FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Wednesday, May 4, 2016

8:00 a.m. to 5:00 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committees

DR. WINTERSTEIN: Good morning, everyone. Welcome to the second day of our meeting. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Sara Petticord, back in the back. If you are present, please stand.

My name is Almut Winterstein. I'm the chairperson of the Drug Safety and Risk Management Advisory Committee, and I will be chairing this meeting. I will now call the joint meeting of the Drug Safety and Risk Management Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee to order. We'll start by going around the table and introducing ourselves. Let's start down on my right.

DR. SCARAZZINI: Yes, good morning. Linda

Scarazzini, industry rep from AbbVie.

DR. HERRING: Good morning. William Herring, industry rep from Merck.

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

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

DR. HOFFMAN: I'm Erika Hoffman. I'm a primary care physician from VA Pittsburgh.

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

DR. McCANN: Mary Ellen McCann from Boston Children's Hospital, pediatric anesthesiologist.

DR. GERHARD: Tobias Gerhard, Rutgers University.

DR. HIGGINS: Jennifer Higgins, consumer representative.

MR. O'BRIEN: Joe O'Brien, patient representative. I'm also president of the National Scoliosis Foundation, a condition that impacts about 7 million people in the United States, of which more than 15,000 have surgery in a given

year. And I am also a patient that's had four spinal fusions and fused from T4 to L5.

DR. GARCIA-BUNUEL: Martin Garcia-Bunuel, primary care physician, VA Maryland Healthcare System.

DR. BILKER: Warren Bilker, biostatistician, University of Pennsylvania.

DR. FLOYD: James Floyd, University of Washington.

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

DR. KAYE: Alan Kaye, chairman of anesthesia, LSU School of Medicine, New Orleans.

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

DR. EMALA: Charles Emala, anesthesiologist at Columbia University.

DR. PERRONE: Jeanmarie Perrone, emergency physician and medical toxicologist, University of Pennsylvania.

DR. WINTERSTEIN: I'm Almut Winterstein. I'm professor and chair of pharmaceutical outcomes

and policy at the University of Florida.

LCDR BEGANSKY: Stephanie Begansky. I'm the designated federal officer for today's meeting.

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

DR. SHOBEN: Abby Shoben. I'm a biostatistician from Ohio State University.

DR. MORRATO: Good morning. Elaine Morrato. I'm an epidemiologist and health services researcher at the Colorado School of Public Health, University of Colorado.

DR. GALINKIN: Jeff Galinkin, pediatric anesthesiologist from the University of Colorado.

DR. BATEMAN: Brian Bateman, anesthesiologist, Mass General and Brigham and Women's Hospital.

DR. GUPTA: Anita Gupta, anesthesiologist and pharmacist from Drexel University at Philadelphia.

DR. FRY: Michael Fry, pharmacist, Providence Health and Services, Oregon.

DR. STANDER: Paul Stander, internist,

geriatrics, and palliative care from the VA and the University of Arizona in Phoenix.

DR. BUCKENMAIER: Trip Buckenmaier, director of the Defense and Veterans Center for Integrated Pain Management, Uniform Services University.

DR. TYLER: Linda Tyler, chief pharmacy officer at the University of Utah Hospitals and Clinics.

DR. CHOUDHRY: Good morning, Niteesh Choudhry. I'm a general internist and health services researcher at Brigham and Women's Hospital and Harvard Medical School.

DR. PARKER: Ruth Parker, Emory University School of Medicine. I'm in medicine, peds, and public health there.

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

DR. HERTZ: Sharon Hertz, division director for the Division of Anesthesia, Analgesia, and Addiction Products here at CDER and FDA.

DR. STAFFA: Good morning. I'm Judy Staffa.

I'm the acting associate director for public health initiatives in the Office of Surveillance and Epidemiology, FDA.

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

DR. LaCIVITA: Good morning. I'm Cynthia LaCivita, director of the Division of Risk Management in CDER at FDA. Thank you.

DR. THROCKMORTON: And I'm Doug Throckmorton, deputy director for regulatory programs, CDER, FDA.

DR. WINTERSTEIN: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We

look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of this meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

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

Conflict of Interest Statement

LCDR BEGANSKY: Thank you. The Food and Drug Administration is convening today's joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee under the

authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of these committees are in compliance with the federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts, when it is determined that the agency's need for a special

government employee's services outweighs his or her potential financial conflict of interest or when the interests of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of results from assessments of the extended-release and long-acting, ER/LA, opioid analgesics risk evaluation and mitigation strategy, REMS. The agency will seek the committee's comments as to

whether this REMS, with elements to assure safe use, assures safe use, is not unduly burdensome to patient access to the drugs, and to the extent practicable, minimizes the burden to the healthcare delivery system.

The ER/LA opioid analgesics REMS requires that prescriber training will be made available to healthcare providers who prescribed ER/LA opioid analgesics. Training is considered REMS compliant if it, one, training provided by continuing education providers is offered by an accredited provider to license prescribers; two, it includes all elements of the FDA blueprint for prescriber education for ER/LA opioid analgesics, blueprint; three, it includes a knowledge assessment of all the sections of the blueprint; and four, it is subject to independent audit to confirm that conditions of the REMS training have been met.

The agency will seek the committees' input on possible modifications to the ER/LA opioid analgesics REMS, including expansion of the scope and content of prescriber training and expansion of

the REMS program to include immediate-release opioids.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Joseph Herring and Linda Scarazzini are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Drs. Herring and Scarazzini's roles at this meeting are to represent industry in general and not any particular company.

Dr. Herring is employed by Merck and

Dr. Scarazzini is employed by AbbVie.

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

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

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

FDA Introductory Remarks – Cynthia LaCivita

DR. LaCIVITA: Good morning. Yesterday, you heard from a variety of presenters, and it was a considerable amount of information to digest. I'm not going to try and summarize it. The serious outcomes resulting from inappropriate prescribing, misuse and abuse of these products, assessing the

impact of the REMS, and additional concerns about the immediate-release products are not easy issues to address.

We do really appreciate the work that the RPC and the CE providers have done to evaluate this REMS, and at the FDA, this is one of our top priorities. Speaking on behalf of my FDA colleagues, we are looking forward to the presentations today, the open public hearing, and the advisory committees' discussion with regard to the REMS. I'm sure it's going to be informative and interesting. Thank you.

DR. WINTERSTEIN: Thank you. We will now proceed with today's presentations from organizations, and Dr. Katzman will start.

Organization Presentation

DR. KATZMAN: Thank you so much for allowing me to come here to speak today. It's really a privilege and an honor. I come from the University of New Mexico, where I've been for the last 19 years, coming from Los Angeles, California at UCLA Medical Center prior to that. I direct the

University of New Mexico Pain Center and also started ECHO Pain in 2008.

What I'd like to share with you and was asked to respond to was how the State of New Mexico mandated continuing medical education specific to pain and opioid substance use disorder in 2012, specifically the New Mexico Medical Board regulation. The title of my talk is A Coordinated Regulatory and Educational Approach to the Public Health Crisis of Chronic Pain and Addiction.

The goal at the time in 2012 was such that New Mexico really had led the country for the past decade in drug overdose, not only to prescription opiate overdose, but also to heroin. And as you know, New Mexico has not been new to heroin overdoses in the country.

Northern New Mexico in particular has had an intergenerational epidemic or endemic to heroin overdoses, and it really only has been in the past three years that we have seen a change in the type of heroin, specifically black tar heroin.

But really, we've had a tremendous problem

in Northern New Mexico, the counties of Rio Arriba, Mora County, and Taos County, with opiate overdose deaths not only to prescription but to heroin, with five and six times the national average. And we still have the highest counties in the whole country.

So the goal in 2010, when key stakeholders in this state, when representatives from the University of New Mexico, the New Mexico Department of Health, the New Mexico Medical Board, the New Mexico Board of Nursing began meeting, was to really develop a grassroots exchange of conversation on a monthly basis in how the state can come together with very little financial resources and work to solve the crisis of the undertreatment of chronic pain, the unintentional opiate overdose deaths that we were seeing not only in New Mexico from heroin, but the rising rates of prescription opiate overdose deaths.

We also realized that, because New Mexico is the fifth largest state and quite impoverished, with only a population of 2,000,000 people, we had

to do something quickly.

We wanted to emphasize that prescriber education was first and foremost. We wanted to have a positive effect on dispensing high-dose opiates, realizing that the combination of opiates and benzodiazepines was what was really causing deaths in many of our patients, not only opiates and benzodiazepines, but opiates and alcohol, and opiates and respiratory depressants. And we also wanted to have an impact on our prescription drug monitoring program.

As Dr. Woodcock yesterday and Dr. Compton from NIDA mentioned, the southwest has really been hit hard along with Appalachia and now certain states in the northeast of the United States.

As I mentioned, New Mexico has been not only number one in the country, but it's really been in the top five for the past decade for prescription drug overdose deaths and heroin overdose deaths. I mentioned that it's the fifth largest state with only 2 million inhabitants. We're a very diverse state with not only non-Hispanic whites, but

Hispanic population and a large American Indian population. We have 29 pueblos and much of the Navajo Nation resides in New Mexico.

As you know, the American Indian population has a very high rate of opioid misuse. Compared to the national rate of 4.2 percent of Americans misusing opiates at the age of 12 or older, American Indians, on average, misuse opiates at the rate of 6.9 percent.

The heroin epidemic, as I mentioned, has been going on for decades, so we know a lot about the misuse of heroin, but the death rates due to heroin have been increasing.

This is a little bit of our overdose death rates in New Mexico. Again, Rio Arriba County, Mora County, as well as states throughout, the counties throughout New Mexico, are just studded with a tremendous burden of overdose death rates.

Only two counties in the entire state have averages of overdose death rates lower than the U.S. average, Curry County and Cibola County. So it's not just Northern New Mexico, but it's even

southwest counties in the state.

So for the year and a half or two years preceding the New Mexico Senate Bill 215, which revised the Pain Relief Act, we were meeting on a regular basis, key stakeholders from around the state. We knew as a state we did not want to impose opiate dosing threshold such as states like Washington that had imposed opiate dosing threshold.

We also knew, however, that high doses of opiates were associated with increasing death rates, especially when combined with benzodiazepines, when combined with alcohol. Because New Mexico is a small state, we only have one Office of the Medical Examiner, which resides right at the University of New Mexico, so our autopsy findings are within one purview and rather accurate.

But we also know that there's a great chilling effect in New Mexico, and we did not want to have a chilling effect with primary care providers who are really at the front line very

much so in taking care of patients who are suffering from chronic pain.

We know that, in many small towns, it's one nurse practitioner, one physician assistant, one physician who are taking care of a population of patients who may be suffering from chronic pain, performing palliative care, hospice care on that community. And if you take away their confidence, their care of taking care of patients with chronic pain, that town is really going to suffer.

So we needed to educate the state. So in 2012, there were about three or four bills that were dropped at that time. Three of them wanted to impose opiate dosing thresholds. And this was not okay, really, with many of the folks at the University of New Mexico, our committee who had been meeting for two years prior.

The one bill that we did advocate for and that did pass was this Senate Bill 215. It required all healthcare licensing boards to mandate continuing medical education related to chronic non-cancer pain for all clinicians with

prescriptive authority.

There were no exclusions whatsoever, so that if you were a radiologist, not prescribing opiates, if you were a pathologist, if you were a retired doctor who is not seeing patients anymore but wanted to keep your license up to date, you still had to take continuing medical education specific to pain and opiate substance use disorder, or at that time, we were calling it addiction.

This bill also mandated the formation of a governor's advisory council, composed of key stakeholders, the similar stakeholders that we were meeting about regularly, to review prescription drug misuse, overdose prevention, and pain management.

We realized very much that what the community of clinicians, not just physicians, but pharmacist clinicians, physician assistants, nurse practitioners needed was more tools in their tool chest to be able to take care of patients, with pain and opiate substance use disorder, and palliative care better so that they could learn how

to take care of patients with pain without using opiate analgesics as first line.

We needed to teach them how to talk to patients. We needed to teach them how to screen for opiate misuse. We needed to teach them how to use exercise, integrative approaches. We needed to teach them how to use non-opiate pharmacotherapy.

So what happened is, the bill passed with almost bipartisan support, 68 to 0 in the House; 31 to 8 in the Senate. So what happened is, every clinical licensing board then had to promulgate rules to mandate continuing medical education.

The first licensing board to do this was the New Mexico Medical Board. 16-10-14 was the rule from the New Mexico Medical Board. They said, "You know what? We should treat this like a medical emergency no different than hantavirus, or a bioterrorism attack, or a medical emergency."

So between March 31st, 2012 and November 1st -- and actually, August 1st, they decided on an immediate 5 hours of CME in pain and addiction.

They told their physicians and their physician assistants, who they were responsible for, that between November 2012 and June 30, 2014, in that year-and-a-half time, every clinician who they were responsible for had to get 5 hours of CME specific to pain and addiction, and then again at every renewal cycle. For physicians in New Mexico, it's every three years, and for physician assistants, it's every two years.

After that, it was like a domino effect. Every clinical licensing board in New Mexico, the New Mexico Board of Nursing, the New Mexico Board of Dentistry, mid-wifery board, osteopathic board and so on, followed the same 5-hour immediate rule and every renewal thereafter.

The New Mexico Medical Board 16.10.14 included the following. The 5 hours must include an understanding of pharmacology and risk of controlled substances, a basic awareness of addiction, abuse and diversion, state and federal requirements for controlled substance prescribing. And then the last one is management of pain.

Here is where it also tied in very much with the prescription drug monitoring program. It also required that every physician and physician assistant registered with the PDMP and checked the PDMP if they were going to write a prescription for more than 10 days and every 6 months thereafter.

So beginning in 2012, we had the most robust combination, if you will, in terms of the 50 states, in terms of 5 hours of CME plus checking the PDMP initially and every 6 months. Just two months ago, New Mexico passed legislation to actually make the PDMP more robust legislatively in terms of now checking the PDMP if writing for more than 4 days' worth of opioids and checking it every 3 months.

So our UNM Pain Center faculty decided that we needed to really get on the bandwagon and train as many New Mexico clinicians with prescriptive authority as we can. So beginning in November of 2012, right as soon as this legislation passed, we began setting up courses, and we trained over half the state's clinicians.

Our New Mexico Pain Center faculty who taught these courses included two ACGME pain specialists, a neurologist, an internal medicine physician, physiatrist with pain specialty, two addiction psychiatrists, and a pediatrician. We also had a dentist teaching one section of the course as well. We also studied this with IRB approval from the University of New Mexico Institutional Review Board.

The topics of our course, for the 5-hour course, included an overview of opioid overdose nationally and statewide. We then taught about use of non-opioid medications and other non-pharmacologic treatments for pain management, a significant talk on identification of patients at risk for opioid substance use disorder, misuse, and aversion.

We talked about opiate screening tools as a significant part of the talk. We talked about how to talk to patients about opioid risk and harm reduction. We had a talk on pediatric and adolescent pain management and another talk on

federal and state laws pertaining to controlled substances and the PDMP as well as safe opiate prescribing.

We then asked the clinicians taking the course to choose between two of the following breakout sessions, and these included vignettes. I started the project ECHO Pain program in 2008, so case studies and case presentations are near and dear to my heart, so these breakout sessions followed a typical case presentation.

Clinicians were asked if they wanted to hear about safe opiate prescribing, management of the patient who is misusing opiates, pediatric and adolescent pain. This was particularly pertinent to the pediatricians and family practice clinicians who were taking the course, as well as pain and psychiatric co-morbidities. We began dental courses in 2013.

I might add as an aside that the New Mexico Medical Board didn't only approve these courses at the University of New Mexico, they also approved courses at the New Mexico Medical Society. They

approved courses at the American Academy of Pain Medicine, Pain Management, the AMA, the American Academy of Family Physicians. They approved courses on their website, and clinicians from all over New Mexico, or even physicians that were practicing in other states but wanted to maintain their New Mexico licensure, could take courses based on the approval that was on the New Mexico Medical Board website.

So we studied this. We got IRB approval. We studied pre/post course surveys in knowledge, self-efficacy, and attitudes. I might add that the study participation was voluntary and had no bearing on receiving the 5 hours needed to maintain their New Mexico Medical Board licensure, but we did have a 99 percent voluntary -- they participated in taking this pre- and post-survey 99 percent of the time.

We published this in 2014 in the American Journal of Public Health. We studied six courses. We have continued these courses to this date, but we just studied the first year of these courses.

Four of the courses were located in Albuquerque at two different locations, both at the University of New Mexico and the VA Medical Center at the New Mexico VA Healthcare System. One course was located in Northern New Mexico, in Santa Fe. One course was located in Southern New Mexico, in Las Cruces.

We did study about 1,090 clinicians; 67 percent were MDs or DOs; 30 percent were mid-level providers, PAs or NPs, and 3 percent were dentists, certified nurse midwives, pharmacists, or psychologists. I might add that that bottom number is quite low because the dentists began their own courses.

This is quite small, but you should have this on your handouts. We had very statistically significant improvement pre- and post-course in knowledge, self-efficacy, and attitudes. And I can get you the detailed questions if you'd like at a later time. I can get the FDA these if you'd like.

Again, this is also very detailed, but what I'd like to emphasize here are a few things. This

goes way before the course, beginning in January of 2008, going through June of 2013. There's a few things that I'd like to note here, that we had a significant reduction in the total morphine milligram equivalents of opiates dispensed.

This is data from the New Mexico Prescription Monitoring Program and New Mexico Board of Pharmacy. We did have a significant reduction in total morphine milligram equivalents dispensed since beginning the course. Obviously, this is association and not causal. And similarly, we had a reduction in the total diazepam or value-milligram equivalents of benzodiazepines dispensed. I was very interested in looking at the opiates and value-milligram equivalents dispensed.

What I was also very happy to see, although others might not be so thrilled with this, is that we did not have a chilling effect. In New Mexico, it's very important that we see not a drop-off of prescriptions for opiates because we have such a rural state, and we need to make sure that our primary care providers are not saying, "I'm not

taking care of pain anymore."

I might add, and this is anecdotal, but I do have the CME comments from our ACCME-certified continuing medical education department at the University of Mexico, that we had hardly any pushback or any comments in a negative fashion such as, why do I have to take this course, I'm a radiologist, or I'm not treating patients anymore, or this is stupid, it doesn't pertain to me, things like that. We had very, very high satisfactions related to this course.

This is current data in that my close colleagues at the New Mexico Department of Health added just-in-time data to the older data from the American Journal of Public Health paper. We've continued since the course to see a decrease of high-dose prescribing of opiates.

We can't tell if this is long-acting or short-acting, but clinicians are decreasing their rates of prescribing high doses of morphine milligram equivalents and are prescribing lower doses of opioids 'til this day.

Similarly, there's been a decrease in total opioids prescribed. Unfortunately, what we have seen is a trend in days' supply of opioids. We're also continuing to see a decrease in the percent of clinicians providing opiates, over 100 morphine milligram equivalents a day. It's similar to the two slides previous.

Now, I need to show this to you. I don't like the 2014 data, but there was a significant drop-off after we started the courses in the opioid overdose death rates, and this is when we went from number 1 in the country to number 3 in the country. Unfortunately, New Mexico gets a lot of number 1's in many things because we're such an impoverished state.

In 2014, it's hard to tell why we bumped up. What I just heard from Mike Landon, the state epidemiologist, is it's a little bit unclear. He thinks we're going to go down in the number of death rates in 2015. We think it's related particularly to the number of heroin overdose combined with benzodiazepines and especially black

tar heroin.

What I'd like to just share as my closing slide is a publication that will come out within the next two weeks in the American Journal of Public Health. I've been involved, as you know, with Project ECHO since 2008 and started ECHO Pain, and have been working closely to help other academic medical centers replicate Project ECHO Pain, and been working closely with VA SCAN-ECHO and particularly with the Department of Defense and the Army and Navy Pain ECHO.

We did these 5-hour trainings with the Navy three times. They were quite successful. We've not published these courses, but we did them with two Navy sites both in the Navy Med on the east coast and the Navy Med in Balboa. The trainings were very well-received.

We started a telehealth with the Indian Health Service ECHO three years ago. Then effective January 2015, Susan Karol, the chief medical officer for the Indian Health Service, really saw our program in New Mexico, and she

effectively mandated all Indian Health Service clinicians to take 5 hours of training based on our New Mexico courses.

Since January of 2015, we have given these courses -- our new UNM faculty have given these courses 8 times virtually, through a videoconferencing platform, to 1700 IHS clinicians. We've seen the same results. We've studied this, and we found the same results. We've studied this with qualitative results as well. And I can share them with you once they're published. Thank you.

DR. WINTERSTEIN: We will continue with Dr. McMahon.

Organization Presentation - Graham McMahon

DR. MCMAHON: Good morning, everybody. It's a real pleasure to be here. My name is Graham McMahon. I am the president and CEO at the Accreditation Council for continuing medical education. I am an endocrinologist and, like many of you here, have been a prescriber of opioids and have been affected by my patients, and by my community, who have had both challenges as well as

benefits from those prescription medicines.

We are honored to be here and to be invited to participate, and really appreciate FDA's recognition of the value of accredited CE to be a mechanism to drive change, innovation in the system, and support best practices, and applaud certainly FDA's commitment to listening to stakeholders and to engaging in ongoing improvement.

The accredited CE system that's out there has had a long-standing commitment to supporting clinicians to do right by their patients both in terms of managing their pain, but also limiting and avoiding addiction and dependence.

Our ACCME system essentially reflects a diversity of community values. We were set up over 35 years to reflect community values by this 7-member organizations to be an independent non-profit and to reflect what the community feels matters in education.

In that role, we set the standards for what counts in continuing education to ensure that

clinicians who are attending educational events know that, by attending an accredited event, they will receive education that's balanced and evidence based, that's designed to maximally be relevant for their needs; to address real gaps and needs, not those that are other people's, but are theirs; that the activities are evaluated to guide safe, effective care; and importantly, that those activities are free of commercial influence that would otherwise be working to derive promotion or marketing efforts for particular products or devices.

To make these efforts real, we not only set the standards, but perform audits. We perform surveys. We respond to complaints and engage a wide and diverse network of CE providers who are able to abide by these standards and reflect our community's values in accredited continuing education.

We've worked to establish those values of independence of educational quality in a very dynamic and changing world for clinician learners.

Standards are changing. Expectations of our clinicians are changing. And our expectations of the clinicians themselves are changing.

We used to think that we would be able to launch our clinicians out of medical school, out of residencies, out of fellowships, out of particular programs, and they would be launched out in the community in a ballistic model, and they would maintain a level of performance for a long time, hopefully only reaching that zenith of staying above standards until just the day before retirement.

But that model is obviously defunct, and the continuing education enterprise is really designed to reflect not just over time the change in standards or to reflect or address the persistent and frustrating forgetting curve of clinician practice, but in order to try and address this zig-zag in changing performances and abilities of our clinicians over time to create opportunities for reflection and self-awareness so that clinicians' abilities, their real intrinsic ability

to do right by their patients and do the right thing that is a professional value of our community, is made aware to them so then they can go out and change, and we can sustain their persistent efforts at doing the right thing for a long time.

In order to do that, you really have to think about engagement as a primary currency for learning. Engagement is difficult to achieve amongst professional learners like we have to address. And unless you think about issues of maximizing relevance, making the education efficient, making the education effective, making the learning meaningful, it's very hard to engage the hearts and minds of our community.

It's easy to drive people through box-checking behaviors and complete activities that aren't meaningful for them for the sake of actually achieving numbers. But if you really want to change practice, you really have to create relevant, efficient, effective, and meaningful educational efforts that connect with clinicians

for the long term. That's what drives behavior.

In many ways, our CME community is designed to achieve just that. They know our learners because they are in their institutions, in their localities. They know the challenges that they face, whether they're in New Mexico or in Manhattan, and helping them connect with their learners in a maximal way will most likely drive actual meaningful change in the long term.

We have a very diverse array of continuing education providers that are each represented geographically by these yellow dots in the accredited CME system nationally. We accredit about 1900 providers nationally. Those 1900 providers deliver about 147,000 different activities, culminating up into about over a million hours of instruction across the range of disciplines and enterprises nationally.

That results in at least 13 and a half million physician interactions, but importantly, 11 and a half million other learner interaction. That means the quality of the CE enterprise is

attracting our nurse colleagues, our colleagues who are physician assistants, and pharmacists, and dentists, and podiatrists, and optometrists, and the entire healthcare team.

The reason that we have this data is that our system requires that activities are created that are listed in our databases as they're created, which is a terrific asset to the community because it allows us to drive data, and evaluate programs, and measure all sorts of information about the health of the enterprise.

When it comes to our opioid REMS CME activities, this system allows us to track many components of that. And I think many of you know our database systems, we modified several years ago to accommodate very specifically the REMS modules and track information for the RPC.

From that data, there's a slew of report data in our formal comments that were submitted by written testimony, but a sliver of that information shows that the majority of our participants who are prescribers according to the FDA definition were,

naturally enough, physicians, but included advanced-practice nurses, physician assistants, optometrists, dentists, as well as a range of other professionals.

The programs that were produced that are listed in PARS show 612 different types of course activities that were predominantly based on live courses in hospitals and clinics distributed across every type of organization and every state in the nation, just about.

A minority of the programming was based on the internet-based activities, those enduring materials. But you'll see that it was those enduring and internet-based activities that drew the largest number of participants.

So of the 168,000 learners who engaged with activities that were tracked in our REMS system, the majority of those were participating in internet-based learning. And many of you may have an outdated view of the ways in which our activities are being created now.

While traditionally you might think of

courses as being sage on the stage and internet activities being narrated PowerPoint slides held online, very many of our courses now are case based, interactive, use case-based simulations, problem-solving skills, communities of learning, and all sorts of other types of activities that drive quality in education.

There's a whole series of lessons that we can learn from what we've been doing over the last few years. The first is to recognize that our continuing education providers are at the elbows of their learners. They know their audiences the best, and they're most likely to be successful when you give them permission, flexibility, and liberty to adapt their education and the modular assessments to their learners' needs.

The more in which you mandate or restrict those types of formats, approaches, types of engagements, the least likely you are to actually be successful in your mission because our learners are incredibly diverse, and their needs are incredibly diverse. And the ways to create

relevant, meaningful engagement is incredibly diverse.

I would encourage us to use things like our search engine to be able to direct learners to activities that maximally meet their needs based on their learning preferences and styles because their activities now are listed in our system. They're searchable, retrievable, and that creates a much more nuanced view of what works for an individual learner.

I would recommend that we revise the blueprint to focus on high-level direction regarding risks without constraining educational providers' ability to tailor that education.

I would encourage us to enable educators to use the blueprint as a basis for identifying and designing activities to meet learners' caps and needs.

I would recommend advising participant numbers to reflect the diversity of the types of providers that are prescribers, but also those that engage teams, and also those that sustain

individual clinician-prescribing behavior through teamwork. And fundamentally, we would say we fully support the continuation of accredited CE as a delivery mechanism for prescriber-based training in the early opioid analgesic REMS.

Accredited CE can also support a whole series of other activities. We can play a role in addressing patient safety issues addressed in other REMS, where those are pre- or post-approval or single-product REMS. And we would think that that system is ideally suited to engage the community in maximal and safe prescribing of drugs and use of devices nationally.

Accredited CME is not standing still. We are evolving to try and encourage best practices in education to maximally meet the learners' needs. Our new accreditation standards focus on things like team-based care, integrating patients in public and education, public and population health initiatives, collaborations with healthcare systems and communities, and a movement towards high-level outcomes data to measure change in physician

performance, patient care, and community health.

Our accredited CE system is working every day to make a difference. We are committed to improving the health of the nation and supporting your efforts to reduce risk and promote drug safety. Thank you very much.

Clarifying Questions

DR. WINTERSTEIN: We have now some time for questions. Sorry. Dr. Krasnow, yes?

