontinue them when appropriate.

Our educational objectives are actually mapped back to the practice gaps, and this helps us, again, to focus on how to enable learners to better optimize safety protocols; assess risks; educate and monitor patients; manage worrisome behaviors; safely taper; and manage opioid-use

disorders.

This is really the key question that all the providers have been struggling with since the beginning. The blueprint has a lot of content and it's critical content. The question for all of us is how do we put that into context? How do we help our learners take this information and change their practice behavior effectively?

Our first program was designed around a case. That's the case of Mary Williams. She is a new patient with chronic low back pain and painful diabetic neuropathy on a chronic opioid therapy. She makes 3 visits to primary care with increasing complexity.

In order to encourage the learner to go from Module 1 to Module 2, and then from 2 to 3, we actually wrote cliffhangers at the end of each module so that there were critical decision points encouraging people to continue on. That was 91 percent that actually went from Module 1 to Module 3, which in the CE world is a very big number.

I will say that we condensed the content from 3 hours to closer to 2 hours after a couple of years because we found that by the time people made the conversion from registration to actually start, we went from 60 percent to 82 percent. Again, as it says here, once we got them into Module 1, they were very likely to finish all the way through, but we needed to get them through to the beginning, and the 2-hour content we think helped to do that because time is a very precious commodity for clinicians.

In 2019, we released our new case, the case of Kathy James who has acute fracture requiring surgery and post-operative pain. She returns years later with chronic pain on opioids, and then again, she has acute pain requiring an emergency room visit. Then we wrote 4 potential endings that covered opioid rotation with decrease in morphine milligram equivalents; opioid taper, both voluntary and involuntary; opioid overdose; and treatment for opioid-use disorder. This enabled us to cover all the elements of the 2018 blueprint.

I do not expect you to be able to read this slide, but this is what we call The Grid, and there are five other pages that look like this. Essentially, this is what we use to audit our program to make sure that everything in the blueprint is covered.

This is a quick snapshot of our homepage. As you can see, we've developed over the years a lot of different kinds of programs. We do live webinars online and podcasts. Again, as was mentioned in the beginning, there are a hundred activities currently out there, I believe, and you'll find many different formats.

This is just a snapshot of things we've done to date, including 184 live in-person meetings in 27 States. As of two nights ago, we now have 16 webinars and 12 have been archived. We have a 6-part podcast series that we released in April of 2020, as well as supplemental content.

Our course director, Dr. Alford, also consulted and helped develop content and was a senior peer reviewer on the excellent New England

Journal of Medicine's Knowledge+ program, which is an adaptive learning platform, and just a snapshot of some other videos and microcases that we developed because it helps clinicians address really challenging clinical issues.

This is a key point. All CE providers are expected to evaluate their activities, and many of us follow the Moore, Green, and Gallis model. I'm sure some of you have heard of this. I've been in this work for a long time and, again, it's pretty standard operating procedure that CE providers will evaluate their activities.

We focus on Level 4 and Level 5, which is pretty standard for a 2- to 3-hour program. We're trying to see if we can measure changes in competence and performance. Again, I don't expect you to be able to read this, but what I wanted to say here is that this is our activity assessment. We use case-based knowledge to measure knowledge and competence changes and we write a sample case.

Right here we have the case of Richard. We ask questions about that case, and this shows the

complexity issue. We're hoping that the learner as a result of our program can apply the knowledge that they learn to a new case, in this case, and case-based assessments are shown to predict future behavior.

At the end of our activities, we ask, as a part of the evaluation, whether the learner plans to make a change, or what we call in the CE industry commitment to change. If they say yes, we give them some suggestions based on best guidelines such as fully implement or improve pill counts for monitoring opioid adherence and misuse.

If they say no, that they're not planning on doing these things, we ask why, and it could be that they're actually already doing these things in practice. If they say yes, we also give them the option to say other, and then we ask them what barriers they anticipate encountering because that will help inform our future activities.

Why do we care about commitment to change statements? Again, it helps us in the CE community to see if we actually have moved a clinician from

knowledge and competence to the next stage, which is predicted performance, are they going to actually go back and make a change in practice? The ACCME says clinicians are expected to deliver safe-effective, cost-effective compassionate care based on best practice and evidence, and an accredited CME can help make that happen.

Again, there's research that shows -- Frank Domino, for example, published a paper in Medical Teacher in 2011 -- that making commitments, whether selecting them from a predefined list or generating them spontaneously, is positively associated with practice change. Kurt Olson reported in a 2012 article, didactic CME and practice change -- don't throw that baby out quite yet -- can be that spark that motivates a clinician to make a change.

This is one of our older papers. We have been publishing our research since we've been doing SCOPE. This was a 2016 paper in Pain Medicine looking at an intent to change, where we looked at the intent to implement a change post-activity and then a 2-month follow-up later. We found that

87 percent intended to make the change towards guideline-based care, and then 86 percent of that group in a 2-month post-program reported implementing practice changes.

So that's it. I just want to say in summary that prescribing opioids, when it's appropriate, is difficult and challenging, and there's no question about that. We see clinicians who are learners, who are definitely making changes, but they still need a lot of support. Thank you very much.

DR. STAFFA: Thank you. That's very helpful to see the implementation of these and to know how some of the CE providers actually try to put the blueprint into action.

Our last speaker in this session, in terms of providing background, is going to be Dr. Jana McAninch, who is going to talk a bit about the history specifically of the assessment piece on this, and bring everybody up to speed on kind of where we've been because that's probably the best launching point for where we need to move forward.

Dr. McAninch, go ahead.

Presentation - Jana McAninch

DR. McANINCH: Thanks, Judy.

Good morning again, everyone. I'm just going to spend the next 20 minutes or so sharing some information that I hope will be useful for our discussions this afternoon in considering different potential approaches to studying the impact of the Opioid Analgesic REMS Education on Pain Management Practice and Patient Outcomes.

First, I'll provide just a high-level overview of RPC's previous work on this and some of the challenges associated with these efforts. Much of this work was done as part of the assessments of the previous extended-release, long-acting Opioid Analgesic REMS, or ER/LA REMS, so some of this might look familiar to those of you who participated in that advisory committee meeting.

In addition to all of the other elements of the assessment that Dr. Manzo described, the main approach that was used to assess the impact of the ER/LA REMS on prescriber behavior and adverse outcomes was to compare population rates of opioid

dispensing and various adverse outcomes before and after the implementation of the REMS, comparing the changes in the REMS analgesics to changes for comparators,typically the immediate-release opioid analgesics, and either benzodiazepines or stimulants.

This slide shows a couple of examples from the 36-month REMS assessment, which was discussed at the 2016 advisory committee meeting. The top panel shows the change in poison center exposure calls involving abuse of ER/LA opioids compared to the changes for the IR opioids and prescription stimulants. The bottom panel shows the change in overdose death rates in Washington state. There were similar pre-/post-comparisons done using a variety of different data sources and outcome measures.

One of the observations in the ER/LA REMS assessment data was that many of the declines observed when comparing the mean pre- to post-REMS period rates began prior to the first REMS continuing education program offering as shown here

for, again, the poison center calls involving abuse of the ER/LA opioid products and self-reported abuse of the ER/LA opioids in people entering treatment for opioid-use disorder. You can see descriptively in these figures that there was not really evidence that the REMS was further bending that curve downward.

We saw similar downward trends in opioid prescribing, and then of course these downward trends have continued since then. But again, one of the challenges that's been mentioned before was that these data don't tell us whether the prescriptions were appropriate or inappropriate, and there really was no consensus on how to define and measure appropriate opioid prescribing.

So did the evidence indicate, then, that the REMS was failing in its goal to reduce adverse outcomes associated with inappropriate prescribing, misuse, and abuse? Well, we couldn't really say that either. One of the challenges was that it was difficult to relate these outcome measures, these population level outcome measures, directly back to

the REMS or the CE training itself. As shown in these examples, different desirable impacts of prescriber and patient education could even have opposite effects on these population level metrics.

Then of course there were many other concurrent interventions and secular trends that could be driving both prescriber behavior and adverse outcomes related to opioids, and it was particularly difficult to determine whether training was having an effect in the environment because at the time of the assessment, or the analyses contributing to the assessment, only about 20 percent of ER/LA opioid prescribers had completed a REMS compliant training, and the completion of training or whether a prescriber had completed training was not linked to either the prescribing or adverse outcome measures.

At that time, we concluded that while the observed decreases in many of these measures were encouraging, we really weren't able to isolate the effect of the REMS or to determine whether it was

reducing inappropriate prescribing, misuse, abuse, or associated adverse outcomes. We did think that population-level prescribing and adverse outcome data would continue to be valuable for surveillance to help inform regulatory decision making, but that alternative designs were needed to evaluate the impact of the REMS continuing education on behavior and on outcomes.

We asked the RPC to explore different approaches that could link CE completion to changes in prescriber behavior and patient outcomes; to develop outcome metrics that are more directly mapped onto the content of the education itself; and to explore designs that would adequately address selection bias of a voluntary education program and confounding by the many secular trends. But there were still a lot of questions about the feasibility of such a study being able to provide clear information about whether the REMS was meeting these goals.

With the next assessment report, the RPC submitted a brief concept paper for a study that

would leverage national prescriber identifier numbers, or NPI numbers, that were collected from participants in one large CE program, the Pri-Med program, and linking those to a proprietary EHR database.

They proposed a difference-in-differences type analysis, so comparing trends in prescribing and patient outcomes pre- versus post-training, using a matched non-completer group for comparison. FDA provided a number of comments to the RPC on this concept paper, but primarily requested further detail on the linkage capability, sample size, and the proposed outcome metrics, et cetera.

Subsequently, the RPC submitted a feasibility assessment and a revised concept paper. This feasibility assessment demonstrated the ability to link prescriber participation using NPI numbers, again, in the same large CE program to two large administrative claims databases.

They determined that such an approach could provide a large enough sample size to assess the impact of training on certain patient outcomes such

as overdose, and then they, again, proposed a difference-in-differences analysis, examining the change in rates of patient outcomes for trained versus matched untrained providers.

In this same assessment submission, the RPC also submitted results of an analysis that linked prescriber completion of the Pri-Med CE program to a national prescription dispensing database, looking at the four prescribing metrics that are shown here under the second bullet. They conducted two different types of analyses, first a self-controlled pre- versus post-REMS training comparison, and second, a concurrent comparison between the CE completers and matched control group consisting of prescribers who had not completed this particular CE program.

What they found was that after CE completion, the trained providers had slightly lower prescribing volume in concomitant benzodiazepine prescribing, but the trained prescribers also had higher opioid prescribing volume than the untrained providers during the

post-training period. There were no meaningful changes or differences in the other prescribing measures.

I think there were a few notable limitations of this study. First, the opioid prescribing volume was quite low in both of the groups. Again, it was unknown whether the slight decrease in opioid prescriptions indicated a decrease in inappropriate prescribing and it was unclear whether either the pre-/post-differences or the differences between the two groups could really be attributed to the education versus to other factors.

There was not that difference-in-differences type of analysis done to compare the change in prescribing behavior in the trained versus the untrained groups, and there were very few variables available for matching in the particular database that was used. Then finally, there was no way to account for participation in other opioid education, even other REMS training, in the control group, which would likely bias results toward the

null.

The following year, as Dr. Manzo mentioned, the ER/LA REMS transitioned to the current Opioid Analgesic REMS, and we encouraged the RPC to continue to build on the work they had been doing under the ER/LA REMS to develop a rigorous plan to evaluate the impact of the OA REMS CE on pain management practice and patient outcomes, considering the expanded focus of the new REMS.

In the 12-month Opioid Analgesic REMS assessment, the RPC submitted a white paper, or essentially a concept paper, again, proposing a study that would link CE completion to national-level claims data but now incorporating sophisticated modeling to control for differences in prescriber characteristics, past prescribing behavior, and so-called environmental factors such as state-level opioid policies and CE requirement.

However, after completing the landscape analysis that Dr. Manzo mentioned, describing the myriad of other CE programs and opioid policies that were implemented during that time period, the

RPC submitted an addendum to this white paper saying that the scope and complexity of these environmental factors likely would create insurmountable challenges to this approach.

I'm not going to say too much more about this because we actually have Dr. Alec Walker, who was involved in this effort, sharing some of his thoughts on the potential for analyses of large electronic healthcare databases to contribute to the evaluation of the REMS continuing education.

Next, I want to shift gears a little bit and share just a few examples of some published studies that have evaluated the impact of pain management and opioid stewardship initiatives that have an educational component on prescriber behavior and patient outcomes. This is just a caveat. This is by no means comprehensive or really a critical review. It's just intended to give a flavor of what some others are doing and some of the other approaches that have been used in this space.

The first study was an evaluation of the Stepped Care Model for Pain Management as

implemented in a network of community health centers in Connecticut, and the lead author, Daren Anderson, is actually one of our panelists today. The Stepped Care Model used here is, I believe, similar to what has been implemented in the VA system, and it includes educational activities as well as other elements to support an individualized stepped approach to pain management.

This study compared a suite of measures during a baseline period to a post-intervention period, including 25 providers and their chronic pain patients at 12 different clinics. Structured EHR data points included things like medications prescribed, use of opioid treatment agreements and urine drug testing; functional assessment; and referrals to behavioral health, chiropractic, and other specialists.

They also conducted a manual chart review of 300 randomly selected charts and abstracted those charts using the Pain Care Quality extraction tool, which has 12 dichotomously scored indicators grouped into 3 different domains: pain assessment,

treatment, and reassessment.

What they found was that comparing the baseline to the post-intervention periods, there were significant increases in use of opioid treatment agreements and urine drug testing, as well as in documentation of pain, functional status, treatment planning, and reassessment, as well as an increase in referrals. They did not observe any meaningful change in opioid prescribing or in pain scores.

The second example I wanted to share is actually a suite of studies evaluating different outcomes associated with an opioid risk reduction initiative in the Group Health system in Washington State, using a control group of contracted care providers and their patients that were not part of this particular initiative but were subject to statewide opioid guidelines and legislation.

The intervention here was a multifaceted, chronic opioid risk reduction initiative that included online training, as well as a number of practice-wide prescribing and monitoring policies,

EHR templates, consultation, performance tracking, and financial incentives.

The studies evaluated the program using outcome measures from a variety of data sources. EHR-based measures included things like the dose of opioid prescribed, access date, supply dispensed, and care plan documentation. Other measures were based on prospectively collected data from patient interviews using standardized pain and depression symptoms scales. Finally, opioid overdose rates were estimated using an EHR-based opioid overdose algorithm linked to state death records.

The investigators here found that against the backdrop of declining opioid dose in both the intervention and the control groups, the intervention group had larger declines in opioid dose and excess days' supply, improved care plan documentation, and no clinically meaningful differences in pain or depression symptoms. The opioid overdose findings were rather complicated, but in essence, the risk reduction initiative did not appear to decrease overdose rates beyond some

modest declines that were already occurring in the intervention group in the setting of statewide opioid dose reduction policies.

Finally, there have been a number of evaluations that have used randomized designs to evaluate pain management and opioid risk reduction interventions on prescriber behavior.

In this study, investigators randomly assigned 53 primary care clinicians and their patients with chronic pain in four safety net clinics to receive either electronic decision tools alone or a multimodal intervention that also included academic detailing or essentially one-on-one education, nurse care management, and electronic registry. Structured EHR data were used to assess use of patient-provider agreements and urine drug testing, as well as early refills, opioid dose, and opioid discontinuations.

What they found was that the intervention group had increased use of patient-provider agreements and urine drug testing, as well as greater odds of opioid dose reduction or

discontinuation. Then interestingly, in a more recent follow-up study by the same group, investigators reviewed charts of patients who had discontinued opioids and found that most discontinuations were for reasons of misuse most commonly identified through aberrant urine drug testing results.

These patients subsequently had fewer primary care visits, no meaningful change in pain-related emergency department visits, and no increase in referrals for opioid-use disorder treatment. The office of the follow-up study noted that this decrease in follow-up care and lack of referrals for opioid-use disorder treatment highlights the need to understand potential unintended consequences of interventions that are intended to reduce opioid risk. This concern of course has been raised by many others in recent years.

So I hope what I've shared will be useful for the discussion this afternoon. We will provide some specific questions to guide those discussions

in each of the sessions, but I thought it might be helpful just to keep a few thoughts or questions in mind, particularly when listening to our upcoming speakers.

First, is it plausible that a single CE training would have a measurable and meaningful impact on pain management behaviors or patient outcomes, and what endpoints would be both meaningful and measurable? What other systems or supports might need to be in place for the education to meaningfully affect behavior or outcome?

What settings and data sources, or combination thereof, might provide the best balance of sample size and the detail needed to capture important outcome measures? And how could a study best address the potential selection bias associated with a voluntary program, as well as the influence of the many other drivers of practice and patient outcomes?

Then again, just another challenge to keep in mind here is the heterogeneity of the REMS

education offerings. As Dr. Liberatore mentioned, although they must be based on the FDA blueprint, they vary substantially in terms of the delivery format, the targeted participants, and the exact focus or content of the training.

So I really look forward to a robust discussion this afternoon, and I want to add my thanks to all the panelists and the guest speakers for their time and their insights on all of these questions. I'll turn it back over to Judy, but I believe we are going to a short break now.

DR. STAFFA: Yes. Thank you very much, Jana. I appreciate it.

It is 10:27. We're just a few minutes behind, but I think that's okay. I'm going to ask if everybody can get back and reconvene at 10:40, and then we'll start with our second session of presentations, which we're going to start with Dr. Walker, and then talk about more understanding what's been done, what's been thought through, and then some other ideas of what some other groups are doing and thinking about in this space. So we'll

talk to you at 10:40. Thanks.

(Whereupon, at 10:28 a.m., a recess was taken.)

DR. STAFFA: Welcome. My computer says 10:40, so we're going to get started again. We'll ask you again to please mute your phones when you're not speaking.

We're going to continue with some of our background presentations, and in this session we're going to begin with Dr. Alec Walker who's going to be talking about some of the work he's been doing in looking at large data sources to try to inform this question.

Dr. Walker?

Presentation - Alec Walker

DR. WALKER: Thank you, Dr. Staffa.

Good morning. My goal in the next few minutes is to remind us all of the utility of existing large data sources on drug dispensing. These data sources I think can have an important role in assessing how continuing medical education programs affect prescriber behavior.

I'm grateful for the opportunity to speak to you. My involvement in the question of evaluating continuing education for opioid treatment arose through an engagement with the REMS program companies, which in turn came out of my involvement with other activities with the Opioid Postmarketing Consortium and member companies. I am not being participated [sic - compensated] for participation in this meeting.

We're here today because a goal of continuing education programs and the REMS programs in general is to affect prescribing practice. The intent is to bring selection of patients and products into line with guidance for best practice. An obstacle to evaluation is that CE programs exist in a world of determinants that are constantly changing.

The elements to determine a prescriber's choice of therapy for a given set of patients are also influencing one another, so the dispensing patterns are dynamic and even turbulent, by which I mean that they affect one another precipitously

over time without necessarily tending to a global steady state.

To make the relations amenable to analysis, it's easiest to lay them out in a directed acyclic graph. Calendar time in this figure runs from left to right and the arrows indicate direct or mediated causation. In the data corresponding to this graph, each note in the graph is available as a series of observations all timestamped. At the left are the notes corresponding to non-time-varying determinants, and along the top is calendar time and its interactions, which represent time-varying proxies for forces not represented in the graph.

To include all the causal arrows that represent the interacting effects of time and place would make the graph unreadable, even in a simplified form. To make matters more complex, the opioid epidemic has spawned hundreds of guidelines, limits, regulatory guidance documents, and educational outreach efforts, all of them designed to affect prescribing.

This figure embeds continuing education into a simplified depiction of the web of determinants. For readability, the figure emits all the diagonal arrows of the earlier figure or the arrows running between different outcome measures at different times. Completion of a continuing education program needs to be considered as a consequence of a history of those same features that we'd often like to call as outcomes in the future.

Availability of extensive data is a prerequisite to statistical control in assessing the effects of continuing education outside of randomized trials. Fortunately, there are both national and regional resources that can provide component information linkable within personand time. The linkability across time means that both prescribers and recipients of opioid drugs can be characterized from dispensing histories. With the addition of insurance billing or electronic health records, even more nuanced portraits are available for the asking.

The idea of deriving patient and provider

characteristics from opioid dispensing files is well established. Dispensing clusters, for example, are post hoc categories of time by place interactions, which have been characterized by further population and micro features. Recipients can be placed into categories on the basis of the providers they see or the dispensing outlets they patronize, as in the many studies of doctor and pharmacy shopping.

In the big data counterpart to a case control study, researchers are first characterized by case, places, and times by such features as opioid deaths, and then gone back into these data to find out how these differ from control places and times. This is just a small sample of the kinds of formal studies that have been done using these data.

The CDC has provided measures for quality improvement that can be easily implemented with large data resources and which provide measures with strong face validity for assessing continuing education. We'll hear much more about these in

Dr. Losby's talk, which comes up next. Let me first point out a few specifics.

These are the CDC's recommended measures to assess adherence to the CDC guidelines. I've added an indication as to whether each can be assessed in a big data environment. Those marked with a red spade require only a comprehensive drug dispensing file and could be implemented nationally. The criteria pertained to form and duration of initial prescriptions, as well as strength and concomitant treatments for both acute and long-term therapy. Where there are insurance or electronic health data available, nearly every measure can be assessed.

Stakeholders could use the data that are available already to prepare interpretable graphics and data on opioid use in the United States. I'd like to propose that we think of analyses whose product was akin to weather maps showing the geographical distribution of key measures in successive slices of time. The unit of analysis could be the prescriber in a block of time. The measures should be displayed and might be informed

by CDC guidelines and by clinical and regulatory experience. The first analytic step would be to look at dependencies within and across places and times.

Coupled with on-the-ground knowledge, geographic visualization is a powerful tool for both research and communication. This presentation could help identify areas that are doing well and poorly with respect to guideline compliance and may suggest plausible areas for action. Such maps might also show where continuing education programs would be evaluable because of relatively stable external circumstances and could even provide the basis for answering the "what if" question that's embedded in a search for causal effects.

While the weather map may serve for evaluating overall progress, the focus of today's discussion is on direct evaluation of CE programs. There are two absolute prerequisites to moving forward with large data. The first is that there be a clear path to data linkage and utilization that identifies individual prescribers. Permission

for external data linkage and use, granted by both CE providers and CE participants, should be integral to any CE program.

Secondly, we need to be willing to identify suitable research venues. There's been a maelstrom of initiatives, all of which we need to consider in principle. But it may be that there are calmer regions of the country or times where one has a hope of embedding a research activity because the external arrows on the DAG are weak or absent. Given the region and time of practice stability, the options for evaluating the impact of CE on practice include the standard designs. I see we will hear more from Dr. Alexander on these at the end of this session.

At the top of the hierarchy, because they take on confounding head-on, or randomized-controlled trials, to set up closest to a clinical RCT would be to identify a high-risk pool, randomized members and groups to possible CE regimens, and do a careful analysis of the impact of CE on the trajectory of prescribing.