DR. KRASNOW: The question is for Dr. Katzman, slide 21. Looking at all the numbers on that slide, all the deaths by year going from the top to the bottom, it appears that there's really no trend whatsoever. Isn't the proper conclusion to your talk that there's been no discernible effect of education on these outcomes to date? I don't see any other conclusion.

DR. KATZMAN: I think we can conclude an association with the decrease in the morphine milligram equivalents dispensing and the diazepam milligram equivalent-dispensing. I agree that the death rate is up for discussion in terms of the

decrease.

I think that there has been a trend until 2014, beginning in 2011 with a trend downward until the 2014 bump-up. But I agree that we can't say anything about the overdose death rate bump-up.

DR. KRASNOW: But if you look at the years before 2011, you also see variations in the same range.

DR. RAGHUNATHAN: Right. That's why I don't think we can say anything about the death rate.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: This is for Dr. Katzman also. On slide 18 -- put that up, staff -- it appears that the percentage of all opioid prescriptions greater than 100 MMEs per day has been static from 2008 to 2015. Is that how you would interpret that?

DR. KATZMAN: In terms of the 100 morphine milligram equivalents?

DR. BROWN: Right. It's been relatively static at 10 percent for, it appears, over the course of time. If you go then to slide number 20

and look at the percent of practitioners providing opioid prescriptions over 100 MMEs per day, there's been what appears to be a significant drop over the same time frame from about, it looks to me, like 78 percent down to about 50 percent.

My question relates to whether or not -- I think these are significant data because it is beginning to identify a separate population of prescribers. And I wonder if the Department of Health or UNM have had an opportunity to -- since you're condensing that number, that population, had an opportunity to look at that more closely.

Maybe those are the people that need the education.

DR. KATZMAN: In terms of where there are some very, very high-dose prescribers that are now prescribing a lot less, is that --

DR. BROWN: It looks like doctor shopping, is what it appears. It appears that there are the same number of prescriptions being written by fewer people and that the folks in New Mexico are doctor shopping to find somebody to write those

prescriptions. And I just wonder if the issue of doctor shopping has come up.

DR. KATZMAN: The issue of doctor shopping has come up. We talk about this at our monthly governor's council meetings. I think that the Board of Pharmacy and the prescription Drug monitoring program does quite a good job with this.

I can look more into this and get you the information about the discrepancy, but I do think that the Department of Health has seen a decrease in the percent of practitioners showing a drop in prescribing the 100 morphine milligram equivalents, but I can get you a decrease in this.

DR. BROWN: I think the important point to be made -- and this relates to continuing education -- is that it appears that there's a special population of prescribers that we could focus continuing education on, and that we would be more successful in getting a better outcome. That's the only point I'm trying to make.

DR. KATZMAN: New Mexico is one of the 16 states that did get the grant from the CDC, and one

of their components is doing a study looking at just those prescribers. Thank you.

DR. WINTERSTEIN: I have a quick follow-up question on this. The denominator on this slide, is this every prescriber, or is this every prescriber who writes for opioids? I mean, it seems to me 50 percent still who write. I mean, this is a fairly high dose. Would that surprise you? What's the denominator there?

DR. KATZMAN: I don't want to be off, so I will get you that data. Thank you.

DR. WINTERSTEIN: Dr. Gerhard?

DR. GERHARD: Also, a question for Dr. Katzman. Toby Gerhard, Rutgers. This obviously was a mandated education effort, and we heard yesterday some comments that suggested that clinicians weren't receptive to mandated education efforts and there would be a lot of resistance or poor learning outcomes in a sense.

What was your experience with a mandated program in terms of the clinicians' receptiveness, and participation, and so on?

DR. KATZMAN: Right. It still continues four years later. Clinicians all around the state are still participating robustly. I just actually participated in a New Mexico Medical Society in Greater Albuquerque Medical Association 5-hour course last Saturday.

I gave 2 hours of the talk. I gave the overview of the national crisis of opioid and heroin deaths. I also gave the non-opioid medication management. Three other clinicians gave the other 3 hours. It was attended by 250 physicians. I heard no comments to why are we having to take this. It was attended by physicians, mid-level providers, dentists, and so on.

Again, clinicians can get their CMEs also through our Project ECHO program. They can get one hour at a time. And with the Indian Health Service program, like I mentioned, they get it through the virtual platform as well.

Like Dr. Graham said, many learners know, as you know, most of them are getting their CME

education virtually, and online, and with case-based learning. Many of our original courses at UNM were with vignettes, and standardized patients, and case-based presentation. With the DoD JPEP curriculum, that's an amazing way for a DoD VA to obtain the CME as well.

DR. WINTERSTEIN: I have a quick follow-up on this as well. Those extra 5 credits, CME, is that part of the total credits that physicians have to take, whatever that might be, 40, or is there an add-on? So in other words, can they basically count that to their total credit. So it's not really an extra burden.

DR. KATZMAN: Yes. So it's not an extra burden. The original thought was that it was going to be a slippery slope. I've heard many things. The original thought was from the New Mexico Medical Board.

A member of the governor's council is also a member of the New Mexico Medical Board, and there was a thought originally, lots of thoughts, well, why pain and addiction, why not diabetes, why not

cardiac? So the member of the New Mexico Medical Board, who also sits on the governor's council, really impressed upon the fact that there's a crisis of undertreatment of chronic pain in this country and also opiate overdose deaths. And it's been working, and we've been continuing down that road, but it was incorporated into the overall CME.

DR. WINTERSTEIN: Dr. Morrato?

DR. MORRATO: I also had a question for Dr. Katzman, and it builds on what we've just been talking. I was really struck by your comment, "treat like a medical emergency," which sounds is important and sounds like it's feasible within New Mexico. If we're being asked how we might scale this, if you will, to take it to a national level, it would be useful to hear your thoughts.

If we think about scaling, it could be state by state, as states like New Mexico have done in trying to affect policies at the state level. It could involve a separate REMS certification system where we've heard about why build a separate system -- that might be adding burden - or one

that's been discussed before is at a federal licensure level through DEA licensing.

Maybe there's other opportunities as well, but what advice would you have to us as we think about taking New Mexico to scale? My impression is that your state numbers probably aren't being counted in the REMS numbers of doctors that are prescribers that have been certified.

So we wouldn't want to complicate things going on in New Mexico by doing something at a federal level, so thoughts on how we might move forward to take this to scale, I guess.

DR. KATZMAN: I've thought about this a little bit. This is my passion. This is kind of what I do on a daily basis. Yes, starting Project ECHO in 2008, and what I do is I educate about chronic pain. And I truly believe that the way to combat the epidemic of unintentional opiate overdose deaths is to really teach clinicians about chronic pain.

You have to teach about chronic pain to get at opioids. You have to teach both. The teaching

of non-opioid pharmacology, and pharmacotherapy, and non- pharmacotherapy has to be built in there as well. And that's why I think it has to be kind of a full program so to speak.

I don't know if the model of New Mexico would be the best approach state by state. I think that's definitely one option. Another option would be a DEA approach in terms of as you renew your DEA license, you have to get the hours.

So that would be kind of my other thought, to go to kind of the federal level. The IHS is doing it. In order to be an IHS employee, you're having to take the 5 hours.

The one thing about New Mexico is we are tailoring our trainings, like Dr. Graham said, to the state. And so cultural sensitivities come into play. Just like the problem in Appalachia, they might tailor their statewide education to the problems in the region. Just like the problems in Alaska, their region might tailor their trainings to their region. So their clinicians might enjoy the trainings better and take it to heart.

We teach a lot about naloxone in our trainings now. We teach about the two FDA products. We teach about the Good Samaritan law in New Mexico. So that might be something to think about if you're going to adopt kind of a DEA approach, tagging it along to DEA licensure, whether you're going to do a state-by-state approach, whether you're going to do a restricted REMS approach -- I mean, there are different ways to do it -- or if you're going to continue along unrestricted REMS.

So that's my thoughts.

DR. MORRATO: Thank you. So it also sounds like, just to confirm that I heard correctly, as we think about this, that content is important, that it might be more of a thematic outline that allows adaptation and that it's important that we teach the broad issue of opioids and pain management as opposed to just, let's say, focusing on extended-release, long-acting in terms of from an educational standpoint, and that it's important that there's allowable adaptation over time

because, if this is a renewal process, it's going to adapt with the messaging of the time.

So whatever's being built needs to allow that.

DR. KATZMAN: Absolutely. For instance, last year, we changed our slides. We have a half an hour slide on federal and state guidelines pertaining to controlled substances, so we had to change our slides. As you know, hydrocodone was up in terms of its schedule.

So we changed our slides; the same with naloxone, the FDA approval of the nasal naloxone formulation. So we're changing our slides every time to adhere to best practices and what's the new rules.

So all of this is changing just so much, so we want to provide just-in-time best practices, delivery, and because some of the schedules change by state. But the DEA approach or the restricted REMS approach, yes.

DR. WINTERSTEIN: Dr. Manzo?

DR. MANZO: Yes, a couple questions for

Dr. Katzman. Is the training required to be live training? That's the first. And I guess the second is, are you considering requiring a module in treating overdose?

DR. KATZMAN: I'm not sure who spoke, but okay. So the New Mexico Medical Board -- and I was asked to speak strictly on that rule, the New Mexico Medical Board rule. If you go to their website, you see that they accredit many different programs, whether it's our New Mexico course, whether it's the New Mexico Medical Society course, whether it's our ECHO Pain course.

You can take a 5-hour course. You can take 5 1-hour ECHO Pain courses, our ECHO Pain program, in which you know ECHO pain has been replicated in many other academic medical centers, by the Army, by the Navy. And they offer 90-minute, 120-minute weekly programs. ECHO Pain now will fulfill the CME for this New Mexico licensure as well.

So the answer is you can take it live or virtually with a videoconferencing platform. The IHS program that's now mandated for all IHS

clinicians, it's a virtual platform.

DR. WINTERSTEIN: Just a quick reminder, we are focusing on clarifying questions right now. The discussion is coming after the public hearing, so just in order to try to get this as efficient as possible, Dr. Fry is next.

DR. FRY: Quick question for you. I worked two years in Rio Arriba County,. and I know some of the issues there would be the proximity to Colorado. Has the Board of Pharmacy reached out for the PDMP to get both states? I had patients that would go both states depending on what they wanted to get, so it would not show up when we did the search.

DR. KATZMAN: Yes. I believe all surrounding states to New Mexico are now included except for Texas. That's been the one stickler so far in terms of the PDMP. New Mexico has a pretty robust PDMP system right now. It's almost immediate. But yes. I hear you on that with the crossover and Rio Arriba County is a real challenge, Rio Arriba and Mora County, in terms of

the heroin and prescription drug epidemic.

DR. WINTERSTEIN: Dr. Buckenmaier?

DR. BUCKENMAIER: Trip Buckenmaier, Uniform Services University. This is for Dr. Katzman. I want to clarify one issue. It's my understanding that you did not have granularity on your death data as to what was prescription related and what was illicit drug use.

My second question that I'd like you to comment on -- and in full disclosure, the DoD has drunk the purple Kool-Aid on ECHO. It's a very important program for us. But could you comment on the knowledge network that's developed?

You're the first clinician thus far that has talked about actually reducing opioid use in providers and using other mechanisms for therapy. And do you have any metric that you could point to on your success in that regard as far as building these knowledge networks and changing the way providers are practicing as far as therapies?

DR. KATZMAN: Thanks, Dr. Buckenmaier. So the first question is that the OMI data in New

Mexico, I can get that for you in terms of what these overdoses are due to. As you know, it's very difficult to tell sometimes, is it heroin or a combination of heroin and prescription drugs. We definitely know that many of these deaths are mixed. Many of them are not just opioids there. They're opioids and benzodiazepines or opioids and alcohol and other respiratory depressants.

The second is that our courses, especially our University of New Mexico courses that we studied, we started with in opening lecture. We talked about the national crisis and why are you here today. And we talked about the fact that you might not prescribe any controlled substances, but you're here because this is a national epidemic, not only because of the undertreatment of chronic pain in this country, but opioid overdose death rates.

You're here because if you don't prescribe opiates, you can still help because you're a healthcare provider and you can teach your community about safe and effective ways to manage

this epidemic. And then we go on, and our second topic is screening for opiate overdose deaths and ways to use screening in talking to patients and getting their psychosocial history.

Our third talk is not about safe opiate prescribing and using opiates, but our third talk is non-opioid modalities because we believe that that's what we really need to be teaching.

We need to be providing clinicians, all healthcare providers, other ways to use opioids -- other ways to manage pain, whether it's non-opioid pharmacotherapy, gabapentin, neuropathic agents, serotonergic oradrenergic reuptake inhibitors, tricyclic antidepressants, and then integrative approaches, exercise, diet, physical therapy, rehab, acupuncture, and so on.

We teach you about best practices, evidence-based approaches, integrative approaches. And then we talk about, if you need opiates, this is how you safely prescribe, beginning with immediate-release, moving up, titrating up to long-acting, extended-release, and so on. And then we talk about federal

and state guidelines.

So that's how we do it.

DR. BUCKENMAIER: Thank you.

DR. WINTERSTEIN: Dr. Emala?

DR. EMALA: So my question is also for Dr. Katzman, slide 21. So we've heard a lot of discussion yesterday and today about the educational impact of the CE activities. But I just want to make a point that the goal of the REMS was not to assess education and prescriber knowledge, but was to assess the impact on adverse outcomes.

Those specific outcomes were addiction, unintentional overdose, and death. So I think slide 21 of your presentation is the one data slide that attempts to get close to the charge of the REMS program. And I just want to reinforce what Dr. Buckenmaier already referred to, knowing what portion of these are attributable to prescription opioids versus heroin overdoses I think it's imperative to understand the impact of this educational program.

DR. KATZMAN: Yes.

DR. WINTERSTEIN: Do you have a direct comment?

DR. KAYE: I have that data. It's from the Albuquerque Journal. And it's 265 for prescription opiates: 154 were heroin, 111 were methamphetamines, and 70 was cocaine. And if you look from 2013 to 2014 and you take out the prescription opiates, 66 of those were from heroin, methamphetamine, and cocaine.

If you go back to 2008 and line up everything, you see that methamphetamines went up from 23 to 111 prescriptions. Opiates we know have gone up, 2 to 4 times depending on the state and what year you compare it to, went from 256 to 265.

So in that regard, you might say with a larger population and with the curve nationwide being as it is that, actually, it is impactful because it's mostly flat, probably statistically insignificant. And if you look at the size, it's probably an improvement per person prescription overdose death.

Does that answer?

DR. EMALA: Yes. But just to follow up again, this is surveillance data over time. And as we saw countless times yesterday, we can't dissect out the impact of this educational program against other efforts that are being made as well.

DR. WINTERSTEIN: Just to clarify, you said from 2008 to 2014, it's 256 to 265. That sounds like a slight increase to me. I mean, it's not a decrease. Basically, what you're saying is, it might have plateaued.

DR. KAYE: What I'm saying that -- I figured someone would ask. I didn't want to be too compulsive. But I'm just guessing that the population from 2008 to 2014 has gone up. So the relative death by prescription opiates, I would think, would have actually gone down. I can pull it up and make a calculation if you want, but certainly it's better than the national average, which over, what, 10, 15 years is anywhere from 2 to 4 times increase in overdose death from prescription drugs.

So in that regard, it's certainly better than trends of the United States.

DR. KATZMAN: This is Joanna. I think that the methamphetamine deaths were -- tell me if I'm wrong, but I think you meant, they've gone up, almost straight up, perpendicular.

DR. KAYE: Yes. It was 111 and that compares to 2008 at 23. So just to be fair, I don't know how much your course or your teachings focused on methamphetamines. Since we're talking about prescription opiates -- because we can't control illicit drug use to be fair. These numbers include cocaine, methamphetamine, and heroin, at least from what I'm looking at on the internet.

DR. KATZMAN: We're Breaking Bad. We're the City of Breaking Bad.

(Laughter.)

DR. WINTERSTEIN: We'll move on with Dr. Auth now for the FDA presentation. We still have a number of questions and people listed here. We'll get back to that after Dr. Auth's presentation, just to stay a little bit on time.

FDA Presentation - Doris Auth

DR. AUTH: Good morning. My name is Doris Auth with the Division of Risk Management. Yesterday, you were presented with a lot of data from the assessment of the extended-release and long-acting opioid analgesic REMS.

Later today, you'll be asked to discuss, among other things, whether the data supports the effectiveness of this program. You'll also be asked to vote on whether any REMS modifications are necessary. And this morning, I'll be presenting some considerations for modifications to the extended-release and long-acting opioid analgesic REMS.

I'll first provide some information on the current state of REMS programs, then walk through the options available for modifying the REMS. I'll also illustrate the operations of two restrictive REMS programs, then provide some numbers of stakeholders that may be affected if a restrictive REMS for the extended-release and long-acting opioids or the ER/LA plus immediate-release

products were approved, and finish with some final thoughts on these modifications.

There are currently 75 REMS programs. Thirty-five of these do not include elements to assure safe use, or ETASU, while 40 have elements to assure safe use. These elements were described yesterday in detail in Dr. LaCivita's presentation.

Of these programs without elements to assure safe use, there's an almost even split between those that are medication guide only and communication plan only, with a handful of programs that combine these two elements.

Of the 40 programs with elements to assure safe use, 33 of those are restrictive and 7 are non-restrictive. I'd like to note that all of these programs with elements to assure safe use may also include a medication guide or communication plan as a component of the program.

This is a slide you saw yesterday. These ETASU programs that are restrictive require some action on the part of the prescriber, pharmacy, and patients in order to prescribe, dispense, or use

the drug. This is most often accomplished through requiring certification or training of stakeholders as well as documentation that a safe-use condition was met prior to dispensing or administering the drug.

An example of a safe-use condition would be the verification that a patient has been enrolled in the program and has completed a patient provider agreement form, or PPA, prior to the pharmacist dispensing the drug.

The only requirement in the current non-restrictive ETASU programs is for the application holder to make training available to likely prescribers. The ER/LA opioid analgesic REMS is one of these programs.

For these REMS with restrictive ETASU, program participation varies widely. The numbers on this slide were pulled from the most recent REMS assessments for restrictive REMS programs. The numbers do not include REMS approved recently as these programs may still be in the implementation phase.

For patients, participation ranges from as few as 75 to as many as 235,000. For prescribers, this ranges 84 to 18,000, and for pharmacies, as little as 3 to as many as 47,000 pharmacies. We have a table in the background document that also illustrates that many of these restrictive REMS programs are relatively small, and roughly 60 percent have less than 10,000 patients, prescribers, and pharmacies participating.

This is likely due to the fact that many of the REMS programs are for drugs that either treat orphan diseases or other conditions with relatively small patient populations.

Next, I'll describe options for modification of the REMS. There are a couple of options, as we heard yesterday, for modifying the extended-release and long-acting opioid analgesic REMS. They're categorized into either the scope, the elements, or some combination of these two.

Focusing our modifications on the scope of the program might incorporate revisions to the FDA blueprint to include general pain management

principles, medication-assisted therapy for addiction, the treatment of overdose, as well as other topics.

Modifications to the scope of the current REMS could also include incorporation of the immediate-release opioids if it's believed that a REMS for these products are necessary.

The ER/LA opioid REMS could also be modified to include additional elements to assure safe use. This would make the program restrictive. This could include the requirement for prescriber certification, pharmacy certification, or patient enrollment.

You may recall from the presentation yesterday that none of these elements can be added in isolation, and the requirement for prescriber education and certification under a REMS almost always requires that pharmacies in turn become certified in order to ensure that prescriptions dispensed for the REMS product are only those that are provided by prescribers who have been educated and certified in the program. And finally, the

program could be modified to include an expansion of both the scope and the elements.

Next, I'd like to illustrate the operation of a couple of restrictive REMS programs that might help to clarify how the modifications I just described could be operationalized for either the ER/LA or the ER/LA plus the immediate-release opioids. Both of these examples are intended to be a high-level overview of operations and do not include all program requirements.

The first example is a transmucosal immediate-release, fentanyl, or TIRF, REMS, which is a shared-system REMS approved in December 2011 that currently includes 8 application holders.

The TIRFs are indicated for breakthrough pain in cancer patients already receiving and tolerant to around-the-clock opioid therapy for management of their underlying persistent cancer pain. The majority of formulations are indicated for patients 18 years of age or older, and only one of these is approved for those 16 years of age and older.

Formulations include buccal tablets, buccal film, a lozenge, a sublingual, and a nasal spray. The TIRF REMS was designed to mitigate misuse, abuse, addiction, overdose, and serious complications due to medication errors associated with these products.

In this next slide, I'm going to walk through an overview of the requirements for stakeholders involved in the outpatient prescribing, dispensing, and use of the TIRF products.

Requirements for inpatient prescribing, dispensing, and use differ. First, prescribers are required to review the educational program and successfully complete a knowledge assessment to become enrolled in the program. They must counsel each patient on the risks and safe-use conditions and complete the patient-provider agreement with the patient.

Pharmacies also have the same education and knowledge assessment requirement. They must provide patients with a medication guide with each

prescription. Pharmacies actually enroll patients into the TIRF REMS program upon the initial prescription as long as the prescriber is enrolled. There is a 10-day window that allows the patient to receive the TIRF product prior to the REMS system receiving that completed patient-provider agreement form.

Pharmacies obtain authorization to dispense based on the confirmation that patients and prescribers are enrolled. Now, for outpatient retail pharmacies, this is done through the claims adjudication system or pharmacy switch system. This allows for that authorization to occur within the regular flow of the outpatient pharmacist workload. This REMS authorization occurs prior to any insurance authorization.

On the other hand, pharmacies operating under closed-system health plans such as the VA, Department of Defense, and some large managed healthcare systems do not use this claims adjudication system. Therefore, authorization to dispense a TIRF in these systems must be obtained

through an entirely different process that entails calling or faxing the REMS program for authorization. And again, patients are required to sign a patient-provider agreement as a safe-use condition.

In this document, the patient is acknowledging that he or she understands the risks, the proper use, safe storage, and disposal of the TIRF products.

The next example is isotretinoin or iPLEDGE REMS. This is also a shared-system REMS that was originally approved in 2005 and currently includes 6 application holders. The indication for isotretinoin is severe recalcitrant nodular acne. Patients typically receive isotretinoin for 4 to 6 months.

The risk that the REMS is designed to mitigate is the risk of teratogenicity. The goals of the REMS are to prevent fetal exposure and educate patients, prescribers, and pharmacies about the safe-use conditions.

There are many similarities between the TIRF

and the iPLEDGE program in terms of stakeholder requirements. Prescribers have to review the educational material in order to enroll in the program, though there is no required knowledge assessment. They're required to counsel all patients and to enroll them by the appropriate risk category.

For patients in the risk category of females of reproductive potential, prescribers have to document that safe-use conditions have been met, both prior to the first prescription and upon each monthly prescription.

These safe-use conditions include ordering and reviewing pre-treatment and monthly pregnancy tests. Prescribers also have to access the REMS program either online or by phone each month to document pregnancy test results have been completed, and counseling has been completed, and the safe-use conditions have been met.

Pharmacies also have educational materials to review in order to enroll. They must also provide a patient with a medication guide each

month. In addition, the pharmacies have to obtain authorization to dispense by the REMS program.

This is where the TIRF and the iPLEDGE programs differ. For the iPLEDGE program, this authorization is done through the pharmacy accessing a phone or web-based system that is outside the pharmacy management software.

Pharmacies obtain an authorization number through the REMS system that serves to document that the safe-use conditions I've already described have been met prior to dispensing. And finally, all patients enrolled in iPLEDGE have to review and sign an informed consent.

Those who are female of reproductive potential have to agree to have pre-treatment and monthly pregnancy tests. Patients also have to access the REMS system each month and complete monthly comprehensive testing questions on the program requirements and document that they are complying with their chosen form of contraception.

The next slide includes data on participation for these two programs. Again, this

is from the most recent REMS assessment reviewed by the FDA. For most of our REMS assessments, we ask that the sponsor or sponsor groups provide the number of active stakeholders during the assessment period, which for prescribers, pharmacies, and patients means those who have written, dispensed, or received at least one prescription during the assessment period, which is typically a 12-month period.

The one exception to this -- actually not the only exception. But the exception for the TIRF program is that we currently receive the number of newly enrolled patients. So this number of just shy of 9,000, all the way on the right in the top column, represents those newly enrolled in the last assessment period. We expect that the actual number of active patients may be higher.

Now, you can see, with the exception of the participating outpatient pharmacies, the TIRF program is relatively small. On the other hand, the iPLEDGE program is larger and is in fact the program with the most prescribers, pharmacies, and

patients currently enrolled.

So if you only consider the number of active prescribers of ER/LA opioids, the number of prescribers potentially impacted by a more restrictive REMS for these products would be over 300,000.

Now, if the extended-release long-acting as well as the immediate-release opioid products were under a restrictive REMS, this could impact up to 1.5 million prescribers. That is currently the number registered with the DEA. Assuming all outpatient pharmacies would participate, the number of pharmacies would be approximately 67,000.

Once again, these numbers are for outpatient retail dispensing. An additional system would need to be put into place to accommodate inpatient dispensing if a more restrictive REMS for all of these opioid products were required.

So if you recall, on both the TIRF and the iPLEDGE overview slides, I mentioned that an authorization to dispense is required each time a prescription is dispensed by a pharmacist and that

the mechanism for obtaining this authorization differs between these two programs.

This is a bar graph from IMS data of outpatient retail prescriptions. It shows dispensing of the TIRF products for the last five years. So beginning in 2012, for each of the prescriptions dispensed, which is the number above the bar, an authorization was required by the REMS program. For 2015, a little less than 91,000 prescriptions were authorized by the TIRFs.

I don't have a similar slide for iPLEDGE, but from the most recent REMS assessment we reviewed, there were approximately 1.2 million authorizations granted, so about 91,000 for the TIRFs, 1.2 million for our largest REMS program. Keep these numbers in mind as I move to the next slide.

I promise this is probably the last time you're going to see this slide for this meeting. It is helpful to look at this graph, though, again in the context of how modifications to the current ER/LA opioid REMS that would make the program

similar to either the TIRF or the iPLEDGE program would impact a portion of the healthcare delivery system. A restrictive closed-system REMS for the ER/LA products alone would require over 20 million pre-dispensed authorizations per year looking at 2015. Those would have to be obtained by pharmacies prior to dispensing.

This number skyrockets if you consider a restrictive REMS program that includes the extended-release as well as the immediate-release opioid products to roughly 150 million.

This may introduce significant burden on prescribers and pharmacies and has the potential also to negatively affect patient access. Again, remember that this slide only shows outpatient dispensing. We know that opioids are used in a wide variety of settings. This would require that additional systems be put into place in order to allow opioids to continue to be used in these other settings.

When considering the development of any REMS program, the elements required to ensure safety

must be balanced with the potential program burdens. We attempt to develop programs, keeping in mind which elements are minimally necessary to ensure safety as well as how those requirements will be integrated into the current healthcare delivery system.

So in summary, there are a number of options to modify the extended-release long-acting opioid REMS. The decision to modify this REMS must be balanced with potential burdens on the healthcare delivery system and potential negative impacts on patient access. We look forward to your thoughtful consideration of these issues and input at the discussion this afternoon. Thank you.

Clarifying Questions

DR. WINTERSTEIN: We'll continue with our questions. Next on the list here was Dr. Garcia-Bunuel.

DR. GARCIA-BUNUEL: I actually have one question for Dr. Katzman, actually, just a general question about your activities in New Mexico. What were the reasons that there was not an opiate dose

threshold included in your initial plan? Was that based on other experiences in other states, and has that been reconsidered?