A variation is a randomized consent design. Here one passively identifies panels of prescribers and then randomizes invitations to CE. The comparison is between those offered CE and not. Assessing the impact of CE availability has a great advantage of assessing what we actually offer. The opportunity for education, differential uptake, or failures to accept CE get rolled into the comparisons, increasing the generalizability of the results.

As in clinical research, an alternative to the RCT is the observational study. The single arm or trial is attractive for its simplicity. The period prior to CE serves as a reference point against which to compare practice after completion of CE. Unfortunately, this assessment is fraught with challenges. Participants may be non-representative of the target population of prescribers because of their self-selection into a particular CE.

Not uncommonly, even if we use our weather maps to identify a suitable research venue, there

will be secular trends in general knowledge and practice that could masquerade as a CE effect if there are no data and controls. Comparative observational cohorts do provide controls and might be set up, for example, in communities of prescribers whose prescribing histories are compatible with a possible need for improvement. In a formal sense, the analysis of observational cohorts resembles that of RCTs.

Closely related to the randomized consent design in which one looks at blocks of individuals who have been offered CE for administrative or institutional purposes and are compared to those who have not had the opportunity for the same training, not the intervention itself but the opportunity for intervention is studied through its effects on groups of prescribers. The impact of offering CE can be evaluated as before. With further assumptions, the impact of the CE program itself can be teased out in instrumental variable analysis.

There are two complementary directions in

which the FDA might move forward using large data systems. The agency is very, very familiar with assistance themselves. Reasons to move forward with a weather map might revolve around low cost and high impact. People in our culture read maps. Spatial and temporal presentations are likely to give visceral understanding of the need for and success of regulation at national and regional levels.

Secondly, large health data systems provide an unparalleled opportunity for program assessment provided the society can set a clear legal and regulatory framework for unimpeded data use. They can also be used to prescreen places and participants for those in whom well-understood research designs can apply. Thank you.

DR. STAFFA: Thank you so much, Dr. Walker.

Our next presenter, to talk about efforts going on at CDC, is going to be Dr. Jan Losby.

Presentation - Jan Losby

DR. LOSBY: Thank you, Dr. Staffa.

Good morning, everyone, and I really wish to

express my thanks to the FDA for inviting me and greatly appreciate having the opportunity to participate in today's scientific workshop. I have no conflicts of interest to report and a standard disclaimer is noted on this slide.

In our time together today, I will share some basic background around the CDC prescribing guidelines, and then really dive into the process that we took in developing the electronic health record, EHR-based, quality improvement opioid measures, which includes an implementation guide that Dr. Walker referred to, so thank you so much for showcasing that in your presentation.

Then also, I will share some information around the quality improvement collaborative that CDC launched. I'll highlight some preliminary implementation results from the collaborative and close with some lessons learned.

In March of 2016, CDC published the opioid prescribing guideline for primary care providers caring for patients 18 years or older with chronic pain outside of active cancer, palliative, and

end-of-life care. The guideline was needed to better align opioid prescribing practices in primary care settings with the best available evidence to ensure safe, effective pain management.

CDC is a non-regulatory agency, and as such, the guideline is not a rule, regulation, or law. The guideline does not deny access to pain medication and includes opioids as an option for pain management. The guideline is intended to help inform clinicians' decisions and discussions with patients and their prescribing decisions based upon the best available evidence about the benefits and risks of opioid use.

The guideline itself contains 12 recommendations, and these are grouped into three conceptual areas: determining when to initiate or continue opioids in chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing the risk and addressing harms of opioid use.

Some examples of a few recommendations are, for instance, checking the Prescription Drug

Monitoring Program, or PDMP, or other prescriptions and high total dosages; avoiding concurrent benzodiazepine and opioids; and offering and/or arranging medication-assisted treatment for opioid-use disorder.

To help encourage uptake and use of the guideline, CDC developed a comprehensive dissemination and implementation framework with four pillars: translation and communication of key recommendations within the guideline; education and training that enhances knowledge, understanding, and application of the recommendation; insurer intervention; and then what we'll focus on today in terms of the quality improvement, where it fits in this fourth area, the health system interventions that help to enhance implementation of the recommendations within point of care.

If we turn to the quality improvement process that we undertook, the goal is really to help support implementation of the guideline within healthcare systems and supporting practice improvement and monitoring. The approach included

three broad efforts. They're listed here, and I'll first go into more detail around the development of the clinical quality improvement opioid measures.

As a reminder in terms of the scope and purpose of the quality improvement measures, it's really to support safe and effective opioid prescribing and pain management and treatment. The quality improvement measures are intended for use by health systems or practices, and these are quality improvements that are based on EHR data, as Dr. Walker highlighted, or chart review data, or other practice-based data. The quality improvement measures are intended for quality improvement and monitoring implementation of the guideline, and they are voluntary. They are not performance measurements.

If we turn to the approach of creating these quality improvement measurements, the initial design the CDC developed is a starter set to look at the content of 12 recommendations in the guideline and what potential quality improvement measures might exist. We looked at the literature,

and then we reached out to a group of external stakeholders, and wish to thank Dr. Daren Anderson who serves as a member of the stakeholder group. We selected individuals that had expertise in opioid prescribing, use of quality improvement measures, IT or EHR expertise, as well as researchers and folks that could represent the patient perspective as well.

These stakeholders provided individual input, and then on the next slide, I'll share the specific steps in terms of the engagement. Many folks on this call are probably very familiar with engaging stakeholder groups, so we asked individually for the stakeholders to rate the draft quality improvement measures, and they were assessed based on importance; acceptability; face validity; timeliness; feasibility; usability; and then overall rating.

We also asked the stakeholders to make a rating of all or some measures, those that are based on need and importance, as well as ease of producing by using EHR data. We wanted to make

certain that we were not trading quality improvement measures that would not be easy to use or accessible through EHR data.

Then we asked the stakeholders, through a semi-structured interview process, just to provide some more detail and background to their assessment of the draft measures. We brought all the stakeholders together really for a group conversation. We weren't trying to reach consensus through a Delphi model, but we really just wanted to have that interaction and exchange of the stakeholders to come together.

This recent publication gives more details around the development of quality improvement measures. The quality improvement measures themselves, we have 16, and these map onto the 12 guideline recommendation statements. They can be tailored to practice policies on opioid prescribing and pain management or reflect state laws or regulations.

We have two categories, new opioid prescription measures and then long-term opioid

therapy measures. You just saw a great slide that summarized these from Dr. Walker. These are the five measures that are tied to new opioid prescriptions. For example, one of the measures that's listed here is the percentage of patients with a new opioid prescription for an immediate-release opioid, and this particular quality improvement measure, which you see on the far-right column, is tied to the specific recommendation number 4 in the CDC prescribing guideline.

We have 11 quality improvement measures that address long-term opioid therapy, and an example is the percentage of patients on long-term opioid therapy. The clinician counsels on the risks and benefits of opioids, at least annually, and this aligns with recommendation number 3 from CDC's prescribing guideline.

If we turn to the second step in the quality improvement process, this is the development of the implementation guide for the recommendations and measures to be used by health systems and

practices. In 2018, CDC, in collaboration with clinicians in the field, developed and published this resource entitled Quality Improvement and Care Coordination: Implementing the CDC Guideline for Prescribing Opioids for Chronic Pain.

The resource is intended to encourage careful and selective use of opioid therapy and facilitate implementation of the guideline. It can help health systems and primary care providers integrate quality improvement measures into their clinical practice, and it includes some practice-level strategy to improve the management and coordination of long-term opioid therapy.

The resource also includes a toolkit of sorts that has materials and tools and resources developed and used by other practices in the field, which have been found to be useful, and then readers can use or modify these for their own needs.

Appendix B gets into more detail. It's the operationalization of the 16 quality improvement measures that goes through the description, the

numerator, the denominator, the measurement period, patient exclusions, data source and guidance for producing the measure, as well as anticipating what those potential challenges might be in operationalizing these measures and some potential solutions.

The resource also includes basic information around encouraging implementation of quality improvement practices. There are five implementation steps that are outlined in the document, and these are steps that providers in a practice or a healthcare system can take to support buy-in, receptivity, and ultimately the use of the quality improvement measures. In the document itself, following the description of each step, there's a self-assessment that implementers can use to reflect on their own progress.

Improving management and coordination of long-term opioid therapy requires not only a refined approach to the clinical care of patients, but also strategies that can be implemented at the practice and system level of care delivery. These

strategies include interdisciplinary team-based approach; establishing or revising internal opioid policies; developing registries and using panel management; and effectively using technology.

In terms of the Quality Improvement Collaborative itself, we felt it was important to develop the quality improvement measures, trace the implementation guide, but then also implement it in practice to see are the measures feasible, are they reasonable, and can they be used with the EHR data. So in 2018, we launched an opioid collaborative, the Quality Improvement Collaborative. The details are listed here.

We have a number of systems, a total of 11 systems, across 12 states, representing over 120 primary care practices. The practices include urban and rural and frontier and tribal, as well as private practices and academically affiliated practices. The participating systems are expected to operationalize five or more of the quality improvement measures and provide baseline as well as quarterly outcomes.

Next, I'll just summarize a few of the preliminary results. As you can imagine, the systems varied in their quality improvement approach, as well as the use of different strategies to implement the recommendations contained in the guideline. All systems completed a formal commitment in the form of a find and review, identifying and working with champions within their systems, and establishing quality improvement goals and assessing their readiness.

All the systems engaged clinicians and stakeholders to some extent, and there were a variety of approaches to do that. For instance, one system established an opioid stewardship coalition with representatives from various entities within the healthcare system, while others engaged clinical stakeholders in a way to provide input into the clinical recommendations that were prioritized, as well as looking at workflows and policies.

All the systems had data experts to work with or on their quality improvement team. All the

systems developed quality improvement and monitoring systems and tools for quality monitoring. Many of them also included dashboards to provide audit and feedback to the clinician to support an understanding of the guideline. In terms of system level changes, they pursued including developing and revising opioid policies, redesigning workflows, and establishing shared medical appointments.

All of the participating systems adopted a range of improvements to better leverage their EHRs. Many of them used clinical decision support tools to help pull information that was in the EHR and bring it to the forefront of the clinician so he or she could make an informed decision in terms of prescribing. All of the systems engaged in some shared learning related to the quality improvement approach that they used. They engaged in robust, multifaceted educational campaigns and training education programs.

Just to close and to summarize some of the lessons learned and the importance of engaging and

recruiting the systems themselves, I've noted a couple challenges, as Dr. Walker also highlighted as well, in using EHR data. Maybe the information is not captured in a structured field; the process of care may be found in notes; and integrating the EHRs may not be easily captured for analysis. There are some inherent challenges and limitations in using EHR data.

Just to close, with many of the systems and practices pursuing improvements in opioid prescribing and pain management, providing a practice-informed understanding of the implementation strategy and their utility can help advance the field of implementation science and the opioid overdose epidemic. Potentially, these EHR-based quality improvement measures could be incorporated into a broader education and training program.

So thank you so very much. We included all of the resources, listed the team members, and I will turn it back over to you, Dr. Staffa.

DR. STAFFA: Thank you so much. That was

very, very helpful, and I'm sure there's a lot we can learn from the CDC's experience here.

Our next speaker is Dr. Caleb Alexander, who is going to be talking about some of the thinking he's been doing around, again, novel ideas to try to think about how to quantify REMS effectiveness.

Dr. Alexander?

DR. ALEXANDER: Thanks. Can you hear me?

DR. STAFFA: Yes, we can.

Presentation - Caleb Alexander

DR. ALEXANDER: Thanks, Dr. Staffa.

I want to acknowledge all of the folks from the FDA and RPC that have worked hard to make today possible. These workshops are like advisory committees in that they're always educational. And I'm a big believer that all of us are smarter than any of us, so it's great to join this group.

Here are my disclosures, which do include extensive work with the Food and Drug Administration in a number of guises, as well as work advising the federal courts in opioid litigation. I also just want to briefly

acknowledge my many collaborators at Johns Hopkins and elsewhere, and also the FDA's Division of Freedom of Information, which has been terrific to work with, as well as FOIA, and Yale's Law School Collaboration for Research Integrity and Transparency.

I've been asked by the FDA to focus my comments on science rather than regulation, and I joked with Judy that I wanted to show her and her colleagues that I'm teachable, so I am going to do so. But these scientific matters don't exist in a vacuum, and as we've heard earlier, it's important to consider the context for why we're meeting today.

The context is that more than seven or eight years after the REMS has been launched, we still don't know if it works. You can't manage what you don't measure, and I think that the FDA deserves some credit here. As our own work has shown in the papers that I'm displaying now, the FDA has made it very clear to manufacturers where their proposed REMS evaluations have fallen short, as well as

recommendations about how to improve the measurement of the REMS, and ultimately the safe use of these products.

I think this brings us to a crucially important question that we're deliberating today, at least obliquely, which is why is it that we don't know whether or not the opioid REMS works? Is it because it's unknowable? There are some briefing materials that were submitted as part of the preparatory materials today from the RPC that seemed to suggest so. Or is it because the right studies have never been done?

Let me turn to the science and just begin by saying that as we've heard a little bit about, the REMS evaluations have relied largely on surveys and surveillance data, and both of these are highly flawed for reasons that I'm not going to go into now, but I'd be delighted to talk more about during the afternoon.

I'm not saying they should never take place or there are not some ways that they may be somewhat informative, but there's a long list of

serious limitations in the ways that both surveys and surveillance data has been used to evaluate the key question, the north star, which is, is the REMS program changing prescriber behavior and patient outcomes?

With this sort of as a backdrop, I think it's important to consider that we're living in an unprecedented information age. Someone could probably tell you what I had for breakfast if you license the right data, and you could certainly know what types of cereal my household likes.

So we have an incredible amount of information that's available to understand prescriber and patient, and frankly, some of this is licensed routinely by firms as they market and promote their products. We also have advancing methods and even new causal frameworks that can be used to understand settings such as this, where a lot of stuff may potentially influence provider behavior.

The key question is, is it possible to assess the effect of an educational intervention in

this context? I'd like to suggest the answer is, of course it is. Can we do so perfectly? No. Can we do so with absolute certainty? No. Can we do so while controlling for every confounder and every potential effect modifier? Of course not, but since when is that the standard for doing evaluative research?

In thinking about how such evaluation should take place, it sounds as if some preliminary looks at the use of longitudinal data linked with the receipt of educational interventions has taken place. I'm sorry that this wasn't incorporated into the initial design of the REMS in 2012, but I'm very interested in the assessments that have been done.

I think that using provider-level data -- and, frankly, you can see patients clustered within providers in readily available data that can be licensed for this purpose -- and linking this to the receipt of educational interventions, one can exploit variation in REMS training over time and over space in order to allow

for assessments of the REMS, and compare recipients with non-recipients of REMS programs.

This afternoon we can discuss, for example, marginal structural models or targettrial emulation approaches, as they're sometimes called, that would treat REMS as time-varying exposures and model the fact that we have variation in this over time and people. A full comparison group of someone who never got the REMS is preferable to comparing with individuals that have received the REMS, but one can also compare people receiving REMS at similar but distinct time periods.

I appreciated, Dr. Walker, you were discussing a little bit the selection of an optimal comparison group, and I fully agree that that has to be done carefully and taking into account factors such as when training is occurring, how the REMS is being rolled out and scaled up, and where state and local policies may be more or less uniform and able to be modeled.

One could also consider an instrumental variable approach that could be used to control for

differences between institutions that are, quote/unquote, "early" versus, quote/unquote "late adopters" of REMS programming, but otherwise matched on other characteristics: geography, state, background policy, milieu, and the like.

Let me say something about the policy environment. There may be hundreds of policies at local, state, and federal levels, but it's not as if providers have necessarily been exposed to these, let alone that they have sufficed to change the culture prescribing around opioid use. Further, as I think we're likely to hear from Dr. Cervero and speaking to the central query that Jana McAninch posed, these exposures need to be reinforced over time.

So my point here is just that it's not like the providers who are out there -- who have had some educational exposure as part of their medical group, or state licensure, are irreparably, quote/unquote, "exposed" or, quote/unquote, "used" -- in some sense can't or shouldn't both receive additional training and also contribute to

rigorous evaluations of the REMS impact.

My last point here is to also say that I was very interested, Dr. Walker, to hear of your suggestion regarding assessing the REMS within hospitals, health systems, physician groups, and other smaller systems of care. It's a smart idea, and it's a bit inexplicable to me that this hasn't been done long ago.

Now, there's a natural concern that this may not be representative. If you go to one integrated delivery network, is that really representative of the country? But since when is representativeness the bar? I think that's holding evaluation to a unfair standard. We don't even require that of manufacturers seeking approval, so why should we do so in this setting? I'm not suggesting that these types of single-system studies should be the only place where REMS are assessed, but surely it should be one place.

I'd like to make a few other points as well. I think it's pretty important that the FDA abandons low-value approaches because they're distracting

and they yield little scientific value. I don't think they're even net neutral. I think they actually diminish the likelihood of a successful REMS evaluation.

I would put many of the contextual measures that have been noted earlier today, and frankly probably the weather maps as well, in this category. I think they're really interesting. I think they're smart. I think they're useful. I think they're important for someone to do. But I don't think that's the central job of the FDA in evaluating whether or not these REMS are changing prescriber behavior and patient outcomes. That has to be the north star of the evaluations.

I'm reminded a little bit, for the clinicians in the workshop today in the room, it's like being on morning rounds and getting reports from your residents about a patient recovering from acute kidney injury and getting a thousand results from them: the WBC; the red blood cell count; LSTs; thyroid function; vitamin D; electrolytes; and EKG. And you just want one number. You want

the creatinine.

So the point here is that I think that these varied approaches really have to be closely scrutinized to be sure not just that they're interesting, but that they really allow for evaluation of the REMS and that they don't distract from the real mandate here.

I also think the FDA and RPC should consider focusing on high-risk providers and patients. We know that there's concentrated morbidity and mortality within subpopulations of providers and patients, so why not focus on them in part? I think revisiting the REMS content is also important. Is it as potent as it should be?

If it's been dosed to hundreds of thousands and we still have some morbidity and mortality from opioids that we're seeing, is it really as impactful as we hope? If it's similar to the content of other CMEs that the RPC reports is out there and that's been designed and offered by others, maybe it should be further potentiated. Does it have to be a one-and-done design given the

content challenges we've heard about from Julie White, and the fact that reinforced training is going to be much more effective?

The evaluations also have to be dynamic. In our prior work, we found that there was essentially a two-year turnaround period between when a problem was identified and when the RPC delivered information to the FDA as to whether it had been fully remedied. You can define the best scientific studies in the world, but if they can't be reported out and rapidly iterated within days to weeks, they have absolutely no chance of meaningfully improving safe opioid use.

This is a bit of a rhetorical question, but I don't know what the alternative would be to not measuring the impact of the REMS. I mean, you can't manage what you don't measure, so how could we have risk mitigation without measurement? The whole premise of having products such as opioids on the market is predicated upon the ability of the REMS to maximize their safe use, and risk mitigation without measurement is no risk

mitigation at all.

Just because it's hard to evaluate doesn't mean that it's not possible. Think about any number of exposure outcome associations: handgun laws and homicides; smoking cessation interventions and smoking rates; or if you want a more timely example, the effect of mask wearing on COVID transmission.

These aren't perfect analogies, but we'd never say that these studies aren't important or that the evidence they've generated isn't valuable just because they're complex, multilevel factors that drive secular trends in these outcomes. We'd never get anything done in our field if we stopped when things got complicated. That's when some of the best and most important work is done.

So in closing, we're now more than 20 years into the opioid epidemic, and as I know all of you are aware, unfortunately morbidity and mortality is stubbornly high, including from prescription opioids.

So are these evaluations going to be

perfect? Of course not. But again, this isn't and shouldn't be the threshold for scientific inquiry, but in this case, rigorous evaluation of arguably the most important risk mitigation program there is and one that's desperately needed by the millions of Americans that are exposed to these products every year.

So again, I want to just thank and acknowledge the FDA's important role in working to improve the design, the structure, and the impact of the REMS, and acknowledge the work that the RPC has done as well. Thank you, and I'll just say I really look forward to our discussion. I am sure that it will be engaging and useful for the FDA as we go forward, so thanks again.

DR. STAFFA: Thank you so much, Dr. Alexander. It was very helpful.

Next, we have two more talks before we're going to break for lunch. We're going to slightly switch gears in trying to think about the areas where if there are challenges to evaluating the impact of the REMS programs directly, are there

other kinds of evaluations that would be useful to additionally be thinking about in this space, too? We're going to start that with our own Dr. Doris Auth from the FDA.

Doris?

Presentation - Doris Auth

DR. AUTH: Good morning, again. My name is Doris Auth, and I'm the acting deputy division director in the Division of Risk Management. I'll be providing a brief presentation on potential additional approaches or alternative indicators for measuring the success of the Opioid Analgesic REMS.

In the very first presentation this morning, Dr. Manzo provided an overview of the REMS assessment plan for the OA REMS. I am going to circle back to a few of her slides now as a reminder of how we're currently evaluating this REMS, and I'll also suggest some additional possibilities for consideration that we can further discuss during the last panel session.

Once again, these are the goals and objectives of the Opioid Analgesic REMS. The full

assessment plan is quite lengthy. We can bucket the metrics that directly evaluate these objectives to first, those that evaluate knowledge since the primary intervention for this REMS is education, and second, those that evaluate the impact on prescriber behavior and patient outcomes.

Once again, we have the evaluation of healthcare provider knowledge, which in addition to being a requirement for the individual CE providers in order to award credits, will also be accomplished through development of a validated instrument to evaluate knowledge before and after completion of a CE activity, as well as at some point in time afterwards. Slightly more distal to the main REMS intervention is the evaluation of patient knowledge, which will be accomplished through surveying patients and also through the evaluation of patient experiences around pain management, which will be done through focus groups.

The next bucket is the evaluation of prescriber behavior and patient outcomes, and we'll

be discussing of course these evaluations at length in both the first and second panel discussion. What I'd like everyone to think about now, however, is whether there are additional evaluations that may not directly evaluate the REMS objectives but that might indirectly inform the impact of the REMS continuing education. I have a few examples, and I am hoping the panel can expand on the utility of these or other potential mechanisms to evaluate the OA REMS.

The first of these is to revisit our knowledge evaluation, and this gets back to understanding the causal pathway of knowledge to behavior change. Is there evidence that if knowledge in a particular area is improved by a certain amount, then positive changes in prescriber behavior will result?

The next example is whether we could identify specific prescribing for monitoring practices that could be measured, and these might be similar to the metrics that Dr. McAninch described in a study she summarized earlier.

Evaluate changes in these metrics over time, for example, the use of urine drug screens; opioid prescribing by dentists and oral surgeons; opioid dispensing from emergency departments; co-prescribing with benzodiazepines; and increased prescribing of opioids with naloxone. These are just a few examples.

Could we then assume that improvements in these were in part driven by the Opioid Analgesic REMS program and focus our future educational efforts on the areas that have not improved?

Another potential area to explore is to further examine the impact of state or healthcare system mandated CE through any evaluations that have been conducted by those organizations. We might also learn whether the 2012 approval of the ER/LA Opioid Analgesic REMS had any influence on these requirements.

The example on this slide somewhat tees up our next presentation by Dr. Cervero, and that is what do we know about the activities that have positively impacted prescriber behavior and patient

outcomes? Can we look at the overall saturation of pain or opioid CE currently or the characteristics of those programs, and determine the likelihood that they have contributed to positive behavior or outcomes?

Finally, we are all aware that there are a lot of concurrent efforts to address the opioid crisis. Some of the interventions on this slide were described earlier and include the use of PDMPs; state or health system mandated CE; prescriber limits; academic detailing; or other prescriber tools such as dashboards and reminders.

If we had a better understanding of the drivers of prescriber behavior in the pain opioid space, could that help us in our educational efforts?

We know that there are challenges, however, to identify which interventions directed at the opioid crisis have been most impactful as illustrated by a recent publication from colleagues at the CDC. The systematic review of over 200 studies evaluated the evidence for 11 different

systems level interventions, including provider education, and found that the quality of evidence supporting these interventions was low to moderate.

The authors identified the intervention with the strongest evidence and also called for the need for further high-quality research on the evidence in order to facilitate the adoptions of programs that are most likely to produce positive health outcomes. The authors also called for research in identifying the best strategy for addressing prescription as compared to illicit opioid misuse and abuse, as well as evaluating the synergistic effect of these approaches and their potential unintended consequences.

We'd like to hear the panel's thoughts about these and other potential indicators of opioid REMS analgesic success and consider, given the multiple interventions targeted at the opioid crisis, again, whether completion of a one-time pain management CE can be the sole driver of prescriber behavior change and ultimately impact patient outcomes, and whether we can assume that the Opioid Analgesic

REMS has contributed to any improvements in prescriber behavior and patient outcomes. Thank you.

DR. STAFFA: Thank you so much, Dr. Auth.

For our final presentation this morning, we are going to hear from Dr. Ron Cervero, who's going to talk more about some of the themes that Doris raised about what we know about CME programs.

Dr. Cervero?

Presentation - Ronald Cervero

DR. CERVERO: Thank you very much, Dr. Staffa. I think I'll end up picking up a number of themes Doris mentioned, as well as several of the other presenters.

I'm going to hope, by the end of my time with you, to answer this question of can we improve physician performance and health outcomes through CME or CPD? The evidence has been accumulating over about 40 years, and none of this is specific to opioid management and so on. But I hope in our discussion this afternoon, we can begin to draw some of the connections.

My disclosures, these views are my own. Of course, I work for the Department of Defense and Uniformed Services University. Specifically, I don't have any financial relationships that will affect my presentation.

I thought it would be helpful -- we have quite a wide range of expertise in the audience, so I thought I would spend a little bit of time at the beginning to talk about the evolution of CME to a more practice-based model, and then speak to the evidence that we have about does CME improveperformance and health outcomes. And finally, really, I think the most important question is how can we design CME to make a difference in these outcomes?

You are all very familiar with this picture, no doubt. CE has historically been focused on what many of us call the "update model," which is basically a knowledge delivery didactic model. What we know, and probably your own experience would confirm, is that this is not really optimal education to improving physician performance and

health outcomes.

So there's been quite a bit of dissatisfaction with the dominance of this approach among leaders of all the professions, really, and policymakers that this is just not good enough. We can and we really must do better. In 2010, the Institute of Medicine had a workshop and produced this monograph, Redesigning Continuing Education in the Health Professions. This is one of many, actually, that were struck around in the 2000s and beyond, but I'm going to focus a little bit on this one today.

What the report really said is what's the problem with the way CME is currently organized, was currently organized then, and that is that it's the process by which health professionals keep up to date. I mentioned this in my original slide. It's an up-to-date model focusing on the latest knowledge and advances in health care.

However, it's so deeply flawed that it cannot really properly support the development of health professionals in that it's become structured

around participation instead of performance improvement. Those of you who are clinicians know this well because you have to accumulate your credits for relicensure and recertification.

I think this report, and many others, with a lot of interest among policymakers, as said, we really need to move to a different way of thinking about continuing education that's really much more inclusive of the variety of ways that physicians and really other health professionals actually learn. The concept we now have that I think is deeply rooted in continuing education is moving from the concept of continuing medical education to continuing professional development.

Dr. McMahon, who's going to be on one of the panels this afternoon, wrote a terrific piece in Academic Medicine three years ago, and he said that, really, CME has evolved to become a multidisciplinary approach for engaging clinicians where they live and work and learn, and that it's about creating teams, putting a mentor at the clinician's elbow, giving clinicians feedback at

the bedside; employing simulation and other technology to support learning; and building longitudinal relationships.

I think a lot of what Graham talked about here, we'll probably be talking about this afternoon, which is the value of multicomponent, multistrategy continuing education that's rooted in practice settings. You really even see this in regulatory systems of accreditation and credentialing where, for example, point-of-care learning is now valued and used to develop CME credit.

What do we know about designing CME to improve performance and health outcomes? I think the thing I'd like you to take away is that this is absolutely not a knowledge problem, that we have hundreds of studies, including many randomized-controlled trials and 39 comprehensive reviews dating back to '77, that inform principles for designing CME that can improve physician performance and patient health outcomes.

What I'd like to do now is just move to the

second part of my presentation to talk about what we know and what the evidence supports, and again, frankly, probably is consistent with what you have found successful in your own learning as clinicians. To do that, I'd like to talk about syntheses that I and my collaborators have done since '96, where we have looked at comprehensive reviews, systematic reviews, literature reviews and so on, that have asked the question, what's the impact of CME? And I'm happy to provide these if anyone is interested.

I'd also note I have an update coming out -- myself and collaborators have an update coming out -- in Academic Medicine, I think later this month, that addresses the additional five years of data. The other is I'd like to reinforce some of what we have found over the past couple decades with the Institute of Medicine report that came out in 2010, that looked at the scientific foundations of the impact of CME.

The research questions really have revolved around these two, which is the one that's in my

title, does CME improve physician performance and patient outcomes? But really, as I mentioned, I think the much more interesting and important question is what are the mechanisms of action that lead to these positive changes in the outcomes?

To the question, we've had 39 comprehensive reviews from '77 to 2014 that I've published across these three syntheses, and what we know is that CME does improve physician performance and patient health outcomes. Of course, as for all the reasons I'm sure we're going to talk about this afternoon and have already been noted, it has a much more reliably positive impact on performance than patient health outcomes because of all the contextual factors that do affect the patient outcomes.

Just to the title slide, can we improve physician performance and outcomes through CME, I think of course the answer is yes, we can. Not every CME program, however, makes a difference, but we know we can improve it through this mechanism, which I think is really critically important as we

talk this afternoon about how this might apply to the REMS program.

I want to move now to the third part of the presentation, the final part, what are the mechanisms of action that we can be focused on, particularly, as Dr. Alexander said, if we're going to look at the impact in health systems and so on? So again, 39 comprehensive reviews, and summarizing that over these three sets of reviews I have done, you'll see we'll have 5 mechanisms of action; first of all, that there has been a needs assessment for practice change, and Julie White mentioned this.

What are the practice gaps for a specific audience, not a generic audience but the audience you hope to serve for your program? Secondly, program intensity, which means more exposures and longer periods of time, leads to these better outcomes, certainly -- and Julie mentioned this also -- using principles of adult learning. What that effectively means is it's more interactive. The learners are engaged in case-based discussions, as she mentioned. Vitally important is that they

were focused on outcomes that are considered important by the learners.

Finally -- and I know we're going to talk a lot about this, and I think several of the previous speakers mentioned this -- CE doesn't exist in a vacuum, that there needs to be administrative support; policy incentives; and, really, in some cases, financial incentives for practice changes. This speaks to the point that several presenters have already made of the notion of multicomponent intervention of which continuing educationis a part. These can be considered planning strategies if you're putting together a CE program and they will all increase the likelihood that the program is likely to make a change.

This tracks with the findings in chapter 3 of the IOM report, which is the scientific foundation for CE. Again, what that review found was it incorporates needs assessments; interactive; ongoing feedback to learners; multiple methods of learning; and simulates the clinical setting. To the question of do we know how to do this and do we

know how to design CME, the answer is, of course we do.

I just want to cycle back to the comment I made at the beginning. We don't have a knowledge problem here. We do know how to design continuing education to make a difference in prescriber practices and patient outcomes. My view is it's a matter of political will, organizational design, and where continuing ed fits into the organizational system. There's really no magic bullets here, but CME can really make a difference.

My final slide is, if we really want CE to impact practice and patient outcomes, let's stay focused on who we are teaching. We're teaching physicians in a social and organizational context; we're not teaching subjects. Of course we have subject matter, but we really have to focus on our learners. And I do believe CME can make a difference in addressing the very serious opioid crisis that we are experiencing. Thank you very much.

DR. STAFFA: Thank you so much. We really

appreciate your perspective and years of experience on this topic.

Before I adjourn us for lunch, I just want to give you a preview of where we're going this afternoon. What we've tried to do is break this down into three sessions, but we're hoping that everyone will be able to participate in all three. They will all be done as a larger group. We're not going to be breaking down into subgroups.

We're going to start with a session talking about the measurable outcomes that folks think are most important to focus the evaluation on for the REMS programs; then move into a discussion about feasibility and study design; and then finally end up with a session talking about some of these complementary and alternative approaches beyond direct evaluations to see where they fit in.

We're going to be working through a hand-raising system for folks to let us know when they would like to speak and try to facilitate the conversation that way. But of course, also, if folks raise questions or comments that are relative

to an earlier comment, we're going to try to make sure we keep that conversation going, so Paul Tran will be helping us with that.

Hopefully, you have learned a lot from both the background and history of this topic, as well as caught some of the enthusiasm and energy from some of our presenters this morning about the possibility of paths forward. We are very appreciative to all of our speakers for taking the time to actually share the information that they have shared with us.

With that, I'm going to adjourn us for lunch, and we will start back promptly at 12:30 with our first session. Thank you very much.

(Whereupon, at 11:47 a.m., a lunch recess was taken.)

AFTERNOONSESSION

(12:30 p.m.)

Panel Discussion - Topic 1

DR. STAFFA: Good afternoon. Welcome back. I hope everyone enjoyed the break and the beautiful buffet lunch we've provided to all of you. I hope you enjoyed all of that.

This afternoon we're going to start with Session 1, so you should all see the specific questions on the screen. Again, we understand that these topics are all interrelated, so we understand that this is a bit of an artificial separation. However, we're going to do our best to try to divide things up the best we can.

Session 1, what we're going to try to discuss for about the next hour or so is talking about the measurable outcomes and, again, thoughts about what those outcomes might be: considerations that we should be thinking about, both scientific

and clinical and research oriented. Again, considering you've heard information about the OA REMS and the goals, as well as the contents of the blueprint, to discuss the meaningful measures of good pain management practice and appropriate use of opioid analgesics.

Again, remembering that the original REMS and the current REMS both focus on prescribers, but the current REMS also broadens to focus on other members of the healthcare team. So if those outcomes might be different or somehow changed to accommodate that, we would welcome discussion about that; then secondly, looking at patient outcomes and discussing those. Again, in the talks this morning, we've tried to invite others who have been doing this work to share what they've been looking at in their work.

The way we're going to do this is if you could raise your hand when you want to offer a comment. I'll ask, since we have limited time for discussion, that folks be as concise as they can with their comments or questions. Again,

remembering if there are specific questions that are very important to the discussion, we welcome you to bring those up now as you make your comments. So raise your hand when you have something, and then after you speak, if you could lower your hand, that will help Paul keep track because we're going to try to go in order the best we can.

I would also welcome my FDA colleagues who are on the line that if you hear something and would like to hear more or expand, if you could just jump in, but just state your name first, and I'll ask all the panelists as well. That will help our transcriptionists make sure they capture the comments correctly. So if you could state just your name, last name, or whatever is most easy to do before you speak so that we can make sure we get that down.

Again, I'm going to let folks know, as Claudia mentioned in her remarks this morning, we have a docket open with this meeting as we do with all public meetings, and we do pay a lot of

attention and spend a lot of time going through transcripts and dockets when we have public discussions. So if by the end of the day, there are other thoughts you think of, or you think of them tomorrow, the docket will be open until mid-February. So we would welcome additional comments, thoughts, and anything you'd like to send us that you think would be helpful to us. We would be very appreciative.

With that, does anybody want to get started? Let's see. Any brave souls who would like to start the discussion?

DR. GOLDMANN: This is Don Goldmann. I put my hand up, so I don't know. Is somebody going to probably call on us when we have our hand up?

DR. STAFFA: Yes. Paul's going to let me know. Yes, Paul will let me know, and then we'll go ahead and let you know to speak.

For those of you who haven't used Adobe Connect before, in the upper-left corner you'll see a little person with their hand raised. If you click on the arrow next to them, it gives you an

option to raise your hand and then to lower your hand. So that's how that works.

Dr. Goldmann, since you're trying to raise your hand, why don't you go ahead and get us started on this discussion, please.

DR. GOLDMANN: One more quick question. I haven't seen anybody's face, so if I turn on my webcam, does anybody see it?

(No response.)

DR. GOLDMANN: I'm happy to turn it on so you can see my backdrop here with beautiful outdoors in Lexington.

(No response.)

DR. GOLDMANN: Anyway, I'm going to make a quick comment about measurement, which is I think our focus here. I'm going to say it in the context of quality improvement, which I'll comment on when we get to that part of this discussion.

I've heard several different types of measures mentioned by the speakers. One presentation talked about measures for quality improvement. Other speakers talked about

measurement for evaluation. There was measurement for getting CME credits, and of course there's measurement for judgment and accountability that might be passed by National Quality Forum, and then incorporated into payment mechanisms.

I just want to be sure we understand that those are all different. My experience with the measures that are intended for quality improvement, such as some of those that the CDC discussed, aren't generally used for that. I was the head of a working group for an evaluation of AHRQ quality and safety measures, and when we did a pretty extensive investigation of whether those measures that were meant for quality improvement were actually used for quality improvement, we found very little evidence that they were, and even less evidence that using them resulted in improvement.

So when we talk about that, the assumption is that people are actually going to use them, have the time to use them, know how to use them, and know how to improve. I think that's probably something that we need to be clear about because in

my experience, that's not what happens. So just a comment, let's be clear. I think today we should be talking mainly about measures for evaluation if I'm not mistaken.

DR. STAFFA: That's correct. That's what we're focusing on, are measures for evaluation. Thank you, Dr. Goldmann.

Dr. McMahon, did you want to make a comment?

DR. McMAHON: Yes, I'm happy too. Hi, everybody. It's really nice to have a chance to chat with you. A couple of quick thoughts based on some of the presentations this morning, and I look forward to the rest of the conversation.

I think it's very clear these are potentially highly dangerous drugs, and training in managing them is absolutely essential. It's particularly so that there's a lot of competence gaps in that more clinicians think they know how to do this safely, and easily, and manage pain, but it's very clear that in many cases they clearly do not.

Secondly, it's worth noting that pain is

obviously complex as well as the entire range of addiction and dependence. Patients are variable. Specialty practices in which this is deployed are highly variable. The practice environments are highly variable. Access to medicines, to treatments, and to care provisions are highly variable.

Compliance with medicines are up and down. And of course you have the intervening variable of time between education, its components, the behavior you're looking for, and its impact on patient health outcomes; so a huge number of variabilities that really constrain the ability to do comprehensive studies, linking cause and effect.

I think thirdly, it's worth noting that we know educational interventions can and do drive learning and performance change. The time when we need to study before and after as to whether clinicians can learn or does change are behind us. We know those things are true. Humans can learn, and they do learn, and they do benefit from education and training.

My specific recommendations for us to think about are first that we should ensure industry and the RPC continue to fund accredited continuing education training because at its outset, it's valuable for the entire community.

Number two, we should probably not require national, broad-scale discussion or studies trying to link health outcomes for large groups of patients, and link those to the educational interventions that we're describing. There's just too many intervening variables. It's ultimately impossible to make a cause-and-effect linkage.

Number three, I think that the RPC should fund, and the FDA should require the RPC fund, educational outcome studies that demonstrate the impact of education on performance in specific environments and with specific educational interventional deployments to look at their effectiveness. And number four, I'd like to see an organization, perhaps the FDA, perhaps another, creating a summary on a periodic basis of those interventional studies to look at the overall

impact and what it means for the entire community.

DR. STAFFA: Thank you for your comments.

Dr. Becker?

DR. BECKER: Great. Hi, everyone. I liked Dr. Alexander's framing of the issues. I'm a believer that the content of the REMS needs to be more potent. I know that's a little out of scope perhaps for right now, but I just want to say that I'm going to try to focus on the measurement issues, but I think, ultimately, where we need to make some improvements are with the potency of the intervention.

That said, the guidance that I think is most -- I'm an internist, I'm a primary care provider, and I've done most of my clinical work in the setting of a busy primary care practice. The CDC guideline to me is the best set of guidelines and the most rigorous and helpful set that are out there. Our speaker from the CDC who was highlighting ways to track metrics that capture adherence to the CDC guideline I think are worth a second and third look.

In that vein, I'm wondering what folks would think about -- or I throw it out there for further comment -- the issue of high-dose prescribing. On an individual patient level, I see the tension of not wanting to say thou shalt not prescribe above a certain threshold because of course you want to design your treatment plan to the individual patient level. But if across one's entire panel there's a high proportion of patients on high-dose therapy, I think that starts to become problematic.

I believe, and I think the data would support this, it doesn't matter your expertise and how much monitoring you're doing; the risk of these therapies become exponentially higher with higher dose therapy. And if that's happening broadly across [indiscernible], there's going to be higher rates of [indiscernible]. So with that, I will lower my hand. Thank you.

DR. STAFFA: Thank you, Dr. Becker.

Could I remind folks to mute your phones because we're getting some echo.

Dr. Becker, could I just ask you, before you

go away, to comment further? You mentioned increasing the potency of the program. Were there specific things you had in mind that, again, might relate to measuring outcomes?

DR. BECKER: Yes. Well, I would like to see -- this is sort of a pie in the sky, and we'd have to get there incrementally. I was really heartened -- the REMS that are out there now are including more guidance related to management of opioid-use disorder. I know that the scope of the pain program -- for example, which I will disclose I'm a faculty member -- has incorporated more OUD management into its materials.

But really, I think anyone who's prescribing long-term opioid therapy needs to also be facile with the use of buprenorphine. And if you're doing this work without facility in that medication, you're hamstringing yourself and you're hamstringing your patients, and I think those two things need to be bundled together more than they currently are.

DR. STAFFA: Thank you very much for

clarifying that.

Dr. Katzman?

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

DR. STAFFA: Yes, we can.

DR. KATZMAN: Okay. Great. I'm a neurologist who practices primarily pain management, but most of my clinical and educational role comes from Project ECHO, and I do a lot of teaching in that realm. I'll just make a comment, if I can, about the topic number 1, about what meaningful measures you might consider as good pain management practice.

I really love the idea thinking about decreasing opioid prescribing, and looking at patient outcomes, and how you might look at educational content let's say from the new and improved FDA REMS, and decreasing opioid prescribing, and decreasing co-prescribing. But I also think it's important to look at things like our prescribers increasing their use of non-opioid pharmacotherapy. Are prescribers referring more to physical therapy, more to behavioral health, more

to integrative pain management? Are they co-prescribing naloxone with their opioids if they're not just for acute pain? Things like that. I have a laundry list of ideas, but those are some things that I'm currently working on with some continuing education studies.

Then I just might mention very briefly a study that I published with a team that I worked on with the DoD, an ECHO pain study where we did a prospective observational cohort study published in 2018 in the Journal of General Internal Medicine, where we looked at Army and Navy clinicians who learned about effective chronic pain management and safe opioid prescribing, coming on to their Army and Navy respective pain ECHOs over the course of many years.

What we found is that those Army and Navy clinicians that participated in ECHO Pain versus Army and Navy clinicians that did not participate in ECHO pain, the patients of the clinicians who participated in ECHO pain had significantly decreased annual opioid prescribing, very

significantly decreased annual doses of opioid morphine milligram equivalents, as well as the most significant thing was decreased co-prescribing of opioids and benzodiazepines. We also found -- which Dr. McMahon reiterated and so did Dr. Cervero -- that it correlated with the increased dose.

So we really believe that continuing education is iterative, as we know adult learning is, and that it's not just one-time, one-stop shopping, but it's interactive, it's bi-directional, and it's not just a one-time thing. But these clinicians were coming onto the ECHO network on average of 4 or more times, and about 20 percent of them came on to 20 or more sessions.

So I think that's what I'll end with, and thank you.

DR. STAFFA: Thank you so much.

Dr. Winterstein?

(No response.)

DR. STAFFA: Are you muted?

(No response.)

DR. STAFFA: Rich, I'm not sure whether we need to unmute Dr. Winterstein's line.

MR. BARNES: Alright, one second.

DR. WINTERSTEIN: Hello? Can you hear me now?

DR. STAFFA: Yes, we can. Go ahead.

DR. WINTERSTEIN: Excellent. Good.

Rather than going into specific measures, I was thinking about a few principles. One is I really appreciated the review of the impact of CME and the effectiveness. There were a few pieces there that I think are really important when we are thinking about evaluating the effectiveness of CME with specific measures, and that is related to how clear the behavior is and how implementable the behavior is that is targeted by a particular CME activity.

It can be something very simple where it's a matter of you should not prescribe drug A but drug B. If that action is very simple and very easy to implement, I have no doubt that this can be reinforced just by providing that specific

knowledge. The problem comes in when the implementation becomes really complicated, and unfortunately in the opioid world, that implementation is incredibly complicated.

I appreciated very much the patient case that was shown by Dr. White very early on, which was the classic chronic pain patient, where it is extremely difficult to wean these patients off opioids as we all know. So those behaviors, then, that would need to be targeted and measured and that are so incredibly difficult to implement for providers are really the ones that are hard to do.

There are issues like follow-up, how do I make sure that I see those patients regularly; issues like tapering and de-prescribing approaches, as was mentioned before; referral for treatment of patients who are suspected to have an opioid-use disorder; and all these cool prescribing alternative therapy options with physical therapy and so on.

None of this is easy to implement as a single provider alone. This has to happen in a

system, and that's where it becomes so extremely complicated, but I think these are the practices and behaviors that need to be targeted. The simple behaviors have already been taken care of. We all know that. The initiation of opioids with very long duration, post-surgery, and things like that, that has been taken care of by state policy in most states as far as I understand. High-dose prescribing has been shown to be now a very poor predictor of outcomes.

So the low-hanging fruit essentially has been taken, so it really becomes the measures and the behaviors that are really complicated that would need to be targeted in measurement approaches. That's one thing to think about.

I think the second thing that really relates to this is that these measures are therefore very dynamic because the world of trying to deal with the opioid epidemic is changing so rapidly. So I don't think that there will be one set of measures that can really do the trick and that will be possible in the next 10 years. There will probably

be re-evaluations of which measures are really needed and which behaviors will need to be the predominant target of the CME programs.

Then the third principle that I was thinking are patient-reported outcomes. We see a lot of discussion and reports of unintended consequences of policies that aim to reduce opioid prescribing. So it seems to me that it is extremely important to monitor not only pain scores, but also other patient-reported outcomes that are directly related to pain, such as depression, when we are trying to change provider behavior.

DR. STAFFA: Thank you so much.

Dr. Thomas?

DR. THOMAS: Yes. Hi. Thanks. I'm really enjoying what I'm hearing here, and I keep changing my response based on what I'm hearing everybody else say, but it is a point.