DR. KATZMAN: It has not been reconsidered at this time. I believe there might have been another bill or two dropped not in the last session, but in 2013 or 2014 legislative session in New Mexico, but it didn't get very far, but it has not been seriously reconsidered.

The worry was frankly kind of the chilling effect of such a rural state, in many towns and villages, the chilling effect of primary care providers being worried about prescribing and the thought that it would be better to take a more collaborative educational approach rather than a regulatory approach to physicians, and nurse practitioners, and physician assistants, and rather educate clinicians about better ways to take care of chronic pain, and take the emphasis off opioids, and put the emphasis more on best practices of pain management.

DR. GARCIA-BUNUEL: Thank you.

Then I was going to ask Dr. Auth, just on her presentation just now, is there data? As we've been trying to discern, looking at the REMS over the last day or so, trying to understand impact and obviously trying to decrease the risk of the ER/LA class, the two programs that you just described in these restrictive programs, in your assessments, have we seen hopefully a decrease in the risks or the adverse outcomes associated with those different agents?

DR. AUTH: I think, as I mentioned yesterday, we're still evolving our science of assessing REMS. And for some of these restrictive programs, we are focusing heavily on knowledge as well as processes and that the processes are being implemented and being followed.

So for example, for the iPLEDGE program, we do in our assessment receive the number of pregnancies that were reported. And as you can imagine, that is fraught with difficulties because these are spontaneous reports. So we've received those, and we ask that the sponsors follow up and

conduct root-cause analyses.

So each year, we are looking at the numbers of pregnancies and what occurred. Obviously, we know what occurred for the pregnancy, but just the program broke down and why the patient became pregnant. Did they not understand? Did they not comply? Did the actual system fail and the patient got an authorization when they shouldn't have?

For the iPLEDGE program, we also look at those pre-treatment pregnancy tests and we look at the number of exposures that were prevented through the program. So we do have some of that information.

I really am not prepared to speak so much about the TIRF program. We do collect some surveillance data. It looks like Dr. Hertz is going to comment on that.

DR. HERTZ: What's important to recognize with the TIRF program in particular is that these products have never existed without some type of risk mitigation strategy. With the initial approval of the first of the class, there was a

risk mitigation strategy. It was before the REMS authority was available to us.

Then each product that subsequently was approved either had a risk map or was already in that context, and then when we got the REMS authority. So we don't have a before and after to the same way we might have with some other situations.

DR. WINTERSTEIN: Dr. Higgins?

DR. HIGGINS: This question is actually for Dr. McMahon or Dr. Katzman. I'm particularly interested in Dr. McMahon's slide 7 regarding the participants, and I'm wondering if there has been any subgroup analysis done on the method by which people choose to be educated. It looks like a number of people really wanted the internet-based coursework. And I'm just wondering if you've looked at age or any other demographics to explain some of the differences in preference.

DR. MCMAHON: Thank you. The learning preference is very substantially intergenerationally, and those are changing

dramatically over time. You're seeing a wide up-spring in the use of digital technology for learning that's episodic and micro-bursts, literally in 2- to 3-minute bursts between patient visits to try and engage particularly younger -- early-career clinicians.

However, you also see wide penetration of internet-based learning for modular components of curriculum in blended learning environments, so those who need consolidation of their learning or look for consolidation of their learning over time turn to digital environments because of its flexibility and its availability outside of office hours or locations of work.

So those trends are continuing. Having said that, it's very important to balance the learning that can be achieved online with that achieved by talking to a peer and collaborating with a peer around solving a case. That tends to drive much more higher levels of reflection and absorption of information that's meaningful for the actual learner.

So you are seeing trends towards an expanding array of the use of digital environments for maximizing learning, but the importance of a variety can't be overemphasized.

DR. KATZMAN: This is Joanna. Do you mind if I just comment on that? Our ECHO Pain program is virtual and, again, the New Mexico clinicians can get their CME for the New Mexico course virtually. So our rural clinicians, who can't drive 4 and 5 hours to Albuquerque, or Las Cruces, or Santa Fe, can sign in if they have internet connectivity. And they find that much more easy. They don't have to take time away from seeing their patients.

Then the prior question answered [sic], why did not we impose opiate dosing thresholds, well, states like Washington did that. New Mexico does not have enough pain specialists to impose opiate dosing thresholds. If you go above a certain dose, you need to get a pain specialist and such.

What I might add is that we teach to this all of the time. If you go above 90 morphine

equivalents or 100 morphine equivalents, we teach about the dangers of this. We're always teaching about best practices, about opiate dosing thresholds. But we have many clinicians that would much rather stay in their home or stay in their clinic and take an online course, just as Dr. McMahon said.

DR. WINTERSTEIN: Dr. Kaye, you did the epi homework. And so the death rates in New Mexico were, as you may recall, 256 opioid-related deaths in 2008, and that's per 2.01 million people. You may recall this went up to 265. There was a slight population growth that equates to the exact same incidence rate, essentially. So it's .127 per 1,000 population. So the message is, it's flat. Thank you.

We should have people on call for stuff like that. That's very handy. Dr. Stander?

DR. STANDER: Yes. Thank you. My question is for Dr. Auth. The examples you gave of restrictive practices were for two relatively low-frequency-use medications, the fentanyl and the

isotretinoin, and there were other examples of cardiac arrhythmics and so forth.

So if I understand you correctly, you're extrapolating that process to the ER/LAs and possibly the immediate-release. But that seems impractical, as you've just described. And I was under the assumption, or at least possibility that, if we tied the training to DEA registration, then you really wouldn't have to check, have a pharmacy authorize each individual prescription. You would simply say that, if this is being prescribed by a practitioner who has the DEA license, then you could go ahead.

I'm just trying to clarify that whole process that you're suggesting.

DR. HERTZ: So I would perhaps suggest that's a little more than clarification and perhaps engaging in discussion. I mean, we gave you examples of what we have and what's involved, and it's going to be part of the discussion. I'd like to hear a very robust discussion about the options. We would like to hear that. So could we do that?

DR. STANDER: I'm fine to delay the further discussion, but the implication was, if we're going to have a restrictive REMS, this is the only way we can do it, and it's going to have a million authorizations or something. And I just wanted to clarify.

DR. HERTZ: It's not so much it's an implication. We have authority that's been utilized, and this is what it looks like when it's utilized. It's just the examples that we have.

DR. STANDER: Okay. So we can have more discussion. I appreciate it. Thank you.

DR. WINTERSTEIN: Just to clarify this, it appears that's the authority that's currently being utilized consists of prescriber registration, which is essentially handled by an external entity, which is not the DEA, but perhaps a commercial entity or whatever. And essentially, the only way for a pharmacy to check whether the physician registration has happened is to query this consistently.

DR. STANDER: Right, which is probably

feasible with those kind of medications that aren't prescribed that often, but it raises all kinds of other implications on a much higher volume of prescribing.

DR. WINTERSTEIN: If there were a controlled substance prescription, which we know can only be done by somebody who is DEA licensed, which in turn might be linked to a particular certification, then that request would go away. That's essentially what you're --

DR. STANDER: Yes, exactly, thank you.

DR. AUTH: Right. That's correct. Each of these programs has a REMS system that manages all of these functions and that is a source of providing those yes/no authorizations and captures all of that. So that is correct. And you are correct that most of these programs are very small, and a lot of them are prescribers or specialists. And it is a little bit easier to manage.

DR. WINTERSTEIN: Dr. Choudhry?

DR. CHOUDHRY: So I have three brief questions, one for each of our speakers. So first,

for Dr. Katzman, I'm wondering if we know anything about patient outcomes, not in terms of adverse effects, but in terms of quality of life, pain and suffering, disability, to the extent that there's obviously a trade-off here. And this is the whole debate about opiates in general and we don't want anyone to suffer.

We all believe that reducing opioids won't cause suffering, especially if there's multi-modality therapy. But it'd be nice to know if that's true. So maybe I'll just state the three questions if that's all right so the other speakers can think about them.

For Dr. McMahon, I'm curious about your thoughts about mandated CME or education -- kind of picking up on Professor Gerhard's comment -- and its impact on behavior change. So what do we know? Ultimately, we're trying to change behavior. We heard a little bit about checkboxes, and ticking the box, and other questions like this.

We all can imagine what that looks like, and just if you had comments on the mandate and what

that does in terms of ultimate outcomes from the adult education learner perspective.

For Dr. Auth, my question really is just a clarification of what scope means. So we heard yesterday about the duration of training, one stop, 2 to 3 hours being a barrier to completion. So I'm wondering if in the mandate of changing the scope is changing the method of delivery. I presume it is, but I just wanted to get some clarification.

DR. AUTH: That's correct. That would all be on the table under scope.

DR. CHOUDHRY: Perfect. So that's an easy one. Please, Dr. Katzman and Dr. McMahon?

DR. KATZMAN: In terms of patient outcomes, in terms of the New Mexico study that was published in the American Journal of Public Health, the IRB-approved study looking at the courses, we did not look at patient level, the Mora's level 5 data in terms of patient-level outcome, unfortunately.

We have looked at practice change effects from our ECHO Pain program, our telementoring ECHO Pain program, and looked at the benefits to

clinicians in terms of how it's affected their practice change, so not directly patient-level data. But clinicians that come in the ECHO network routinely have told us in focus groups time and time again that it significantly affects their practice change; that their patients benefit, that they feel as though they are improving their knowledge, their confidence, their skills, and the way they manage their patients.

We have published on that as well. Thank you.

DR. WINTERSTEIN: One announcement for the -- oh, sorry.

DR. MCMAHON: I was just going to follow up Dr. Choudhry's question. Behavior change is obviously very complicated, and mandates have a complicated effect on behavior. If you really want to drive somebody to change their practice behavior in a formative way, you have to engage their heart, and their soul, and their mind and generate durable reflective practice.

Mandates are complicated because, while they

create an audience and our clinician community are rule followers, you often engage them at the lowest possible level. And you have the greatest difficulty through mandates of engaging those who need it the most in many cases.

So most educators feel that mandates can be very counterproductive to actually changing behavior. If you want to change behavior, you need to engage people voluntarily so that they're actually listening, they're open-hearted, open-minded, and there to learn, not there to follow a rule.

So we have to be very thoughtful about the effect of mandates on potentially breeding in fact cynicism and the worst possible outcomes for the behavior change of our community.

While it may drive some numbers, it may not create the behavior change that you're looking for unless you offer the type of robust longitudinal engaging materials that are attractive to learners, that will ultimately engage them in self-reflection and drive actual behavior change.

DR. WINTERSTEIN: One announcement for those who have registered for the open public hearing, there are a few people who haven't checked in at the front desk yet. During the break, please make sure you do so, so that we have you on the list for speaking.

Among those, we still have at the list here, in the interests of time -- are there anybody who really has a clarifying question, not a discussion question? I'd like to finish those and then have the break. I see Ms. Shaw Phillips, and Dr. Raghunathan, and Dr. Floyd, so maybe in that order.

Anybody else? Okay. Just a number, that sounds short.

DR. PARKER: Marjorie Shaw Phillips. This is for Dr. McMahon, and this is related to outcome assessments, evaluating continuing education. And obviously, the long-term outcome evaluation data that we got from the CE registrants nationally was horrible if they only got follow-up for a few hundred people.

I know it's certainly a trend, and I know in pharmacy education, too, in querying attendees at programs and saying how did you change your practice, what did you do different.

Can you give us some feedback on what the latest innovations are in continuing education and what you would recommend for doing that evaluation to ensure that attendees have that change of behavior or have those skills, and what you would suggest doing differently for a really meaningful evaluation of educational programming?

DR. MCMAHON: That's a big issue. The first reflection is that education is not an event; it's a process. And think of education as completing a series of tests and off you go; you're ready to do whatever you need to do. It is a fundamental misunderstanding of how our clinician community prescribes, how they learn, how they practice.

Education has to be embedded in the system of care in which they operate. Education that does that is, for example, our accredited providers who are based locally and disseminated around clinics

and hospitals around the country to develop a curricula that ultimately supports clinicians to do right by their prescribing practices.

Those systems, when correctly constructed -- and about 60 percent of our accredited providers, for example, are integrated into quality systems in their institutions and environments -- they can do much more sophisticated outcomes-based assessments. They can look at their own electronic medical record systems. They can do audits of practice behavior locally and tie those outcomes to local behaviors.

When you do that, you prove time and time again that education is very effective. We know that people can learn. That question has been answered for millennia. But we know educational structures, when put in place correctly, not only drive learning, but meaningfully affect behavior. And it's very hard to extract the value of education and those outcome delivery systems from the outcomes that you're seeing in terms of patient outcomes because there are so many variables that

affect that.

The last thing I will tell you is that the education community in the post-graduate space is progressively augmenting their outcomes assessment quality to the highest levels. So for example, right now, though 60 percent of our activities are designed to change performance, only about 40 percent are measuring some of those performance outcomes nationally across every dimension of curricula.

Although about 30 percent are designed to create patient-outcome change, only about 11 percent are actually measuring that patient outcome change because of the real challenge of connecting patient outcomes to education.

But that number is rising fast and there are plenty of efforts and structures developing to support additional connection between the quality of the education and the quality of outcomes and trying to understand how to maximize that impact.

DR. WINTERSTEIN: Dr. Raghunathan?

DR. RAGHUNATHAN: I have this question for

Dr. Katzman. In your pre-post study, do you have data on prescribing behavior of before and after of your participants? So can you see whether or not there has been a shift in the dose recalibration?

Are they changing from opioid to non-opioid and also whether they are going from a high dose to a low dose? And my second question is that your online system, is that marginalized or is it one setting for 5 hours?

DR. KATZMAN: The first question is, we do not have particular data on those that took the University of New Mexico course, what was their prescribing behavior exactly before and after, are they prescribing more or less opiates. We just have the Board of Pharmacy dispensing data in aggregate, unfortunately, to show because, for instance, many of the University of New Mexico Pain faculty taught in many of the other courses around the state. So we were teaching all over the state at the time and still are. So it's been a big kind of public health endeavor.

The second is that the online, or the

video-conferencing platform, is one hour at a time. So for the Project ECHO Pain, it's 1 hour or 2 hours at a time. The ECHO Pain is offered 12:00 to 2:00 in New Mexico, for instance, on a Thursday afternoon. So they can get 2 hours of CME, no-cost CME for free. Or they can claim 1 hour if they attend for 1 hour.

DR. WINTERSTEIN: Dr. Floyd?

DR. FLOYD: So this is a clarifying question for Dr. Auth about restrictive and non-restrictive REMS. So you gave a couple examples of restrictive REMS, which seem to have been effective in preventing some adverse effects or reducing prescribing.

Do you have any examples from all the other REMS of voluntary REMS that were actually effective in preventing adverse effects or reducing prescriptions? Then the second part is, do you have examples of restrictive that were just education that were effective, so in either of those areas?

DR. AUTH: I'm not quite sure I'm following

the question. I think you're asking whether we have any data from the non-restrictive ETASU where training is being made available. We do, and we're particularly looking at uptake of the training. That's one of the metrics that we use.

So just comparing this program with some of those other programs, if you calculate, if you ignore our performance metrics and just look at 320,000, there has been 66,000 educated. That's about 21 percent. These other programs, the highest we've gotten is 22 percent. And again, it's a much smaller prescriber population.

I'm not quite sure I follow the second part of your question.

DR. FLOYD: That's okay. Quick follow-up --

DR. AUTH: You were asking about outcomes. Right?

DR. FLOYD: Yes. So I'm not interested in uptake or knowledge assessment.

DR. AUTH: Right. Sorry about that.

DR. FLOYD: I mean, actual prescribing

levels and adverse effects, do you have any evidence that other REMS for other products have been effective that were voluntary?

DR. AUTH: Again, we're using the same metrics. We are looking primarily at knowledge. We do ask for adverse event reports and look at those in some of the programs. But again, that data is often confounded by the spontaneous nature of the reports.

I think probably where we get some really good data is for the very restrictive programs, where patients are required to enroll in a registry. So we can actually capture what's happening with those.

One of those programs is a Tysabri program, where every 6 months, there are 4 filled about events and continued use of additional drugs that may impact the risk for PML. So for programs like that where we have a very, very tight system, we're able to get that information.

DR. WINTERSTEIN: But that wouldn't be a voluntary education program.

DR. AUTH: Right.

DR. WINTERSTEIN: Dr. Morrato?

DR. MORRATO: My question is also for Dr. Auth on the slide, I think it is 16, where you talked about the stakeholders impacted. So this is talking about the current isotretinoin program, which is the result of many years of going from voluntary efforts to a previous stage of smart labeling, which is sort of in between where it is.

So to help us understand, really, the impact on access, and burden, and chilling effect of usage, do you have what the prescribing numbers or the active patients or prescribers were when it was at the voluntary level?

My sense is, it was much more widely used by pediatricians, for example, and primary care. Now it's largely by specialist. So that would give us a sense of --

DR. AUTH: We had a public meeting about the iPLEDGE program in 2011. I'm not sure if you attended that. And I can give you some of that information, but I think, just very basically, what

we did see was, when the iPLEDGE initially was implemented, there was a dip in prescribing.

Then over the course of -- maybe Claudia can help me out on this -- a period of time, the prescribing levels were, again, about as high as they were prior to the implementation. So there were a lot of growing pains in just getting that program implemented. But I don't think we've seen a whole lot of difference in the actual numbers of those who are prescribing.

DR. MORRATO: So that's good to know. Thank you.

DR. MANZO: I think there probably were prescribers that procedure it at very low levels that decided not to prescribe it. But again, with regard to the number of prescriptions, they almost went up to what they were prior to the restrictions.

DR. WINTERSTEIN: We will break now, and we'll resume the meeting at 10:20.

(Whereupon, at 10:04 a.m., a recess was taken.)

Open Public Hearing

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with today's industry group, its products, and if known, its direct competitors. For example, this financial information may include industry's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson, and thank you for your cooperation.

Will speaker number 1 step up to the podium, introduce yourself? Please state your name and any organization you are presenting for the record.

DR. RUPP: Good morning. Thank you for the opportunity to speak today. My name is Tracy Rupp.

I was previously a clinical pharmacist at Duke University Medical Center and am now the director of public health policy initiatives at the National Center for Health Research.

Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from the drug or medical device industry, and I have no conflicts of interest.

Our center strongly supports research and programs to improve the safety and appropriate use of opioids. In 2012, healthcare providers prescribed enough opioid prescriptions for every adult in the United States to have a bottle of pills.

In 2014, more Americans died of opioid overdose than in any other year on record. Amidst a crisis of mounting deaths from opioid overdose, we must reexamine whether REMS for opioids are actually reducing the risks associated with their use.

REMS were developed to enable the FDA to approve drugs with serious risks like opioids by providing a mechanism to mitigate those risks. But as we've heard at this meeting, data from the fourth REMS assessment show that we still don't know whether opioid REMS are effective at reducing either inappropriate prescribing or opiate overdose.

Since only about 20 percent of long-acting opioid prescribers have completed the voluntary REMS training and 41 percent of prescribers are not even aware such training is available, it's not realistic to expect the program to have a significant impact.

Of those who have completed the training, the prescriber survey indicates gaps in knowledge about initiation, modification, and discontinuation of opioid therapy. Scale in these areas is critical to safe and appropriate opioid prescribing.

It's very disappointing that so few prescribers have been trained, and after repeated

REMS assessments, we still don't know if opioid REMS are effective even when prescribers are trained. For those reasons, we support a mandatory prescriber training program that is linked to a prescriber's DEA registration and rigorously tested for its ability to mitigate the risks of opioid use.

The less-than-rigorous approach to studying the effect of REMS should not be acceptable to any of us, given the scope of the opioid overdose problem. FDA reviewers pointed out many limitations in the applicant's patient and provider surveys.

For example, the prescriber's study sample was not randomized or self-controlled with pre- and post-test comparisons. Self-reported behavior was not validated out of prescribers or patients, and we don't know how the survey population compares to the targeted population. It's also not possible to know whether the REMS training itself is responsible for the observed changes in opioid use since the changes began prior to the implementation

of REMS.

We strongly urge the FDA to require a more rigorous evaluation of the REMS training where actual behavior rather than self-assessed behavior or knowledge is studied. The study should be a well-controlled longitudinal study with the behavior of prescribers who have taken the training compared to behavior of those who haven't received training.

The study should also be designed to tell us whether the opioids that are prescribed are being prescribed appropriately at the patient level. We also support expansion of REMS to include immediate-release forms of opioids. Most patients who start taking opioids are initially prescribed immediate-release products.

There is some evidence of an increase in the use of some immediate-release opioids under some circumstances. For example, drug patterns and prescribing data show that, despite a decrease in overall immediate-release opioid use, the use of immediate-release oxycodone actually increased.

Similarly, self-reported non-medical use of short- and long-acting opioids increased among college students in the years since REMS have been required. Effective REMS could potentially help reduce the inappropriate use of immediate-release opioids.

Lastly, we urge the FDA to perform its own assessment of the effectiveness of opioid REMS on an ongoing basis and make the data publicly available on FDA's website. Currently, REMS assessments are completed by the application holder and reviewed by the FDA. This process cannot ensure that assessments are unbiased, accurate, or rigorous.

Given the enormous cost of opioid abuse in terms of human life, quality of life, family tragedies, and lost productivity, we must be certain that REMS assessments are providing unbiased information about the effectiveness of the program. Making the data publicly available would allow stakeholders to perform their own assessment of the program's effectiveness.

In conclusion, if we want to reduce deaths and addiction due to opioids in the United States, we must demand more from everyone involved. Prescribers must be better informed, REMS assessments must be more rigorous, and the data must be transparent.

We must all work together to find a more effective solution to the challenge of opioid abuse. Thank you for the opportunity to comment today and for consideration of our views.

DR. WINTERSTEIN: Thank you. Would speaker number 2 step up to the podium, introduce yourself? Please state your name and any organization you are representing for the record.

MS. ZIMMER: Good morning. I'm Phyllis Zimmer, president of the Nurse Practitioner Healthcare Foundation, a faculty member at the University of Washington School of Nursing and a board-certified nurse practitioner. The Nurse Practitioner Healthcare Foundation is a member of CO*RE. I have no conflicts of interest to report.

This testimony was prepared with

consultation from Dr. Paul Arnstein and Dr. Barbara St. Marie, national experts in the area of pain management. Many patients with serious conditions experience chronic pain and deserve safe and effective treatment to achieve a reasonable quality of life. Some of these patients require the use of opioids to effectively manage their pain.

At the opposite end of the spectrum, however, is the drug-seeking individual, who may abuse, misuse, or divert opioid meds. In the middle are patients who begin with legitimate opioid therapy, but who may become addicted to their medication, or may become drug seeking.

The clinician has to make a series of complex clinical decisions each step of the way, balancing safety, efficacy, and harm reduction. Healthcare professionals are not adequately prepared to address these patient care conundrums.

The term "medical signature" is used to describe the way you've always done it, meaning that you have adopted usual ways of practicing, or in this case, prescribing. Most medical signature

is congruent with training as clinicians, and most of the time, it's a good thing, where the usual care that you provide your patient is evidence based, safe, and meets guidelines for best practice. But medical signature gets you into trouble when it's based upon a practice that is outdated or incorrectly applied to the case being considered. Then medical signature leads to incorrect care or medical error.

To prevent such errors, we need to replace outmoded or inaccurate medical signatures with new, more appropriate ones that will lead to better clinical practice.

Education is absolutely the key to converting to a new more appropriate medical signature, especially with a clinical issue as dangerous and complex as opioid therapy. Significant, varied, consistent, and ongoing interprofessional, educational efforts are required.

Through our educational programs, the Nurse Practitioner Healthcare Foundation has educated

thousands of NPs on just these clinical issues. The result has been relearned medical signatures and improved practice. Prescribing behavior, practice protocol, and systems of care delivery have been upgraded and monitoring has been put into place. The outcome has been improved quality and safety of care for patients on therapy.

With that brief background, we would like to offer the following comment and recommendations.

The ER/LA opioid REMS have been a positive step for changing practice. The program has propelled healthcare professionals to examine their practices and adopt new practice patterns. The REMS have not been an undue burden and have not limited access for those who require therapy. Continuing education is an effective method for achieving learner engagement and practice change.

When provided by peer experts, education is one of the most effective approaches to breaking poor medical signature and adopting safe and effective practice patterns. Although we're well on the way to achieving a new, safer, and more

effective medical signature in opioid management, all of our efforts must continue.

However, we would offer the following changes to enhance the effectiveness of the program. One, the immediate-release, short-acting opioids should be included in a blueprint that addresses both the ER/LA opioids and IR/SA opioids. A particular education point would be the role of opioids as part of a multi-modal therapeutic approach.

Two, chronic pain management is most often an interdisciplinary team effort, not the sole responsibility of one prescriber. Therefore, education should include all appropriate members of the team.

Three, the revised FDA blueprint should be incorporated into the pharmacologic curriculum of health professional educational programs across the health disciplines. Resources such as the core curriculum could be used to achieve rapid implementation of that recommendation. In addition, it may be helpful to work with program-

accrediting agencies to align curriculum with national guidelines.

Currently, a number of REMS-compliant education programs are done outside of the RCP-funded mechanism and are not reported to the FDA. The tracking and reporting system should be modified to include these learners. And it's important to streamline the process as the current system is quite burdensome.

Thank you for the opportunity to present testimony.

DR. WINTERSTEIN: Thank you. Will speaker number 3 please come to the podium? Please introduce yourself, state your name, and the organization you may be affiliated with.

MR. PHILIPS: My name is Julian Philips, and I am an ambassador with the U.S. Pain Association, a foundation. First off, whatever I say today, please don't get away from the fact that I do applaud the FDA for trying to create a good training basis for our practitioners, nor do I want you to think that I am in any way not empathetic or

sympathetic to anybody that may pass away from the use of opiates or any other medication or drug. That's far from the truth.

However, with all of that said, just let me give you a brief outline of who I am and why I'm here. I started off, as you can probably tell, in the United Kingdom. My pain started 34 years ago with a dislocation of that finger that is no longer there.

From that dislocation, ultimately, they decided that the best thing to do to get away from the pain was to remove the finger. Well, that didn't work because it just spread.

I went through all sorts of modalities, whether it was acupuncture, regular medication. I went through everything they possibly could throw at it, and all that happened was it consistently got worse. I came to the United States in the hopes that maybe I could have a better quality of life by living in Florida. Well, that really didn't work out too well because, again, the pain continued.

I ultimately had a spinal column stimulator implanted. That's helped a little bit. I came up to Pennsylvania and, due to the work that I was doing, I became more and more pained, and ultimately more and more medication was tried and started to help give me a little bit better quality of life to the point now that I am on opiates.

Do I like it? No. I suffer with horrendous OIC, opiate-induced constipation, not a topic that anybody likes to talk about. But let me tell you, it's not fun. Would I want to get off opiates? Absolutely. But the point is -- and this is what everybody forgets -- we are human beings and we feel.

I feel pain every day. I can't get away from it. It doesn't matter whether you make my doctor do more education or less education. He can't get away from the pain. All he can do is help me go through and have a slightly better quality of life.

It wasn't long ago, approximately five years, that for the first time in my life, I

seriously considered suicide. I very seriously considered it. There are people that have gone through with suicide because they can't find pain management doctors who will prescribe opiates. In fact, in Tennessee, two pharmacists just recently have refused to give out opiates. I don't mean give it out, but you know what I'm saying? They won't give opiates out now because there's too many restrictions. And yes, you need to continue education, but you've got to make sure that it doesn't become overburdening.

When I was in business, especially in England, right at the beginning of the EEC, we had business. We could do certain things. And then, suddenly, we couldn't do X, Y, or Z without this form or that form. And then there was another restriction that came in, and then another restriction. And eventually, it came to the point where business was no longer fun to do because we were becoming overburdened with things that we had to do by law.

You can see the same thing happening here.