First of all, with Project ECHO, I heard there were 20-plus sessions. This is one 2-hour session. So I think you have to have realistic expectations about what you can get out of a 2-hour

training session. It's also not -- as was discussed before -- how CMEs can be refreshers, but a lot of these clinicians have very little training in this to begin with. So it's not like reminding them of their years of training and just update them on the most recent information; you're talking to a lot of clinicians that aren't trained.

So if we're looking at metrics from this CME that's like global, change-the-world sort of metrics, I think that's a bit unrealistic. There are so many other things going on at the same time. I go back to Dr. Becker's comment about some potent questions. I think if you can put in this training just some key questions, some key things that we think could make a difference, and a clinician without a huge amount of experience in pain and opioids, if they knew that, it could make a difference, and then I think that would make both the REMS better and also the evaluation.

I like the idea, potentially, of tying it to the CDC guideline because there are some very good things in the CDC guidelines, plus there are some

misconceptions. There was a New England Journal of Medicine paper put out about some of the misconceptions of the CDC guideline. So if we could just focus on some key things that clinicians should know, given that they probably don't know that much to begin with on this topic, and some key misconceptions, then if we can just change those, I think in those people you would be making a difference on a local level.

Just to give you one example, we have a program at the NIH where we created online modules, and our first module was just trying to overcome a misconception about back pain. I won't get into the module, but the people gave the module to medical students, and then six months later they tested people that got the module versus don't on that specific misconception, and the people that took it no longer had that misconception or had that misconception less.

So in that way, that was a real tangible way of at least showing that there was a lasting impact. And I think a similar thing could be done

with a REMS, where if we can just show some key changes in what is believed and not believed, I think you could say you did make a difference.

DR. STAFFA: Thank you, Dr. Thomas.

Dr. Alexander?

DR. ALEXANDER: Yes. Can you hear me?

DR. STAFFA: Yes, we can.

DR. ALEXANDER: Great.

Great questions. There's so much morbidity and mortality from prescription opioids, still, that I think anything is on the table. I'm not sure that I would agree that any potentially problematic prescribing behavior has, quote/unquote, "been taken care of." Whether high dose, or chronic use, or concomitant benzo and opioid use, or otherwise, I do think it's a reasonable point that a lot of opioid volume goes to people for one-time prescriptions, and I think that's a reasonable point. But if those are unnecessary prescriptions, then that's a problem.

With respect to these questions, I'm going to just focus on question 1 for a second, and then

question 2. So question 1, I think many meaningful measures of good pain management can't be captured but some can, and I would focus on the prescriber-centric ones. I think these are a great place to start, and given the role of opioid supply driving a lot of the epidemic, other members of the healthcare team are much more difficult.

So my suggestion would be walk before you run, and pick off the easier stuff first, which is by no means the slam-dunk, which is to look directly at prescribers where the data is very rich. These are directly related to the second question; that is, the outcomes that I think are most meaningful are patient-level measures that are clustered within prescribers.

There are a large number of patient outcomes that can be assessed using measures such as those developed by the CDC, so I would agree with many former speakers about that one. These measures have several strengths. One, they're automated; two, they allow for approximations of appropriateness. They're not perfect, but they

allow for some approximations of appropriateness. Three, they can be licensed, and they're routinely used by healthcare technology companies; four, they can be clustered into providers; and five, they can be analyzed in almost real-time fashion.

So I'm thinking here both in terms of a national view of prescription claims alone, so measures that -- I think Dr. Walker had a nice depiction of measures, some of which only require pharmacy claims and others which would require additional information. I would just dichotomize, as you think about this, those measures that can be examined only using pharmacy claims that are available from just about everybody in the country, including you and me. So I'm talking here about things like high dose; high-dose chronic use; redundant therapies; concomitant opioids with other controlled substances; initial days supply; and so on and so forth.

Then the second type of measures are those that would require more additional patient information. So these might be limited to specific

systems of care, EHR records, and they would allow for analysis of things like incorporation of nonpharmacologic interventions, integration of care, adequacy of follow-up, and so on.

The last point I'll make is just about smaller randomized trials -- and again, Dr. Walker, I think your comments were spot-on -- and the potential value of these within specific systems of care. Here, if you're doing pragmatic trials, which is an interesting design, what you're collecting would be limited to measures that are typically captured in clinical records. So we're back to having more than pharmacy claims, but less than what you can ask if you're designing your own instruments.

But to get at some of these outcomes that people have spoken to, where there's also an appeal to gathering them but it requires primary data collection, you could do randomized trials or, like Dr. Walker said, a randomized consent trial where you can collect lots of stuff because it's up to you what you're gathering from participants.

So I think that, as a general framework, may be helpful in thinking about these measures of the REMS that are going to allow for direct assessments of the impact of the REMS on the outcomes that we all should care about the most, which is prescriber behavior/patient outcomes. Thank you.

DR. STAFFA: Thank you.

Dr. Morrato?

DR. MORRATO: Yes. I'm going to try my webcam as well. Maybe that will work. There I am. Okay. Very good.

First, I want to say thank you very much to the FDA and everyone on the presentations. It was wonderful to see everything integrated in a very cogent and easy-to-follow way. The comments I want to add to everything others are saying is maybe to use the logic model framing that was mentioned earlier.

I think it's important to tie our outcome measures as to what might be logical, proximalthings you might expect immediately in terms of having the CE, and then what might become

more distal and therefore more complex or more difficult because you're now operating within a real-world setting that gets more complex based on multilevel factors, as many speakers have talked about.

So it's well-established in implementation science that as you go from those proximal to distal, you'll get what's called often a voltage drop. And I think it's very important to be understanding where along that pathway towards effectiveness and health outcomes we're losing the voltage drop most greatly; and if we think of this as the continuous process improvement and learning system, where further focus should be.

So in terms of proximal, I was really impressed with colleagues that presented on the work being done in Boston on the CE, and that makes me wonder to what degree are all of the REMS-producing CE providers following such a rigorous and thoughtful approach in how they're linking from the blueprint to the outcomes measure.

So a first assessment would be are we

getting the dose delivered consistently across all of these? And I would go back to what colleagues are talking about are standard outcome measures around quality in this kind of CE, and in that context, not just knowledge, but I really appreciated the measure related to commitment to change, which is very analogous to behavioral intention.

At least as they're walking away from this one CE intervention, has there been a change in attitudes, and therefore a commitment to the change? Because frankly, if that's not occurring, it's hard to believe that the CE is having much of an effect on the more distal outcomes.

Then with regard to the distal outcomes, I would echo also Dr. Walker and Dr. Alexander in arguing could we be doing targeted RCTs that are now trying to -- in the context of that CE being delivered, we know that this is a complex problem that requires multilevel, multimodal interventions, and we saw evidence from some of the published work that was shared that it's possible to do these

kinds of pragmatic trials in partnership with community health systems. And putting now the CE embedded in that, can we now start to look at, as was mentioned, that behavioral intention being linked to actual individual prescribing behavior, or clustered, as Dr. Alexander was talking.

I think that now helps us understand are we translating from intention to behaviors, and we can get the data that's needed to know in that context and setting. When I think of outcomes there, I would draw on many of the speakers in saying we're not trying to do a national representative. Where are the specific use cases, scenarios, either high risk or populations, where they were concerned most about the care gap, in which we think that the CE -- just like when we do a trial design, you're wanting to test an intervention where you think there's sensitivity to detect a difference.

We know now, more recently, the CE is being directed more broadly in pain, immediate release. So are there particular healthcare settings that are still not tracking as well? And therefore in

terms of quality that we're hoping for, the RCT is directed there. Then the outcome measures or behaviors are very much like what we heard from the CE providers; it's case-scenario based and what makes sense in that care setting, and those become the drivers of the behaviors, or outcome measures, that we want to be tracking.

So there's, in other words, good logic linkage between what the CE is evaluating as behavioral intention, and then how is that being translated to outcome measures that we're looking at in prescribing. And I would stop there, frankly, as outcomes, and really do, as the FDA is doing, just broad CDC surveillance around what's going on nationally as opposed to trying to link a specific, one-time CE to everything going on nationally in terms of outcomes; important for surveillance for FDA and CDC, but not necessarily an outcome measure tied to the CE delivery. Thank you.

DR. STAFFA: Thank you, Dr. Morrato.

Dr. McMahon, did you have a comment to make

directly relating to Dr. Morrato's comments?

DR. McMAHON: Sure. Thanks.

Just briefly, we at ACCME have been conducting audits on the REMS compliant educational programs that are funded by the RPC for several years and have found clean audits in terms of the ability of these organizations that are funded to demonstrate that their provider groups are attesting to change and committing to change exactly like she described.

I think her point is very well made, that our sense is that the research efforts and the outcome evaluation efforts should be activity- and program-based, rather than trying to take on a national question that has so many intervening variables, that makes the feasibility of such an approach very challenging indeed.

But we do have lots of evidence that educational interventions are being effective, but the effect of teaching a pain management specialist about recognizing patients with potentially addictive behaviors versus teaching a primary care

clinician how to avoid using narcotics in patients with low back pain are such different outcomes, you can't generate unifying outcome variables for such broadly and different issues.

DR. STAFFA: Thank you.

Dr. Morrato, did you want to respond to that?

DR. MORRATO: Yes, just briefly. I know there are other speakers. I think that's outstanding. I'd like to see it public. I'd like to see that audit public so that we can all be understanding that. I think your point around there's very different variability in what an outcome measure is, depending on the case scenario or a clinical setting, is really underscoring what I was saying, to understand where the gap is most critical, and then an effectiveness study be designed for that specific setting, recognizing it's hard to have one unifying global indicator. Thank you.

DR. STAFFA: Thank you. Good discussion. Let's move on.

Dr. Floyd?

DR. FLOYD: Hi. I have some brief comments on the measurements, but also some more general ones on the role of voluntary CE that may not fit in the other section, so I might just mention them now.

Most of my relevant experience in this area has come from serving on a credentialing panel, actually, for L&I in Washington State. The big focus for our group over the last five or six years has been identifying the most problematic opiate prescribers and prescribing that has caused harm, or deaths, or evidenced by really high dose or prolonged opiate prescribing.

I would just echo what others have said, that the process measures, especially in the CDC guideline, look excellent. The things we've relied on such as duration of use, MED equivalence, and co-prescription of benzodiazepines, I think the CDC goes much further than that, and we found those to be quite helpful.

I agree, I think, with Dr. Alexander making

the point that the patient-specific outcomes are more important; things like deaths, overdoses, misuse, and abuse. Those are very hard to identify with structured data, and I know the FDA is doing some ongoing work on trying to improve surveillance, but there are ways to do some of this with EHR.

The more general comments about the role of the CE, I have a little bit of skepticism about the impact of a voluntary CE activity on perhaps some of the most problematic opiate prescribing, and part of it is because I think we found that the prescribers who cause the most harm and cause deaths, that were prescribing lots of high-dose opiates for long periods of time without justification, probably weren't the ones who were going to be affected by a voluntary CE. They often trained very long ago. They were isolated. They weren't in a group practice or an academic center.

I think others have made the point that perhaps trying to target the providers or areas that are having the most problems might be more

useful. This also has to do with evaluating the effectiveness of a CE or any public health intervention. If you simply study the people who are signing up, I don't think that's necessarily where the most harm is being done.

DR. STAFFA: Thank you so much.

I'm going to just remind folks when you're done with your remarks, if you don't have anything else that you wanted to say in this session, please remember to go back and put your hand down. That's going to help Paul identify who still wants to speak. But again, if you've spoken once and you would like to speak again, you can put your hand up again.

Dr. Larochelle?

DR. LAROCHELLE: Hi. Thanks. I just wanted to make a couple quick comments. One is, like the CDC measures do, I think it's important to stratify these measures, and I'll suggest three categories where we have increasing evidence about appropriateness.

I would start with incident opioid

prescribing for acute pain conditions, and then starting opioids for patients with chronic pain. Then the last one that I think is the stickiest that others speakers have alluded to is approaching patients on prevalent long-term opioid therapy for chronic pain. I think that's an area where the evidence is much weaker and really hard, much harder, to develop appropriate guidance around, and an area where we're still collecting data on what the best practices should be.

The second thing I just want to advocate for, we've heard a little bit of this, but really make sure we're thinking about potential externalities from these practices. The first I'll mention is making sure we're not widening existing recognized disparities in the treatment of pain, especially by race ethnicity. The second is that we're not discouraging providers from continuing to manage these medications for patients who have been on them and that we're not leading more providers to exit actually doing this, which could be leading to orphaning of patients, for lack of a better

term, who have been on these medications for some time. I think epidemiologically we still have work to do to really identify how prevalent that is.

Then lastly, some of the evaluations I've done have identified less harm due to opioid analgesics themselves but without recognition of the transition to illicit opioids, first heroin and later fentanyl, of which much scientific debate has existed around the influence of efforts to reduce opioid prescribing may have contributed. So I think those are some externalities that need to be considered.

DR. STAFFA: Thank you so much.

Dr. Losby?

DR. LOSBY: Thanks so much, Judy. I really appreciate this rich discussion. Some of my comments may not be most relevant to the later speakers, but I was jotting down some notes and just really appreciate the earlier comment about the difference between outcome measures that are intended for evaluation or outcome measures that are intended for quality improvement, and

absolutely agree.

The intent of sharing the quality improvement measures that are aligned with the guideline, just to say that these are available and certainly support all of the previous speakers who stressed the importance of tying any outcomes that are selected by the FDA and that they closely match the content, and the intent, and the intention of the intervention dose; and being very explicit in what could be expected with a 2-hour exposure to content, and then being able to clearly identify what are those short-term intermediate and long-term outcomes.

I certainly appreciate and support the comment that Dr. Morrato mentioned about logic models. In and of themselves, logic models can just be very clear about teasing out the exact expectation of what is the content, and then how can we closely tie those to the particular expected outcomes.

The last comment, I think someone made the note about the misapplication of CDC's guideline,

and I think it was perhaps someone from New York who mentioned that even in the training scenarios and then with some of the feedback, it was important to include misapplication as a potential question so that people are prompted to recognize what are those misapplication times that may happen, either misapplication to a patient population or misapplication in terms of what the guideline recommendation was itself. So those are my comments. Thanks.

DR. STAFFA: Thank you so much.

Dr. Anderson?

DR. ANDERSON: Hi. Sorry. This is Dr. Anderson. This is Daren. Can you hear me?

DR. STAFFA: Yes, we can.

DR. ANDERSON: Great. I had actually taken my hand down because some of the previous comments pretty much covered what I had to say, so I'm good. Thanks.

DR. STAFFA: Alright. Thank you.

Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: Once again, like the

group, this is very a mind-expanding time, and I will try not to repeat what's been said, though I'm very impressed and appreciative of all the input.

I was trying to step back. I know we're trying to discuss measures, but actually where that took me to -- and I apologize if I tend to deviate a little bit, but when we were talking about REMS in the years past, and I had the opportunity to be involved with this group, the picture that I drew for myself is a funnel in that what we've been discussing, whether it be through the CDC guidelines or the blueprint, I think at that point we had such a national crisis going on, and I think we felt we were coming in late already. But I think we cast a pretty wide net with especially the changes that were made to the REMS when we went from the extended-release to the short-acting and how we broadened the REMS.

And now I wonder is it time that we use the evaluation tools that we're discussing, and the science, again, to help narrow the funnel of the REMS, so to speak, and really identify what are the

risks, and maybe prioritize what we're defining as risk in terms of prescribing opioids, and is the RPC model and continuing medical education one of the tools that could be used to foster the innovation in terms of the science around this; so allowing, one, for the FDA to consider is this another moment to look at REMS and, once again, focus it, scope it, because we're more informed about risks already.

I really like the comments about looking at prescribers and systems and patients. I'm a primary care physician. I have the luxury of working for the VA, where we are a system and we actually have a lot of these signals and feedback loops already available to us. But I think we can further define what we're really talking about in terms of what are the risks that we need to associate, to consider, and then start looking at the dose of education maybe in a more discrete content, frequency, and once again, who is the provider we're talking about, the primary care provider versus the specialist, and the geography

of it. I think the comment about risk of discontinuation and the risk of lack of access to good pain management is a potential risk that we know could be an unintended consequence of the large net that we cast.

So with that being said, I would close with saying, yes, consider leveraging the RPC to foster more innovation around education, targeted education, and then the measures that are already being discussed, that I agree with, whether they be the transactional measures of prescribing frequency amounts, doses, and using data to inform you on that, could be a step forward to narrow the funnel of assessing risk and trying to impact risk. Thank you.

DR. STAFFA: Thank you so much.

Dr. Goldmann, did you have another comment?

DR. GOLDMANN: I did, actually. Let me see. I like to go on camera just because it seems more personable.

First, I'm really happy that, Marc, you brought up stratification and equity. I've been to

whole-day meetings where the issue of equity is not brought up, so we've really got to be sure that the data is adequately stratified. Sometimes the data we have available does not include the necessary level of granularity, but stratification around neighborhood, social determinants, people of color, Latinx, ethnicity, these are all really, really important to understand where we're making progress and who's being left behind. We may improve and actually widen the gap of disparity between those who are having improved care and those who aren't.

I also like this discussion of dose. But remember; it's not just the dose we administer, its documenting that the dose was received. RAND did a study with us that really emphasized this. We were so sure we were delivering multifactorial dose in repeated segments and all that, just like Julie White nicely described, but we didn't know, really, whether the dose was being received.

One thing that I haven't heard mentioned is we talk about bias, and who's taking up the CME activity, and who's improving because of it, and so

forth, but what about the people who have said no and have not taken it up? How do we measure who they are so that we know who's being left behind, or who's not interested, or who we're reaching in the wrong way? There's got to be some measurement strategy to really elucidate the characteristics of the people who are saying no to these programs.

Finally, there are a number of epidemiologists on the phone, and sampling is really powerful. So if we need more granular information about the various programs, sampling can be efficient and relatively economical to do. There are lots of national sampling efforts to look at the health and well-being and practice in American health care, so we ought to be using it here if we're not already. Thank you.

DR. STAFFA: Thank you, Dr. Goldmann.

Dr. McMahon, did you have another comment?

DR. McMAHON: Yes, sure. Thanks very much; a few quick things. First of all, outcome assessment can actually interfere with the quality of the learning and the behavior change that you're

looking for. Educators always are very thoughtful about engagement, like you heard Julie and Ron mention earlier on in their remarks, and outcome assessment by itself can create a new burden on the learner that will actually disincentivize their engagement in the behavior or in the learning materials themselves.

The same is true for the dose that Don just mentioned. Higher dose educational activities may be much more effective, but they're not going to be effective if people don't participate. So in a voluntary program, you've got to be thoughtful about the balance between outcome burden and dose burden on the individual learner. That's one of the challenges here. We're not talking about pharmaceuticals where you can just dose adjust within the same size pill and the burden on the patient is no different. That's very different in these circumstances of human behavior.

Two last things just to mention are, first of all, I'd love to see the FDA, the RPC, and the CE community work together to define levels of

outcomes that could be assigned to educational activities that get to higher levels of performance outcomes. I think we can certainly continue to obligate organizations that do education to at least generate commitment to change and generate from that what people are planning to change qualitatively. That's very interesting from a human performance issue and often anticipates what their actual behavior change will be.

The fourth suggestion is the joint accreditors put together the independent grant review committee for all the RPC grants this last year. They could be an ideal group under Ron's leadership -- Dr. Cervero -- to select educational activities that are associated with research outcomes that could be very usefully summarized as an aggregate via leadership groups like the CDC and the FDA.

DR. STAFFA: Thank you so much.

We're coming down to the end of the hour, but there are a few more people who would like to comment. So I'll just ask you to be as concise as

you can so that we can fit all the remaining comments in.

Dr. Katzman, did you have another comment?

DR. KATZMAN: Yes, and I'll be very brief to end here. I just wanted to make an observation that there's just been many, many studies over the last 5-10 years looking at CME outcomes related to best practices, pain management, safe opioid prescribing all across the country, showing, really, benefit, showing kind of Moore's level outcomes 3, 4, and 5 with improved knowledge, self-efficacy, and even intent to change practice. But it's really the patient-level outcomes that I think would really benefit us all with regard to looking at how the FDA blueprint is going.

So that's just an observation that I had, that I think weshould really be focusing on patient-level outcomes, and I think that's it. Thank you.

DR. STAFFA: Well, thank you for making sure we don't lose sight of that.

Dr. Morrato, did you have another comment?

DR. MORRATO: Yes, I do. I'll keep it -- I can't do two buttons at once. Hold on.

I really appreciated what Dr. McMahon was just talking about and what can be done within the companies. But the question I wanted to say is I wanted to note that it is quite impressive -- it looks like in just a year that there was a hundred thousand that did do -- the completers, as you say; 60,000 that directly have a license to prescribe a controlled substance.

So I would like to see measures that can help us better understand -- I know it's voluntary, but is there anything we can be collecting to help us better understand the selection bias and/or type of clinical setting or care setting? Not just like prescriber's specialty, but a setting that will help us understand where this is being delivered and where there might be other areas that we need to incentivize in, quote, "a voluntary way."

Then related to that is I think it's a missed opportunity for trying to understand context better and understanding what policies or levers

are in their system that are influencing how they're delivering care. What do I mean by that? State requirements around the use of a prescription drug monitoring program, or local system, this is a priority or not. These kinds of indicators have been shown as being very influential in whether or not people actually engage and adopt.

So I recognize that there's balance between outcome burden and dose and assessing that, but I'd like to see more emphasis in trying to understand who are the people that we are training, and how representative, and where are there gaps in which CE needs to be spread. Thank you.

DR. STAFFA: Thank you.

Our final commenter in this first session, which again I know the sessions are going to kind of blur together a little bit, but Dr. Alexander.

DR. ALEXANDER: Yes. I just want to say when we're talking about whether or not educational interventions are effective, I think we have to specify with respect to what outcome. At five years, again, the FDA and ER/LA manufacturers, the

FDA determined that they could not conclude whether or not the ER/LA REMS had reduced inappropriate prescribing or improved patient outcomes.

So I think commitment to change is important and I understand that there is data to support its value, but I would argue it may be necessary, but it's surely not sufficient. I don't think that a national evaluation is summarily too complex. A national evaluation could mean a lot of different things, so I wouldn't be so quick to write off the potential for doing something that's not that deep a dive but that's broad in scope using automated methods.

This addresses the last point I want to make, which was a follow-up to a comment about the burden on learners. It's a very important comment and is exactly the reason why the sorts of measures that have been suggested and that I've suggested are so valuable, because they're automated and they don't require the collection of data from individual participants, so it would be invisible to the participant.

So again, I don't think that that sort of linked design approach is the only assessment that should take place, but it seems to me a really low hanging fruit in terms of using automated methods, near real time, low burden or no burden on the participating learner, and a means to examine patient behaviors that matter and to see them clustered within prescribers.

Panel Discussion - Topic 2

DR. STAFFA: Thank you.

That's a nice way to wrap up that portion where we focused on the outcomes to measure, and I think you've given us a lot to think about. But I want to move now into Session 2, where we talk more about -- and again, as we're thinking about these outcomes, I think this will influence what we're thinking about in terms of the feasibility of studying these outcomes: what kinds of data systems; what kinds of environments; what are the key issues to try to figure out; and what are feasible ways to do this: observational versus interventional, traditional methods versus more

innovative methods, and different kinds of designs and data.

As we heard in the presentations this morning, we have so much electronic healthcare data, it seems crazy to not try to use it in some meaningful way with many of the questions we try to study, but on the other hand, to acknowledge some of the key limitations and to realize that we're not going to be able to get everything we want, and figure out whether there are creative ways to make the best use of what we have, and yet add to it as we need.

So I'll ask if folks could go ahead -- I think folks have largely lowered their hands, so that's good. So we'll start with a clean slate, and it looks like -- who are we going to start with at this point? Who would like to start the discussion going in this area? Again, broader than the outcomes, but thinking more about the design and data, as well as, I think, in this session also thinking about some of these other issues going on.

I know some of our speakers spoke to the

other issues and all the other things going on, and trying to separate out effects due to any one intervention as opposed to the entire environment changing, and changing in different ways and different places, and in different healthcare environments.

Any initial thoughts to get us started? It looks like Dr. McMahon is going to be brave and get us off the ground, so go ahead, Dr. McMahon.

DR. McMAHON: Just to get the conversation going, I think you're probably, really, more looking at rather than a system-wide intervention to track all of the learners and accredited education around pain management education to try and separate out the efficacy and dose effect of the intervention, you're probably looking at a summation of more modest studies at the program level. That can be large programs like we heard from BU earlier on, or other national-level programs of which there are many different models, some of which are many hours long and the full curricula.

But I think if you try and differentiate the elements of each of those program level effects and create more of a narrative review of the effectiveness of this education at achieving a variety of endpoints, that's not going to satisfy those who are very quantitative. But in fact a lot of the value of educational interventions, particularly on an open framework where there aren't placebo interventions, and the only comparison you can make is either non-engagement or a time-based crossover study, you're really limited in what you can do from an epidemiological perspective with these types of issues, particularly when the secular trend is towards improved knowledge and changes in performance over time.

So I think that you're better off looking at a narrative and a summative meta-analysis view of program-level outcome variables to differentiate the overall effect of the intervention over time.

DR. STAFFA: Thank you, and thanks for starting the conversation and laying out some of

the challenges here.

Dr. Winterstein?

DR. WINTERSTEIN: I actually have a question, and no answer yet, that relates to the landscape of the -- can you hear me?

DR. STAFFA: Yes, we can, but no fair. You're supposed to have the answers, right?

(Laughter.)

DR. STAFFA: Sorry. Go ahead.

DR. WINTERSTEIN: Yes, that comes later.

Related to the landscape of CE -- I think that's extremely relevant when we're talking about use of observational designs -- do you know what is the proportion of states that have mandatory CE versus involuntary CE? And then among those who take CE, what is the proportion of people or CE programs that follow the blueprint versus not?

DR. STAFFA: That's actually a very good question. I'm going to ask, Dr. Auth, do you have any information on that? I think some of that was in the landscape analysis that I think was in our issues paper, but I'm wondering if you have that at

your fingertips.

DR. AUTH: Hi. This is Doris. I actually don't, but if you give me a minute, I could probably pull it up and let you know when I have it. I think nearly all of the states have some sort of required education for different types of their providers, but I'll get you that exact number. And I also think we do have some information on how many of those programs were blueprint compliant, but I'm not sure that we have a full understanding of that.

DR. STAFFA: Dr. McMahon, did you have anything relevant to add?

DR. McMAHON: Yes. Forty-two states require some sort of education about pain management, addiction, or opiate prescribing, but those requirements, as has been referred to earlier on, are not the same as the REMS blueprint whatsoever and are often subcomponents of it. The elements of the education that are deployed nationally obviously are not all registered for REMS or funded by the RPC.

There's a huge range of educational programs happening at the local level and at the national level around pain management, OUD recognition and management, all across the country, with every member of the healthcare team all the time. This is a hot topic, and continues to be, and appropriately should be. But those educational programs that are registered for the OA REMS are audited for compliance with the blueprint, and those activities are required to be and are compliant universally with the blueprint. We audit as a regulator that compliance and have found a hundred percent compliance with those who are participating in the program with the FDA and the RPC.

DR. WINTERSTEIN: Okay. Thank you. That is very helpful. Given that description, if you're thinking about use of existing databases, if it is essentially impossible to define what kind of exposure a control group would have, it appears that there would be at least one component of prospective data collection that could potentially

be in some sort of case control design, right? But it would essentially have to ascertain what kind of exposure to a CE program a given provider has had in the past, and when that happened, and whether this was a blueprint CME program or whatever else was there; just as the first start for the answer.

DR. STAFFA: Right, right. Thank you. Thank you both.

DR. WINTERSTEIN: The big problem there is, really, if there was no effect found, is that caused -- the CME is not effective or the comparator essentially had the same exposure, and we don't know. We saw one of those earlier studies this morning, and this was mentioned where there was some sort of matched control group, but this is the same problem. If the CME program shows effectiveness in some sort, then the control might be adequate, but if it doesn't, we don't know whether the control really was adequate or not.

DR. STAFFA: That's actually an excellent point.

Dr. Howley?

DR. HOWLEY: Yes. Hi. Can you hear me?

DR. STAFFA: Yes, we can.

DR. HOWLEY: Hello? Wonderful. Thank you. Hi. This is Lisa Howley from the Association of American Medical Colleges and thank you for including me today. I really enjoyed the presentations and then this conversation.

I wanted to follow up and just share a few comments. I'm an educational psychologist in medicine and I work across the continuum. So I have a bit of a broader lens, if you will, looking at this issue and this challenge to better prepare and train our physicians, whether they're medical students, residents, or practicing as clinicians and faculty out in practice.

I'm delighted that we're talking today so much about outcomes. As most of us on the call today are aware, we've been shifting to an outcomes approach or competency-based approach education model for decades, again, across the continuum of education; and just actually some comments that Graham, Dr. McMahon, you made much earlier today,

and it was about the fact that, yes, education does work.

We know, yes, we can and do change practice via education. We should keep in mind, though, as many have said, that education itself is an incredibly complex endeavor. It's a social science and involves educational research, and a variety of methods should be taken to study and really understand the effectiveness of our approaches that are different from those that we take in the natural sciences. I agree with those who said that we should be taking a more targeted approach and not a national broad look at this because educational interventions really need and take a targeted approach because of the complex environment that our physicians are working in.

I wanted to comment, as our colleagues at Brown Medical School show with their scope of practice model, that we should be matching our measured outcomes with specific learning modality and objectives that it's intended to measure, but also not expect higher level outcomes from a single

education module or activity, and also not to underplay or undervalue the importance of improving or increasing knowledge.

I feel that we have demonstrated, and we do demonstrate, that these shorter, smaller interventions do affect knowledge, gains, and growth in knowledge, which is really important. It's certainly not sufficient for necessarily changing behavior and practice, kind of those higher level outcomes that we also want to expect, but I think we need to take a broader perspective and take more from a logic model, which has been mentioned already, about when we evaluate our program, our broader educational programs, differentiate that from the specific educational targeted intervention. Thank you again.

DR. STAFFA: Thank you.

Dr. Morrato?

DR. MORRATO: Yes. Thank you. I'm going to comment on two things. One is I think it's not a single study design but, as many are saying, I think we need to approach it as a comprehensive. I

know there are multiple study designs answering different questions, and I know FDA's evaluation assessment plan with the company's approaches is that way.

Then the second one, I want to build off of what Dr. Alexander has been really underscoring, is this sense of urgency. And here we are how many years into it? So when I see words like "can we do a pilot study," that doesn't speak to a sense of urgency in the sense that we have a lot of information, and things have been published already, and that we should be able to move forward more quickly. I think I've been informed a bit. We are in a COVID environment in which things are moving very rapidly, and I think we can bring a lot of that same kind of can-do urgency for this crisis as well, which has not gone away.

So in that context, I think a study design that is feasible, which we haven't really talked about, is just really clarity on the knowledge transfer, and that it's feasible, it's ongoing, and it needs to be a part of the evaluation, that

pre/post. We're not talking in depth about that today, but that is feasible and is happening.

We've talked about this idea of comparative effectiveness, is the CE making a difference,ongoing, from intention to actual behavior? I hear Dr. Alexander in which we need to be looking at outcomes such as mortality, drug abuse, and addiction metrics as well, but I'm also thinking pragmatically on what can really be accomplished and targeted, a short-term kind of study that we can actually say that the outcome is related to taking a CE event.

I'm thinking of feasibility related to how do you power a study or size it, and I think in that kind of sense we could be doing a comparative effectiveness pragmatic trial or comparative effectiveness embedded observational study using secondary data in partnership with the health system; that that can be feasibly done, and as we've seen by some of the published work, it has been done.

So I expect the companies to be able to do

what any academic can do as well, and even faster and better, with the resources that are available for this very important problem. I might say a primary endpoint needs to be something feasible that can be collected in the short term, and that maybe the secondary endpoint -- just like we have an RCT for drug development, a secondary endpoint might be related to these larger safety profiles or other kinds of metrics. So that can be feasibly done versus trying to size the study, say, on a very difficult-to-measure outcome.

Third, as I've been listening and reflecting on what others are saying, I really like the idea of this national surveillance. I guess the question is whether or not that's something that is FDA, the company, or CDC. I'm not sure who's really responsible for it, but I do love the notion. And what comes to mind, if we think about COVID, is the utility, for example, some of these large data sets have played and understanding the rollout of the pandemic and also a sense of what's happening on state policies.

So I look towards the IHME and its dashboard. They are tracking at state level things like mass policy, social distance, et cetera. That's very analogous and akin to what we're talking about in terms of prescription drug monitoring programs or mandated CE, et cetera. And it just seems to me that we should have a similar kind of dashboard, at minimum, that is really trying to help us understand those metrics in semi real time, and just have national reporting of that in some surveillance way.

I know a lot of the data we're dealing with is lagged, but if we've put the same energy we have towards COVID reporting that we have for this, there are ways to get this accomplished. We're seeing it happen right now, and I think we should be demanding the same amount of urgency and investment in opioid-related indicators as well. Thank you.

DR. STAFFA: Thank you, Dr. Morrato, and thank you for pointing out some of the similarities for urgency between the two crises, actually.

I just want to circle back. I think Dr. Doris Auth has some more information about the question that Almut raised earlier.

Doris, did you want to share information that you have?

DR. AUTH: Sure. I believe Almut's question was, do we know the proportion of mandatory CE from state, for example, and the proportion of those that follow the FDA blueprint? Actually, what the RPC included in their landscape analysis is a little different, I think, than your question, but they did summarize whether the REMS CE would fulfill the state requirements. So they looked at the state requirements individually, and then they looked back at whether the REMS blueprint would cover that.

Sorry. Can you all still hear me?

DR. STAFFA: Yes, we can hear you.

DR. AUTH: Sorry. Unfortunately, I was getting another call at the same time. It's very strange.

What they found is in the landscape

analysis, so I would just direct you all to that. That is included in the background attached to the appendix to the issue paper. However, I will just share that of the 40 states with physician CE requirements, specifically Doctor of Medicine and Doctor of Osteopathy, the standard REMS CE would totally fulfill those state requirements for 26 states; partially fulfill the requirement in 10 states, and failto fulfill the requirementin 4 states.

Again, I would have to take a closer look at this to find out exactly what those failures were and what was not covered, so I apologize for that. But in the landscape analysis, this is included for all of the different professions, so physician assistant, pharmacist, nurse, et cetera.

DR. STAFFA: Thank you very much, Doris.

Julie White, did you also have information that you thought was responsive to that question?

MS. WHITE: Yes. I just want to respond, though, to what Dr. Winterstein said because she was pointing out that individuals could say whether

or not they participated in a REMS-compliant program, and I want to say that most people have no idea. They don't know what REMS -- I'm talking about the clinicians that are accessing education. They don't understand what REMS is, so I don't think that you could get a great amount of data looking backwards.

I also wanted to point out that clinicians really access education because they have a clinical problem that they need to solve. That's what motivates them. That's really what's behind it, and mandatory requirements may not be the best way to go.

Also, one other thing I wanted to comment, and a couple people brought this up, is I want to echo what Dr. McMahon said. If you put too many barriers in the front of the education, we already have to ask them a lot of questions just to ascertain whether or not they're a prescriber, et cetera. If we add a whole lot of upfront questions about pre/post, et cetera, that will be a barrier. Lastly, people will not want to

participate if they think they're being tracked. If they had to give us their NPI number, for example, and I know we can look it up, that would scare people away. So I just want to put that kind of reality check out there.

DR. STAFFA: Thank you.

Dr. Floyd?

DR. WINTERSTEIN: May I respond to that briefly? That's ok.

DR. STAFFA: Almut, why don't we have Dr. Floyd, and then you can get back.

DR. WINTERSTEIN: Sure.

DR. STAFFA: Thanks.

Dr. Floyd?

DR. FLOYD: On the topic of evaluating feasibility, I do think for reasons that were really nicely described in the briefing materials and in the reports, it would be very hard to interpret a study that tried to estimate some causal effect of the CE on either the process measures or on patient outcomes, both in terms of looking at secular trends just because of all the

other public health interventions over the last 5-6 years of which the CE is just one part of.

Also, in an active comparator design, back in 2016, I think I advocated for some type of mandatory CE, but the report and the briefing material suggest that, actually, we kind of have de facto mandatory CE. Most states have some regulation requiring some type of opiate CE, so I'm not sure that's really useful, and other panelists have made the comment that that presents barriers or breeds resentment, potentially.

I do think that having the CE available, the high-quality CE, is valuable just as a resource in and of itself without having to demonstrate that it has some kind of efficacy or effectiveness in terms of question 2. I really like the idea of surveillance. There's been a lot of talk about process measures, what patient outcomes are important, and can they be studied. I think they're most valuable in the context of a national surveillance activity rather than a conventional pharmacoepi study that tries to link these outcomes

to a specific CE activity, which I think you'd have problems making any kind of inference about.

I think there's a lot of value in the discussion and talking about which outcomes to look at, but it may be different than what was envisioned in the these questions.

DR. STAFFA: Thank you for that perspective.

Dr. Goldmann?

DR. GOLDMANN: Yes. Thank you.

This is really an interesting discussion, and I really appreciate the comment about showing causality. Let me frame it a different way, as one of association versus causation and attribution. I don't want to get too radical here and say that we shouldn't look for attributable effect of this program, but I take us back to the concept on a logic model.

A logic model assumes there's a program theory, and so far I have not heard articulated what the program theory is, let alone the natural outgrowth of a program theory, which is a prediction of the attributable effect of the

intervention. The more I listen to this, the more I realize just how difficult it is to imagine a program like this with its limitations and all the barriers that people practice and face, let alone the patients.

I can't come to an attributable fraction or attributable effect of this program that's going to be large enough to be appreciated in an observational study. I'm thinking about pragmatic trials, and large simple trials, and leveraging the data sets using latent class or propensity analyses. I'm trying to think of all of the statistical tools that would allow me to get beyond a crude association with a large confidence interval and true attribution or causation.

I love the example that was shown early on of a time-ordered data analysis. I don't know if it was a statistical process control or whether it was an interrupted time series. I'm not sure of the method used, but that's what we need to see. We need to see that, overall, as a country, or region, or health system, that we're making

progress and be happy that we may have contributed to that. But without a real prediction, I don't know what I think about the effort of evaluation.

That said, where I think we need to go, whether we can attribute or not, is to make sure that we have a learning health system. I don't want to use a buzz word that's being overused, but there's an enormous opportunity for a learning health system. It was mentioned this morning that Julie White's program at BU incorporates all kinds of pedagogically sound behavioral science-based approaches to better learning through scenarios, vignettes, and iterative testing the way we now know reinforces learning.

How widely used is that? Do we understand where the best practices are and how can we spread them so we can say with confidence, we're using the very best techniques that we know about for education to move behavior? I gather we're nowhere near that. Then people like Julie can do evaluation in their own milieu to see whether or not using best practice actually changes behavior,

and we'll be able to learn from that. But at a larger scale, I don't think we're going to be able to do that, but we definitely should be using the best possible behavioral science and the best possible education science to try and accomplish what we think we should.

DR. STAFFA: Thank you.

Dr. Goldmann?

DR. GOLDMANN: That was me. I already --

DR. STAFFA: Oh, I'm sorry.

DR. GOLDMANN: -- just gave you -- I gave you a whole lecture on my feelings about attributable fraction.

DR. STAFFA: And hopefully I'm not going to attribute it to someone else. Thank you.

Dr. Alexander, I believe you're next.

DR. ALEXANDER: Yes. I practice and I prescribe opioids sometimes, and I think it's easy to overstate the concerns about the potential impact of other training that individuals may or may not have received. I don't think that people that have received training are essentially done

with and can't be, quote/unquote, "used or studied or something." But I do think that it's really important that there's careful selection of controls in any comparative cohort studies that are done, and I think looking at a similar group of prescribers within a state, within a time window, or maybe within a payer, that those sorts of factors would be important to consider in thinking about what a comparable group might be.

I think we're using the term "national" pretty loosely, me included, so I just want to try to see if I can sharpen this. Sometimes when we're talking about national, I think we're referring to surveillance studies or population-level studies, and I'm not enthusiastic about those.

I think the FDA has very astutely pointed out the limits in the use of surveillance, or, quote/unquote, "national data" to evaluate the REMS in information that's in the public domain, and that national can also sometimes mean -- when I've used it, I've been using it partly just to refer to analyses of programmatic impacts that are beyond a

single system. I'm simply referring to using individual prescriber data, individual patient data, but in more than just, for example, the state of Massachusetts.

Some of the concerns that I hear seem to lead people to be enthusiastic about things like surveillance, or national mass, or other things. If the direct impact of the REMS is tough to assess, I don't see how the solution is measuring something else. And if the concern is that we'll never show the REMS impact -- one recent speaker said I'm not sure we'll ever show that it's impactful. This is my words, not yours, but what I was hearing was it's a one-time intervention. But I don't think the answer, then, is to study something else; it's to revisit the REMS program.

Don't you want a REMS program where people that participate in it look different than those that don't? I don't mean their race or gender, but I mean, don't you want providers that after the program are somehow different fundamentally from before the program? If you don't, then what's the

point of the REMS program? I thought we're talking about a program to approve the safe use of opioids.

So I don't know why we're so discouraged that we're looking to measure something else. It's like wondering if someone with diabetes can be treated with lifestyle modification alone, concluding that they can't be. But instead of starting insulin, deciding to monitor their lung function instead of glycemic control.

The measures that you're talking about for surveillance nationally, they're vital, they're important, they're useful, and they're interesting. I'm all for them, but it's not the FDA's regulatory mandate. That doesn't have to do with the REMS; there are a thousand different levers. We've all said that there's a ton going on in this space.

So I just don't understand why we would want the FDA, with their limited resources, to take their eye off the ball and focus on something that's just going to propagate the status quo, because it's not going to provide direct feedback of whether the REMS program is working or not. I

think this bleeds over into question 3 or Session 3, but I just don't see why looking at whether there are hot spots around the country where more people are dying from overdoses helps the FDA in regulating manufacturers' conduct of this important post-approval safety program.

DR. STAFFA: Thank you, Dr. Alexander.

Dr. Katzman?

DR. KATZMAN: I just realize -- sorry about that. I kind of agree with this last speaker that -- I'll just say my comment in the chat. I just wondered if there was any evidence that a one-time CE for pain education really changes practice or patient outcomes, and I agree with the last speaker that it's really not your role to change the process you're doing. But maybe we ought to look for some other way to kind of study effective best practices using more iterative training and interactive training. I'll just leave it there. Thank you.

DR. STAFFA: Okay. Thank you.

Dr. Winterstein, did you want to get back in

the discussion? I know you wanted to respond directly to the answer to your question, but if you have other thoughts to add, that's fine.

DR. WINTERSTEIN: Yes. I have some thoughts to add. I'm still chewing on the whole notion of other CME programs, and I would like to throw some thought out that might be, at least in my opinion, fairly important. And it also resonates back to some of the DSaRM meetings that we have had around exactly that topic.

The REMS typically adds specifically a layer of safety on top of existing practice and policy and whatever else is in place. So the existing practice and policy that is in place is that there are 42 states that have a requirement for CE. And I acknowledge that that requirement may be different from the blueprint, but there is some educational and some duration that providers have to do pretty much nationally, close to nationally, of various quality.

And now we are talking about a REMS program that is a voluntary component, which obviously is

somewhat redundant given the fact that there's already mandatory requirements in place. Then we infer that because that blueprint -- and I'm very impressed by the blueprint and the comprehensiveness of detail that has been prescribed in there. But we're assuming that this blueprint is extraordinarily better than other programs that may not follow that blueprint, so we're comparing this really not against nothing anymore; we are comparing it against something. And now we are thinking that that additional blueprint, essentially, or that additional information that is provided in a 1-hour or 2-hour CE, whatever is required, really moves the needle.

I have started to think about this from an evaluative perspective because that's my training, but now I'm also starting to think about it as what's the value of the program given where we are now. In 2012, things were quite different than where we are now, so how do we really extract it out of the current landscape and infrastructure that is in place and that has been put in place by

state policy?

My direct comment back to Dr. White, when we were thinking about how can we actually capture what kind of exposure -- and still it's basically an exposure comparing different exposures to different educational interventions, or even these CME programs -- I imagine that all states that have a mandatory CME in place require certification that the CME was completed, which probably would be issued by the CME provider. Technically, working with the boards might be able to produce that information, but then again, I'm wondering to what extent we really would be able to distill the difference out of non-blueprint CME programs and blueprint CME programs, given the acknowledged weakness of an isolated educational intervention in itself.

DR. STAFFA: Thank you. Those are really I think key points in this.

DR. WINTERSTEIN: Yes, and I hate to be destructive, but --

DR. STAFFA: Right. As I've told folks

who've been on our advisory committees before, we don't bring you the easy questions. We try to figure those out ourselves. We only bring externally the hard questions, so that's OK.

Dr. McMahon?

DR. McMAHON: Thanks very much. It's just a terrific conversation and great to be part of it. How wonderful that we all feel so passionately about something that's so important for the public health.

I come down to a couple of observations in my mind. First is that these drugs are indeed dangerous, and the manufacturers have to participate with the community and have an obligation to facilitate their deployment effectively and safely in the community.

I think secondly, we know CE works. Whether it's for the team or for the individual, educational interventions do have the capacity to meaningfully change performance and patient outcomes. The best strategy for how to do that and generate the best possible outcomes is entirely

activity-dependent on who you're trying to change the behavior, what behavior trying to change, et cetera.

I think where we're having difficulty is not agreeing on the importance of measuring outcomes. All of the educators on this conference are passionate about measuring outcomes and being evidence-based in the educational interventions that we deploy. That's what we have developed our careers on, that's what we think about every day, that's what we care about. We care about the performance of learners who give us their time and their minds for a while, and we want to make a change that's going to be most helpful for them, and their patients, and their communities.

I think the difficulty that we're trying to navigate is at what level of analysis can we perform the outcome assessments, and my encouragement to us is to recognize the complexity of trying to do outcome assessments on anything other than the program or activity level.