There's too many factors occurring. Nobody should die from opiate overdose. I don't even understand how anybody can. I have never had a high from opiates, never. I have one doctor to prescribe. I have one pharmacy that gives them out. My wife keeps them in a locked container. And she puts them in little doohickeys, whatever you want to call them, so that this time, I know I take that, and at that time, I take that, and et cetera, et cetera, et cetera. So I never have the opportunity of overdosing. I just don't see how it's going to happen.

Remember something else I found out yesterday. Yes, again, it's important to stop opiate overdose, but the third reason of death in this country, one, heart; two cancer; three, medical errors in hospitals. We need to remember priorities.

DR. WINTERSTEIN: Sir, please end in a second, just as a --

MR. PHILIPS: I thought I could have extra time because I'm sure there won't be somebody here

that's talking.

Thank you. Thank you very much for listening to me.

DR. WINTERSTEIN: Thank you.

For all the public speakers, you are given five minutes, so you will see a light start blinking in yellow when the last minute is starting.

Will speaker number 4 come the podium and please introduce yourself? Please state your name and the organization you are representing.

MR. PITTS: Thank you. My name is Peter Pitts. I'm the president of the Center for Medicine in the Public Interest, and I have received no stipend or compensation to be here today.

To paraphrase Peter Drucker, the information revolution will shift from the generation of data to figuring out the meaning and purpose of the data with the patient's perspective in mind.

Nowhere is this more pertinent than in the discussion of the future of opioid pain medicine,

and the role of the FDA, and advancing both the science and regulatory approaches to appropriate pain care management. But cutting the Gordian knot of what appropriate means demands more than current REMS programs. It requires working with the providers of continuing medical education to develop better curriculum. It means ever-better-validated risk evaluation and mitigation strategies with more thoughtful purpose.

It means enhanced and validated reporting tools for post-marketing surveillance. It means using real-world data to provide real-world advice. And it means using the tools of the 21st century, such as patient and physician apps.

The FDA can play an important role in working to develop and share with broad constituencies validated tools for physicians to use in determining which patients may be more prone to slide into abuse so they can choose their therapeutic recommendations more precisely.

One improvement will be to improve the accessibility of the ER/LA opioid and analgesics

REMS website so that interested healthcare providers can more easily access accredited REMS-compliant material. We must also work to continue and expand REMS to include the extended healthcare team, as you've heard already this morning.

Education of team members beyond analgesic prescribers is critical for implementation of REMS learning. We should revise the FDA blueprint for prescriber education to reflect stakeholder input and feedback.

We should link Schedule II and Schedule III narcotics DEA registration and re-registration to either completion of prescription opioid education or other acknowledgements such as board certification in pain medicine. We should include IR opioids in the REMS modification discussion. It's where the overwhelming volume is.

With the data collected from REMS programs, a logical next step is to utilize that real-world data to amend product-specific labeling to indicate lessons learned outside the verified world of the

randomized clinical trial environment to assist physicians in using the right product for the right patient.

Real-world evidence doesn't just mean recognizing new risks, but also communicating new benefits learned through patient outcomes, and such evidence is both available and exciting.

Beyond the REMS programs discussed during the course of this meeting, the FDA has required all sponsors of brand-name products with approved abuse-deterrent labeling to conduct long-term epidemiological studies to assess their effectiveness in reducing abuse in practice.

Then there's the thorny question of FDA labeling. Product labeling is the basis for articulating the value proposition of a product. As you are aware, data definition and generation are very much still a work in progress, as is their relationship to clinical relevance.

No absolute magnitude of effect can be set for establishing product characteristics. And the FDA continues to talk about the ambiguous totality

of evidence standard, which really means using their best regulatory judgment, and that's appropriate.

One crucial question that deserves more conversation is the nature of the evidence used to decide whether or not a given product works to reduce abuse in the real world. Given the data challenges, it may be almost impossible to ever demonstrate a causal link between a new formulation and an impact on patient abuse.

But is that because the product didn't have an effect or current measurement methodologies and data systems are inadequate to detect it? The path forward is unclear. Is real-world data reliable and robust enough? Should the FDA define and then assign various statistical weights to comparisons and population studies?

At the end of the day, the agency can't only look to REMS for risk mitigation, but must also seek out data that supports more aggressive labeling language. Obviously, more work needs to be done in order to refine optimal data sources,

study design, statistical methods, and epidemiologic outcomes of interest to developers, physicians, patients, and regulators.

No one group can do it by themselves. We need a more aggressive, creative, and collegial approach to the pain management ecosystem. Thank you.

DR. WINTERSTEIN: Thank you. Will speaker number 5 step up to the podium, introduce yourself? Please state your name and any organization you are representing for the record.

MS. LOWE: Good morning. My name is Maria Lowe, and I'm representing Patients Like Me. I currently serve as a pharmacist on the health data and clinical informatics team at Patients Like Me, and I have no financial conflicts to disclose.

Founded in 2004, Patients Like Me is the largest online patient-powered research network with over 430,000 registered members reporting data covering more than 2500 different conditions. Patients track their health, connect with others like themselves, and learn from patterns in their

own data or from data shared by others in the community.

Together, with our patients, we have led the advancement of patient-generated health data over the last decade. By using both quantitative and qualitative data collection methodologies, we proactively and transparently engage our patient members as true partners.

Patients share their data and contribute to innovation across the health ecosystem from clinical research and regulatory science all the way through care delivery. Our research portfolio includes over 70 publications of internally- and externally-initiated projects to help answer questions that matter to patients.

At our core, we try to help patients answer a fundamental yet complex question. Given my status, what is the best outcome that I can hope to achieve and how do I get there?

As of March 1st of this year, 24,646 members of our community had reported taking an opioid medication at some point, with nearly 3,000

reporting the use of an ER/LA product. No doubt, our patients want to ensure the safe and effective use of opioids while minimizing barriers to accessing effective pain management. Yet, we suspect many of these patients are not even aware that the products they are using are subject to this REMS program.

Increasing transparency for patients provides an opportunity to engage them in sharing accountability for achieving the goals of this REMS and for better understanding if they are deriving benefit from these treatments.

As a result, Patients Like Me is proposing two specific recommendations for the committee's consideration, framed in the context of empowering patients as partners to help mitigate risks and prevent adverse outcomes when using these agents and to proactively participate in assessing and measuring the effectiveness of this REMS.

Our first recommendation is the development of a blueprint for patient education. While the results of the patient knowledge survey offered

encouraging findings for key domain questions, we found the questions posed to survey respondents offered more detailed examples of potential adverse events and used more patient-friendly terms than the information provided in either the patient counseling document or medication guides that are currently available for use in clinical practice.

While these individual documents could be improved, we instead recommend that the FDA develop, in partnership with patients, what we are calling a blueprint for patient education. Such a resource could provide patients with the information needed to build their knowledge and understanding of these products.

A blueprint for patient education could serve as a companion to the available blueprint for provider education, with both documents aiming to facilitate the education of a key stakeholder in the prescribing and use of these agents.

Pairing patient-focused educational materials with provider education programs supports shared accountability for treatment decisions and

outcomes and encourages patient empowerment by providing access to relevant educational information and data about opioid use.

The goal is to ensure that patients are equipped with sufficient information to self-identify their real or potential risks and participate as true partners in their treatment planning.

Our second recommendation is to create a patient-reported ER/LA REMS evaluation tool. We feel it is important to provide patients access to an automated tool for evaluating their experience with ER/LA medications and to the associated REMS requirements. Through the use of a patient-facing data collection platform such as Patients Like Me, patients can monitor and track their experience with these products, including their perceived effectiveness along with the occurrence and severity of side effects.

Such a resource should not only allow patients to share insights, but share data back with them to allow patients to learn from others

regarding their experience with pain and pain management intervention, further empowering them to feel like partners in their healthcare decision making.

We believe these two recommendations represent innovative methodologies that can support the goals of patients, providers, and the FDA. Thank you for your attention.

DR. WINTERSTEIN: Thank you. Would speaker number 6 step up to the podium, introduce yourself? Please state your name and the organization you are representing for the record.

MS. KULKARNI: Good morning. I'm Shruti Kulkarni, and I'm a policy advisor to the not-for-profit Center for Lawful Access and Abuse Deterrence, CLAAD. Our organization works to reduce prescription drug fraud, diversion, misuse, and abuse, while advancing consumer access to high-quality healthcare. CLAAD's funders include treatment centers, laboratories, and pharmaceutical companies and are disclosed on our website at CLAAD.org.

Thank you for the opportunity to offer comments regarding risk evaluation and mitigation strategy for extended-release and long-acting opioid analgesic medications. Today, we're discussing REMS for ER/LA opioid pain relievers, but CLAAD encourages the FDA to apply REMS safety measures to reduce misuse and abuse to immediate-release opioids as well as controlled medications and other drug classes.

We base this recommendation on the following fact, among others. Seventeen percent of college students abuse prescription ADHD medications. Benzodiazepines are present in 50 percent of drug-related overdose deaths in some states. Controlled sleep medication is the most common date-rape drug, and now, there's even a so-called Ambien defense to crimes, including murder.

Like FDA, we support mandatory prescriber training on responsible prescribing practices. Our analysis has concluded that mandatory prescriber education can be structured under current FDA REMS authority. Specifically, elements to assure safe

use may include specific training, experience, or special certification for prescribers.

Currently, before dispensing a prescription medication, pharmacies utilize switch systems that transmit transaction details to a third-party payer and wait for approval, a process that generally takes less than a second.

The RPC could work with pharmacy industry to develop a database for integration with existing pharmacy switch systems to verify prescriber certification. This plan provides for mandatory prescriber education without changing federal law, involving the Drug Enforcement Administration, overburdening the healthcare delivery system, or hindering consumer access to medications.

Like the RPC, we recognize the value of educating the extended healthcare team, including healthcare providers who are not prescribers of opioids. The extended healthcare team plays a vital role in care coordination and can prevent inappropriate prescribing, medical mistakes, and other adverse events. The RPC has earned our

appreciation for educating so many members of the extended healthcare team.

Finally, CLAAD reiterates the RPC's recommendation that federal agencies like FDA and NIDA work together to develop consistent professional education curricula. Newly-integrated provider education courses should include greater detail on best practices for prescribing controlled prescription medication, including verifying through definitive urine drug testing that patients are taking prescribed medications and not illicit substances or medications not prescribed to them, and referring patients with inappropriate substance use to a higher level of care, which may include addiction treatment.

CLAAD is available to FDA and RPC to provide more information on our prescriber certification analysis and the other recommendations we have shared with you today. Thank you.

DR. WINTERSTEIN: Thank you. Would speaker number 7 please step up to the podium, introduce yourself? Please state your name and any

organization you are representing for the record.

MS. FOSTER: Good morning. My name is Wendy Foster. I'm the senior state advocate for U.S. Pain Foundation. Neither U.S. Pain Foundation nor myself receive any compensation or have any conflicts.

U.S. Pain is a national organization founded by people with pain for people with pain. Our mission is to support, empower, educate, and advocate for the chronic pain community. U.S. Pain is the largest pain organization in the country with more than 75,000 members nationwide. Today, though, I come before you as a person living with chronic pain.

I have an undiagnosed neuromuscular disease for nearly 24 years, which causes bilateral restrictive lung disease secondary to a proximal myopathy. I have asthma, severe migraines, spinal stenosis, arthritis in my hands, effects from a stroke, and Parkinson's disease.

The pain in my spine severely limits the time spent standing and sitting, and I am unable to

walk very far without sitting. The Parkinson's tremors in my hands and legs causes increasing pain daily, pain that I can't escape from.

In the past, I have used opioids, and it has allowed me to go camping with my family, attend concerts and plays that my children were in, and attend family functions. I love to read and crochet, and the medication would allow me to sit and enjoy what I was doing. It would also allow me the time to work with my service dog and take him for brief walks.

I'm not alone on this pain journey. Thousands of our members live with severe disabling pain. Unfortunately, finding the right combination of medication, physical therapy, complimentary therapy is trial and error for each pain warrior to find what works best for them to keep their daily pain at a manageable level.

The Institute of Medicine has reported that 100 million Americans live with pain, and at least 10 percent of those, or 10 million Americans, have pain so severe that they are disabled by it.

Opioid analgesics don't help everyone who lives with chronic pain, but they do help many thousands of Americans to function and have some quality of life.

For these people, their medication is often a lifeline that can make the difference between a life worth living or an existence too painful to endure. In my case, opioids can help somewhat with my spine and hand, but not with my migraines or Parkinson's.

The question at hand is to consider what changes should be made to the extended-release, long-acting opioid analgesic REMS program. The central component of the program is the medical education that has been created for providers and it is imperative that prescribers are trained on understanding the appropriate use of medication they select for their patients.

I believe the FDA should be commended for the efforts that have been made so far to create high-quality training materials for practitioners. However, I also feel that it is critical that any

efforts to expand and enhance the REMS training programs for healthcare providers do so in accordance with the professional education and training objectives and strategy called for in the recently released National Pain Strategy.

National Pain Strategy takes a more comprehensive approach to pain assessment and management from acute stage to chronic and across the lifespan. It also emphasizes a biopsychosocial approach to pain care, where medication is one component of a multi-modal integrated model of care.

While a good deal is being spent on the development and delivery of the REMS training, the future training dollars might be more effectively allocated using the training recommendations set forth in the National Pain Strategy.

I know that training has been encouraged but not mandatory. But I would be concerned that, if you create mandatory requirements and if you expand REMS to include immediate-release opioids, that they may become hurdles that our practitioners will

choose not to deal with.

I would caution you to be sure you give appropriate weight and consideration to the critical importance of access to these medications for the many in severe pain who depend on them, like me and thousands of our members. I'd be concerned that if it becomes too much of a burden for providers to take the required training, the patients will suffer. This can lead to dangerous self-medicating chronic-pain sufferers.

The level of pain that I and those like me face day in and day out is something that those who are fortunate not to have chronic pain simply cannot understand, a level of pain that can and does drive individuals to take their own lives. When patients are stable on and secure with their chronic pain regimens, any upset in the routine can have dire consequences. Thank you.

DR. WINTERSTEIN: Thank you. Will speaker number 8 please step up to the podium, introduce yourself? Please state your name and any organization you are representing.

DR. WOLFE: Thank you. I'm Sid Wolfe, Public Citizens Health Research Group. I have no conflicts of interest.

The CDC announced that, in 2014, more than 14,000 people in the U.S. died from overdoses involving prescription opioids. The data on this in the next chart comes from the U.N. Associate International Narcotics Control Board, and they point out in a report that came out last year that U.S. leads the world's 168 countries in the consumption of defined daily doses of all Schedule II opioids per million people per day -- that's all of the Schedule II combined -- 50,142 such doses per million population per day, more than one daily dose for every 20 people in the U.S.

The next slide looks at other countries, so we start out with the 50,000 in the U.S. And if you extrapolate it to the whole population instead of per million, you get 15.7 million for the entire population, daily doses per day. Most of these people in the whole country are not using opioids,

so on an average day, tens of millions of people are using a daily dose of opioids.

Canada is a little bit behind, about 60 percent of the United States, and Germany a little behind that. But of the 168 countries, 165 of them have less than 25,000, less than half of these per day, or less than 1 in 40 people. And as you can see on the bottom, 129 of these 168 countries have less than 2500, as opposed to 50,000, defined daily doses per day, in which less than 1 out of 400 people rather than 1 out of 20 are getting the drug.

These are other data from a paper published a few months ago by Berterame based again on the U.N. International Narcotics Control Board. And they're looking at the increase from early years, 2001 to 2003, all the way up to 2011 to 2013.

Worldwide, there was an increase of 4.3 billion per year daily doses. And of that, 2.74 billion, or 63 percent, was in the United States. Now, there is the interim increase in that 10-year period when opioid prescribing in the U.S.

was larger than the entire increase in the rest of the world combined. And as you can see from these figures, the U.S. has roughly two-thirds of all the opioid prescriptions in the world with far less than 5 percent of the world's population.

This is from the same paper, and if you'd just look, the X-axis is age-standardized rates of cancer. We all agree that severe pain of cancer is clearly the most important and probably the largest use for chronic opioids.

What you can see on the right, or at the 300 age-standardized rates, is that the U.S. is way up on top, off the charts, as it was in the previous slide, and that many other countries, including ones in Europe and other places, for the same amount of cancer, use far less opioids.

The conclusions of the authors were that much of this increased usage has occurred in high-income countries, probably due to long-term prescribing for non-cancer pain, a difficult concept, but one which I think involves a lot of the overuse and inappropriate use of opioids.

I was a member of the Drug Safety and Risk Management Advisory Committee that met almost six years ago to look at pretty much the same issue. This was the drug industry collection of companies that came up with a REMS program, and 25 of the 35 of us voting on that day concluded that the individual components were not adequate to address misuse and abuse of IR opioids.

It stressed the need for appropriate adjusted legislation, including the DEA requirement for condition of getting a license or renewing it, to have training and ability to pass a test.

I'll skip over these slides. The conclusions are, then, that, obviously, key decision-makers -- dentists are obviously included and others who have narcotics licenses -- are doctors. And I would imagine that most doctors -- I don't know what fraction -- are doing very appropriate kind of prescribing, but too many are a complicit cause of this.

The concluding sentence is, what more needs to be done? Mandatory training and testing to get

a narcotics license with as little opioid industry involvement as possible. Legislation is needed. Thank you.

DR. WINTERSTEIN: Thank you. Will speaker number 9 step up to the podium, introduce yourself? Please state your name and any organization you are representing for the record.

DR. HORN: Yes, good morning. My name is Matthew Horn. I am a physician with many years managing pain in clinical practice. For the last 10 years, I've been focused on developing continuing medical education, including many pain management activities.

I am currently employed as a senior medical director at Rockpointe Corporation, a medical education company, and we are currently working with several partners to implement an opioid REMS educational series supported by a grant from the RPC.

For the last six years, I've also served on the Board of Directors of the National Association of Medical Education Companies, where I've had

discussions with others developing opioid REMS education. So my opinions have been shaped by input received from many colleagues involved in pain management and the development of education on pain management as well as patients in pain. I would also like to mention that I have received no compensation to cover my time and travel to speak here today.

First, I would state my general agreement with the FDA that pain management education is both necessary and effective in improving pain management and reducing the risks of opioid abuse and addiction. Preliminary outcomes from our ongoing series revealed that 99 percent of participants rated the education as valuable in terms of improving their practice, and over 95 percent of participants stated that they were better able to meet each individual goal of the educational blueprint as a result of participation.

Yet, despite the success of such programs, there are several areas where the REMS program could be improved. For one, the program is

considerably behind stated goals for educating prescribing clinicians. One reason for this is that there simply aren't enough opportunities with the RPC having difficulty keeping up with demand.

My company alone applied for seven different grants over the course of four years before receiving a grant for our current series. Another provider that we work with created an activity based on the blueprint that resulted in over 32,000 completions by class 2 and 3 DEA-licensed prescribers, and over 10,000 self-reporting ER/LA prescribers. But those completions will not be counted towards the FDA's goals because the education was not funded by the RPC.

There are a great number of activities that are not being counted towards the FDA's goals. A wider acceptance of education that covers the material should be considered. A single REMS program covering all opioids should also be considered.

The implementation of a program that only applies to extended-release and long-acting opioids

is likely leading to more use of immediate opioids over long-acting forms. And this is not necessarily in the best interests of patients nor efforts to curb opioid abuse and addiction. A single REMS program that encompasses all opioids would prevent any other unintended consequences.

The program being voluntary for physicians also plays a part in the low participation rates thus far. Clinicians are very familiar with continuing education credits being required for state licensure and hospital privileges. I recommend that the DEA-issued license required for prescribing controlled substances be linked to a certain number of hours per year or relicensing period.

This would be seen more as a sensible approach to safe prescribing rather than a potential regulatory burden or punitive measure. This approach would also ensure that all opioid prescribers receive educational updates rather than a subset receiving a single certificate for completing a single activity.

Requiring all elements of the blueprint on each activity results in far too much information to be learned at once, lessening the skills gained. A completion-of-hours approach would allow for a broader range of pain education to count towards the goals while also allowing for more in-depth coverage of education that permit learners to increase abilities according to their specific needs.

This approach would also be better at overcoming the lack of adequate education that clinicians receive when initially trained, especially those in primary care where most pain is managed and most opioid prescriptions are written.

Finally, I would like to address the fact that continuing education alone is unlikely to be enough to fully impact our pain management and opioid abuse problems. Several system changes are needed, including more comprehensive pain and pain management education in medical, nursing, and pharmacy schools; increased government and private insurance coverage of other treatment modalities,

including physical therapy, acupuncture, chiropractic, and other complementary methods; and a less stigmatic and punitive approach towards pain suffers and prescribing clinicians than is currently seen in other government agencies' approaches towards managing these issues.

In summary, I would like to recommend that the panel consider a single REMS program for all forms of opioids that includes continuing education as a critical component, but that ties this ongoing education to DEA licensure and allows for a wider range of educational activities that cover individual elements of the blueprint without the need to cover all of it at once.

The FDA committee should also lead the call for other government agencies to work together to implement some of these other solution-oriented recommendations that you will hear from our speakers today. Thank you for your time.

DR. WINTERSTEIN: Thank you. Would public speaker number 10 step up to the podium, introduce yourself? Please state your name and any

organization you are representing for the record.

MR. ROSENBERG: Thank you. Good morning. My name is Andrew Rosenberg, and I'm here representing the Continuing Medical Education coalition, the CME Coalition, an advocacy group representing nearly three dozen CME stakeholders from across the spectrum of education providers, supporters, and physicians.

CME is critical to the success of the REMS program. Under REMS programs, the FDA reviews and approves programs developed by drug sponsors, and healthcare professionals must then heed the program rules. In order to ensure that healthcare professionals understand the rules as well as their roles in making sure the rules are followed, CME courses and activities are essential.

There have been numerous studies done as to the effectiveness of CME. Over the course of 39 systematic reviews published between 1977 and 2014, the overall impact has been settled. CME courses can more reliably change health professionals' knowledge, and competence, and their performance in

patient health outcomes.

CME courses accredited by the ACCME have stringent criteria and standards that must be met. In 2010, a prescriber education working group stated, "The stakeholders in the working group recommend that the REMS prescriber training be designed to exceed the goal of traditional CME methods, i.e., knowledge acquisition, and instead aim to demonstrate optimized practitioner performance and improved patient outcomes."

As such, the ACCME has worked to streamline and align CME's purpose with the ideas of the working group and the needs of practicing physicians.

Today, the types of CME offered for REMS include general information about the use of opioids to aid in patient selection and counseling, specific information about the individual drugs in the class, and information on how to recognize the potential for and evidence of addiction dependence and tolerance.

This is not the first time CME has been a

part of REMS. As such, lessons have been learned from past REMS, including the following. Educational venues must be engaging. We have to address educational needs that underline the practice gaps of each intended audience.

Finally, hypotheses must drive the scientific development of audience samples for measurement. CME as part of REMS is helpful to practitioners because the FDA controls the needs assessment and content requirements and because it encourages evidence-based debate on risk versus benefit.

ACCME-accredited CME is especially helpful because the scope of evaluation of effectiveness is actually measured in one of three ways: change in competence, change in performance, or change in patient outcomes. This helps to evaluate how well physicians understand the REMS and opioid effects on their patients.

Moving forward, we believe that the FDA should consider standardizing the REMS process while allowing more flexibility in content. The

strength of CME is that it can produce myriad educational activities that are targeted to physicians based on their professional practice gaps, individualized needs, and stages of learning and change. Added flexibility will allow prescriber education to better address individual prescribers' educational and practice needs.

The effectiveness of REMS can also be measured in terms of how successfully it promotes access to education and draws the attention of the medical profession to a problem.

Several government agencies have also been helping to educate physicians on the dangers and special care that patients who have been prescribed opioids need. Many organizations have previously provided REMS education, but have not dotted every I and crossed every T when it comes to following the blueprint. CME has worked very hard to comply with the blueprint while supporting these programs as part of a larger risk education project.

We believe that REMS should also be expanded to include short-acting opioids. While extended-

release and long-acting opioids can be abused, short-acting opioids are even more likely to be abused and therefore much more difficult to manage.

We agree with the FDA's stated position that REMS be expanded to SAIR and that we create a single blueprint for all opioids. We encouraged that FDA sees CME as a valuable tool in combating the opioids epidemic. Our members have created hundreds of hours of pain education programs and have delivered them to hundreds of thousands of physicians.

Through their research and experience, we believe that rather than requiring the whole 3 to 6 hours of content outlined in the blueprint, the counted credit hours towards a goal of 3 hours of REMS education should be considered.

Finally, we recommend expanding the target audience to include other practitioners, NPs, PAs, pharmacists, and nurses. Thank you very much for your time.

DR. WINTERSTEIN: Thank you. Will speaker number 11 step up to the podium, introduce

yourself? Please state your name and any organization you may be representing. Speaker 11?

(No response.)

DR. WINTERSTEIN: Will speaker number 12 please step up to the podium, introduce yourself?

DR. TWILLMAN: My name is Bob Twillman. I'm the executive director of the American Academy of Pain Management. I have no relevant relationships to declare.

The Academy is the largest and most multi-disciplinary pain management organization in the United States, and the only one that, from its beginning, has educated about and advocated for an integrative approach to pain management.

Yesterday, as I viewed the presentations from both REMS sponsors and the FDA, I was struck by this realization. In the ER/LA REMS, we've created a program that's cost pharmaceutical manufacturers millions of dollars, dollars that have been diverted from other vital pain management education efforts.

We've created a program that essentially

everyone thinks we have to force prescribers to complete. And we've created a program whose effectiveness we have no way to accurately evaluate. That's what I call a regulatory triple play.

We're all acutely aware that we're wrestling with two public health crises in the United States, namely prescription opioid abuse and chronic pain. Finding solutions that address both of these crises without creating a sort of zero-sum game is a major challenge.

We believe the only real solution to this challenge lies in the ability of clinicians to engage in the appropriate practice of pain management, a practice that uses opioids when necessary, but supplements opioid use with other medications and, most importantly, with a variety of non-pharmacological treatments that relieve pain.

Teaching this model of pain management is, we believe, the only way we're ever going to really succeed in effectively addressing these two

problems, and that's not what the ER/LA REMS program does. In short, the ER/LA REMS puts the emphasis on the wrong syllable.

I think it's ironic that critics of the pharmaceutical industry often talk about how incredibly effective the industry-supported medical education was during the quarter century that began in the mid-1990s, so effective in their view that the industry allegedly created an epidemic of prescription drug abuse.

Yet, when we set about to fix this problem four years ago, rather than refocus those effective methods on teaching effective pain management, we forced industry to abandon them in favor of funding the ER/LA REMS regulatory triple play, to which I referred earlier. Perhaps we should now explore ways in which we can resurrect those methods, using them to teach an effective model of pain management that will address the twin public health crises that we face.

In that light, here are some suggestions for you to consider. Number one, effective pain

management is a team sport involving clinicians from a variety of disciplines who, when working together, can effectively address all aspects of a person's chronic pain experience.

Why not focus on educating not just prescribers, but healthcare teams about safe and effective use of opioids as part of a comprehensive, integrative approach to pain care so that all team members share a common understanding of their roles in addressing pain?

Number two, effective pain management requires far more than just opioids. If we want to reign in the perceived overuse of opioids, isn't it incumbent upon us to provide alternative methods to treat people with pain? Effective education about the safe and effective use of opioids oddly requires that we effectively educate clinicians about other treatments that may reduce the need for opioids.

So let's teach people how to treat pain without just writing another prescription. Let's teach materials such as that highlighted in

Dr. Katzman's presentation this morning.

Number three, given the apparent reluctance of prescribers to volunteer for 3 hours of continuing education about opioids, there needs to be some form of mandate for this education, recognizing that such education may be necessary but not sufficient to solve the problem.

There has been much discussion about using renewal of DEA registration as the vehicle for this requirement. I'm decidedly not excited about that idea because even if you could pass legislation to permit this mechanism, I'm personally not in favor of handing the keys to the continuing medical education bus to our friends at the DEA.

So instead of this requirement, why not consider something that may be almost as good and much more expedient? What if FDA consulted with another HHS agency, the Centers for Medicare and Medicaid Services, and together they decided to write a new rule that makes completion of a comprehensive REMS program a condition of participation in Medicare?

I understand that this creates the risk of prescribers opting out of being Medicare providers, but I'm not sure there's a way to mandate education without running the risk of prescribers opting out with one excuse or another.

This is, as I said, a challenging and complex problem. And there is no simple solution to it. Despite this, I believe there is considerable potential for progress if we free ourselves from the same flaw in our education as we have in our clinical practice, namely an inordinately constricted focus on opioid prescribing by one clinician. Thank you.

DR. WINTERSTEIN: Thank you. Will speaker number 13 please step up to the podium, introduce yourself? Please state your name and any organization you are representing for the record.

DR. WITTENAUER: Hello. My name is Justine Wittenauer. I am a psychiatrist speaking on behalf of the American Academy of Addiction Psychiatry, also known as AAAP. I have no financial conflicts of interest to disclose.

AAAP is an organization that represents addiction psychiatrists nationwide. AAAP is a leading source for the latest evidence-based research on substance use disorder treatment and education and seeks to ensure that research findings are applied to clinical practice.

Although the FDA blueprint has good intentions in providing continuing education on opioid prescribing, we have concerns regarding key missing information.

As a result, AAAP recommends modifications to the ER/LA opioid analgesic REMS, including not only the expansion of the content of prescriber training to include immediate-release opioids as proposed, but also to require more comprehensive prescriber training, highlighting the risks of prescribing opioid medication.

We are specifically concerned about the lack of emphasis the blueprint has on screening for mental disorders, suicidality, as well as opioid and non-opioid use disorders. Emerging evidence reveals a significant number of prescription opioid

deaths are suicidal in intent. In fact, a report from a national surveillance database of poison control centers from 2006 to 2013 noted an alarming 75 percent of prescription opioid-related deaths occurred with suicidal intent. The percentage rises to 86 percent in individuals 60 and older. This is all the more alarming, as these statistics are glaringly absent from public discourse regarding opioid risk.

We strongly advocate prescribers have training for screening in mental disorders as well as the risk for self-harm and suicide, both of which should be reflected in the blueprint.

With the rising number of opioid-related overdoses, the blueprint should also include a recommendation for naloxone, the opioid overdose rescue medication, and should outline steps to direct an individual to treatment after experiencing an overdose.

Screening for mental and substance use disorders as risk factors is imperative and will contribute significantly to addressing the misuse

of opioids. These are enduring risk factors for the misuse of opioid medication and need to be assessed as part of a patient's ongoing care.

One example which could have ended tragically is a case of a 65-year-old married man, Mr. C., who was taking prescribed opioids for lower back pain. It wasn't until Mr. C. overdosed with a combination of opioids and alcohol in the context of attempting to taper off opioids, that he was referred to a psychiatrist who diagnosed him with severe major depressive disorder. After beginning a therapeutic trial of an antidepressant, Mr. C. was able to transition to non-opioid treatment and physical therapy that was ultimately effective in addressing his pain.

While the blueprint does highlight screening for opioid use disorders when there is a change in patient behavior, it does not emphasize the need for longitudinal assessments or clearly explain how to manage any at-risk patients. This may mislead prescribers not to perform routine ongoing screening for mental disorders in patients with the

potential for chronic opioid therapy.

If there is any history to suggest a substance use disorder, chronic opioid analgesic therapy should not be initiated without consultation with an addiction specialist. It is important to note that prescribers should not deny opioid treatment if deemed appropriate, which would have enhanced safety practices in place and carefully monitor the patient's response to treatment.

Recommended monitoring practices include reassessment at regular intervals and callbacks for pill counts and toxicology. For further algorithmic guidelines, please refer to the Centers for Disease Control and Prevention checklist for prescribing opioids for chronic pain.

In regards to the development of independent audits to confirm completion of mandatory REMS training for ER/LA opioid prescribers, we have concerns regarding its effectiveness without available peer and expert feedback on challenging cases. PCSS-MAT, a national education initiative

funded by SAMHSA that provides mentoring at no cost, may be a good model for reference.

In summary, AAAP strongly recommends expansion of the current FDA blueprint to include key information regarding the risks of prescribing opioid medication and the importance of thorough and longitudinal mental health and substance use screening. Thank you for your time.

DR. WINTERSTEIN: Thank you. Will open public speaker number 14 please step up to the podium, introduce yourself? Please state your name and any organization you are representing for the record.

DR. LEMBKE: My name is Anna Lembke, and I'm chief of addiction medicine at Stanford University School of Medicine. Today, I am representing my views, and I'm also speaking on behalf of PROP, Physicians for Responsible Opioid Prescribing, a multispecialty professional organization with a mission to reduce opioid-related morbidity and mortality. I have no financial conflicts of interest to report.

I'm going to limit my suggestions for improvement today to two areas, the curriculum and dissemination of the curriculum. The curriculum has much useful information within it. The problem, there is not sufficient emphasis on the risks of opioid analgesics.

Communicating the risks of a given medication is the very purpose of REMS. For example, there is no need for the blueprint to contain material on opioid rotation, basic drug formulation facts with brand names -- brand names in any case should not be included in CME educational material -- or overly simplistic case scenarios which do not simulate the real world. Indeed, the inclusion of this non-essential information dilutes the message of the REMS. We are losing the forest for the trees.

What should the REMS focus on? The REMS should include the new CDC guidelines on opioid prescribing. The REMS should highlight the risks of opioid analgesics and correct misinformation from past educational efforts, which minimize the

risk of addiction and exaggerate the effectiveness of long-term use.

Physicians and other healthcare providers need to understand there is no evidence for the use of chronic opioid therapy in the treatment of chronic pain and that the risks of opioid analgesics increase with increasing dose and duration.

Those risks include but are not limited to death due to overdose, even for those taking their medications as prescribed, particularly when combined with sedatives such as alcohol or benzodiazepines; misuse and addiction, even in those with no history of addiction, tolerance and physiologic dependence, an important and underappreciated concept by patients and doctors alike, and a relative contraindication for ongoing use; hyperalgesia, a paradoxical response to chronic opioid therapy whereby pain is increased, not lessoned.

In addition to being familiar with these risks, doctors need to know how to communicate

these risks to patients, how to monitor for and mitigate these risks, including how to interpret a prescription drug monitoring program and a urine toxicology screen, how to taper patients off of opioid analgesics when the risks outweigh the benefits, which is to say, slowly, particularly for patients who have been on chronic opioid therapy from months to years.

The REMS blueprint should also address the emotional toll on doctors and patients around opioid analgesic misuse, addiction, and withdrawal. Educational content should suggest tools for coping with real-world complex clinical scenarios. Lack of training in this area has already contributed to burned out, overwhelmed doctors, and abandoned fearful patients.

Dissemination of the curriculum. The opioid analgesics REMS curriculum is currently disseminated through continuing medical education lectures. CME lectures are vulnerable to speaker and conference sponsor bias. Furthermore, physicians in practice are not the only providers

who need this education.

Family practice and internal medicine doctors prescribe the highest volume of opioid analgesics by specialty, but they are followed closely behind by nurse practitioners, physician assistants, and dentists. Medical students and residents, the next generation of opioid prescribers, arguably need this curriculum more than any other group, as they will be the face of medicine in the years to come.

We recommend some novel strategies for targeting a broader audience, create online enduring courses, developed by experts not affiliated with the pharmaceutical industry, and make these courses available free to key stakeholders for further dissemination, for example medical school and residency programs, professional societies, the Center for Medicare and Medicaid Services, and state medical boards.

Launch a multimedia public health campaign to educate consumers and potential consumers of opioid risks. Thank you for this opportunity to

provide these suggestions to improve the opioid analgesic REMS.

DR. WINTERSTEIN: Thank you. Will speaker number 15 step up to the podium, introduce yourself? Please state your name and any organization you are representing for the record.

DR. LEMBKE: So I am speaking for speaker number 15.

"My name is Dr. Andrew Kolodny. I have no financial relationships to disclose. I am the chief medical officer of Phoenix House, a national non-profit addiction treatment agency. I'm also the executive director of Physicians for Responsible Opioid Prescribing. I am speaking today on behalf of Phoenix House.

"Nearly 20 years ago, when media reports of OxyContin addiction and overdose deaths first began to surface from Appalachia and New England, FDA was asked by policymakers and consumer advocates to address the problems. Meetings were held. And as opioid prescribing continued to soar and as the death toll continued to mount, FDA was asked

repeatedly to help address a crisis devastating families and communities across the country. More meetings were held.

"At each meeting, opioid makers and their physicians and patient spokespersons tell FDA that opioid harms are limited to so-called drug abusers. Millions of pain patients are doing wonderfully on opioids, so they can claim and they can tell FDA, 'Don't worsen the problem of untreated chronic pain in your effort to reduce drug abuse.'

"Unfortunately, FDA has consistently accepted this framing of the issue, which is why the opioid REMS program is so weak. The notion that we have two distinct groups, so-called drug abusers, who are harmed by opioids, versus millions of pain patients who are supposedly helped is false.

"Evidence suggests that at least 80 percent of chronic pain patients on opioids are not doing well. Over the past 20 years, millions of patients prescribed opioids for pain have become addicted and thousands have died from overdose.

Compassionate care for patients suffering from chronic pain is not jeopardized by more cautious opioid prescribing. It demands it.

"In a recent New England Journal of Medicine editorial that accompanied the roll-out of the CDC guideline, the CDC director wrote, 'The science of opioids for chronic pain is clear. For the vast majority of patients, the known serious and too-often fatal risks far outweigh the unproven intransigent benefits.'

"This straightforward message in the CDC opioid guidelines should become the centerpiece of an overhauled REMS curriculum. Education on opioid prescribing should emphasize starting fewer patients for shorter durations and at lower doses.

"The educational curriculum must take into account the fact that opioid prescribing has skyrocketed in response to an industry-sponsored campaign that minimized risk and exaggerated benefits. Prescribers need education that explicitly corrects this past misinformation.

"I urge the FDA to take the following steps:

"Number 1, change the curriculum from one that suggests opioids are safe and effective for chronic pain to one that emphasizes that daily long-term use may not be safe or effective.

"Number 2, implement firewalls to prohibit faculty with financial ties to opioid makers from teaching REMS courses.

"Number 3, implement firewalls to prohibit organizations with financial ties to opioid makers from administering REMS programs.

"Number 4, for patients on high-dose opioids, require registries to ensure close monitoring.

"Number 5, extend the REMS to include immediate-release opioids and;

"Number 6, create a new component to the REMS that goes beyond patient and clinician education by requiring opioid makers to fund a wide scale social marketing campaign for the public on opioid risks, especially the risk of addiction.

"These common-sense changes to the existing REMS would help promote more cautious prescribing

and help control a devastating epidemic of addiction." Thank you.

DR. WINTERSTEIN: Thank you. Would speaker number 16 please step up to the podium, introduce yourself? Please state your name and any organization you are representing for the record.

DR. JOHNSON: My name is Chris Johnson. I'm an emergency medicine physician from Minneapolis, Minnesota. I'm speaking for the Steve Rummler Hope Foundation, the Minnesota chapter of the American College of Emergency Physicians, and the Minnesota Medical Association, though they didn't pay me a dime to come here. I'll have to see about that.

In any case, I have been an emergency medicine physician for the last 15 years, so I've had a front-row seat as I've watched this tragedy just erupt right in front of me. I have seen multiple patients dying right in front of me. Some, I can save, and some, I can't.

While five minutes is too short to offer a detailed recommendation on curriculum, I do want to send home one take-home point based on my years of

experience fighting this problem. And that is, as far as the human brain is concerned, all opioids are heroin. And this may sound inflammatory, but it shouldn't, actually.

Heroin has a scientific name, diacetyl morphine. And actually, heroin was never its street name. That comes to us from Bayer Pharmaceuticals in the 1890s. They tested it on their employees and asked them how it made them feel. And they replied, "Heroish," which means heroic or strong.

So here it is. We remember our organic chemistry. Here's an acetyl group of carbon double-bonded with oxygen in a methyl group. You put one of these groups, a morphine molecule here and another one down here, and there you have it, diacetyl morphine, heroin. And look how similar it all looks, the basic ring structures of oxycodone, hydrocodone, Dilaudid, which is actually stronger than heroin, all look the same. They all bind the same brain receptors.

In fact, heroin is used as dimorph. It's

not some malevolent compound with a moral component to it. When used properly, it is medicine. It's used every day in the United Kingdom. You have a kidney stone in the U.K. You go to the ER. You're likely to get to a dimorph.

All opiates act in the same way. They bind the same receptors. There's no different receptor for oxycodone or heroin in the brain. They modulate the release of dopamine, which increases your mood and decreases the experience of pain, which is an emotional experience. And since every brain has a reward center, every brain is at risk. And because every brain is at risk, the only way to reduce the morbidity and mortality from opioids is to reduce overall opioid prescribing, period.

We have seen this slide before. This is what prescriptions have done in the last 20 years, which is approximately triple. The U.S. now consumes 80 percent of the world's opioid painkillers, comprising just 5 percent of the world's population.

Here's the other key factor. You watch the

sales go up, and you watch the treatment admissions go up, and you watch the deaths go up. The slope of the curve is almost identical. They are directly correlated.

In fact, if something is inflammatory, this should be it. If you total up the number of Americans who have died from accidental prescription overdose in the last 15 years, from 2000 to 2014, it's almost 190,000. That is more than the number of American soldiers lost in the European theater in World War II.

Deaths are just the tip of the iceberg of misery. This is from the CDC data. For every one overdose deaths, you have 15 abuse treatment admissions, 26 emergency department visits, and countless others who are abused, or dependent, or non-medical users at tremendous financial cost.

Then there's a question, do these drugs even help? We get personal stories of success, which are compelling, but we're told that they give people their lives back. But look at the nationwide data. It's not helping people go back

to work. Disability has more than doubled in the last 20 years, from 1994, from 5 million, to 2014, to 11 million. And the number one causes are back and joint pain. These are the conditions that these medicines are supposed to treat safely and effectively.

So when we consider education requirements for short- or long-acting opioids, we should be asking, really, how many guidelines and how much education is sufficient for you to feel safe putting someone on heroin indefinitely.

So I might break the education down in this stretch. If you're deciding who to put on heroin, you have an exit strategy or you don't. This is where traditionally we have been. When far fewer patients were dying, you treat it for acute injury because the exit strategy was, the wound heals, the kidney stone passes.

You treat aggressively but briefly, or terminal cancer because a dependence is not a relevant factor in their health outcome when the diagnosis is fatal. If you don't have an exit

strategy, ask yourself, are you okay if they become dependent. In some patients, who are already very limited by their other health conditions, you might consider, they can have that discussion with their doctor. But let's stop pretending you can predict who's going to have a problem, because we can't.

In the end, I want to say that, in my experience of treating patients, we're not trying to punish anyone by reducing opioids prescribing. Addiction and dependence is hopelessness, misery, and in some cases death. And reducing opioid prescriptions will prevent this misery for many. Thank you.

DR. WINTERSTEIN: Thank you. Will speaker number 17 please step up to the podium, introduce yourself?

DR. ARCHER: Yes. I'm Dr. William Archer. I'm a former health commissioner for the state of Texas, and I'm currently employed by Adapt Pharma as director of medical affairs. I greatly appreciate the opportunity to present before the committee on the modification of the ER/LA opioid

REMS.

Firstly, to add education about opioid overdose risk and risk evaluation and mitigation strategies, and secondly, to add a new element to assure safe use for clinicians to offer a prescription for an FDA-approved naloxone aside, high-risk opioid prescriptions, Adapt Pharmaceuticals distributes the first and only FDA-approved naloxone, NARCAN Nasal Spray, for the emergency treatment of opioid overdose.

We greatly appreciate the FDA having dedicated the resources to rapidly review and approve NARCAN Nasal Spray in late 2015. It's a very simple and easy-to-use product. This is a saline demonstration.

We are already receiving reports of saved lives across the country. As is well known, prescription opioids are implicated in about 19,000 deaths per year in 2014. Most of these have been in community, 54 percent at home.

In response to this challenge, a wide group of stakeholders have galvanized around three

initiatives, firstly, changing clinicians' opioid prescribing practices, which we've heard a lot about; increasing access to opioid use disorder treatment; and thirdly, expanding access to naloxone.

I'm going to focus on expanding naloxone access. This has a tremendous opportunity and potential to educate and prepare a patient and a bystander about opioid risks and increase the possibility that a bystander may be in a position to treat an overdose where and when it happens.

In order to achieve this goal, though, we need to look at a few things. First, we need to congratulate our EMS, law enforcement, and harm reduction groups who have shown us the way in the power of this product. Indeed, lives are being saved.

For some of these groups, the newly-approved FDA naloxone products offered opportunities to expand even further these important community-based activities. Second, the new FDA-approved naloxone formulations are uniquely suitable to allow non-

medically-trained persons to rapidly administer naloxone.

The challenge is to increase the likelihood that the antidote is in the right place at the right time. This is where the activation of clinicians to offer naloxone prescriptions alongside the highest-risk opioid prescriptions, otherwise known as co-prescribing, comes into play.

Co-prescribing has the potential to be a critical component of expanding naloxone access. In support of co-prescribing, there are a number of things to consider. This idea is widely supported by key opinion leaders, medical societies, state and federal health agencies, and most recently, the CDC and their opioid-prescribing guidelines.

The challenge is, what is the systematic means to implement this goal? Current guidance and recommendations of some medical groups in states are voluntary. As such, we've seen 40,000 prescriptions written for naloxone against 250 million prescriptions for opioids.

This is also despite the really

forward-thinking efforts of states like Massachusetts and the city of Baltimore, who have actually written to physicians to encourage them to co-prescribe.

But why is this voluntary approach likely not working? Kaiser did a study in which they showed that physicians acknowledge a lack of awareness of the problem, and secondarily, that they feel that there is a stigma with having to speak to patients around this issue.

To support a policy that moves from good idea to effective activation, our suggestion is for clinicians to offer naloxone aside high-risk opioids, consistent with CDC guidelines and prescribing as a condition of safe use of opioids.

As set out in our written submission. we believe this is a necessary medical intervention and consistent with similar ETASU-based requirements. It is also within the FDA's regulatory powers.

Importantly, listening to physicians and medical groups, we have learned that this is an

opportunity to move from a voluntary opt-in to an opt-out approach to offering naloxone on a patient-by-patient basis using their medical judgment. The patient would retain the option as to whether to accept or fill the naloxone prescription.

Why will this work? Again, moving to opt-out gets at the root of prescribing, and it's a condition for safe use of identified higher-risk opioids. It also moves from risky patients to risky opioids.

It allows physicians to understand the role that they have in educating their patient and also has the potential to reduce prescribing. This would be about 3 percent of the cost of opioid prescriptions. We request that the committee consider seriously this option.

DR. WINTERSTEIN: Thank you. Would public speaker number 18 please step up to the podium, introduce yourself?

MR. FALLON: Good morning. My name is Jay Fallon. I'm the executive director of the New England HIDTA, the High Intensity Drug Trafficking

Area. I have no financial conflicts to disclose. I'm here to offer testimony regarding the HIDTA heroin response strategy. But more importantly, I'm privileged to be able to highlight our ongoing long-term relationship with the Boston University School of Medicine, as we strive to collectively address the heroin epidemic that plagues us.

Nine years ago, I retired from the FBI after a 23-year career to work for the New England HIDTA program. As a Boston division FBI supervisor, I coordinated our drug program throughout four states. I later was assigned to supervise all FBI investigative and administrative matters in New Hampshire.

For the past 33 years, I have experienced firsthand the effects that heroin and opioid abuse and addiction has had, certainly from a law enforcement perspective, but also witnessing the effects on first responders, medical professionals, treatment providers, and our educational system, certainly the backbones of our society. The devastation to families is incalculable.

It is clearly evident that heroin and abusive controlled prescription drugs, opioids, are the greatest drug threats in New England. For the last several years, New England has suffered more drug-related overdose deaths than motor vehicle fatalities.

Now, at HIDTA, we pride ourselves on being nimble, thinking outside the box, and taking steps to address an emerging threat in fairly short order. HIDTAs are comprised of initiatives, cooperative efforts among law enforcement agencies, working together in a task force environment to dismantle the most prolific and dangerous drug-trafficking organizations in the area.

But the overarching question is, what can we do to best address this epidemic of heroin and opioid use, misuse, and abuse? What should our strategy be? What entities should the strategy be composed of?

One of our solutions was to partner with non-law enforcement agencies, in this case the Boston University School of Medicine, in an effort

to educate a key stakeholder, the medical community, regarding adopting a more temperate approach concerning opioid prescribing.

SCOPE, the safe and competent opioid prescribing education, is the beginning of a public health public safety partnership that the HIDTA program so fervently believes in. The HIDTA role in assisting SCOPE is a relatively simple one. We consult with Boston University School of Medicine regarding possible locations to sponsor or to co-sponsor CME seminars and liaise with the appropriate medical professionals in an effort to encourage as large a turn-out as possible.

We providing funding support, meeting costs, as well as to seek to provide appropriate leaders from the law enforcement community to speak to this concept of growing a public health and public safety partnership. Our heroin response strategy develops regional strategies designed to curb the epidemic number of deaths and overdoses brought about by the use, misuse, and abuse of heroin and opioids.

The ultimate goal of this strategy is to reduce drug overdose deaths across the region by instituting a partnership designed to enhance public health and public safety collaboration. The foundation for this strategy is a network of two-person teams, a drug intelligence officer and a public health analyst. These teams will interact with public health and public safety agencies in each state and develop strategies in an effort to reduce fatal and non-fatal overdoses.

Let me be clear. It's quite certain, we're quite certain, that we cannot arrest our way out of this epidemic, or prevent our way out of this epidemic, or treat our way out of this epidemic, or educate our way out of this epidemic, when each of these entities works in a vacuum, unaware of the existence of the other.

Our best chance to successfully address the epidemic of heroin and opioid addiction is one which will encompass a partnership comprising education, prevention, treatment, and enforcement professionals working collaboratively to achieve

the overall goal of safe and healthy communities throughout the nation.

As you are well aware, ongoing education of the medical profession is a component of the ER/LA REMS strategy. Research shows that education works best when it's continual, and the medical profession is no exception to this research. In fact, follow-up studies by Boston University School of Medicine show that following CME of SCOPE, prescribers are likely to adopt a more cautious approach in the prescribing of opioids.

In short, this is a well-placed tool that is proving to be highly effective. HIDTA is proud of the strategy, and we remain optimistic that these efforts of the public health and public safety partnerships will continue to build safe and healthy communities. There is not a moment to waste. Thank you very much.

DR. WINTERSTEIN: Thank you. Will speaker number 19 please step up to the podium, introduce yourself?

DR. ADAMS: Thank you for the opportunity to

address you. My name is Joseph Adams, MD. I have no conflicts of interest to report. I'm a diplomat of the American Board of Addiction Medicine and of the American Board of Internal Medicine. And today, I am representing the National Physicians Alliance, an independent non-partisan organization, which unites tens of thousands of physicians across medical specialties who advocate for patients and avoid conflicts of interest.

We believe that the REMS educational component needs a complete overhaul. It needs to convey the following points in a very clear and unequivocal manner.

One, evidence of effectiveness is lacking for long-term use of opioids and chronic non-cancer pain. This is completely missing from the current curriculum.

Two, for headache, fibromyalgia, and non-structural low back pain, there is good evidence that long-term opioids are likely to be ineffective and harmful.

Three, the educational component should be

based on the CDC guidelines.

Four, any organization that administers the program and any speakers who present it must have no financial relationships with opioid manufacturers.

Five, immediate-release products should be included; and six, mandatory education and certification for prescribers should be included.

Personally, I am sorry to report that I have overprescribed long-term opioids, causing harm to patients because I was subject to education that minimized risks and maximized benefits. We have an opportunity to correct this misinformation, which is something that the current REMS does not do.

In fact, the current REMS curriculum makes opioid overprescribing more likely, not less. A prescriber taking a course entitled "The Safe Use of Long-Acting Opioids" is much more likely to get involved in this kind of prescribing. It's like a how-to manual. It reassures prescribers. It sends them down the path of prescribing for chronic pain. That's what happened to me.

The safe use of long-acting opioids is the phrase from the FDA blueprint, and it has caused huge unintended consequences. The courses give the impression that bad patients are the issue and suggested screening for risk factors where misuse and abuse can prevent problems, but there is no evidence for this.

The focus on misuse and abuse is a serious error and is seriously misleading because fatal overdose tends to occur in those taking medicine as prescribed by mouth, who are middle-aged or older, and is very often unrelated to misuse and abuse, but this information is missing from the current curriculum. The current curriculum is similar to courses that pharma was providing shortly before the REMS went into effect, and that's not a good thing.

The last five years have shown that the REMS program has been ineffective. It needs to change. The program must stop emphasizing a balance between risks and benefits, which is unhelpful to prescribers who desperately need more guidance than

that. Instead of being told simply to balance risks and benefits, prescribers need specific guidance, such as the need to document a significant functional impairment and documented significant improvement in functional impairment before opioids should be continued.

If a new drug were introduced today and it killed 18,000 Americans a year as a side effect, with no clear evidence of long-term effectiveness, of course it would not be approved for long-term use. But unlike opioid pain medicines, suboxone, for example, is a relatively very safe medicine and it requires prescriber certification, which is mandatory.

The advisory committee has got it right in 2010. You voted 25 to 10 against the REMS program. And as reported in the press at the time, "The majority who voted no felt that educational programs must be mandatory." That was from MedPage Today. You were right.

In summary, the REMS program must communicate the following points clearly and

unequivocally. Evidence for effectiveness for long-term use is lacking in chronic non-cancer pain. We're just saying that prescribers need to be clearly informed as to what the evidence does or does not show.

For headache, fibromyalgia, non-structural low back pain, there is good evidence that long-term opioids are likely to be ineffective and harmful. The educational component should be based on the CDC guidelines. Financial relationships between opioid manufacturers, and organizations, and individuals affiliated with the REMS program should be strictly prohibited. IR products should be included. And education and certification for prescribers of long-term opioids should be mandatory. Thank you.

DR. WINTERSTEIN: Thank you. Will speaker number 20 please step up to the podium, introduce yourself?

MR. BRODINE: My name is Joe Brodine, and I am a medical student at Georgetown University and a future primary care provider. I am speaking today

on behalf of myself and my future patients. I have no conflicts of interest or financial relationships to disclose.

In the clinics and hospital wards where I've been training, there is collective frustration among practicing physicians who have received mixed messages regarding opioid prescribing. Medical students and residents also are in need of clear evidence-based education that emphasizes appropriate indications for prescribing opioids and teaches them how to distinguish risks and benefits for those indications.

The current REMS is inadequate and insufficient to this task and must be modified. The FDA's blueprint for prescriber education should be updated to reflect the guidance provided in the CDC's recently published guideline for prescribing opioids for chronic pain.

Educational content should follow this guidance and make clear to providers that opioids are not first-line therapy for chronic non-cancer pain. The educational content should emphasize

that opioids may not be safe or effective for chronic pain and may not be appropriate for patients with certain chronic conditions.

Regarding the question of whether REMS should be required for immediate-release opioids, the stated goal of the REMS is to reduce addiction, unintentional overdose, and death. Many patients are initially prescribed immediate-release opioids for chronic non-cancer pain. Immediate-release opioids can be just as addictive as extended-release opioids.

Considering addiction is one of the drivers for the current epidemic, it is crucial to have a REMS that addresses both immediate and extended-release formulations.