That doesn't mean to say you can't include a

whole region, or you shouldn't include just a single institution like Julie's program that she described earlier on. But you can't amalgamate all of these variety of educational interventions because they address such variable learners across so many different disciplines, and across so many different learning outcomes, who are on so many different types of institutions that have access to a whole different range of actual abilities to change the performance and compliance of their community with these pain management and OUD avoidance efforts.

So I think that's where the issue is, at what level is the assessment made, not should we be accountable for and demonstrate the results of the interventions that we do make.

DR. STAFFA: Thank you for your comments.

Dr. Floyd?

DR. FLOYD: Just to follow up on some of the comments I made earlier, if the scope of the discussion is narrow just on the existing REMS, how can we best evaluate it? I do think it's hard with

observational designs, and in the list of questions is do we need randomized-controlled trials? And if that's the objective and the priority, that probably is the best way to do it.

I think my argument is that given limited resources, what is going to be most useful in terms of public health interventions and evaluating them? The kind of surveillance systems that have just been discussed by several others on the discussion I think have some utility in terms of REMS but also have more broader applicability as well. And from a regulatory perspective, it may be that that's a non-starter; that you simply can't mandate that companies do that. That's acceptable, but if the goal is to talk more broadly about what would be useful given the limited resources, I think it's worth discussing.

Another point to bring up is the REMS itself. This current REMS is considered a non-restrictive one. It's voluntary continuing education. There are other aspects of REMS that could be considered an implemented. We had some

discussion about this back in 2016, and I think that was unpopular; things like provider registries and restricting prescribing at certain high doses or for certain products, but that's also something that could be discussed as well.

DR. STAFFA: Thank you for your comment.

Dr. Larochelle?

DR. LAROCHELLE: I think I'd echo what Dr. Alexander was saying during his presentation, that if we really want to study whether or not the REMS is having an effect, I agree we need a design with causal inference. We just talked about RCTs. I don't think it's impossible to do a cluster RCT here for some of the reasons that were discussed.

I think the observational design that gets at causal inference is much trickier.

Dr. Alexander mentioned emulated trials, and this is really just a thoughtful systematic way of approaching your observational study to mimic or emulate a trial, where you clearly delineate the inclusion/exclusion criteria for your population, the intervention, and the study question you're

trying to ask and answer, rather than just do a cohort study where you look at myriad exposures and outcomes without givingthought to those considerations you by definition need to. I also think an important aspect of that is pre-registration of whatever this observational protocol would be prior to delving into the data.

The other thing from a design perspective that I wanted to mention is that we've talked a lot about potential confounders, but I want to make a plug that some of the things we're talking about as confounders could also be effect modifiers. So I think your practice environment really will influence whether or not this educational intervention could be effective.

I'll make a likening to some of the DATA 2000 trainings. You get an 8-hour training, and then whether or not you're effective or actually choose to prescribe buprenorphine I think has a lot to do with the practice setting you're in. I'm in a large academic practice that happens to have a really robust nurse management program to

help support us with buprenorphine. When I started doing buprenorphine prescribing, that really helped my ability to take off, whereas had I been in a different setting and gotten the same exact training, I probably would not have been doing it near as much.

Finally, if this is too much to chew for FDA, given the limited resources, I think there's an opportunity to think creatively about working across agencies. CDC is very interested in this. I know Dr. Losby may have had to step off for a little bit. There are examples of people doing this. I'm involved in the HEALing Communities Study right now, which is joint funded by NIDA and SAMHSA. So if people are looking to study different interventions in this space, there could be an opportunity to bring this in as a component of what's being studied.

I agree with Dr. Alexander. I don't think we need to throw out the potential that this could be directly evaluated with some robust design.

DR. STAFFA: Thank you.

Dr. Thomas?

DR. THOMAS: Yes. Hi. Thanks. I was going to echo Dr. Alexander also, but then I started listening to everybody else, and I really like this discussion. I agree that if we set our sights too high and look nationally, and expect a broad impact of this one educational effort, first, you can't tease it out very well at all; and second, it's probably not going to be that much of a difference compared to all the other things.

But I agree that we want somebody who takes this education to look different afterwards, and I think that we can detect. We're not going to turn them into pain experts or opioid experts, but education works. I learned that in school. They should be different in some ways, and we have to be thinking about what those critical ways are. Some of them could be not starting at high doses and we're not just cutting people off opioids. I've heard horror stories. If we can just get some people in the clinical field thinking that way, I think it will make a difference, whether we can

detect it on national data or not.

The other point I wanted to make is that it's just one 2-hour module, but most clinicians, the average MD gets about 6 or 9 hours of pain education in medical school. So 2 hours on top of that, that's 25 percent more or so, so that might make a difference. We did one pain module, which was 45 minutes long, that made a difference on a very specific belief that clinicians had. I think it was the first pain module where success was ever published in a journal.

So I do think that you can make a difference with a 2-hour module. It's not going to be a global difference that we'll be able to detect, but I think if we're strategic in terms of what changes you're looking to make and have those changes that actually could make an impact, I think these 2 hours can be impactful. Especially since so many people are taking these modules, this 2 hours can add up; but, again, strategic in terms of what changes in those individuals we would like to see that could potentially have an impact.

DR. STAFFA: Thank you.

I want to thank you guys. This is exactly the kind of discussions that we've had internally, and I'm really happy to see the differing viewpoints. It's really helping us a lot.

One point that I'd like you all to think about -- and I'm going to keep going down the list, but if you have thoughts on this, please raise your hand, and we'll get to you -- is this idea that evaluating specific programs really does require the ability to link the NPI information to prescriber practice, behavior, or whether it's prescribing EHR. It does require that step, and we understand that there are some challenges there.

So if folks have insights into what those challenges are and ways that could possibly surmount those challenges, we would love to hear that. So with that in mind, I'm going to keep going down the list and keep the discussion going.

Dr. Morrato?

DR. MORRATO: Yes. Thank you. I can't answer your question on the linking, but I wanted

to come back to this question of we're trying to evaluate whether the REMS is effective. Right? I think that's what FDA is asking, what measures and what's the study design?

It makes me come back to we haven't really talked about the goals of this particular REMS and, really, what is the intervention, which is a single CE. Really then, based on that, what is the expected effectiveness out of that when you think of that as a weaker intervention in and of itself and you think of that in the perspective of all of the complex health systems that we have, which includes federal and state regulation, as well as difficulties in mental health and addiction services more broadly in the U.S.

I think it would be useful for the FDA -- is it reasonable to expect not just this intervention, but any action that FDA takes that's going to solve this larger societal problem, other than to be contributing to be part of the solution. I think that informs what we set as our expectations for what level of evidence is needed to say has the

REMS been effective.

I might argue that the REMS has been effective and that the CE, although voluntary, has helped to prime the pump and help contribute to CE more broadly. Probably when FDA takes action, it has indirect influence on state actions and the fact that more states are having CE, if that's the case, and it could all be seen that this policy action has had some effect.

If in fact we feel, really, the goal of the REMS is to mitigate the problem of misuse, abuse, death, et cetera, from prescription opioids, then it would make us say, well, one CE is not going to do that. So do we have the right REMS program or should other interventions be added? And that's a different question than saying are we getting the most out of what we could expect from the single CE?

To that regard, there's probably evidence that it's shown to be effective, and what we're arguing with is, is that intervention enough in light of the magnitude and complexity of the

problem, and then is that really in the purview of FDA's authority to be able to control all of those elements?

So I think that's what makes this a real thorny problem to try to say what is that magical study design or outcome measure because I think of it in the context of, really, what's reasonably expected in FDA's authority in this regard, given the complexity of addiction and the misuse of this type of prescription medicine? So it's more of a philosophical comment maybe than an answer, but I just wanted to share. Thank you.

DR. STAFFA: Thanks for sharing. Philosophy is welcomed.

Dr. Cervero?

DR. CERVERO: Yes. Thanks. I agree. This has been a really productive discussion and I've learned a lot. I have several points to make, but I wanted to pick up on -- I forget the speaker just before this last one, about can a 2-hour program make a difference in prescribing. I would use that to say, of the five characteristics that I talked

about, one was that there was a needs assessment for practice change and that the physician believed these were important.

So I think it illustrates that, yes, a 2-hour program can make a difference if it's done with some of the key strategies in mind, however, we know there's many other CE programs that are 2 hours, or even 20 hours, that won't make a difference at all because of the design.

So I want to come down on the side of I think that this can be done. We could evaluate the effectiveness of the REMS, but we have to do it at the activity level, not at a national level. And the reason for that, as I just illustrated, is continuing ed is not a generic thing. One of the downsides of the metaphor of a dose is that you can dose drugs because you can send out the same pill to all over the country, but you can't do that for continuing ed because it's multifaceted, it's done well, and it's done poorly.

So I think we have to do this at the activity level, and I know there's a lot of really

expert people on the line of how you can link a variety of study to look at the overall impact, so I would leave it to those folks.

I want to make three points. First of all, from an educational point of view -- and this is why it has to be done at the activity level -- you have to link the outcome measures to what was actually taught and what the learning objectives were. As one of our speakers said earlier in the first discussion, not just what was taught but what was received, and what did the learners take away. So that's my first point, why I think it needs to be at the activity level.

The second is, as I said, I think continuing ed is not generic. There are some that are better and some that are worse, and some that incorporate needs assessment and some that don't. So we need to be able to disaggregate the kind of features of what effective CE might be.

My third point -- and we've talked about this a lot today -- is that continuing ed exists within a larger system so that you can think about

designing interventions that are not just the education and training but other components such as quality, QI process, academic detailing, and there are a variety of things you could put together as a package.

The final thing I would say is I don't think this is just about proving or disproving whether this program works, but how can we create a process by which we learn how to do it better? I think if we can have the pharma companies be part of the design of the studies that look at the impact of the interventions they are funding, we can learn a lot if those kinds of evaluation studies are done well. So, over. That's my last comment.

DR. STAFFA: Thank you very much.

Dr. McMahon?

DR. McMAHON: I really appreciate those comments from Ron, and it's obviously important to think about the pragmatic nature of how CE works, and in what audience, and in what time, and the importance of educational design. I think all of us here could spend a lot of time thinking about

educational design, but it's not necessarily the function of this particular conference today.

Just to go back to the key question that you had about linking prescriber behavior with NPI and trackable information for a population or patient health outcomes, I would just say there are a couple of factors that you have to think about.

The first is that behavior and performance of a clinic or practice really depends not just on the behavior of the individual physician or clinician who's a prescriber, but on the performance of the team that wraps themselves around that patient, and many of our communities are of course working in teams. So thinking about team-based outcomes ends up being very important.

But then you need to also establish a relationship of trust with that person and their team if you're going to track and manage them over the long term because only in a relationship of trust are people going to allow themselves to be tracked and develop a relationship with you and get feedback from you that they'll actually leverage,

believe, and implement into their practice.

That means that in many cases, those who have access to data on which patient outcomes can be monitored and those who are also in a position to establish trust and trust with the team are often local educational units based inside clinics, and hospitals, and other health centers. Those CE providers in that local circumstance can serve these roles and be the nexus around which a lot of these studies and the outcome assessments are made, and they're there willing and able to help in many cases.

DR. STAFFA: Thank you for providing your thoughts on that.

Julie White, I know you had raised this issue, too, in your previous comment. Can you speak to that?

MS. WHITE: Yes. I just wanted to say -- back to your question, Dr. Staffa -- about the NPI number, I think the problem with that is that looking at prescribing patterns doesn't necessarily give you what you're looking for.

For example, our course director, Dr. Alford, he ends up inheriting patients that other clinicians have abandoned because prescribing opioids or dealing with complex patients is difficult, and they don't want to deal with it anymore, so his prescribing numbers have probably gone up. So I wanted to say that would be the concern in our minds about looking at prescribing behavior.

The other thing I wanted to mention -- I think it was Marc who mentioned this, Marc Larochelle -- is that the system really needs to support positive change. This is kind of what we've seen in the transitions during the time that we've been offering this education, that I don't think it's a question -- I think it's gone way past knowledge and competence, and more to do clinicians work in systems that support positive pack practice behavior? So if you're in a system that gives you all kinds of support, that can make a difference. So you kind of need that coupling of ability and skills of a practitioner, but also the support of

your team and your system.

Then the last thing I wanted to say is I think that the challenges that clinicians are dealing with today is different than what it was back in 2012-2013. One of the things we're hearing, for example, is that safe tapering is a real challenge for people. I also want to support what Dr. McMahon and Dr. Cervero were saying, that I think there are reams of data that we could be looking at, and there's probably a way to tease that out and get it up to the higher level of what this whole enterprise is accomplishing. Thank you.

DR. STAFFA: Thank you for those comments.

Dr. Roach, you had a comment in the chat room about tying outcomes to payment from the CMS perspective. I'm wondering if you could talk about that a little bit for the group.

DR. ROACH: Can you hear me?

DR. STAFFA: Yes, we can.

DR. ROACH: Okay. This may be a case of just -- I'm the CMS person, so if all I have is a hammer, everything looks like a nail. But there

are mechanisms for which to put improvement activities into our quality payment program and to have some degree of it tied to payment. Since this is such an important thing as how much should we be pushing this, what do people think the limitations are of that?

One of the limitations of our programs are stopping people from using this as an improvement activity because I do feel if we tie some of these behaviors to payment, we would get some to stick. So it doesn't help necessarily in determining I guess the impact of the CME and how effective they are, but I do think that we can get some of the outcomes that we want easier if we work through the payment program.

But that being said, I realize there are limitations and some of it's voluntary. So any ideas on what we could do, because this is something that we looked at a lot at CMS. We're trying to develop measures about opioid use in various settings, about concurrent opioid, and benzodiazepine use, and just other aspects of this.

So what would you say to increasing the uptake of it? That's what I was just wondering. And Dr. McMahon just put a note that there is a CE already approved, so I guess how would we get more uptake of that and what do people perceive as problems with what we have currently?

DR. STAFFA: Thank you.

Do other folks have comments on that specific topic?

DR. ALEXANDER: I would just say it's a clear example where the administrative support -- this is Caleb Alexander. We've heard from speakers about these factors that can promote the value or the impact of CME, and one of them was administrative support or policy incentives.

So I would just say in selecting locations, for example, that might be good ones for single-system studies or trying to find settings where you could both identify REMS recipients and comparable non-recipients, that looking at things like payment incentives or other incentives that promote practice change sounds very smart.

DR. STAFFA: Thank you.

Dr. Katzman, did you have a comment on this or something else?

DR. KATZMAN: Sure. That's a really interesting idea about the REMS CE already being approved, the MIPS. I would just feel a little worried if there was any kind of underlying payment incentive and if that might bias any provider behavior in terms of their practices. I don't know if that would at all or not, but that would be my unconscious worry I guess.

I would just like to comment about how difficult it is to link clinician education -- we were talking about a couple minutes ago -- to NPI number or in big systems like the VA or the DoD, to expose them to take their training, and then to expose them down the road to see how they're doing in terms of prescribing behavior. When I was working at ECHO with the DoD, we couldn't do that, even after getting very secure and high-level data sharing agreements. I think it's just fraught with a lot of -- providers really shy away from that,

and I think that's very reasonable.

I agree with Dr. McMahon about the fact that what needs to happen is trust in smaller systems, getting to know the clinicians, getting to know the leadership and the clinic, and working with them; then studying smaller systems, then working with educating them, and then maybe perhaps getting medical records after developing trust in smaller settings. Over.

DR. STAFFA: Thank you.

Other comments or things that folks would like to add to this particular discussion? I'm also checking in with my FDA colleagues. Anything you want to hear more about or things you would like to clarify that you've heard? Be thinking about that. And I see that Dr. Cervero has raised his hand.

Please go ahead.

DR. CERVERO: I just want to reinforce what Dr. Alexander said, is that these evaluation studies are quite plausibly done within closed systems. It's much more difficult to do when you

have learners coming in from multiple systems. It's very, very difficult to track them because they're going back to many other types of effects on their practice. But if you're in a closed system, it's much more doable to do the kind of evaluation I think the FDA is thinking about here. Over.

DR. STAFFA: Thank you. I think that's consistent with some ofthe comments we've heard, that it's more important to get the detailed information we need, rather than to worry about the generalizability or the national-level nature of this.

Let's see. I believe, Julie White, you raised your hand again.

MS. WHITE: Sorry. No, I actually took it down.

DR. STAFFA: Okay. No problem.

Dr. Alexander?

DR. ALEXANDER: Yes, Judy. I was going to ask you or your colleagues, given that this has come up several times, can any of you speak to the

degree to which enrollment and privacy concerns limiting participation was a really important or formidable barrier in the study that the RPC did provide at 72 months, based on the concept brief that was provided at 48 months?

DR. STAFFA: Dr. McAninch, I don't know that we have any insights into that, but what I really was hoping folks to speak to is exactly what you heard from Julie White and Dr. McMahon, that there are concerns and issues with trust. And I think that there is some hesitance on the part of prescribers or healthcare professionals to be providing information where perhaps they're not entirely clear where that information may end up.

It looks like, Dr. Auth, did you want to speak to that?

DR. AUTH: Judy, are you recognizing me? This is Doris Auth.

DR. STAFFA: Yes.

DR. AUTH: Sorry. I didn't hear what you said.

Yes. I just have one point that I would

like to make, and that is since beginning of the ER/LA Opioid Analgesic REMS program, where we started having the companies fund the CE, there has really only ever been one CE provider that captures routinely NPI numbers, and that was a company who did the study that Dr. McAninch described.

We have heard some concerns from CE providers and the accreditors, and I think those folks are on this meeting. I will let them speak to those. There are potential issues with providing this information to CE providers. I think there are some concerns that it's going to be used for marketing purposes; that if it's provided, they know that there might be studies.

So we haven't required that these grantees be required to capture this information. We've been trying to work within the system that's already set up for accredited CE, for the accreditors and providers. But I'm just wondering if Julie or Graham have any comments on that issue of capturing NPI numbers.

DR. McMAHON: This is Graham here.

Remember, much of the funding here is coming from the REMS program companies, which are pharma companies and their data nexus. Sending information about the prescribing patterns, or just the identities of participating clinicians to pharma companies, is kind of antithetical to the promise of accredited CE, which guarantees separation between clinician behavior, education, and those companies. So that's been the obstacle so far.

On a theoretical basis, there's no limitation to providing consented data through educators for data analysis and linking with prescriber information. The issue is just sharing that with pharma companies would be considerably unpopular and probably problematic.

DR. STAFFA: Thank you for that comment.

Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: Yes, just a couple somewhat random comments. I do want to make sure, yes, that I reiterate the importance of, yes, education not being a stick to change behavior, and

obviously the sensitivity, too. And I appreciate all of the comments related to how do you design and deliver education so that it is positive; obviously influential, ideally; and affecting patient outcomes. So that has got to be a key factor.

With that being said, I don't know if there are mechanisms for being able to benefit from linking information. We're talking about the NPI number, and once again, I appreciate the comments, too, about how sensitive that is. Obviously, NPI numbers are public access numbers. You plug in a name on your Google, and there's an NPI number. So it's not that they are private inaccessible numbers.

I think where we are getting into the issue of how do we utilize that and, obviously, how would that data be identified, I'm wondering are there mechanisms to still take advantage of that linkage but at some level of analysis or data sharing that we're not necessarily always, in terms of reporting findings and informing ourselves, linking that data

to individual providers.

Then lastly, another thought once again; one, that we have obviously a medical record system that we have access to all the information, much of the information that we've been discussing here. For good or for worse, there are really some major players nationally, Epic, Cerner, and others to name a few, including Cerner that will become the EMR for the VHA, and are there ways to using the same idea, identifying practice patterns and potential outcomes using the electronic health record but, once again, de-identifying it, but informing ourselves by looking at systems of care. Thank you.

DR. STAFFA: Thank you.

Dr. Larochelle?

DR. LAROCHELLE: Yes. I just want to say that I think it's possible to actually get informed consent from the providers here. These are prospective training programs if your evaluation is going to be prospective, and at the time of that evaluation, I think it would be reasonable to have

an informed consent where someone is able to provide that. I think that would be the concern about provider privacy, and I know those rules vary by state.

We have a lot of experience in Massachusetts with our state Department of Public Health linking a whole slew. It's now nearly 20 data sets that are across state agencies that have been linked at the individual level, which was accomplished through legislation and a really strong commitment to privacy.

Despite that, I would recommend if people want to look, after this, at an article by Liz Evans from UMass, who interviewed a bunch of stakeholders with concerns about using big data in this way to study this issue and had some really thoughtful outputs in ways that there may be a conversation that could be had to address some of the ethical concerns upfront and engender more trust. So I think there are some paths forward there, and consent is not completely out of the question.

DR. STAFFA: Thank you. That's very helpful.

Julie White, did you have another comment you wanted to make?

MS. WHITE: Nope. Sorry if my hand's up. Somebody responded.

DR. STAFFA: Okay. Great.

Are there any other comments that anyone would like to make? This has been a fantastic discussion, and I think you've hit on a lot of the topics that have come up in our internal discussions.

DR. MORRATO: Judy, this is Elaine Morrato. May I just add on to the last comment?

DR. STAFFA: Yes, sure. Go ahead.

DR. MORRATO: This really highlights -- we haven't really talked about it in the context of who runs the studies and conducts them directly. I think the last point, in general, around the trust and privacy underscores maybe a different model of how the RPC is going about doing some of its work as well, and that I would request that they reach

out to the academic kinds of communities that are already doing this kind of research; whether it be in partnership with state public health agencies as we've heard, or embedded within healthcare systems, there are folks that are tackling the challenge of linking and integration of data, and doing it in a trusted way.

I think in that context, informed consent and understanding why we're doing this and why there's value, and perhaps in a pragmatic trial approach or in an observational one, would go a long way in the feasibility of doing this difficult work. So I would encourage the companies to be thinking in other ways of approaching doing this kind of evaluation. Thank you.

DR. STAFFA: Thank you.

Dr. McMahon?

DR. McMAHON: Just briefly, I think it would be most appropriate for the pharma companies, the RPCs, not to do these studies themselves. I think these studies should be in the hands of the CE providers and the academic providers that are out

there doing education and doing research work in this area. A mechanism that I'd encourage the RPC to use is, again, the independent committee set up by the joint accreditors, the nonprofit regulators in this space, that was chaired by Ron and has agreed to convene again next year, to look over these grant applications.

We can make stipulations about the research outcomes that might be expected from some of these projects or create a separate category for the grant allocations to encourage those that have a research outcome for some of them. But I would encourage the REMS program companies to use that vehicle and recognize that independent selection of who receives these funds is in everyone's interest.

DR. STAFFA: Thank you.

Dr. Floyd?

(No response.)

DR. STAFFA: Dr. Floyd, did you have another comment?

DR. FLOYD: I was on mute. Just to follow up on the questions about who's doing the studies,

isn't it the case that the RPCs put out RFAs, and the work to date has mostly been done by academic institutions? For example, I just recall some of the work on ER/LA opiates that I was involved with through one of the Kaisers, where they had some oversight and were involved but mostly were the funders.

DR. STAFFA: Right. I'm going to ask Doris Auth to address that question. I think she has some more information to share.

DR. AUTH: Yes. I would like to clarify that the majority of the studies evaluating the effectiveness of this REMS has not been done by the RPC for the extended-release and long-acting opioid REMS. Industry was involved in determining which programs got funded, however, it has been mentioned several times today that for the OA REMS, they did use an independent grant review committee, which was great.