In summary, the opioid REMS must be robust, comprehensive, and provide clear guidance to current and future physicians. For the sake of patients, the FDA must require a REMS that addresses immediate-release opioids, and the FDA must also revise the blueprint for prescriber education so that education curricula reflect the

guidance laid out in the March 15th CDC guidelines for prescribing opioids. Thank you.

DR. WINTERSTEIN: Thank you. Can speaker 21 please step up to the podium, introduce yourself? Please state your name and any organization you are representing for the record.

MR. BEALS: Hello. My name is Dean Beals, and I'm the president and CEO of DKBMed. We're a medical education company. Thank you all for allowing me to speak today. I was not compensated to attend today's meeting. I came because I believe this is a vitally important issue.

I want to disclose that we have been awarded three REMS grants in partnership with the Post-Graduate Institute of Medicine, the practicing Clinicians Exchange, and Johns Hopkins University School of Medicine. We have developed 18 live activities, print, online, and recently an Apple and Android smartphone app, all covering the FDA blueprint. We have educated over 2300 clinicians with over 883 completers, that is learners who are both opioid prescribers and successfully completed

the curriculum.

Let me focus for a moment on our live meetings, which were concluded in 2015. We had over 1400 learners, 619 of those were completers. Almost half of our learners were actually not completers, and the reason behind that is because they were not either DEA registered or did not prescribe long-acting opioids in the past 12 months, and I'll come back to that in a moment.

By all measures, the course was very successful based on learner outcomes. It featured lectures, simulated patient cases on videos, and audience participation. We also provided tools such as patient contracts. Across all 18 meetings, more than 95 percent of learners agreed that the program will help improve the clinical outcomes of their patients.

There were significant gains in knowledge when measured directly after the activity, and importantly, those gains remained 16 percent higher, statistically significantly higher, 45 days later. More than 80 percent of participants

indicated that they have or will make changes in practice as a result of attending the activities.

We also received a number of substantive comments echoed by multiple learners, including, I will conduct an evaluation of risk assessment on patients before prescribing medications for pain, and I am now more confident and willing to order medications appropriately to better manage my patients on long-acting opioids.

I'd like to spend the rest of my time discussing recommended improvements. First, let me say that I commend the FDA for supporting the CME community. Opioid abuse is clearly an enormous problem that must be addressed. I believe it would be ill advised not to utilize CME for future opioid education. We are the right community to be doing this important work. We are the experts in continuing medical education.

That said, I recognize that the supported activities have not achieved the agreed-to number of learners and are well below the goal. While I am not aware of how those goals were set, I believe

they were overly optimistic for three reasons, one, the length of the curriculum; two, the fact that no governing body requires completion of the blueprint; and, three, that non-prescribers were excluded from the completer counts.

First, while the FDA blueprint is well written and thorough, it's simply too long. It takes between 3 and 4 hours in a live meeting setting. To their credit, the RPC supported programs which were highly rated, but the challenge remains getting learners through the door, or for that matter, to participate in online activities.

Despite extensive promotional efforts, only so many learners are willing to spend 3 to 4 hours to attend a program. Our surveys for reasons for not attending included either other commitments or simply did not have the time. We need to take a hard look at the blueprint and find ways to manage that.

Secondly, there's no requirement that the curriculum be covered. While several states require varying degrees of pain management

education, it may or may not include long-acting opioids. It is not required by the DEA for licensure, nor by any medical board, to my knowledge, for maintenance of certification. These would have made an increase, a great increase, in the number of people taking this important education.

Third, just because the program attendees are not an opioid prescriber, it does not mean that they will not benefit from the education or have an impact on patients taking opioids. Forty-four percent of our activity learners were not prescribers, but they decided to attend the program anyway. Why? Because they recognized how important the topic is, and they wanted to ensure the safety of their patients.

So in summary, I would recommend shortening the blueprint to increase adoption, requiring the curriculum for MoC and licensure, and redefining who a completer is to include not just people who are DEA prescribers; and finally, to continue to support CME in developing this important education.

Thank you.

DR. WINTERSTEIN: Thank you. Would open public hearing speaker 22 please step up to the podium, introduce yourself?

DR. ADAMS: I'm Joseph Adams again, but I'm reading a statement from Don Flattery, who is not able to be present today.

"Thank you for the opportunity to speak as you consider the effectiveness of the REMS as it applies to ER/LA opioids. I believe that the REMS program is based on flawed assumptions and is inadequate.

"My name, it says here, is Don Flattery, and I live in Alexandria, Virginia. I am a former federal manager at the U.S. EPA, a member of the Virginia Governor's Task Force on Prescription Drug and Heroin Abuse, and most importantly, an impacted parent, having lost my only son, Kevin, who was 26 years old, to an opioid overdose 20 months ago.

"My talented, highly-educated, and loving son became addicted to OxyContin as a working adult, pursuing his career passion in the film and

entertainment industry. Like thousands of others, including members of the medical community, he had not fully comprehended the highly addictive power of opioid drugs, and that misunderstanding led to his demise.

"The epidemic of opioid addiction is a public health crisis that continues to worsen, despite all efforts to contain it. The horrific loss of life continues to grow as policy experts and federal authorities deliberate. Today's proceeding is but one of dozens of contemplative moments at a time when common sense demands more aggressiveness, more realism, and unquestionably more urgency.

"In 2014, CDC reported that there were over 29,000 opioid-related overdose deaths in the U.S. Drug poisonings are now the leading cause of accidental death in Americans and are driven by dramatic increases in overdose of prescription opioids.

"The direct association between the growth of opioid prescribing and the explosion of opioid

addiction and mortality is well known. The cause is clear and the solution is intuitive. Return to more cautious prescribing.

"Opioids prescribed unnecessarily are flooding our communities, schools, and medicine cabinets and leading to overuse, non-medical use, and addiction. The solution is not to make these highly addictive and inherently dangerous products to be abuse deterrent, but rather to change the fundamental risk assessment factoring in this epidemic of opioid-caused mortality.

"Deficiencies in medical education related to pain management and addiction are well documented, and this gap has sadly been filled by pharmaceutical representatives, who suggested that risk of addiction was under 1 percent, up until 2007, when Purdue Pharma was convicted for misleading marketing practices.

"In 2009, the FDA missed an opportunity to promote more cautious prescribing at the request of industry and industry-supported pain management organizations. FDA abandoned its plan for

mandatory training and registries. FDA's REMS proposal is so weak that its advisory committees voted against it.

"I offer the following comments and suggestions as the committees consider the content of REMS for ER/LA opioids. The REMS should include immediate-release products. Entities or individuals with financial relationships with opioid manufacturers must not be permitted to administer the REMS curriculum or to serve as faculty.

"The REMS curriculum must reflect a more realistic risk-benefit calculus, which recognizes the exponential increase in addiction and mortality due to prescription opioids. The REMS curriculum should not imply that long-term opioids are either safe or effective for chronic non-cancer pain.

"The curriculum must change its current focus on how to prescribe, and it must be based on the recent CDC opioid guidelines. The curriculum should end its focus on the 'misuse and abuse of opioids' and instead emphasize that opioids have a

significant risk of addiction in patients taking them as prescribed.

"The curriculum should include a public education component and be broadly available on social media, an essential mechanism for reaching wider audiences.

"I implore the advisory committees to recommend significant changes to the opioid REMS program, which is seriously inadequate, so that the FDA can fulfill its role in protecting the public from highly addicting and dangerous opioid drugs. Thank you."

DR. WINTERSTEIN: Thank you. And our last public speaker, number 23, would you please step up to the podium, introduce yourself and any organization you are representing for the record?

MS. CHAMBERS: Yes, thank you.

My name is Jan Chambers. I'm the president and founder of the National Fibromyalgia and Chronic Pain Association. I have no relevant relationships to declare. We connect with 157,000 members and 160,000 people on Facebook. Thank you

for your services and for the opportunity to make public comment today.

Pain is a disease with neuroplasticity that increases over time if not treated. Undertreated and unmanaged pain has clinical, psychological, and social consequences, including limitations on life activities, lost work productivity, reduced quality of life, and stigmatization. Families become care providers and relationships get burned out.

Chronic pain affects 100 million American adults. Our organization conducted a 2015 survey of chronic pain patients and had 6,420 responders. It was published in Pain Medicine in December of 2015, which is the Journal of the American Academy of Pain Medicine. This survey was the only snapshot of what happened to people, the unintended consequences to people with chronic pain 100 days after the rescheduling of hydrocodones from 3 to 2.

We are now conducting the second part of that survey to understand what is happening to people one year out from the rescheduling. I'll give you some of the statistics from that report.

27.2 percent reported having thoughts of suicide since the rescheduling. Of those who could no longer get hydrocodone, 18.1 percent were on pain medications, 17.1 percent turned to marijuana, 13.1 percent used alcohol, and 2.3 percent used illicit drugs. Most respondents had to visit their healthcare providers more often, 64 percent, and 30 percent reported some type of issue interacting with their pharmacy.

Eighty-eight percent felt that the rescheduling was neither a fair nor appropriate solution to the abuse of hydrocodone. For those still working, 46 percent reported that they had missed work because of the strict regulations.

The significance is that the unintended consequences for people with chronic pain that have been caused by the rescheduling effort to impede hydrocodone abuse are negatively impacting thousands. These consequences include suffering from being placed on less effective drugs, increased cost, inconvenience, and negative influence on physician-patient and pharmacist-

patient relationships. We think that the REMS blueprint should include screening for mental disorders and suicidality.

Recent policies and legislation are focusing only on prescription opioids in the big picture of drug addiction and overdose. Street heroin and illegal fentanyl patches need to be accounted for in the war on drugs and in the statistics that are used. Abuse-deterrent formulations on all opioids, including methadone, paid for Medicaid often, are necessary. The FDA must help in this important strategic approach to get serious about preventing opioid-naive young people from trying these medications.

These medications are serious medications for serious pain. Please make recommendations to stop villainizing and torturing the people with chronic pain. As I've indicated with that report, the consequences do affect thousands and thousands of lives. Just like other medical conditions, they need medical care and access to pain medicine in an integrative treatment between a physician and a

patient. Thank you for your time and attention.

DR. WINTERSTEIN: Thank you.

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

First, we will break for lunch. We will reconvene again in this room in one hour from now at 1:10. Please take any personal belongings with you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any other members of the audience. Thank you.

(Whereupon, at 12:10 p.m., a lunch recess was taken.)

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

(1:10 p.m.)

DR. WINTERSTEIN: You are a very well behaved committee. Everybody's already quiet and here. Wonderful.

All right. Coming to the final potion of this meeting, we're starting with Dr. Auth, who will provide us with our charge.

Charge to the Committee

DR. AUTH: Since the ER/LA opioid analgesic REMS was approved in 2012, the FDA has continued to receive inquiries regarding the effectiveness of the program. The purpose of this meeting was to publicly present the data evaluated thus far and to have an open discussion as to whether these data support the continuation of the current extended-release and long-acting opioid analgesic REMS program, or whether these data are or whether these data are not sufficient to support the effectiveness of the REMS, or whether modifications are necessary to ensure safe use.

As has been mentioned several times, the

multiple efforts to address the opioid crisis make the evaluation of this program particularly challenging. As was the case in the early development of this program, many continue to advocate for a program that is broader in scope, while others caution that additional restrictions on opioids can negatively impact patients with a legitimate need for opioid analgesics.

You've heard presentations on the many other concurrent efforts to address the opioid epidemic, the challenges and successes of the ER/LA opioid analgesic REMS, as well as recommendations for future educational programs, a presentation on the results of a mandatory state education program, as well as public testimony both in support of and against further REMS restrictions.

Your input on a wide variety of discussion issues is needed, including, again, whether the data submitted for the evaluation of this program are appropriate and sufficient to support a determination of program effectiveness; whether the program should be broadened to include immediate-

release opioids; and whether a voluntary educational program can impact prescriber behavior and patient outcomes.

You will also be asked to vote on whether the current REMS should be eliminated, stay the same, or be modified, and to support your rationale for your vote. You will also be asked to provide your ideas on what the recommended modifications should entail and how the modified program should be evaluated, should you choose to vote for modifications.

If you believe that there are other mechanisms to ensure safe use of ER/LA as well as ER/LA and immediate-release opioid products, that might be less cumbersome than a REMS and serve the same purpose. We would also like to hear those ideas. Thank you.

Questions to the Committee and Discussion

DR. WINTERSTEIN: Thank you, Dr. Auth. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is

open for public observation, public attendees may not participate except at the specific request of the panel.

Before we get started, you may or may not know that my task is to summarize the discussion for each question. You would help me tremendously if you focus on the question at hand and don't deviate into anything that we are not supposed to answer right now, and try to be concise, and focus. That will all bring us out at 5:00, and not by 6:00 or 7:00, and I get to summarize what we actually really are supposed to answer.

So please, please, please, try to do this. If you don't, I will start to make funny faces, and at some point, I will start throwing things at you.

We had some questions from over before the break. There were a few more people who we had noted. I will just go down the list and see whether there's any clarifying questions left that we need to address. That will be starting with Mr. O'Brien.

Do you still have a clarifying question?

MR. O'BRIEN: [Inaudible -- off mic].

DR. WINTERSTEIN: Okay. Dr. Gupta will come later. Dr. Bateman is good. Dr. Israel? Dr. Kaye? That's probably all related to data. You're good? He's good. And Dr. Brown?

Everybody is good. All right, good. Then we'll start with the first question to the committee.

Considering the number of participants and completers in the extended-release and long-acting opioid analgesic risk evaluation and mitigation strategy continuing education programs in the first three years of the program, please discuss, A, the expectations for the reach of an education program that is voluntary for prescribers and whether the number of completers and participants are satisfactory; B, whether the goal of training 80,000 prescribers of ER/LA opioid analgesics within two years was appropriate, if not what is a reasonable expectation in light of the many competing programs?

Are there any clarifying questions to

clarify this question? I'm supposed to ask this. This is in my script.

Okay. All right. Anybody ready to answer this question, discuss the question? Dr. Brown?

DR. BROWN: I think the expectation of the reach of this educational program, for what some people have been calling a national emergency, is that we involve every person we can. I've listened to the folks in the public part of this, and I agree that it's really a team effort and everybody should be involved.

I think that this goal of 80,000 prescribers is a laudable goal, but it is not a laudable goal if there are no teeth behind the continuing education to make it mandatory. So I'd like to suggest, if I can, another way other than having every prescriber in America involved in a REMS program, and another method because there may just not be enough political will at this point to drive that which is necessary to make this available or restricted for everybody in the United States.

Another method would be, which might be more

palatable, to identify problem prescribers. And I go back to Dr. Katzman's data, which I focused on before, where she showed some interesting information about those prescribers that continued over the years to prescribe more than 100 MMEs, despite the fact that they had been educated. And that might be the group that we need to focus our attention on, and that might be more politically palatable, and that might be an easier throw for the FDA to improve this program.

DR. WINTERSTEIN: Dr. Stander?

DR. STANDER: In answering the specific questions, I think, if I understood the information we got, while it appeared that the goal was not achieved, there was so much uncertainty among the people taking CME courses as to what exactly they were taking in terms of REMS qualification, that everything I saw from the CME presenters, it seemed like far more participants took CME courses related to opioids than actually technically met the qualifications.

So to me, the goal was actually reasonable,

given the number of people prescribing ER/LAs and immediate-release. I think we had 1.2 million people actually prescribing these meds, and you had a goal of less than 10 percent of those.

So I think the goal was laudable and reasonable. And I think, actually, technically, even though it didn't meet this very restrictive definition you set, it probably was achieved. And we heard a lot of presenters talk about redefining what's acceptable CME around REMS qualification or not.

So I think if you open up what is considered reasonable training that meets the blueprint, which will probably be revised -- then I think the goal was, if anything, in my view was actually under -- is too low. So that's my two cents.

DR. WINTERSTEIN: Dr. Raghunathan?

DR. RAGHUNATHAN: The reach of any program really depends upon how it was marketed, and how it was conveyed, and how the recruitment went through. So I think, given that there are 839 programs or 839 courses that are available for people to take,

and having a thousand people taking the course per year -- 500 people taking the course per year is not a big challenge.

So I don't know whether there was a lack of reach in terms of how urgent it is needed. I think that the marketing may have been lacking in that respect. So I think it is a reachable goal. But again, given that it is a voluntary nature of the program, it's quite likely that they didn't think this is serious enough to take these courses.

So I don't know. Some sort of a mandatory -- somehow I think the urgency has to be conveyed in order for these programs to succeed.

DR. WINTERSTEIN: Dr. Floyd?

DR. FLOYD: I agree with Dr. Raghunathan's comments. I don't think that a voluntary effort is actually going to reach the providers who are causing the most harm from using opiates, and I would advocate for a very different type of educational program, but one that's mandatory.

My comment actually is about the questions in general. The first five questions or so have to

do with evaluating the REMS, if it stays the same. And I suspect, if we're recommending changes or differences, it's not going to be very relevant. But if I have comments about what I think the REMS should change to, should I save those for later, and comments are only for the current REMS? I guess it depends on what the FDA wants comments on.

DR. WINTERSTEIN: Right now, just comment on this question. If you take a look at all the questions that have been posted, that you see in the briefing material, we will have time to discuss how to change the REMS. Right now, we are talking about this particular question. Thank you.

Dr. Krasnow?

DR. KRASNOW: Thank you. One of the problems I see with this is, I think the numbers are too low. And I think that one of the reasons is that I don't think the course is particularly attractive because of, number one, the length of the course, and, number two, the restriction to ER/LAs.

I think if you put out a course that is

going to be burdensome in terms of time and very restrictive in content, you might expect an optimal number of people are not going to take it. So I don't want to get into more details about recommendations, but I think the structure and length of the course needs to be addressed in order to attract more people to voluntarily take it.

DR. WINTERSTEIN: Dr. Kaye?

DR. KAYE: Thank you. To me, it's about lifelong learning. When you think about all the changes in opiates and the epidemic or opiates as a whole -- when you think of people in medical school, there's a tremendous lack of education in this field.

I give lectures across the country, and I'm changing my slides every week just on opiates. And I'm interested -- and I have a very good background, and even I am taxed to try to keep up. So I think of the primary care physician, who is leading the pack in prescribing, who voluntarily, if they feel like it, can get an hour or two, it just seems like we should, as was said, put meat in

it, make it mandatory, make it user friendly. Education nowadays can be done online. You don't have to go somewhere in a room. You can learn by your computer. We have the technology. There should be teeth.

To the point of the outliers, the bad or problem prescribers, I think that we haven't said anything about it, but I will. The pharmacy surveillance programs that are run through each state should include national oversight for people, for patients, for problem patients that we don't know are problem patients, who are going to more than one state and will have problems surviving their futures.

That's not the prescriber's fault, but I think that's something in the gestalt of this epidemic that is not mentioned nearly enough, that we should have national surveillance as we look at pharmacy surveillance in kind of a report card of all the strengths and weaknesses of where we are in moving forward. Thank you very much.

DR. WINTERSTEIN: Thank you. Mr. O'Brien?

MR. O'BRIEN: Looking at the question specifically in terms of some it asking us for the past, I think the 80,000 goal was reasonable. It was calculated reasonably at that time. Just de facto evidence, was it satisfactory? No. it wasn't. It didn't reach the goal. So to that extent -- but that doesn't necessarily mean it's totally critical.

The big question for me is, is it a reasonable expectation? No. It shouldn't be Russian roulette for a patient to go in, to expect care, whether or not that person is trained in what they're going to provide. That should be for everyone that goes in. It shouldn't have to be Russian roulette to go in there.

So I think the expectation should be every prescriber should in fact be educated.

DR. WINTERSTEIN: Dr. Galinkin?

DR. GALINKIN: So in answering this question specifically, I think, in terms of reach, it did in many ways meet its goals because the number of programs that sprung up at the same time as this

REMS, it seems like, have been inordinate, a large number, and greatly exceeded the 80,000 people that were trained. And they unfortunately suffered from the fact that there was many competing programs, including one by NIDA and other things that didn't necessarily address all the things the FDA wanted, but they were programs addressing opiate use.

So in that sense, it did meet the goal, and I think more than 80,000 people were trained across the country. However, the goal of consistency is a different question. And I think, comparative efficacy of these programs, at some point, it'll have to be looked at, and whether a uniform set of guidelines or a uniform set of continuing education that can be developed across all spectrums.

I mean, now, you have something separate in New Mexico. You have something separate everywhere else. And I think a lot of people have been trained with this REMS in mind, but I don't think that it necessarily met the FDA definition, but I do think they had reach.

DR. WINTERSTEIN: Dr. Parker?

DR. PARKER: I think it's just a restating of some of what I've heard, but I would say that, for the ER/LAs, the REMS were required for those products, which made sense. They were non-restricted from the beginning, which I think we now know didn't work. Being non-restrictive, being voluntary, it didn't reach the numbers, given the high risk of the products and the number of deaths that have been -- you can go down from death, but death's such a big one, you can just start with that. It's not adequate.

DR. WINTERSTEIN: Dr. Buckenmaier?

DR. BUCKENMAIER: It is somewhat hard to frame this just for this question. On some level, this was successful, but I think the effort was myopic in the face of the national scale of the problem that we're trying to deal with. So my suggestion would be to claim a Bush-style victory --

(Laughter.)

DR. BUCKENMAIER: -- and then recognize that your initial approach was not enough, and that

trying to divorce the issue, as stated in the National Pain Strategy, from the problem is not going to work, and then develop a program that massages those issues.

Providing every provider with some modicum of understanding of pain in our society would be a very good thing. And at the same time, you can provide the information that those providers who prescribe would need to do that effectively, and therefore actually move the ball on this issue; because, if you divorce the drug-specific issue from the thing that's driving it, which is pain in this country, you're doomed to failure, in my opinion.

DR. WINTERSTEIN: Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: So my comments are this. I think the FDA got what it expected and asked for, historically. I think when this idea was proposed and supported, the fact that you got very inconsistent data, we're left with very little solid information here; we are three years later. So I think the expectations were met, but it was an

anemic attempt at addressing a high-risk situation.

So having said that, yes, in my mind, it's clear there are a couple things. My sense is, historically, at some point, we lost the key, which I think is part of what this committee is here for, is to talk about risk and trying to identify risk on a national scale as public health practitioners, as clinicians, all of us.

So I think what got lost in the shuffle here is that the risk got drowned out by trying to make a big program. The risk message got drowned out because it's a voluntary program, and the risk message got drowned out because there were hundreds of people trying to do it in a hundred different ways.

So my recommendation on this question is, yes, it should be mandatory, and I can comment later on how I think that should look. But I think if we don't make changes, we'll just go down the same road.

DR. WINTERSTEIN: Dr. Israel?

DR. ISRAEL: I just want to say I've been

working with NIDA for the last 15 years on drug epidemiology and drug abuse issues and been watching the evolution of the opiate addiction problem from heroin, including all these prescription opioids.

I just want to make a comment. I agree with a lot of the things that are being said. But I think, also, this idea of voluntary participation, you don't know what you don't know. And those of us that are working in the area, or that are acutely aware of what's going on, obviously understand how these are bridged together. But the rule providers, people that aren't particularly taking CEs in this area, don't know that they really need to have the CEUs or CMEs to understand what their responsibility is and how to handle these patients.

So I would agree that it needs to be more mandatory in nature.

DR. WINTERSTEIN: Wonderful. Dr. Bateman?

DR. BATEMAN: I was just going to echo Dr. Israel's comments. I think, to me, the issue

is not just the absolute number of providers that are enrolled, but whether the program is reaching those providers that most need the training. And I think with a voluntary program, you're likely to attract providers that are attentive to this issue, that are eager to improve their prescribing practices, but you'll miss those that are at highest risk for using opioids inappropriately.

DR. WINTERSTEIN: Excellent. Okay. So I think the committee agrees that the goal of 80,000 was not too high, that it may in particular not address prescribers who may be in the greatest need for training.

The committee pointed out that, as science changes so rapidly, it is a fallacy to rely on prior training of physicians or PAs and RNPs, and that they need to be continuing training on opioid issues. The committee pointed out again this is a national epidemic and that every patient should be able to expect that he or she gets adequate care as it relates to appropriate pain management.

I'd like to add, just in terms of numbers,

that if we are thinking that it took about three years to train about 20 percent of all prescribers and we extrapolate this to the approximate year when all prescribers would be trained, we are looking at another 8 to 10 years, assuming that there was some ramp-up time; and that seems to be not an adequate projection, considering that this is a crisis.

There were a few suggestions made for improving the reach, and I expect we will talk more about this in the next questions. The committee commented that the marketing and the outreach may not have been sufficient to really get prescribers involved in the CME; that the voluntary nature is not effective; that the structure and the length of the training may need to be revised to become more attractive; that there are clearly competing programs that may have trained to various extent -- or may have provided training to various extent and that there should be some standardization to ensure that the appropriate messages are communicated throughout all available

CME programs.

Does that summarize everything that we're thinking? Dr. Morrato?

DR. MORRATO: You did a great job summarizing. But I had two other things to add before that, so I'm sorry if I'm out of order. Just to add, maybe two things I thought related to metrics. We talk about prescribers, but I think a metric can also be the proportion of patients that you're reaching.

So it kind of relates to the problem prescriber, but we saw yesterday that there's different prescriber specialties that are writing at different volume, so you could have a more targeted approach in how we think of the prescriber number. And hitting 25 percent if they're writing 80 percent of the prescriptions could be a very good number. We just don't know based on the data that we have right now. So that was one comment.

Then the other, in terms of just where FDA may have chosen the tipping point of 20 percent or 25 percent, it's useful to remember diffusion of

innovation theory and tipping point that's been popularized, that 25 percent is sort of where things really take off.

If at two years you're only hitting half of that goal, you're hitting the 12 percent, which tends to be people who are more innovative, who are more involved, the more eager learner, that is not necessarily translating in the population.

So it's hard to know if we're just getting the people who are already eager learners for this kind of voluntary, and it certainly doesn't address the point you raised on the speed of the curve and how long it takes it to happen, and that's probably too slow, what they had.

DR. WINTERSTEIN: Moving on to the next question -- more to question 1, Dr. Stander?

DR. STANDER: No. I was ready for question 2.

DR. WINTERSTEIN: You're ready for question 2. All right.

(Laughter.)

DR. WINTERSTEIN: Get in the queue quickly.

Question 2, many parts, the effectiveness of the data sources and methodologies used by the RPC to evaluate the impact of the ER/LA opioid analgesic REMS, particularly the expectations for the reach of an education program that is voluntary for prescribers and whether the number of completers and participants is satisfactory; B, whether there are more effective short- and long-term approaches to measure the success of ER/LA opioid analgesic REMS in reducing serious outcomes resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications; C, whether the potential effects of the ER/LA opioid analgesic REMS on reducing abuse, misuse, addiction, overdose, and death can be differentiated from the many federal, state, local, and health systems activities with similar goals; D, what is the anticipated length of time for an educational intervention to broadly impact prescriber knowledge and behavior.

Dr. Stander?

DR. STANDER: Thank you. I think the first one, A, if we go in order, I think everybody is more or less coming to a consensus that the voluntary is probably not the best way to go.

While it's tempting, I agree with Dr. Morrato that it might be tempting to try to hit a targeted group. I think that's going to be difficult because there's often nurse practitioners prescribing because their supervising physician might have recommended. I'd be more inclined towards something, as we'll see, perhaps talk more about later, linking it to DEA or something.

I think it's very difficult. I think the presentation yesterday from our epidemiologists about really tracking these outcomes is going to be extremely difficult to measure the success, but I think there have been a lot of people that talked about registries for prospective tracking, seeing if we can track not just the numbers of prescriptions, but the numbers of pills and the morphine equivalents, as I think New Mexico had done; trying to correlate it with what diagnoses

they're being used for. We especially heard some of our experts talking about fibromyalgia, and non-structural back pain, and so forth, and it's really evidence that they may have adverse effects; and if on tracking the overdose deaths, if we can segregate out illicit versus prescribed opiates.

I think it's going to be very difficult, if impossible, to segregate out the effects of education versus the myriad other interventions that are going to happen. And it's going to come down to an argument, are we going to look for proof of efficacy to determine whether we keep educating people about this or are we going to accept the intuitive belief that education, it's hard to see how it's harmful unless it's unduly burdensome, and that we all believe that if you're prescribing a dangerous medication, you ought to be taught how to do it as optimally as possible.

I think that -- I'm not sure for D -- the anticipated length of time to have a broad impact on prescriber knowledge and behavior is probably almost immediate. It's difficult to measure, but I

think many of the CME programs can assess their impact.

I would get away from, if possible, the "did you think this program was good" and so forth. I think pre- and post-testing is probably the best way to determine that, but I think that, from the impact on knowledge and behaviors, it can be almost immediate. Thank you.

DR. WINTERSTEIN: Dr. Choudhry?

DR. CHOUDHRY: So I do also agree that the effectiveness, data sources, and methodologies have thus far been somewhat lacking, and I very much appreciate the effort of the FDA and the industry to actually develop a framework for evaluating REMS.

What I think was absolutely right is the idea that there's a multi-modal approach here, that there's not one solution; that there's the ultimate randomized controlled trial that looks at opioid deaths, or something like this, or overdoses, and therefore, we know whether the REMS worked or it didn't. The story is much more complicated than

that, so I think that the reliance on two or three at least different modalities is right on. And as we think about modifying, we maintain that philosophy.

So I'd make a couple of very concrete suggestions, some of which actually came out of directly from the FDA's own presentation yesterday, from the epidemiologists and statisticians.

In the survey realm, the idea of the length of the evaluation almost certainly has something to do with the completion or likelihood of participation. So recommendation number one would be that we actually propose to shorten the surveys that are done for evaluative purposes.

Number two, a much better sampling approach be used. We heard about the non-systematic models that were used at that point, and therefore the large selection effects that resulted. So clearly, we need more generalizable and larger sample sizes, and using better sampling methodology; we ought to go there.

For the second group of stuff, whether we

call it surveillance or drug utilization, a couple of thoughts. First of all, as was brought up yesterday, there is an emerging body of integrated data sources that we all use in our research lives now, which married together in some cases electronic health record data, with claims data, with some in cases registry data, with laboratory data, and so on, and so forth; so the idea of reliance on a broader set of those sources, which not only will give us more granular data on indications, but therefore on appropriateness, which is clearly a metric which we really haven't gotten to, to date.

The challenge of evaluating programs when there are multiple competing alternative things happening is clearly one which confounds most people in observation in epidemiology and will almost certainly continue to confound the evaluation of REMS.

That said, there are methods for this. So to the extent that there are multiple states doing multiple things, to some extent, states which have

all the attributes less or plus one serve as controls for the other states.

We've done this in other contexts, for example, where we tried to evaluate complex systems like insurance benefit design, there are 5 or 10 or 15 attributes they may be going in and out of at different times. And there are strong quasi-experimental approaches that can be applied to actually to make inference on that basis.

So I would suggest that, with the right data, which should be available, that there are in fact ways to begin to tease apart some of the effects here, and that should really be the action of further intent.

The last comment I'll make is with regards to D. We're talking about behavior change from a single continuing educational intervention. So what in general we know is that in order for behavior to really change, it has to be sustained and ongoing. So I would be hard-pressed to imagine that a single intervention would actually meaningfully and durably change prescribing.

I think the answer to the question is that if you're going to see a change just from that, it will likely be there, but then short-lived. So at the very least, that sort of leads itself to one of two possibilities.

Either we encourage not a one-and-done kind of thing, but a multiple ongoing iterative idea, and then you might need a year to see an effect, or conversely, if you are going to do one, you ensure the durability of the effects, so both over the short term and over the long term. I'll stop there.

DR. WINTERSTEIN: Thank you. Dr. Higgins?

DR. HIGGINS: I wanted to talk a little bit about the data sources and the methodology used for this. I'm quite surprised that a representative sample was not used and a random sampling method was not used for this, which I think really would have bolstered the results that we have here.

It's hard for me to compare people who responded with those who don't respond when those target populations are not really being

represented. I'm also struck by the fact that CMS data was not used and the reliance solely on private commercial insurance. I think that was a huge mistake.

I do hear that there were some challenges using those data, but I think it really would have enhanced the quality of this survey.

DR. WINTERSTEIN: Dr. Raghunathan?

DR. RAGHUNATHAN: I was thinking about this. After hearing all those presentations from the analysis, it was kind of disappointing that this was not carefully thought out, an evaluation strategy. If this were a phase 3 trial, evaluating the effect of treatment on patients -- where I think this is an effect of evaluating the effect of intervention that is designed on prescribers, I would have thought about evaluating that intervention on the prescribers using several outcome measures and several carefully crafted design experiments as well as sample surveys.

So I didn't see the blueprint of analysis or designed experiments that was recommended, but I

think this needs a careful redrafting of the evaluation plan using measurable outcomes, carefully crafting the various design of experiments and sample surveys, using longitudinal data of detecting the change in the behaviors.

So I think that this whole plan was not adequately addressed in the current REMS evaluation.

DR. WINTERSTEIN: Dr. Bilker?

DR. BILKER: Yes, hi. There are just a couple of points I wanted to bring up. The first thing is -- and I think somebody mentioned this just a minute ago -- the current REMS program measures the level of prescribing, which is very helpful, but it doesn't address at all whether any of the prescribing is appropriate or inappropriate. And I don't think moving can be made without that. You can't just look at the level of prescribing. And as Dr. Stander pointing it out, we may be able to address that at least partially by looking at the prescribing patterns within specialty areas.

One other thing I wanted to bring up

is -- and I know this has come up at least in part -- there's a lot of different federal agencies that are looking at this issue, but it doesn't seem that there's a lot of collaboration between the agencies.

So we've got the FDA, the CDC, the DEA, NIDA, and this isn't a federal agency, but the American Association of Medical Colleges, CMS, all the CME providers. But it doesn't seem like there's enough cooperation between all the groups. And that may have to be done through legislation to make that happen, but it seems like something needs to happen along those lines.

DR. WINTERSTEIN: Dr. Emala?

DR. EMALA: I would just like to add a few comments about question 2B, about the effectiveness of the evaluation. And I have to say I'm pretty struck with the lack of studies that attempted to address the major goal of the REMS, which was to look at outcomes. And in some ways, it appears that the lower-hanging fruit was approached with looking at prescriber education and knowledge base.

So I think, based on the recommendations of the epidemiology group at FDA itself, that recommended a longitudinal study of prescribers that do and don't take the training, as well as studies as we started seeing a little bit of yesterday, the Pri-Med study using electronic data sources and administrative data sets to look at true outcomes, I think, is imperative.

In fact, if I had any reluctance whatsoever in recommending mandatory training or expanding training to IR formulations, it would hedge on the fact that we're really looking at an inadequately evaluated system at this point and whether the REMS have really met its goals of achieving its primary objectives. Instead, we're really discussing some secondary measures of prescriber education rather than outcomes.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: I want to reiterate what Dr. Bilker was saying about something that I just said, and that was relating to inappropriate prescribing. I think, in my mind, that's the crux

of the point here. That's the identification of the group that is probably causing quite a lot of the problem that we've been seeing.

It may require us to have some whole new method surveillance system, develop a whole new surveillance system. But I think it's worthwhile for one of the federal agencies to look in some detail at pulling together all the information we have, including pharmacy surveillance from individual states and DEA records to try to determine if we can't create a database of who's really causing the problem.

DR. WINTERSTEIN: Dr. Parker?

DR. PARKER: Just to underscore a couple things and add a slight bent to a couple of them, I'm really going after the B and D components here. I totally agree with C being multi-modal. If it's starting to work and everything's working, don't spend too much time figuring out what it is. Just be glad, because, right now, we need to make it better.

So regarding B, it seems to me I totally

agree with going after the inappropriate prescribing behavior and getting to that. So I want to throw a couple other words in here that relate to some of what has been said. It's incredibly ripe for analysis of big data.

So we're hearing about data analytics, using big data. There are a lot of data sources. There are a couple that are not in the room that I think are important to highlight. One is the payers, the insurers, and the ones who are paying for the prescriptions to get filled, and what data you could actually garner from that source, and how that could be added into understanding what's really happening, also data that comes from the retail sites, but looking across these multiple sources with analytics to try to get at what's really going on with inappropriate prescribing behavior, so that we have a better handle on what it is we're really trying to go after.

I think the other thing relating to D that's worth underscoring, educational interventions and particularly prescriber behavior. And I'm going to

speak mostly from the bias of being a physician myself, but I think it relates to most prescribers.

Behavior is hard to change. Most people know more than they do. All of us do. I had a bag of Cheetos for lunch, and I wouldn't have bought them. We know more than we do. So when you get at the behavior of actually doing, that's a tough, tough thing to go after. And if what we're really after is the prescriber behavior of inappropriately prescribing, you've got to think very long and hard about how we're going after that.

Certainly, incentives, and opportunities, and quality offerings are important, but consequences are as well. So what happens when you don't and when you violate? So I think a very careful look at whether or not something like REMS can really get at that, which does not get at what happens when you don't and what happens when inappropriate behaviors continue, is worth highlighting and thinking about as part of this.

So in other words, what are you really asking the REMS to do? And consequences per se are

not necessarily a part of that, but the inappropriate prescribing behavior is obviously a target. So it's sort of a very careful model that tells you where you're going, what you're going after, why, what you can expect.

It's a comprehensive look at something that really has absolute dire adverse outcomes, and it's highly recognized in our country.

DR. WINTERSTEIN: Ms. Shaw Phillips?

MS. SHAW PHILLIPS: Lots has already been said, so I'm trying not to repeat anything. But to tag onto what Dr. Choudhry was saying, I think, depending on what you're trying to get out of your education, if you're trying to get that knowledge, the knowledge of what the alternatives are, or how to approach a patient with pain, I think it's one kind of assessment. And you would expect that change to happen very rapidly, but also hopefully to be maintained in that knowledge and ability to apply to be retained. I think the practice change and outcome change is something that's going to take longer to see on a population level.

What I'd really like us to be thinking about is who should be doing those assessments. And rather than putting that in the hands of the RPC, I think it would be better handled as a responsibility of the education providers, particularly as we move for education being more innovative and targeting, changing practice and changing outcomes rather than just imparting knowledge.

There are certainly innovative educational models that include those follow-ups, so what did you change in your practice or encouraging the health systems, or the target sites, or the targeted populations to measure the outcomes themselves?

Even some very simple outcomes that we saw did not occur with the REMS in the first three years would be very helpful, so ensuring that there's a contract for every patient on long-term pain management to ensure that the patient counseling guide as revised is used with a discussion with the patient.

I think there are some very simple things that organizations should be monitoring, and step up in alternative care, and referral to specialists, and so on that could be put back in the hands of the attendees in the systems or organizations that are being educated.

DR. WINTERSTEIN: Dr. Floyd?

DR. FLOYD: So I think a number of very good recommendations have been made about better study designs, data resources, improved collaboration, focusing on adverse outcomes, bad prescribing in particular. I would just urge the FDA that whatever changes are made to the REMS, they not be delayed for this evaluation to happen on the previous ER/LA REMS, that this be the plan for assessing whatever new REMS is implemented.

I think that's important. Some of these study designs or investigations could take quite a while to do, and I don't think that should delay any changes that are recommended.

DR. WINTERSTEIN: Dr. Galinkin?

DR. GALINKIN: This is in regard to

question 2B. What does inappropriate prescribing mean? I'm still not entirely sure after all of these discussions. Is it the amount, the type of drug given to the patient archetype? And how do you measure these outcomes? I think that's a key question.

If our key outcome is death, you need to develop patient adjudication committees to actually adjudicate the deaths, and see if they're associated with opiates, see if they're associated with the opiates that are prescribed for that patient because really, in some ways, you're directing these REMS specifically at -- it seems like chronic pain patients and patients inappropriately getting this for chronic pain, when I'm not sure if that's really what the goal is of getting these opiates off the street, which is a much different question.

If there's somewhere around 25 percent of opiates -- at least, that's partially -- somewhere between 8 to 25 percent of opiates end up on the street, what are we actually measuring? And I

think this is going to end up being a multi-pronged, multi-organizational effort. There's just no other way to do it because to get the death data is not something that the FDA can do.

To get a lot of this prescriber data is probably more something that the DEA is going to help with. So the organizations have to work together to do this, and this can't be a feuding match, which is what seems to be going on between a lot of the organizations.

DR. WINTERSTEIN: Dr. Bohnert?

DR. BOHNERT: I wanted to acknowledge that I think the RPC was somewhat handicapped in doing their evaluation by the fact that they were not able to have the identifiers for who did the training, in that I think being able to link that to pharmacy records would have given the panel some of the data we were interested in understanding in the program.

The other thing I was thinking about, when I think of wanting to do an intervention study or a trial with an intervention that's readily

available, I think of Christine Timko's work that she's done around 12-step groups, where her actual intervention that she randomizes to is a facilitation of using that intervention. And it's given to people who have not yet availed themselves of this readily available -- we're currently doing a similar design of the trial around crisis line, and then to be able to look at the outcomes you're able to use, a mediation model to better understand the underlying process of effect.

But that said, I agree about not delaying the implementation of any changes that are made based on being able to do an evaluation, and doing anything that would be a trial would be very challenging if the timeline in which all the people are expected to have done training is fairly short.

DR. WINTERSTEIN: Mr. O'Brien?

MR. O'BRIEN: To answer again, I don't want to repeat a lot of the things, but clearly, for the question here, the data sources and methodologies, I think, were very poor and did not reflect what I thought were the goals of REMS that were there.

We heard and saw that in things like surveys self-reported, non-representative samples that did not reflect perhaps even the prescribed community for patients, and we didn't even have any correlation to the adverse events, adverse outcomes population.

If we looked -- which again gets to the need of more granular data to determine are we reaching the goals. And to Dr. Brown's point and looking at Dr. Katzman's presentation, the number being concerned about inappropriate prescribers, from my perspective, it was not clear to me that we can make a link between those charts of a reduced number of prescribers with an increased number of volume with the death rates and the adverse outcomes. Are they really related? We don't know that.

I think it was just mentioned by Dr. Galinkin that the data does not give us a clear indication are we reaching the target audience that we want, the target population for the crisis that's here, that we've got to resolve, and to

reach the two goals that are very clear within REMS.

In terms of potential methodologies on a short-term basis, and we've discussed it a little bit, I think patient committees are necessary. I think patient involvement is necessary. The second part of this goal includes patients. And to make sure there's no adverse effects, I think we have to include more patients in here. Nothing I saw really included patients other than a non-representative sample after the fact of perhaps non-related people to the problem.

I think that perhaps some of the things to look at, in addition to outcomes studies, quality of life instruments there, et cetera, to see what the true impact is, in terms of access we may be able to utilize, or I suggest we take a look at live reporting. We have adverse effects and NIH for other agencies, et cetera, where we can go in and patients can report if they have troubles with access, if they can't get what it is.

I think we can perhaps get some live data as

to what's happening out there in the community rather than after the fact. I think, for adverse effects, for caregivers to be able to also communicate in that event and to increase the amount of data we're getting on more of a live basis may be helpful.

If we're going to start to look at the crisis of opioid deaths, then in terms of Dr. Katzman, it would be great. On one side, we have the data more granular in terms of dosage levels for prescriptions, but we didn't have that data, we know, for the 265 in New Mexico, what that was by level. Then we may be able to correlate one to the other and begin to see whether or not it is inappropriate, whether it's doctor shopping.

Is it doctor shopping in a negative way in terms of those that are really abusing the system, or is it doctor shopping because they can't get access to it, and the chronic sufferers who really need it can't get it anymore because their prescribers are not there, so they have to go to someplace else who is doing it?

Those are two different things, and I think we have to get a better understanding of what that is in the data before we start making the crisis that's here and we have to respond to. But you also have the problem of the tail wagging the dog, and we want to make sure that we can ferret out and get to the appropriate level. And I don't think it accomplishes that at this point in time.

DR. WINTERSTEIN: Dr. Gerhard?

DR. McCANN: Just a couple of additional points. Obviously, we've seen a lot of issues with the REMS evaluation in the past, both in terms of methodology as well as data sources. Some of them were structural by the way this was mandated.

The point I really want to make, though, is I believe, although this requires me to look into the future and vote on future questions a little bit, if we are going the route that this will be greatly broadened or even mandated, the challenges for evaluation will be very difficult and even more complicated than in the past because we basically won't have a comparator anymore.

If we mandate that everybody is trained, we can't compare trained people to untrained people, so we are limited to looking at changes in behavior or changes in knowledge over time, while many, many other things are going on at the same time.

So I think we'd have to be okay with stepping back from trying to distinguish what makes the impact here, just trying to design a program that is as strong as we can design it and a program that focuses on the right issues.

I think the issue that's really central and has been largely ignored is this issue of appropriateness. And particularly, I think appropriateness in the sense of use for non-evidence-based indications or chronically in ways where there is just no evidence that the opiates are actually effective, I think that's probably where the biggest -- or in situations where alternative approaches weren't sufficiently tried out, the latter will be really complicated because there are many places in the country where those alternative approaches might not be available.

But I think that's really an important thing to realize, that if we go that route of mandating something, we won't be able to compare physicians with and without the intervention and make these evaluations.

The one thing I want to caution, although we're obviously all looking at these overdose death numbers, and they're the most striking example of the problem, I think they, in many ways, might be the worst specific target for the intervention.

Trying to evaluate the effect of this program and other efforts just by looking at these overdose death numbers I think is equally likely to get you to declare a false victory or false defeat because they're influenced by much stronger alternative factors, the availability of naloxone that might reduce death rates, although the underlying problem is even increasing, or a real start of tackling the prescription opiates while availability of illicit drugs is increasing at the same time.

All of these factors, illicit drugs,

naloxone, affect death rates very immediately, so I think it would be problematic to just focus on that number. I think if we can -- and that's difficult to measure -- get a handle on appropriate use or maybe even abuse, which is even more difficult to get, that's I think a more important goal for this and other efforts.

DR. WINTERSTEIN: Dr. Fry?

DR. FRY: To kind of second what Dr. Gerhard was saying, you can't just look at death data. If you're looking at prescribers, you're missing the fact that some of the overdoses are for drugs that are being diverted. You know, I broke my foot. Babysitter comes in, steals the rest of my oxy, sells it, that patient dies.

So as you're looking at all these surveys, you're not going to get accurate data with prescribers and how it correlates to overdose and death. I mean, there will be some correlation for patients that are taking their prescriptions as is and overdosing, but there is a large subset of diverted drugs that are causing death that would

not be seen in these studies.

DR. WINTERSTEIN: Dr. Morrato?

DR. MORRATO: The point I just wanted to add was, I think the need for some harmonization of metrics that are being measured by health systems and that maybe there's an opportunity, at least in those measures, for more real-time surveillance.

So these kinds of reports that we've been discussing the last day only become available to the public when you have forums like this and they get synthesized into briefing documents. So all you hear in the public surveillance is about the deaths and the emergency room. We're not seeing things as it relates to the prescribing in a similar way. I think that's a role that the FDA could play in making some of this evaluation more transparent. I know that was common in the public hearing.

Just to reiterate or underscore a point that was raised yesterday, CMS is in the process of developing quality indicators. It looks like they might be implemented as soon as 2017. They're

getting reviewed now. They focus on opioid high dosage as well as multiple prescriber and multiple pharmacies and thinking of this as an overutilization monitoring system.

So I think there's opportunity with the REMS evaluation, a component of it, to be looking at harmonizing with these kinds of metrics, and it's through these kinds of audit feedback that many times, health systems will then implement programs that are affecting these kinds of metrics.

So it's a way of helping institutionalize the REMS measures as well.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: There are a couple -- as we go around the table, we talk about all that we don't know, but there are a couple of things that we do know. One thing that we at least believe that we know right now is that higher doses are associated with poorer outcomes. And, of course, association is not causality, but it sure is an observation.

The other thing we know is that the pain community recommends that we stay away from doses

of drugs that reach that level and when people are prescribing and get close to 90 to 100 MMEs per day, they begin to really be thoughtful about what they're doing.

If indeed the CMS is going to use this as a quality indicator, then that would be a first step for us to be able to look at something, which I think is important because it's something that we can all agree on.

DR. WINTERSTEIN: Dr. Israel?

DR. KAYE: There have been some really good comments made by the last couple people that have spoken, so I just have a couple quick things. In all fairness, in 2009, when this was all started with the development of this program, no one had any idea that the heroin epidemic was going to explode like it has or have all these prescription opiates involved.

So in hindsight, it's great to say, well, we should have done things differently with the RMS, but there's no way to really know that back then. There was inklings that was going to happen.

So I think it's important to move forward, and I think everybody at the table has been saying that rather than worry about what's in the death data and how we're going to tease that apart from the heroin, which you'll never be able to do.

I mean, I've sat down with years' worth of death data from just the state of Missouri trying to figure out how all this stuff falls out, just looking at the actual MME data. And it's very difficult to figure that stuff out, and it's probably a waste of time. We need to figure out what we're going to be doing with prescribers and moving in the direction we're talking about. If CMS is going to make those changes, that's going to help us quite a bit along the way.

DR. WINTERSTEIN: Dr. Raghunathan?

DR. RAGHUNATHAN: Yes. Focusing on death is such an extreme outcome. To me, I think that is like an end-stage renal disease, so you have lots of other steps that you can do in order to prevent it going to that stage.

So I think there are a lot of outcomes that

you can study that I think can prevent going to that stage. But I think not focusing on those early stages of outcomes that can have an impact would not be appropriate; for example, whether the non-opioid treatment options have been exhausted or not and whether the dosing was done correctly or not, whether number of prescriptions that are being given is appropriate or not.

So there are so many other things that we can measure based on the longitudinal data of the prescription behavior that I think can have an -- our programs can be tuned to that. So all those outcomes could be measured rather than just hanging on this one outcome, which so many other factors affect that outcome.

DR. WINTERSTEIN: Dr. McCann?

DR. McCANN: I know nobody has said this, but Dr. Gerhard's point that 80 percent of prescribers have not taken the course, I think does provide great opportunity. I don't understand why nobody has brought up the idea of doing a randomized controlled trial of a random sample of

the 80 percent who haven't taken the course.

It would be quite easy. I don't think you'd need that many patients, and it wouldn't take very long to do. If enticing them to enroll would involve some money, I would think that that could come from the RPC., and it would be another way -- it would be a very easy way, I think, to measure the impact, whether the REMS is actually affecting whatever outcome measures we come up with. And I agree with everybody else that we don't really have good outcome measures at this point.

DR. WINTERSTEIN: Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: Just a couple comments about other ways of looking at maybe bridging with what Dr. Choudhry had said. So other opportunities, I think we're having a discussion obviously nationally and trying to get our arms around this one in a big way, and then the flip side being I think one of the luxuries or resources we have in this country is, one, healthcare is delivered locally. A majority of healthcare occurs

locally, and we can ask questions at the local level, whether it's looking at states and obviously having to compare different programs once again, whether it's Washington or New Mexico.

Another thought that comes to mind is, as healthcare changes, and it's going to continue to change -- so for instance, in the state of Maryland, where we have gone to global budgets through the waiver, through our HSCRC, now we in the state of Maryland -- and I'm interested in it, too, because of just looking at the VHA as a system.

But we are looking at regionally, in our state, hospital systems that are now essentially responsible for the population. And there's been a lot of work put into looking at who these patients are, where do they live, and then interestingly, obviously, paying health systems to take care of those people.

So within that, in their intervention to decrease risk, those healthcare systems are going to have an interest in looking at utilization of

EDs, utilization of multiple resources, complications, hospitalizations, readmissions.

So that's also another area, I think, that we could consider leveraging, as well as the other systems of care throughout, whether non-profit or for-profit healthcare systems throughout the country.

So a couple different layers, but probably with CMS involvement, I know, once again, in the state of Maryland, there might be some opportunity for partnering to understand how some of those interventions may play out in actually a local healthcare system.

DR. WINTERSTEIN: Dr. Bateman?

DR. BATEMAN: So I guess a number of people have brought up the idea of creating longitudinal data sets that would allow us to evaluate the impact of the training program. But I have to say I'm a bit skeptical about the feasibility of an observational study that would define the causal impact of a training program, particularly if we're talking about a voluntary training program, because

while there are databases that can capture with fairly granular data characteristics of the prescribers, their specialty, their patient panel profiles, you won't be able to capture their engagement with the issue of appropriate prescribing.

That's going to make them very different than those that don't seek out training and would likely confound any observed association that you would see in terms of taking the training in and changes in prescriber behavior.

So I agree with Dr. McCann that this may be a place where an RCT is really necessary to define the effect of the training intervention.

DR. WINTERSTEIN: Dr. Krasnow? Go ahead.

DR. KRASNOW: I was just going to say, just a caution about a randomized clinical trial, though. It was stated that it might not take that many subjects, but then we're not clear what our outcome measures are yet. The outcome measures determine the number of subjects, and I found that one is usually surprised by the number of subjects

you need in a randomized clinical trial.

So I think that would have to be very carefully thought out.

DR. WINTERSTEIN: Dr. Raghunathan?

DR. RAGHUNATHAN: I think something was brought up about the confidentiality and data sharing, but there are protocols for setting up data coordinating centers where the education providers can provide the data to the third party under some strict confidentiality rules, which you can then analyze the data.

I agree. I think longitudinal data under the randomized clinical trial framework would be the ideal way of doing it. But observation studies also can be done, which are carefully crafted comparison groups. And that may be hard to do in this context of completely voluntary samples.

But I think, if it is done mandatory and if it is phased in, then there is an opportunity for us to evaluate it because, then, you can compare the immediate treatment versus the delayed treatment group.

DR. BATEMAN: Like a step-wise type design, and that might be helpful. Yes.

DR. WINTERSTEIN: Dr. Stander?

DR. STANDER: I'm going to say something that's probably a bit politically incorrect. But I think we're maybe letting the perfect become the enemy of good. There are a lot of very smart people here and epidemiologists who really want the perfect study to determine, or maybe the FDA needs this for political purposes to prove that REMS training or education about opioid training can produce an outcome.

But with all due respect to our CME providers, the requirement to do a certain amount of CME to maintain your license, I'm not sure has ever been proven to provide quality. I can do 40 hours of training, CME in whatever kind of courses I want that may or may not have anything to do with what I do in practice, and it gets my license.

We're trying to prove something I'm not sure we can easily do. And I thought we heard an

overwhelming consensus from most of our outside experts that, empirically, teaching people how to use these dangerous medications makes sense. And I'm not sure that we're ever going to be able to get much beyond that. And I think, personally, I think that's kind of where we have to lean towards.

DR. WINTERSTEIN: That was a good introduction for what I was going to start out with. So we started out -- or Dr. Stander just stated that, whether proof of effectiveness of an educational intervention is really necessary or not, if we are assuming that this is just a given that prescribers should be aware of opioid risk and proper prescribing practices.

Looking at the quality improvement literature -- that was my personal comment -- there is overwhelming evidence that educational intervention usually does not really effectively change behavior. So if we were to extrapolate this to this particular case here, then our expectation and thinking that a CME program in itself will fix the problem is probably a little bit

overenthusiastic.

Now, thinking about this question here, it's really about how do you evaluate a REMS and not how do we evaluate an educational intervention, so the REMS could perhaps contain completely different elements that we haven't even talked about yet.

So I'm introducing everything else that has been described under this idea that it's not only about evaluating an educational intervention, but it's about evaluating the REMS itself.