But yes, all of these studies have been contracted out, some by, I think as Dr. Floyd mentioned, Kaiser that he was involved in and

others through the CE providers. So they are actually doing some of this work, and I would have to go back and look at who else has been doing this, but it's not the RPC.

DR. MORRATO: May I ask a clarifying question, Dr. Auth? This is Elaine Morrato. Maybe there's a differentiation between all of the work that's going on. If we look at the comparative effectiveness study, whether it's an outcomes-based, or a trial, or what-have-you, that has not been asked of the independent CE providers. Right?

I guess what I'm trying to encourage is what we heard from Dr. McMahon, is if we are to expand evaluation, that that go back through the mechanism that's been established and funding goes there. The landscape analysis was not performed using what I might call basic academic standards if someone did a landscape policy analysis, and it appears that their responsiveness, based on the study outline to do the comparative effectiveness, did not necessarily consider all study designs for that

or they did not reach out and present information in partnership with the healthcare system. It was looking very narrowly at just observational large data sets.

So I think in that regard, if there is a mechanism now with the RPC CE providers to be doing more than just delivering CE and evaluating that, that could be something to further expand upon.

My question is, do you know if they are reaching out more broadly to other sites to talk about your question around comparing the effectiveness or to answer the question of has the REMS been effective other than the CE evaluation?

DR. AUTH: That is a question that we would have to take back to the RPC. I'm not aware of that.

DR. STAFFA: Dr. Floyd, did you want to get back into this conversation or did you have another comment?

DR. FLOYD: Yes, related to some previous comment. I think several people made the really great suggestion that some of this work should

perhaps be carried out in integrated healthcare systems, where you have really rich EHR data and the ability to implement changes based on what you see.

But one limitation, potential limitation, is that many of these candidate healthcare systems have already implemented really robust systems for reducing some of the most inappropriate opiate prescribing behavior such as -- I think when some of the early ER/LA work was going on, it was very hard to find, in the Kaisers, physicians prescribing ER/LAs to opioid-native patients, which was kind of one of the questions.

So it might be a little bit hard to find the ideal systems that don't have some of the bad behavior that you actually want to look for.

DR. STAFFA: Thank you.

Again, we are approaching the end of the time frame for Session 2. I know we haven't gone through the questions specifically, but if there are any remaining comments on value, and feasibility, and study design, populations -- I

think we've hit on many of the issues. I guess the one that we haven't talked about that much is the heterogeneity in the CE programs. Again, I think we've hit on that a bit indirectly, but if anybody has any remaining comments before we go to break, this would be a good time.

Anything anybody didn't get to say before they get their afternoon coffee? Dr. McMahon?

DR. McMAHON: Just very briefly, I would certainly welcome lots of other input, but as Ron, and Julie, and several of my colleagues in the world of CE have mentioned earlier on, program activity format largely reflects on the needs assessment for the learner community and the educational outcome that you're looking for. So there is broad variability in educational design and format for exactly that reason. In some cases, you'll want to do a simulation with patient actors for example, and other experiences you want to focus on getting people to learn a particular adverse effect profile.

So there's a huge variety in educational

format and delivery depending on the need of the activity itself, and increasingly what you see is mixed model formats of education, some of which uses video, some of which uses participatory active groups and involves peer and mentorship, and others which involves reading and consumption of other informational activity.

So that's why there's such broad variability, but also you want to be very cautious about fixing educational format because that might constrain the innovation and the flexibility that the accreditation system currently allows in educational format to allow that diversity of approaches for maximal efficacy.

DR. STAFFA: Thank you. Yes, there's that tie, that tailoring, to what we determine the most important outcomes would be. It's very much related to that.

So with that, I am going to suggest that we take a break, and we will reconvene at 3:10. We'll have a 15-minute break and start maybe just a few minutes early for our last session, during which

we'll be talking about some of these complementary or alternative approaches beyond a direct evaluation and get your thoughts on that. Then we'll also hear from a couple of folks who have signed up to speak from the public to share their thoughts. So have a good break, and we'll be back online at 3:10. Thanks.

(Whereupon, at 2:56 p.m., a recess was taken.)

Panel Discussion - Topic 3

DR. MANZO: This is Claudia Manzo. I will be moderating the third session with Doris Auth, so I'm going to go ahead and get us started. During this session, we'll be discussing alternate study approaches to broadly evaluate the impact of continuing education on prescriber behaviors and patient outcomes.

We did pose a couple of questions here that can maybe begin that discussion, so if the panel would consider whether inferences can be made out of the effectiveness of Opioid Analgesic REMS to be programs based upon evidence of the effectiveness

of CE programs more generally, and whether there are approaches that could inform our understanding of the contribution of continuing education, in general, to improving pain management practice and patient outcomes.

I guess I will just wait and see if we have anyone that wants to start. It looks like Alec Walker has his hand up.

Dr. Walker?

DR. WALKER: Sorry. I didn't have my hand up intentionally, so I'm taking it down.

DR. MANZO: Okay. Thank you.

Elaine Morrato?

DR. MORRATO: I had a clarifying question as we start this. Do you want us to discuss broadly just thinking of this as a REMS strategy broadly or just very focused around the OA REMS CE program, or would you like both?

DR. MANZO: Well, I think the intent, really, was to discuss whether we could look more broadly at various outcomes and whether or not there needed to be an attribution to the REMS CE or

could information or evaluation of CE generally be applied to the REMS CE. I hope that clarifies it.

DR. MORRATO: Yes. I think there might be, also at the end, maybe some reflection on what have we learned from this that could have been built in; if we were to start the ER/LA REMS today, some of these things that many years down the road we're building in the next time you do one of these. But we'll focus on the immediate, so thank you.

DR. MANZO: Okay. Thank you, Dr. Morrato.

Dr. Katzman?

DR. KATZMAN: I don't have any comments right now. Thank you.

DR. MANZO: Okay.

Dr. White?

MS. WHITE: Hi. Thank you. I know the answer to number 1 is yes because just linking back to what we've been saying earlier, I suspect many of us, not just BU, Boston University, has data about intended practice change or maybe even actual practice change towards more guideline-based practice. So I think there's potentially a lot of

data out there that could be analyzed.

DR. MANZO: Okay. Thank you, Dr. White.

Dr. Winterstein?

DR. WINTERSTEIN: I think this is a really difficult question, and we had a really good talk earlier on this topic, but I would like to offer two thoughts to this concept. One is that the evaluation of any kind of quality improvement intervention has been reviewed for decades, at least three of those, and there are some common themes that have been summarized by IOM, or NAM, and ARC, and many others that have been very active in quality improvement, which is that quality improvement initiatives often don't come isolated, so they are in this record of all kinds of things that are happening.

That was presented in this talk this morning as well that a good CE program requires the institutional support and incentive, which is a separate intervention product, CE program. Obviously, there are all kinds of interventions going on relatedto the opioid crisis, but right now

we are talking about an isolated CME program and what this can accomplish.

The second thing, based on what I have seen with respect to educational interventions, I don't think that there is any systematic review out there that has convincingly concluded that a CE program can improve patient outcomes. I think that there are intermediate process measures such as knowledge or certain behaviors that have shown positive effects. I think that's the second part to think about.

Then the third that might be really important in this context is that -- now I lost my train of thought. It will come back, but right now it's gone. So I'll stop here. Sorry.

DR. MANZO: No problem. Thank you, Dr. Winterstein. Yes, if you think of it, definitely feel free to raise your hand again.

DR. WINTERSTEIN: I will for sure.

DR. MANZO: Dr. Alexander?

DR. ALEXANDER: Thanks. Can you hear me?

DR. MANZO: Yes.

DR. ALEXANDER: Great. These are great questions and very interesting ones. I also would probably say yes or perhaps to the first question that's posed, but I don't really understand the intention of the question. In other words, I don't think that the fact may be, perhaps or yes obviates the need for the opioid REMS to be directly evaluated. So I guess I'm not really clear on how this gets the FDA where it needs to go because we're back to you can't manage what you don't measure.

I think you could use the analogy of risk communications that the FDA conducts. We've done a systematic review of these that's been published, and the bottom line is -- so you could ask can you infer something about the effect of the next risk communication based on the dozens of risk communications that have already been performed by the FDA and the very good studies that have evaluated these, and I'd say yes and no, again, because context matters, and all of the factors that Dr. Cervero identified matter.

So I don't see that just because we know that CE programs can work -- I guess I'd like to hear more from you, Doris, or Jana, or your colleagues, as to what you're trying to get from the panelists today with respect to this first question.

Regarding the second, we have enough here for an IOM report and three systematic reviews. So again, we're back to the fact that there is an enormous evidence base and that we know that CME can work. So I just would like to hear more. I guess maybe the smartest thing I should have begun with is just asking for more clarification, again, from the FDA regarding what are you hoping that we can help you with or where are you headed with these questions?

DR. MANZO: This is Claudia. I'm going to try to answer the question, but I'll ask other folks from FDA to chime in. The second panel, there was a question, of course, of the value and the feasibility of conducting a study that would isolate the impact of REMS CE. In this third

session, it would be, well, should it not be feasible or considered feasible, are there alternative approaches? In any case, even if it is feasible for us to conduct this study and isolate the REMS CE, we're still interested in understanding if there are any complementary approaches that could help us to evaluate more broadly the impact of CE on prescriber behaviors and patient outcomes.

Does that help to clarify?

DR. ALEXANDER: It does, but it does feel a little afar from evaluating the opioid REMS. I mean, there's lots of good work that I could see the FDA getting behind, and frankly there were some interesting ideas, creative ideas, I thought from multiagency collaboration that I think would improve the science and ultimately the clinical delivery of care for people with pain, but a lot of those I think are beyond the purview of the REMS. And, again, as I said before, I think there's a very serious concern and risk that you might move to measuring things that are measurable but not

necessarily focused on evaluating the REMS.

We had a long discussion about surveillance data and national data that would be at a population level, and all of these outcomes that one could imagine examining. But as soon as you give up on trying to understand whether the REMS is responsible, I don't see how you're doing REMS evaluations anymore. So it might be good for the FDA to do it, and maybe it should come out of the commissioner's office, or OSE, or some other agency or office, some other office or center, but I don't think it should be part of the opioid REMS program. I just don't see how it's evaluating the impact of the REMS.

DR. MANZO: Okay. Thank you.

I am going to ask Doris -- I think, Doris, you had a follow-up question for Dr. Winterstein; is that correct?

DR. AUTH: Well, yes. This is Doris Auth. Actually, it was really a question directed toward Dr. Cervero because Almut made the statement that she doesn't know that there has been any systematic

review that can show an impact of continuing education on patient outcomes. So I would just like to toss that back to Dr. Cervero because this is primarily a lot of the literature that he has reviewed and studied over the years, and if he could just comment a little bit on whether it does indeed exist and what types of education was that impact on patient outcomes; what sort of areas was that shown in.

DR. CERVERO: Yes. Thank you, Doris. The reviews that we did incorporated syntheses or systematic reviews that looked at both outcomes, that is physician performance as well as patient outcomes. What we found, I think I mentioned in the presentation, was that there was a less reliable impact on patient outcome. It happen less frequently simply because of all the factors we've talked about, the contextual factors that go on in patients making decisions about whether to follow the advice given by their clinician.

So yes, there's plenty of evidence in those reviews, individual studies, as well as the

comprehensive reviews. I think we know it can make a difference. It's harder to make a difference in patient outcomes but it does happen. So I would leave it at that. I think you'd have to go deep into the individual studies to find those that included the prescribing behavior, but I know there were some. I think the presentation this morning, I think by Dr. McAninch, included some of those studies. I could be mistaken, but I'm pretty sure I saw some individual studies there that did talk about patient outcomes. Over.

DR. AUTH: Thank you for clarifying that.

DR. McANINCH: Yes. Hi. This is Jana McAninch. Some of those studies, yes, did look at certain patient outcomes such as pain scores, depression symptoms, and that sort of thing, and for the most part did not detect really much of an impact.

DR. MANZO: Thank you, Dr. McAninch.

I think Dr. McMahon, you had your hand raised next.

DR. McMAHON: Sure. Thanks for all those

comments. I appreciate them. I'd take us back a little bit to Dr. Alexander's question, which is what's the actual intent of the question, and I think it leads to an important one, which is what's the intent of the evaluation itself? Is the intent to inform the development of better educational interventions for the future or is the intent to try and answer definitively is the education effective or not?

I would say if you take the former approach of saying the intent of the evaluation is to get information and evidence that informs the continuous quality improvement of the overall educational program, that is very achievable and actionable and valuable. I would say an effort to obtain a definitive answer to the question is does the entire program work is likely to be unfeasible and broadly spoken.

I say that because if you think about very specific short-term intervention, you teach a surgeon how to use a trocar in her laparoscopic surgical approach more effectively to reduce

insufflation errors in abdominal surgery, you can demonstrably show that effective training like that meaningfully affects a patient's outcome very quickly and easily.

There's none of us on the phone here that would think that education like that is ineffective or inappropriate; of course it is. The challenge is making an extrapolation to patients with complex comorbidities who are getting cared for by a team in clinics that are complex in their array and their access to a variety of therapeutic approaches. All of those confounders and other factors make it very difficult to show an expectation of aCE program on a patient outcome when there are so many intervening variables.

I think the third point I would just make is that I would encourage the FDA not to think of this as one study. I think you've got to think of this as a program evaluation that funds and incorporates multiple smaller studies that inform the overall question. To emphasize my first point, that question to be answered is what advice can we give

to future CE programs in the following year that a grant program can allocate accordingly and leverage to improve the quality and impact of those educational interventions?

DR. MANZO: Thank you, Dr. McMahon.

I think next was Dr. Winterstein.

DR. WINTERSTEIN: Yes, I found my train of thought back, and it might also be relevant to this discussion whether CE works or not. I think that is a really complex discussion to have, that the most important part is, really, whether whatever evidence we have about other CE programs really is applicable to the problem of the opioid epidemic and opioid prescribing, and that's what I was trying to talk about.

If changing behavior with respect to opioid prescribing were easy, we all wouldn't be here. So it's very clearly a very complicated matter, and all the interventions that have been thrown at it obviously haven't really had the desire or magnitude of effect they we all would have hoped to see. So what that means is that we are talking

about behavioral changes that are complex.

If we are looking at the CE literature as a whole, we would need to find similarly complex behavioral changes that are targeted to a CME program, and there is probably not that much analogy there where we really have something similar.

Oftentimes, the evaluations that I'm thinking about are specific prescribing guidelines where people are supposed to follow a certain evidence-based approach or have implemented certain monitoring behavior or something like that. But there are distinct pieces, which is very different from what we're trying to focus on here, where the magnitude of behavioral change and the various processes that have to be put in place and that a provider has to think about are much more complex.

A good example is perhaps thinking about antibiotic prescribing in children, where there's lots of pressure from parents that an antibiotic is given, and there are a lot of guidelines that say you shouldn't do this for otitis media or

what-have-you, or they're prescribed all the time. And there are guidelines out there for this, and there are CME programs out there for this, and it's still extremely difficult to change this behavior and this practice in the environment where we are.

This is by far not the appropriate comparison for opioid prescribing, but I think that's just what we need to think about when we're trying to make inferences from the general evidence on general CME programs to the problem that we're dealing with here.

DR. MANZO: Thank you, Dr. Winterstein.

DR. WINTERSTEIN: The other piece that I --

DR. MANZO: I'm sorry. Go ahead.

DR. WINTERSTEIN: I have one more piece that's just important as in this discussion, and the FDA knows way more about this than I do. The purpose of a REMS is to prevent a specific adverse outcome, and I think the adverse outcomes that we're talking about here is opioid-use disorder, and overdoses, and so on. I don't contest that offering appropriate CME to prescribers to improve

pain management practices is a very important tool; the question is whether it really does justice to a REMS program with the focus on reducing OUD and OD.

DR. MANZO: Thank you.

Dr. Alexander, did you have your hand up?

DR. ALEXANDER: I did. I'll just briefly say I think there's a bit of a false dichotomy if the choices are either we do evaluations that help us improve the process and learner experience or we definitively quantify the impact of the intervention on the outcomes that really matter, which is the outcomes that affect our patients.

I think if you're looking for a reason not to do evaluations, direct evaluations, of REMS impact, you'll find them; whether privacy concerns, or potential confounders, or the difficulty of finding a good comparison group, or concerns that a single intervention, such as the REMS is currently designed, is simply not going to have an effect.

I do think that there's general consensus here. I certainly haven't heard a lot of disagreement that considering the unique features

of different programs is important; that you need multiple approaches; and that we're not talking about a single study. And insofar that there's value in looking at specific systems of care and that insofar as you do attempt to compare recipients with non-recipients, that you have to think carefully about the characteristics of the comparison group.

Over, as one of our panelists would say.

DR. MANZO: Thanks, Dr. Alexander. I did actually have a question. What about the thought of even understanding the impact generally of CE versus some of the other policies that have been put into place to impact prescribing behavior? Any thoughts on how or whether it's even valuable to try to understand that?

DR. ALEXANDER: I'll just say very quickly that any -- this is Caleb again -- CE, whether this CE or otherwise, you're still going to do better with all of the considerations that have been identified today. So if you're going to try to disentangle CE from all of the other potential

drivers of prescriber behavior and patient outcomes, I think all of the considerations today are still relevant. I may not have understood the question, but that's my first take.

DR. MANZO: Thank you.

Dr. Morrato?

DR. MORRATO: I didn't have my hand up. I have nothing to add with what others are saying, other than to maybe underscore I think it may have been what Dr. McMahon was saying. To what degree is what we're learning here. Gathering it so we're informing not just this program but future programs and lessons learned. That would be the ideal learning. I don't know if regulatorily you can require that, if a company, or set of companies in this case, is required to focus on their own evaluation, but that would be the only thing to add.

I think you may be wanting -- I'll just add one more thing -- to -- we haven't talked about other mixed methods. We've talked very quantitatively, whether that be survey, trial,

observational. We haven't talked about qualitative really. I know you touched on it briefly, Dr. Alexander, in terms of focus groups, I think, with patients.

If we were to really have a robust evaluation, it would include qualitative, not just with prescribers and patients but to really understand health systems so that you're trying to evaluate the CE in the context of the healthcare setting and policies that are occurring. That helps us understand how the delivery of this intervention fits in more contextually.

Typically, in robust program evaluations, state of the art is to do mixed methods. That does not replace what we've been talking about, so I would agree with everything that Dr. Alexander has said. It's not an either/or, nor to replace. It would be an augment,and leave it at that.

DR. MANZO: Thanks, Dr. Morrato.

Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: Yes. Thanks. I feel like it's Friday afternoon now, and the discussion

is just fantastic, and I think my mind's exploding a bit. But I wanted to just contextualize a couple things.

I'll go back to the framing, the context of where at some level we've started earlier on years ago with the REMS and the discussions around it. I will just share with the group, one, I was trying to recapture that in my brain. From a primary care perspective, I think an important perspective for me, when we were discussing this and recommended expanding the REMS, there was a lot of frustration, obviously, in the country.

Many of us who are looking at health systems, and most of all the crisis in the country, I recollect that we saw the REMS as a must. And it was a must, I think, also based on some frustration, which was based on different interpretations of how our partners in pharma were supporting or not necessarily supporting changes that many of us felt were very important. I think we felt somewhat helpless.

I recall that there was even discussion of

could we linked the REMS to -- and I can't remember if Jana or others brought it up to the DEA numbers and sort of connecting the dots between different regulatory components of the delivery of health care, in this case around prescribing opioids.

With that context and listening and reflecting on today, and I think my previous comments may parallel this, I think we're at another place. I don't think we are where we were, and I think we're trying to figure out what the impact of this REMS was that we came up with or that we supported years ago. Then I think Dr. McMahon, some of his comments and other wonderful experts on this panel, someone brought up the whole concept of, obviously, in education, the importance of needs assessment.

That makes me just want to add the comment that from an FDA perspective and from this REMS perspective, is there a role for a needs assessment, either looking at what we already know is going on here and now around risk and harm related to opioid prescribing and the management of

pain, and could a needs assessment also help make this a more focused effort on behalf of FDA because there's so many angles to it.

So it's an arm of this I'm very supportive of and always excited about the big data approaches. I think Dr. Alexander talked about those invisible looks at data that don't impact the providers and the teams, and in some ways may not bias certain things because we can just look at big data, once again, invisibly so to speak. So I think that continues to be an innovation that I would be very supportive of.

Then I'm also intrigued and supported by, once again, thepotential for partnering through the RPC with the examples we've seen of more refined research on education, clinical education, and the potential impacts, and doing that, once again, maybe in more targeted ways around health systems or particular identified risks that we have a little bit more sophisticated knowledge of.

Lastly, I think the challenge with looking at opioid-use disorders and overdose, one thing I

think we may be able to agree on, too, is that there has been a decrease in prescribing, but we know there's been an ongoing increase in terms of looking at overdose and the impact of opioids. In this case, many people are just not utilizing the organized healthcare system, so that's another area that I'm not so sure the REMS is as relevant, and I'll stop there.

DR. MANZO: Thank you.

I'm going to see if anyone from FDA wanted to respond to that. Dr. McMahon, I see you put a comment in the chatbox, and if anyone wanted to respond to the last comment?

DR. AUTH: Hi. This is Doris Auth. The discussion of the first couple of sessions was a bit overwhelming; lots and lots of good discussion there. I think what's falling out for me is maybe this idea that several have touched upon today. When you look at the goals of the REMS, in particular the ER/LA REMS, they were very broad goals.

We thought we were going to impact all of

these different prescribing practices and patient outcomes. But I think what I'm hearing now is the need to look at potentially -- and, Dr. Alexander, you mentioned these sort of hot spots or problem prescribers, looking at the needs in particular areas and trying to understand better the behaviors that are leading to the outcomes, and then design a program which may include education but certainly other supportive activities to address those.

I think that's probably getting a little bit beyond the direct evaluation of the REMS and CE, but I think that's what I'm hearing. So I just wanted to put that out there and see if anyone else has any comments on that.

DR. ALEXANDER: I do. I just want to clarify for the record -- this is Caleb Alexander -- I do not think doing broad surveillance looking at hot spots is a good use of the FDA's resources evaluating the opioid REMS. I just want to be clear. I do not think that broad surveillance approaches allow for one to understand if and how this program is working.

The other point that I'd make is that the opioid epidemic writ large has not been driven by problem prescribers. They play a role, they're important to identify, they certainly have contributed, but the thrust of the opioid epidemic is not problem prescribers. I did suggest, however, considering some focus of one component of the REMS evaluation considering looking at high-risk prescribers and high-risk patients.

So I'm not necessarily referring to rogue prescribers here or prescribers that are openly bucking decent standards of care, but I am highlighting the epidemiology of opioid prescribing is not evenly dispersed across patients and clinicians. So I think as you're thinking about where to potentially target the REMS, I think it's worth considering whether or not there are subpopulations of prescribers and patients that would be most likely to benefit from this sort of educational outreach that the REMS provides. Thank you.

DR. AUTH: Hi, Dr. Alexander. This is Doris

again. I do just want to clarify I think I was speaking mostly about getting back to the needs assessment. The needs assessment can include, I think, a lot of the things that we were talking about: are there high-risk prescribers; are there areas of the country where there's a particular issue that we need to address?

So I wasn't necessarily talking about using large surveillance databases as I think we've done in the past to look at prescriber behavior and make some sort of determination as to whether we think it's improving or not. I was just basically, I think, agreeing with a lot of what I heard about the importance of the needs assessment and how that can drive some of the educational activities.

DR. ALEXANDER: Okay. Well, that makes good sense, and I think Dr. Cervero and others highlighted that was both from the Institute of Medicine and from his own work, kind of where it all starts. And if you look at scope of pain, of course, the speaker nicely highlighted how the practice gaps are really what motivates the design

of the program. So I totally agree with you on that one.

DR. MANZO: Okay. Thank you.

Dr. White? Julie White?

MS. WHITE: Hi. Thanks. I'm sorry, because I feel like we're kind of ping-ponging back and forth, but I wanted to just pick up on something that Dr. Morrato was saying. In getting prepared for this day, I was trying to find more information about the impact of CME in the literature, and that article that I mentioned by Kurt Olson does offer a potential way to evaluate CE that is qualitative.

He basically says that rather than looking at continuing education and whether it's effective at changing performance or improving patient outcomes, he says when change in clinical practice is observed, what role, if any, did continuing education play? He uses a retrospective case study approach, and then the theoretical framework -- which I'm not familiar with and maybe some of you are -- is the soft knowledge systems. His study actually looked at changing the use of

antibiotics, actually, trying to get at overuse.

Again, just going back to what Elaine was saying, maybe there's some qualitative approaches we could use to back into where there are successes of the REMS program.

DR. MANZO: Thank you.

Well, I just want to see if anyone else who hasn't spoken up has any thoughts or anything they want to share with regard to this particular topic.

(No response.)

DR. MANZO: Then I guess, since we have a little bit of time, any more general comments regarding any of the three topics that we discussed over this afternoon?

(No response.)

Pre-Registered Public Participation

DR. MANZO: Okay. Hearing none, I think we can go ahead and conclude this particular panel session, and we will start with our open public portion of this meeting, so I'm going to turn this over to Michael Harned.

Are you on, Dr. Harned?

DR. HARNED: Yes.

DR. MANZO: Okay. Go ahead.

DR. HARNED: Great.

Good afternoon. My name is Michael Harned. I'm here on behalf of the American Society of Anesthesiologists. I'm the vice chair of the ASA's Committee on Pain Medicine. I'm also the past president of the Kentucky Society of Anesthesiologists. I'm a board-certified anesthesiologist and pain physician, and I currently serve as the medical director for the University of Kentucky Health Care Interventional Pain Management Clinic, and I'm also the fellowship director for the Multidisciplinary Pain Fellowship. I've also spent some time in private practice. I appreciate the opportunity to come speak with you today.

The ASA has a long history of weighing in on the FDA REMS program, and we've monitored its growth and change over the past several years. Prior to its expansion in 2016, the ASA actually recommended that the REMS education be required for

all classes of opioids. The society also asked that the FDA update its educational blueprint to include the complexities of care for chronic pain patients.

We were pleased with the FDA's announcement in 2016, which then became effective in 2018, first, that REMS education would be expanded to include the immediate-release opioid analgesics; that information on pain management would be incorporated more broadly into that FDA blueprint; and the inclusion of other healthcare professionals that are involved in the management of patients with pain. The blueprint focused on fundamental pain management concepts, acknowledgement of principles of the CDC guideline, and when to refer patients to pain management specialists where necessary.

As I am sure you've seen, over 76,000 people have died from drug overdose from April 2019 to April 2020. This is unfortunately the most ever recorded in a 12-month period. So given the ongoing opioid crisis, as well as new challenges

that are now present with the COVID-19 pandemic, the ASA does support the continuation of the REMS program.

While it's difficult to evaluate any one program's efficacy, access to free continuing education is important. As the FDA acknowledges in its own issues paper, it is difficult to evaluate a single educational activity with expectations that completion of a single activity will result in immediate effects in practice change; yet, we know that CME can improve physician performance and patient health outcomes.

The ASA understands that the FDA is interested in specific measurable outcomes that might demonstrate that the REMS training is effective in educating prescribers and other healthcare providers involved in the treatment and monitoring of patients in pain. The ASA recommends that the REMS education follow traditional ACGME standards for accredited CME providers.

The goal should be to measure change, competence, performance or inpatient outcome. We

suggest analyzing these changes by providing pre- and post-tests, as well as a 90-day follow-up to ensure the changes the physician committed to are reinforced. If barriers to change are encountered in making that change, it should be acknowledged, documented, and subsequently, educational interventions can be developed to minimize those barriers.

In 2019, the ASA was fortunate to receive a REMS grant from the FDA, and we administered education through four on-demand interactive modules and four live meetings. There were 3,257 participants, and 3,101 of those completed the training. Our data relies on pre-and post-tests, as well as self-reporting after follow-up, but we did find most learners experienced positive changes.

We found a more than 90 percent relative average increase in knowledge gained across all learning objectives. The program documented a 51 percent increase in both incorporating nonpharmacologic treatment options and

incorporating an individualized approach to pain relief. However, we still identified persistent learning gaps and needs.

Thirty-five percent of the responders reported continued low confidence in knowledge of and competence in safe and effective opioid pain management, as well as prevention and management of opioid-use disorder. Less than half indicated specific practice to change they would make regarding opioid pain management and preventing or managing opioid-use disorder. Therefore, we feel these results demonstrate a role for both continued education and reinforcement.

Another challenge that the FDA is highlighting is with the changing landscape of the opioid crisis. We were already seeing a decline in the opioid prescribing, so it has been difficult to measure whether the REMS program has had a direct impact on the decline of opioid prescribing.

Because it has not been possible to link prescriber participation in the REMS training to changes in practice or patient outcome, the FDA

advisory committees have recommended that the agency explore feasibility of a study that examines the association between trainings and desired changes in practice, and some of these proposed concepts have already been studied and recognized that challenges remain.

The FDA has again posed the question in light of today's workshop. The AC believes it would be challenging to specifically evaluate the effect of a REMS CE activity on prescriber behavior and patient outcomes. There are many concomitant strategies, state-mandated training, state laws on prescribing, and local policies to try and address the opioid crisis that it seems difficult to disentangle the effects of a REMS CE activity.

One possibility for a pilot study would be to partner with a specific health system or institution to assess prescribing practices and patient outcomes between a group targeted with the REMS CE education versus a non-education group. A one-year post-intervention time period seems reasonable to assess for these changes.

Prescribing practices could be assessed by well-defined metrics such as MMEs per day, co-prescribing of naloxone, and rates of co-prescriptions with benzodiazepines and opioids, et cetera. Patient outcomes could be rates of overdose, opioid-use disorder, and long-term opioid prescription. Pain-related outcomes might be more challenging to assess and may not even be directly impacted by a REMS program.

The ASA would also recommend efforts to try and mesh REMS with state requirements. There would likely be a further uptake in the training if state or other licensing board requirements were met with REMS participation. One challenge the ASA experienced when trying to engage our own members in REMS education was this competition for time of the provider and other CE requirements that were urged or required by their own health system instead of our training. Greater alignment in education across multiple credentialing bodies would increase uptake.

Last, the ASA encourages the FDA to revisit

some of the studies discussed in its issues paper. As the climate around prescribing has changed, some of the studies could now more feasibly be done. The past 5 to 10 years saw a dramatic shift in opioid-prescribing behavior that could be attributed to a multitude of educational opportunities, as well as federal CDC guidelines and individual state recommendation.

The rapidly changing environment made assessment of the efficacy of a specific REMS intervention difficult to calculate. Most of these education programs and adoption of guidelines has occurred, and there's now a more, quote, "steady state," if you will, "of opioid prescribing," so revisiting these REMS studies as they pertain to a single REMS program may in fact yield more accurate information than in times past.

In conclusion, the ASA concurs with many of the sentiments expressed in the FDA issues paper and understands the challenges in evaluating an effective REMS training. However, we still believe there is value in the program even when you can't

conclude that any one improvement in provider practice or behavior is the result of that education. The benefits of widely accessible and free education outweighs the barriers to measuring how effective the program is specifically. In addition, we know that constant reinforcement increases learning, so ensuring the availability of education through REMS training is preferable.

Again, thank you for the opportunity to provide feedback for you today.

DR. MANZO: Thank you. Dr. Harned.

Our next speaker is Robin Heyden.

Robin, are you on?

MS. HEYDEN: Yes, I am. Can you hear me ok?

DR. MANZO: Yes, we can hear you. Go ahead.

MS. HEYDEN: Okay. Terrific.

Good afternoon, everyone, and thanks for hanging in here until the bitter end to hear these last comments. My name is Robin Heyden, and I'm here representing CO*RE. CO*RE, The Collaborative for REMS Education, has been an OA REMS grantee from 2013 through 2019. I'd really like to thank

the FDA and all the panelists for the thoughtful discussion here today. It's been a very rich day. I'd also like to thank the RPC for the important work that they do in the background to make this possible.

This is the organization of our CO*RE collaboration. As you can see, we are made up of nine association partners. Their logos are represented here at the top. These nine association partners work exclusively with CO*RE, and the lower boxes show our executive team and our operations project management team of which I am a part.

While CO*RE has educated more than 435,000 clinicians and 881 activities since 2013, today we'll focus on our 2019 results summarized here. As you can see, we educated over 72,000 learners in 2019.

For the purposes of our conversation, I'll focus on the learners who took our new online adaptive learning course, which we refer to as REAL CORE, because those 18,000 learners provide us with

some learner data insights that are quite relevant to the purpose of this forum today.

We started this work in 2018, developing a common outcomes framework in order to align our clinical education to the FDA's desired objectives as expressed in the blueprint. We very carefully designed this framework in consultation with an education consultant with a PhD in educational design, a psychometrician, and our own interdisciplinary expert clinical faculty to identify practice gaps.

Let me explain this diagram you're seeing here. Starting from the top with the FDA blueprint, we created measurable learning objectives; then we built the assessment items to evaluate learner understanding; and then once we knew exactly what we were measuring, we built the content that served our 115 live and other online courses around those objectives. This made for consistency across courses and our own ability to compare apples to apples and draw more compelling data conclusions.

I want to concur here with Dr. Morrato about the importance of careful and rigorous approach to design with good logic linkages. In fact, I could see quite a few similarities between our outcomes framework and the logic model that Dr. Morrato showed.

So now let's move into the outcomes data and what we learned from our 2019 experience. This graph shows our post-test scores; that is the learner scores on our standardized 14-questionpost-test from three different types of CO*RE education: live at the top; the REAL CORE, the adaptive learning in the middle; and in the bottom bar a more traditional online course consisting mostly of reading and videos.

As you can see, the live learners outscored the online learners, but note that the REAL CORE adaptive learning results are very close to the success of the live learners. It's the more traditional online course that suffers from lower outcome results.

So why is this? We have some preliminary

understanding on this. One has to do with the audience mix who takes the various courses, which I'll get to on the next slide, and the other contributing element that we've gathered into our follow-up qualitative interviews and focus groups is that the adaptive learning environment adheres more closely to the established principles of effective adult learning that we've been talking about here today; that is repetition; formative assessments' chance to practice; feedback to the learner; and the opportunity to test out of content that you already know.

Now let's talk about the audience mix, taking the various forms of the course that I mentioned on the last slide, but first I want to draw your attention to the fact that all prescribers, regardless of clinician type -- NP, physicians, or PAs -- have post-test scores that are within an acceptable range. RNs, however, shown in the dark purple bar, deserve a closer look.

RNs are the profession that have the

greatest representation in all our online courses, both the traditional online and the adaptive learning. Across our CO*RE courses in 2019, the average RN post-test score was 10 percent below the average prescriber test score, which in part explains the pattern you saw on the previous slide. Since there are more RNs in the online courses and since their post-test scores are low, they are in effect pulling down the average of the online courses. But it's important to note that the RNs post-test scores were not as low in the adaptive learning course compared to the traditional online course.

We along with all of the other stakeholders here are glad that RNs are now included as target learners in the REMS since they're key members of the pain management team and often have the most contact with patients who are prescribed opioids. But these results indicate that the blueprint's current version is not wellmatched to their scope of practice; hence, the lower scores. In other words, the current course includes content for

which they're not trained or do not regularly perform. A good example of this would be opioid rotation calculations.

In our follow-up work, we've interviewed a number of RNs and RN educators, and they suggest re-examining the blueprint in light of RN needs and consider course adjustments to support them. Another CO*RE finding is that learners with individual DEA registration score higher than both learners with no DEA authorization or those who are prescribing under an institutional license.

We wanted to give you a peek at the REAL CORE, the adaptive learning project's data dashboard. We've been talking a lot about data and dashboards today. I know there's a lot going on with this slide, but if you could just bear with me.

This is the user interface of the Tableau data warehouse that we built along with our adaptive learning course. Since adaptive learning delivers a veritable mountain of interesting learner data, you really need a sophisticated

platform like Tableau to slice and dice the data in order to make meaning of it and provide some deep reliable insight into learner behavior.

I'll draw your attention to the top gray bar here. We are currently on the high level chapters metric page, but you can navigate from here to other pages to see participants by state, to examine shifts in confidence ratings, to take a deep dive into post-test scores, or to analyze intended behavior change.

Moving down to the middle blue bar row, you can look at completion by chapter. You can look at who tested out by chapter and the average time spent by chapter. And on the far right, you can see a series of slicers by clinician type; time in practice; region of the country; DEA registration; et cetera, which allow us to cut the data on any of the pages in a number of helpful ways.

For instance, we could take a look at outcomes data for, say, physicians in West Virginia versus physicians in Utah, or we could also use this to take a much more nuanced look at exactly what

content areas, what concepts, learners had the most trouble with.

I was very taken by Alec Walker's analogy for a weather map that he made earlier today, and I think this sort of data dashboard is a good way to think about it; and, Dr. Morrato, we could easily add other factors into these slicers that appear over here on the right, such as the clinical setting that the provider is in to understand better who it is we are educating and where the scores are represented.

We can also think of this adaptive learning project as a preliminary proof of concept to the possibility of a clinician testing out of the information. This test-out concept has been discussed among REMS, grantees, and stakeholders since 2012. This of course is just a static screen shot of our data dashboard. If anyone would like a live tour of the actual data, we're happy to provide that.

One of the most exciting aspects for us as content developers is that we can take a deep dive

into precisely what our learners know and what they do not know and why. Here on this slide, I've just plucked out two particularly challenging topics for our learners, opioid rotation calculations and using the ORT OUD screening tool. These concepts are good examples of the kind of knowledge that drives prescribing behavior, the kinds of changes mentioned by Dr. Auth earlier.

We are able to follow the learner path through this content and evaluate their progress: which wrong answers they select, how much time they spend, and what help they avail themselves of. For this slide, I've just pulled out the number of attempts at completing the activity, the percent correct, and the shifting competence on the topic from pre-exposure to post.

You can see that these two topics require multiple attempts that eventually the learners arrive at a reasonable score and their confidence delta increases from before exposure to the learning module, to after. In future iterations of the CO*RE course, we will be able to use our data

to further hone the activities in order to better address misconceptions and conceptual problems.

Now we'll turn to some higher levels of outcomes. The data in the top row of this slide show the percent of respondents who selected the change associated with each chapter. For example, although learners intended to make changes related to all chapters, slightly more chose changes associated with patient assessments. Here we're looking at changes that the learners thought they would make.

Moving down to the second row, we emailed the follow-up survey to online activity completers 4 to 8 weeks after the activity. This is self-report data on changes made. We see that the same change related to patient assessment was the highest at 44 percent.

The third row, while a low sample size, is interesting because it reveals documented changes in practice. Here we conducted chart-stimulated recall interviews by phone and asked clinicians who'd taken our course to look back at what was

documented in their patient charts. You can see that more changes were documented under creating the treatment plan here.

As any CE CME provider will tell you, getting practice change data is challenging. It's difficult to get clinicians to respond, and the realities on the ground -- for instance, what all is tracked in the EHR -- influence the shape of the results. We would like to point, however, to the fact that the CME providers consistently do this work as part of their accreditation process. We are accustomed to the work and we enjoy trusted relationships with our learners.

From the learners' perspective, such an interview feels like an extension of the learning that they already started, and thus they're more likely to participate. It's important to also understand that gathering this level of data is complex as we've discussed today. The higher level, 5 and 6, are more expensive and the process is much more complicated.

Here's what we see as the implications going

forward from our experience. A common outcomes framework is critical to measuring effectiveness of any CE CME program. We suggest that there be some commonality among future REMS grantees in outcome design and assessment questions. This could allow for collective evaluation of the OA REMS. Online adaptive learning certainly works, and that's good news since online learning will continue to be the method of choice in our pandemic world.

We believe that the RNs need additional support, and perhaps the FDA could consider adapting the blueprint to their scope of practice. We'd like to make the final point, that has been made many times here today, of the absolute critical importance of data to inform educational development decision making. And with that I'll end,and thank you very much.

DR. MANZO: Thank you.

I'm just going to open it up to the panelists if they have any questions or comments for the public speakers.

(No response.)

DR. MANZO: Okay. Then I think we can move into the final portion of this meeting, which Judy Staffa and I are going to make an attempt to provide a high-level summary of what we heard during this three-panel discussion. I'll turn it over to you, Judy, if you'd like to get started.

DR. STAFFA: Sure. But I do notice Elaine had her hand up, Elaine Morrato.

Do you want to ask a question or make a comment about what you heard from either speaker?

DR. MORRATO: I just wanted to say thank you to both speakers. That was really outstanding, and it was really nice to hear your synthesized comments resonate with a lot of the discussion for the day, so thank you very much.

DR. STAFFA: Yes, totally agree.

DR. HARNED: Thank you.

High Level Summary

DR. STAFFA: Thank you for taking the time to talk to us and to share your thoughts. This has been a really fantastic day, and I want to, again, thank all of our panelists, as well as our two

public speakers, for taking the time to discuss this challenging issue with us and to share your thoughts and opinions.

We didn't get a specific plug-and-play recipe, but I don't think we thought we would. But we got a lot to think about, and as we pore through the transcript comments -- again, the docket will be open until February 11th -- we'll be able to flesh out the comments and what we heard even further.

But what I heard was that there was some difference of opinion that rather mirrored some of the discussions we've had ourselves of understanding the need and the importance of evaluating the REMS program, but at the same time recognizing the challenges with doing that pragmatically.

But overall, personally I heard that even though it's not simple, it may be doable, but perhaps not in the way that we originally had envisioned it. And that may be where some of the challenges lie for us: to broaden our thinking and

to think about these from the point of view of a suite of studies rather than a single study, taking into account things like needs assessment to use those to carefully pick apart some of the elements of the blueprint and the training and to tailor and pick the outcomes that seem to be most important.

Again, these will be judgment calls to prioritize what are the outcomes we really want to see and perhaps do them separately or sequentially; to be actually picking some of the lowest hanging fruit and of course leaning heavily on some of the work that our colleagues at CDC have already been doing, and that there may be a lot for us to borrow from there; to follow the pathway according to the logic model of looking at what is in the training, what are we trying to teach, what behaviors are we trying to influence, and then model those outcomes on that, and to do that up front.

I also heard the desire to share prespecified protocols in a public way, and again, we can take that back. I heard that we can possibly be able to use big data as possible, in

that some of these elements that we're looking at may be readily captured. But for some of these outcomes, we will need to go beyond that.

We should be thinking more along the lines that a prescriber's behavior is part of a team, and I think that's reflected in the broadening of the education to the other healthcare professionals on the team. But that team resides in a specific environment, and we need to think broadly about looking at prescriber behavior in the context of that team and that setting, or health plan, or environment in which that prescriber practices.

I heard strongly against any kind of a pilot study; that, really, we probably know enough to be able to proceed with this at this point. I didn't hear a lot of enthusiasm for that idea. I did hear that another challenge we've heard about, which I think is a substantial challenge, is the NPI, and the availability of it, and the linkage. I heard it acknowledged as a problem, but I also heard that it's probably a surmountable problem if we proceed in a careful way; that this is probably a problem

that can be overcome.

I also heard that using mixed methods, using some pragmatic trials, again, not looking at this evaluation as a single study. I didn't hear that there should be a single study. Again, I heard this idea to focus locally, that the national data can be very helpful. But to be looking at this, we should probably be mounting, again, multiple efforts, looking and bringing in the different dimensions to look at some of the proximal outcomes here, but to be able to stratify and look at some of the dimensions of prescribers, such as their specialty; their geography; their specific level of experience; their setting of care, but also characteristics of patients such as race and ethnicity and geography; and also the elements of the programs, what kind of programs are we looking at in relation to the outcome of focus, and really tailor these knowing that not all of these elements and these different domains will be available in big data. That's where we need to be thinking more granularly into other data or linking data in.

Then finally I heard that continuing to do surveillance at a national level and looking at this big picture is important, to continue doing that. Again, as a federal agency, that's always part of our purview, and this kind of high-level weather map type of approach could be useful to identify perhaps populations in which we may really want to dig in and evaluate the outreach, the penetration, and the impact of a REMS program if we see that some of the outcomes seem to be trending upward.

So that's kind of my high-level take. I know I didn't hit on everything, so I'm going to turn it over to Claudia to see if you had other elements to add and some of your take-aways.

DR. MANZO: Thanks, Judy. I think that you summarized it very well. I guess I would say that what we heard is there is definitely a need to isolate the impact of the REMS CE. But as you mentioned, we would use multiple approaches and maybe mixed methods to do that and some qualitative types of evaluations as well.

So I don't really have much to add, and I just wanted to open it up to other FDA folks that might have heard some additional things that either Judy or I didn't capture.

DR. LaCIVITA: Claudia, this is Cynthia. I think that Judy and you captured it very nicely. I don't really have anything to add right now, but thank you.

DR. McANINCH: Hi. This is Jana. I agree. I don't have anything to add.

Adjournment

DR. STAFFA: This is Judy Staffa. I will add one more thing from this last session. I think we got the idea of these other broader more global efforts, and to be looking at its influence on prescriber behavior and patient outcomes in general, that maybe a lot of that information is already out there, and that it may be just a matter of targeting that and looking at that more carefully.

There may not be a need to do that kind of work, at least as part of this, but that we might

be able to draw on information that hasn't been synthesized in a way that's useful to us but that perhaps we could draw on.

I don't see any other comments from the FDA folks, so at this point, I would like to thank everyone, and remind you if you have other comments that you didn't get to share for whatever reason, please consider submitting them to the docket. We really do look at these dockets and pore over them, and we gain a lot of useful insights. There's really not a lot of things more valuable to us at FDA than hearing from folks outside the agency to help us with our thinking through difficult problems.

Thank you for taking the time to do that. And again, it will be open until February 11th, so if it occurs to you in the middle of the night at some point, by all means jump up and put it in the docket; we would love to hear it.

So thank you all so much for your time. Thank you to all of our presenters for taking the time to organize and share your thoughts, and thank

you to Rich and Paul and Wendy, our folks in the background making all of this happen. We very much appreciate it. I hope you all have a wonderful weekend and a very peaceful holiday season. Thank you.

(Whereupon, at 4:20 p.m., the workshop was adjourned.)