So to question A, there was very limited discussion, but I think one part that was made clear is that it's really important to evaluate the reach of the REMS, in particular with respect to the prescribers who may cause the major problems, so rather than just looking at the global impact, looking at the impact where the impact is really needed.

With respect to measuring success or measuring outcomes, I think the committee agrees that service that evaluates knowledge don't really evaluate the REMS. They perhaps evaluate the short

term or the quality of the CME program as such, but not the effect of the CME program on outcomes that really matter and that the REMS is focused on.

My personal comment to this might be that the surveys that looks at knowledge is essentially a quality improvement strategy for the CME providers to see whether the CME is well-crafted, but it really is not an evaluative tool in itself.

With respect to the surveys, there were comments that the sampling approach would be improved. We addressed yesterday that assessment of baseline knowledge might be important to really see the effect of the education itself after it's been provided.

So then moving on to outcomes that the committee felt more strongly about, there were two types. One is drug utilization types of outcomes or outcomes that address change in behavior versus outcomes that directly affect the patient.

With respect to changing the behavior, that might actually be an adequate focus or inadequate outcome that could be addressed in pre-post designs

even if CME became mandatory because there's always a time when people didn't have the CME yet, where pre-post comparisons could be made, so changes in behavior.

I think the committee struggled with defining what exactly that would entail, specifically how to define appropriateness of prescribing. Ideas that were presented are use of adjuvant therapy, trial periods with other medications other than opiates, use of high doses of opioids and tracking that.

Of course, then we also have the CDC guidelines that have come out, like urine tests or urine screening in patients who might be at risk for substance use disorder or using of provider contracts. So that's the drug utilization portion, and I think most of the committee members feel that looking at those types of outcomes would be the most immediate effect of the REMS that we would want to look at.

Then the second part is real patient outcomes about death. There were concerns raised

that death in itself is, number one, very rare and requires large amounts of patients to really track. Secondly, we have issues in connecting death to prescription drug abuse versus other exposure to opioids.

As a personal comment, there as much, claims data could fix that problem, so I could easily see where claims data could be linked to NDI in order to get a better handle on what the history of prior prescription opioid use looked like before death occurred.

Then of course, we also have just overdoses that could be tracked, so we don't have only death, but we also could look at hospitalizations or ER visits for opiate overdoses, which would give us a much broader handle on patient outcomes.

Then lastly, an outcome that was mentioned that might be much harder to measure and that might really require collaboration with other DHHS agencies is diversion, which clearly we wouldn't get from claims data, but which is an important piece. And I remember that one committee member, I

believe Dr. Galinkin, stated to get the drug off the streets, and that obviously is another important outcome.

In terms of isolating the education from other efforts, there were recommendations for between-state comparisons that could look at timeline of introduction of various approaches to mitigate problems related to opioids with respect to PDMP programs, and mandatory CE programs, and so on that would allow us a little bit of a glimpse on what the CME program itself does.

The other recommendation or suggestion that I had were pre-post comparisons that could specifically look at behavior changes. And then there were some suggestions about RCTs. They were mixed evaluations of whether an RCT is really an appropriate tool to evaluate the CME program, specifically the sample size.

An RCT would not provide sufficient sample size to look at patient outcomes such as death. It might be able to look at evaluating changes in behavior, but even that would need to be obviously

very clearly defined. And then one thing that needs to be considered is that in an RCT of educational intervention, blinding and randomization becomes extremely difficult. I mean, there may be some ideas with lagging the intervention and the control group, but it's not as easy as it sounds.

Then lastly, D, when can one expect an effect? There was little discussion on this item, but I think it seemed that most committee members felt that this would be a fairly immediate effect that one would see if a CME program really affected a change in behavior that should surface fairly quickly.

Did I forget anything?

(No response.)

DR. WINTERSTEIN: Good. Okay. One more before the break, 3, please discuss the impact of the ER/LA opioid analgesic REMS on patient access to opioid analgesics. Provide examples of how best to evaluate patient access. Mr. O'Brien?

MR. O'BRIEN: My answer to this is I don't

know. Based on the data that I saw, I don't know if I have any confidence in what I have seen. There was nothing to indicate there isn't, but I don't know. We heard from the public communities, the fibromyalgia community that they believe it is impacting. But like we've seen with other things, there's so many confounding issues, I'm not quite sure what may or may not impact it, whether it's insurance or in my own state.

We just passed a law that says you can only get seven days at a time, that that may have more impact on accessibility than REMS has. I spent a couple of days going through. We have a patient online forum with about 8,900 registered members that have posted over 150,000 posts. That's a searchable database.

So I put in OxyContin, and pain management, and REMS. First of all, no one knows what REMS is. There's no post, really, regarding REMS. But in terms of looking at pain management, accessibility did not pop up as an issue. There are clearly issues with the community. On average, these are

mostly post-surgical patients who are getting a regimen of long-acting OxyContin for 20 milligrams twice a day; oxycodone, 40 milligrams every 4 hours; Valium, 5 milligrams every 8 hours; and Tylenol, 1,000 milligrams 3 times a day. So they're getting a pretty high regimen for up to 2 or 3 months at a time.

But what you see in the community, if you read it, is that they're concerned more not with accessibility but with their quality of life. They are very aware of the problems that come with this type of regimen. Their concerned. They are dealing very much with constipation, sweating, and all of the symptomatic issues with being on that type of regimen.

They are very grateful because it does relieve the pain that affects their quality of life, but they're very concerned with how do they get off of this. But there's a stigma. They don't want to be associated with addiction because, to their mind, they're physically dependent. They realize that may happen to them, but they're not

addictive in their nature for the most part. And they don't want to be associated in a negative stigma with that group of individuals because that's not their case. They need what they need in order to survive.

So as I said, I guess, at the end of the day, I don't know. I don't see any evidence that accessibility directly related to REMS is an issue.

DR. WINTERSTEIN: Dr. Craig?

DR. CRAIG: Thank you. Yes. I don't think it has had any impact at all, actually. I'm in the state of Florida and primarily deal with cancer patients. But I don't think the REMS has had any negative impact. I think the pill-mill laws or other things and availability had more of an impact on our patients. And it's something I deal with every single day in trying to find our cancer patients access to medication.

So I'm an access kind of advocate, if you will, but I don't think the REMS, and especially the voluntary nature of the REMS, has had any impact at all.

DR. WINTERSTEIN: Dr. Galinkin?

DR. GALINKIN: I want to agree with the past two speakers that I don't think it's had an impact on the availability. I do want to differentiate the comment that was made about the fibromyalgia patients. The hydrocodone rescheduling was, I think, before the long-acting product came out, so it really did not impact the ER/LA availabilities.

DR. WINTERSTEIN: Dr. Shoben?

DR. SHOBEN: The other part of this question was about examples of how to best evaluate patient access. And I think that's really difficult to do without sort of defining this issue of appropriate and inappropriate prescribing that we had before, because how can you possibly evaluate that a patient who should have access to this drug had trouble until you've really defined who should really have access to the drug.

DR. WINTERSTEIN: Dr. Higgins?

DR. HIGGINS: I'm interested in talking a little bit about what Dr. Auth found with the previous examples of REMS and how there was a

slight dip in prescribing as a result of the institution of REMS. And then it came right back up, the prescription level.

So I'm interested in talking a little bit about that and whether people think that is maybe a proxy for what might happen with the opioids. I'm not sure.

DR. WINTERSTEIN: I think the committee feels that the current REMS that has reached 20 percent of prescribers who voluntarily participated in a program that presents the FDA blueprint for appropriate prescribing guidelines has not really affected access to medications and should at least not negatively affect access to medications because it summarizes best practices in pain management.

As to the second portion of the question, that really addresses not global access to opioids, but it really addresses access for those patients who need opioids, which brings us back to the appropriateness question, which of course is much more difficult to define in both terms of

inappropriate as well as appropriate access.

Mr. O'Brien?

MR. O'BRIEN: I apologize for post-issue, but to that extent, the question to me is not does the patient have access to the treatment that they need, but they really would prefer something else. They want the best thing that it is, so the need for research, really, for better ways of pain management, I think, is highlighted by that.

DR. WINTERSTEIN: Dr. Gupta?

DR. GUPTA: I can give a patient example. In my own practice, I've had patients who have had end-stage cancer, very, very painful, and requiring some of the products that are in the TIRF REMS category. And it has been a deterrent. It has delayed access for them because I had to go through the process of completing the training, and I also had to have the pharmacy dispense the medication.

So the barriers with insurance to get approval plus completing a REMS, plus completing the pharmacy, making sure we're all on the same page, it was absolutely a deterrent. And that

patient was critically ill, was in hospice, needed care at home. So it was a terrible situation.

So I absolutely think it was a deterrent for me rather than actually helping a patient getting access. It really limited my ability to give that patient quick access to that medication.

DR. WINTERSTEIN: The ER/LA REMS? Are you talking about ER/LA?

DR. GUPTA: I'm talking about TIRF REMS, like when you have to have an immediate-release sublingual product for someone that has, say, cancer pain, it was a deterrent. Maybe someone else can give me another example, but this was actually a patient I had.

DR. WINTERSTEIN: Dr. Craig?

DR. CRAIG: I'll just echo Dr. Gupta. The restrictive REMS with TIRF, basically, our institution eliminated that modality entirely. It went to zero. So if you take the restrictive approach to all opioids and make it mandatory, make it more restrictive than it currently is, I'm not arguing that opioids would disappear. I think it

will change. Whether the change makes things more appropriate or not obviously is in question.

I think you have to be sensitive when you're talking about proposing new REMS or adding to what we currently have in existence and making it mandatory versus voluntary, you run the risk of doing very similar kinds of things, the enrollment, the burden of the sheer volume of the number of patients.

I'm already having problems with my cancer patients as it is now. What will it look like if that's our new reality? I can't imagine. But in regards to the TIRF REMS, they no longer exist in our institution because of the potential barriers in getting them access to patients and having pharmacies actually have them in stock. They're no longer tools available to us.

DR. WINTERSTEIN: I think we're addressing the impact of proposed changes to the REMS in later questions, so perhaps we can focus on this one right now.

Dr. Floyd that was later? Dr. Krasnow,

later? Okay. This one? Okay. You get to say something.

DR. MORRATO: Just listening to this made me think we haven't really talked about access as getting the drug, but there is a stigma in the process of getting the drug. And I know I've heard qualitative information from folks that the going of the process through that can create that kind of anxiety or stigmatization, am I a drug addict or things like that.

So I was wondering if any of the other researchers who focus on this particular area have seen anything that would be evidence, good or bad, around stigmatization.

DR. WINTERSTEIN: Moving on to question 4, considering the information provided today regarding the current ER/LA opioid analgesic REMS, please discuss, A, whether the REMS is meeting its stated goal to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release or long-acting opioid analgesics while maintaining patient access to pain

medications; B, whether the REMS assures safe use of ER/LA opioid analgesics; C, whether the REMS is unduly burdensome on patient access to ER/LA opioid analgesics; and D, to the extent practicable, whether the REMS is minimizing the burden on the healthcare delivery system.

Dr. Gerhard?

DR. GERHARD: I think, in my mind, this question is pretty straightforward. The answer very much relates to the current REMS. So for the first question, we really have no idea what the impact of the REMS is. Given what we've seen on the adverse outcomes, we don't know.

Does it assure safe use? We've seen a lot of numbers and statistics that clearly say, no, it does not. And regarding the burden, again, we don't know to what extent it has. But again, as we're focusing going forward, I think this question is probably not the most relevant to spend a lot of time on.

DR. WINTERSTEIN: C, the burdensome, was pretty much addressed under 3. So we probably

don't have to -- everybody is nodding. And the response is we can probably skip C.

Dr. Perrone?

DR. PERRONE: Thank you. I tried to restrict some of my comments so we could get to a setting where we're talking about appropriate prescribing. So under B, I'm really concerned that we couldn't possibly assess the safe use of these drugs because one of the things that we really need to focus on is who gave that prescription to that patient for their very first opioid. Before they had a chronic opioid situation, who started their appropriate prescribing?

So really, part of the CDC guidelines have tried to address acute prescribing. But I don't know -- the patient may need long-term opioids now because it was started, but was it ever started for an appropriate reason?

So we really need to address, if you want to limit an epidemic, you have to limit new cases. And we're never really going back if we're already looking at people with chronic pain or chronic

opioid use. We're not really looking at how they got there.

So these high-dose long-acting drugs, somebody initiated a short-term drug for that patient that may or may not have gotten them to the long-term drug. So appropriate prescribing in this setting has to include sort of backtracking for the next wave and how we can really focus acute prescribing to appropriate situations?

DR. WINTERSTEIN: Dr. Craig?

DR. CRAIG: This is actually a follow-up to a comment you made about the current access. On C here, I don't think there's currently any burdens, but if there was discussion about changing things, I think that raises the questions about access becoming more burdensome, especially if there's much more mandatoriness of the new program, whatever that is, the lot of proposals to make things mandatory, make more teeth, make it better to evaluate.

I think, when you start talking about those things, that raises more concerns about access,

just in general.

DR. WINTERSTEIN: Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: I guess, on B, the question -- maybe I'll try not to slice this up too much. But the question saying about did the REMS assure safe use, and I think just maybe to reiterate, one of the themes that's come up is that's under, I think, what we've been talking about, how we measure what's appropriate use.

I would still bring up the question, the REMS should also be focused on helping us decrease risk as opposed to promoting safe use. So I think that might actually be -- I think one of the issues that's come up is what are we focused on with this tool? What's the tool for? And I think what's come up in regards to that is the idea of, are there prescribers who are causing a lot of harm?

So is there a role for a REMS tool, maybe not to promote and teach safe use, but to decrease some of the most risky interactions between practitioners, prescribers, and patients. That's my comment on B.

Then, on D, my comment on the burden to the healthcare delivery system, which I may be looking at through a funny lens, the REMS has at this point hasn't at all increased the burden. And I would say, I would see it from another thing. There is a huge burden on the healthcare delivery system right now due to the overprescribing, the diversion, the abuse, and the addiction.

So right now, the burden on the system, for primary care physicians, the burden is massive. Once again, there is utilization both in primary care, urgent care, the emergency department. There is utilization related to hospitalizations.

So right now, I would say that, if we wanted to look at it from that perspective, we would need, once again, potentially a more targeted tool or a tool that can really be much more aggressive. My fear is -- and we see this in primary care, and I think it's been mentioned by others -- that this issue has the potential to take an already beleaguered generalist's specialty, the family physician, the primary care physician, taking care

of a variety of chronic/acute conditions, counseling on prevention, the common mental health issues that enter a primary care practice, doing indirect patient care, phone calls, filling out forms, coordinating care, all the things that we see building around the patient center medical home, all very interesting and potentially a very beneficial approaches to the delivery of healthcare.

When you layer upon that, what we're seeing in the primary care, the practice of primary acre, there are practitioners who are leaving the practice of primary care, who are not going into the practice of primary care. I think we heard from a medical student as well. There is a tremendous burden.

So I think there is an onus for us, if it's possible, to utilize this tool to decrease risk, but also to decrease the massive burden on the primary care delivery system.

DR. WINTERSTEIN: Dr. Choudhry?

DR. CHOUDHRY: So I very much agree with

that last comment in terms of D. So to the extent, just briefly, right now, the REMS as it exists is not burdensome, I think. It's very much in the context of continuing education, which is standard bearer of how we all practice and get accredited. I think it needs to be more burdensome, but as it stands right now, the REMS is not.

DR. WINTERSTEIN: Dr. Floyd?

DR. FLOYD: I don't know the best place to put this. I don't see it in the other questions, but I think it's most relevant to the idea of risk assessment, of reducing risk. There's another side of this that's a benefit. We usually evaluate therapies in terms of risks and benefits, and we want the benefits to outweigh the risks.

I think it's worth stating. I don't think it's really been stated that for non-cancer pain, there is no evidence from well-controlled studies that there's an average treatment effect in the population that the use of opiates is more beneficial than the harms.

That said, we think that there are patients

who do benefit, and the way that we assess benefit is individually. We had an example from the public speakers about the ideal candidate patient who has reasonable expectations about the benefits. It improves function. It improves pain. It is aware of risks, uses the drug safely, and that happens on an individualized basis.

So I think that when we're talking about risks, we also have to talk about, are we actually prescribing the drugs to patients who benefits. And I don't think it's probably true that the vast majority of patients getting long-term chronic opiates are those ideal patients who are actually achieving benefit that outweighs the risks.

So I think, as we move forward, not only talking about the ER/LA REMS, but any other future REMS, we need to really focus on whether we can restrict the drugs to patients who have some measure of benefit, not only ones who don't have excessive risk.

DR. WINTERSTEIN: Dr. O'Brien?

MR. O'BRIEN: I just follow up with that

comment. It just reminds me that the REMS goal is for patient access, but I do think it's more about better patient management, effects. I think, anecdotally, in my own case, after four spine surgeries with a large regimen of opiates managed by an orthopedic surgeon, there was no adverse effects.

Two years ago, with an acute disc herniation and a cervical disc herniation with a nurse practitioner looking up drug.com and giving me a regimen, I ended up addicted after a 7-week period of time on both long-term OxyContin and oxycodone.

So there's a difference there. So my hope is that a REMS would end up with better management, not only in terms of what the prescription is, but how to manage and how to wean me off, when to get the patient satisfactorily through the treatment that they need, and get them on to a regular life without opiates in their life.

So I think it's beyond just access that's there, so I think that's a good point.

DR. WINTERSTEIN: Dr. Raghunathan?

DR. RAGHUNATHAN: The data itself shows that 71 percent of the patients were able to obtain a prescription when needed for pain, and 78 percent of patients were satisfied with access based on the data that was reported. I'm not sure whether they are, the right medicine, but I think they are getting access to what they wanted.

DR. WINTERSTEIN: So I think the committee feels that it is very difficult for us to evaluate whether the REMS and current REMS meets its goal or not because of the lack of appropriate data. As a personal comment, I think in thinking through this, it's difficult to draw the line at what the FDA can regulate, or has to regulate, and what somehow falls outside of the purview of the FDA.

What I mean with this is, the diversion issues, if somebody really sells the drug on the street, I think no REMS will ever be able to take care of that in a meaningful way unless we have patients essentially swallow their pills at a clinic every single time they take one.

So there is this issue of, we really don't

know how much of the opioid-related deaths or overdoses are related to inappropriate prescribing and inappropriate pain management versus just losing practices of dealing with these medications and selling them on the street.

That makes it so hard to evaluate whether the current REMS meets its goal or not, and that really is, essentially again, related to the missing evaluations, assessments, the appropriate metrics that should be used in those assessments, that haven't been used yet.

We all feel that safe use is not assured. I think we all are in agreement on that. And then we also agree that the current REMS as it is not burdensome in terms of patient access or the healthcare system. But as we are moving on to the next questions, how to keep that balance if we move forward with proposing a more restrictive REMS, that might be a separate discussion.

Yes? Okay. Break. Yes. Everybody feels a break is a good idea? Great. So it's 2:55, a 15-minute break. So we will be back here at 3:10.

(Whereupon, at 2:54, a recess was taken.)

DR. WINTERSTEIN: Let's get started. Everybody ready for question 5? Discuss whether the scope of the current FDA blueprint is sufficient. If not, what should be added or deleted from the blueprint? Dr. Stander?

DR. STANDER: Thank you. We've heard a lot from our public comments, and a lot of us have been impressed by the CDC guidelines. And I think including them or at least making people familiar and recommending that they become familiar is one thing.

I agree with Dr. Floyd and others who spoke, with particularly that I think the passion with which our addictionologists spoke, that we are underemphasizing the risks of these, and there should be much more of an emphasis on -- and, I mean that ED doc about equating it as starting heroin was maybe a little simplified and overly dramatic, but I think also, are we really emphasizing enough how potentially dangerous these are?

I think it's clear now that if you prescribe this medication to anybody, you have no idea where it might end up. And that's not necessarily because everybody is diverting it, but I've heard stories about people having it in their bathroom cabinet, it being stolen by construction workers, or realtors who come, or their kids, or whatever.

So I think that we really need -- as was outlined, I took a lot of notes about the speakers from the public commentary, again, the CDC guidelines emphasizing the risks, the lack of efficacy in chronic non-cancer pain.

To me, I know we're concerned about access for people who truly need it. I think that that's a concern, but a far greater concern right now is it's clear that our society is flooded with these medications.

I know I'm going to say something probably controversial and political, but it's analogous to the gun control issue. We have more guns and, gee, we have more gun deaths in this country than anywhere in the world. We have more of these

opioids in circulation in this country, and we have more opioid deaths. I mean, it's not that different.

So I think there should be a focus on reducing the amount of opioids out there, and I think the concept of better pain management education is also important, but you can't accomplish that in the kind of CME program that we're going to potentially mandate or ask for; but an emphasis that opioids is one part and probably a small part of management of pain, particularly chronic pain, and is kind of the last resort versus the multi-modal approaches that people want to emphasize. Thank you.

DR. WINTERSTEIN: Dr. Tyler?

DR. TYLER: Thank you. I think the blueprint provides a really strong framework for what should be our educational agenda for all health professionals in terms of the knowledge, skills, and abilities that they need to have. I really like the thread that came through in many of the comments, that this is not just about training

prescribers, but training healthcare teams. So from that standpoint, I think the blueprint could provide that framework.

I think one of the things that we struggled with in some of our comments is for a variety of reasons, the FDA and the RPR is going to focus on the drug-specific issues, when what really we need to think about is how do we treat the disease state, how do we treat patients in pain.

Obviously, as part of that, then, when is it appropriate to use opioids, when isn't it appropriate to use opioids falls as a part of that discussion, and then falls some of the drug-specific stuff. But spending some time emphasizing what should be the appropriate use of these agents in the context of other modalities for treating pain should be the emphasis of what we do as we build and modify the new blueprint, so taking that into account.

I think if we consider those things as we amend the framework, adapt the framework to what are the needs for what we need now, then that will

help guide us for what we need in the future.

DR. WINTERSTEIN: Dr. Choudhry?

DR. CHOUDHRY: So I agree as well. Clearly, there's some modification that I think would be beneficial. I think one thing will be duplicative with question 7, which is what else should be added, which is immediate-release products. So perhaps we can note that now. I suspect others will have an opinion about that.

I think the other substantive idea I wanted to raise in terms of the blueprint is the nature of what's required in terms of the structure of the education, and that's something that should be rethought.

We've heard this several times. I made comment on this earlier. Powers of continuous education one time may not be the optimal way to change behavior. So proposal for some flexibility in the way the course is set up or can be delivered, a requirement that it actually be not one time, even if you sat and did it all at one time, that would be insufficient. But there may be

an hour or two -- at one point, an hour or two at six months down the road, and perhaps periodic check-ins to encourage this idea of sustained behavior change.

So I think that all falls within the idea of changing the scope of the blueprint itself.

DR. WINTERSTEIN: Dr. Shaw Phillips?

MS. SHAW PHILLIPS: I would echo Dr. Tyler's comments about putting everything in context. One of the things that obviously needs to be updated is the role, where the role for prevention with the co-prescribing of a naloxone product would come in. That would need to be added.

I also was really struck by the comments both from the CE providers and in the assessments about probably the less beneficial inclusion of the aspect 6, which is the details of the specific drugs. And I think it would be much more appropriate to have that in a resource that could be accessed later as needed and really focus more on the high-risk class effects, like how to dispose of it properly and what happens if a patch gets

overheated, that are the more high-risk aspects, but then focus on really more the broad context of pain and multi-modalities of treatment instead of specific drugs that may not be appropriate for the particular participant.

DR. WINTERSTEIN: Dr. Galinkin?

DR. GALINKIN: Being a pediatric provider, I think that it's essential that the scope be increased to cover pediatric patients, especially now that we have two of the ER/LAs actually labeled out for children. And if we are considering making this mandatory and adding instant-release medications, pediatricians will be required to do this training, and you need to expand the scope to make the training relevant for that population.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: I've been looking through the blueprint on the Web for the last 10 or so minutes, and it's fascinating. It's almost frightening in its detail relating to the individual drugs that we are considering here. And I agree, and I would put a finger on this and say that there is no adult

learner in the country that is going to be able to manage that much detailed information, and that could be taken out.

Since that's seven pages out of 15 pages of the blueprint, what we could put in there are alternatives to use of medications or work on issues of physical therapy, occupational therapy, increasing function, or non-opioid approaches to pain management.

So we talked a little bit yesterday about the fact that this was so much information and how were we going to get it on at the end, and we couldn't apply new information on top of old information. But I think there's a lot of information in the blueprint that we can release and let it go to its death without any problem whatsoever retaining other information that will be much more useful in reducing risk to patients.

DR. WINTERSTEIN: Mr. O'Brien?

MR. O'BRIEN: To Dr. Stander's point, I agree that risk has to be the emphasis there. I still do think that patient education and patient

management are important issues.

To the comment that was made, when I look at it, a blueprint is almost like there should be a separate adjunct arm specifically to patients. The NIH and the FDA, they're very good at patient-centered care, and having informed patients, and involving patients, but I seem to see that's absent from this process for the REMS. We have it as a goal at the end, but we really don't have it integrated within the REMS process in the blueprint.

So to me, there would be a benefit in actually reaching the goal of reducing usage of opioids through a very positive educational campaign for patients in a blueprint to include what a patient should be told. Right now, it relies on just the provider informing or counseling. I don't think that's adequate enough.

I think that we would benefit by having an enhanced program for patients and allow the informed patient to be part of that process. If we're going to include a team and everybody agrees

on team, I think the most important part of the team is the patient, and that's where the outcome is going to come from.

I think we have an opportunity to positively impact that outcome by being more inclusive of patients.

DR. WINTERSTEIN: Dr. Parker?

DR. PARKER: So it seems to me that across HHS, we need to really have clarity and alignment. And the CDC guidelines from 2016 seem to need to be at the crux of it, since that seems to be the recent, most up to date. So I think really making that clear because, right now, it's possible to go to multiple components and get some mixed messages, and we really don't want that. And if there is indeed agreement that the guidelines for prescribing opioids out of CDC are really the crux of the chronic pain management, we need to be very clear that this is where -- it's just got to become very coordinated.

So it needs to be coordinated. And I know there are a lot of efforts going on within

different efforts to address it nationally, but clarity and alignment with the CDC guidelines to me seems to be just a high order. They weren't available at the time the blueprint was done, so that's one thing.

The presentation by FDA also mentioned the treatment for overdose as a possibility, I believe, for increasing the scope. That came up in some of the comments from the public. That seems very appropriate. The other thing came up that seemed very relevant was addressing mental health within this, and mental health needs, and how that's addressed as part of it.

But I think the coordination, the clarity, here it is, rather than, okay, so you might want to go to that site, too, and make sure you're not missing this, would really help as well.

DR. WINTERSTEIN: Dr. Gupta?

DR. GUPTA: I wanted to just agree with what Dr. Choudhry said and just take it a step further regarding how the blueprint information is being delivered to providers. We heard from some of the

graduate medical education leaders that there really needs to be intergenerational forms of this information. Older physicians or older individuals learn differently. Younger physicians learn very differently.

The way that the information is currently delivered, in my opinion, is not effective. And I do think that it needs to be interoperable to other systems, meaning pharmacies, the communication that exists, and also making sure that blueprint integrates a lot of what we're seeing from the CDC and integrates with other organizations' recommendations.

DR. WINTERSTEIN: Dr. Bateman?

DR. BATEMAN: So I think there should be some flexibility in the blueprint in a way that allows the CME providers to make the training tailored to the specialty or the care for the person receiving the training.

The content that's going to be relevant for primary care physicians is different from what emergency room physicians are going to need to

know, which is different from what surgeons need to know. I think the training is likely to be most impactful if it directly relates to the clinical situations that the specialist or care provider is seeing day in and day out.

DR. WINTERSTEIN: Dr. Morrato?

DR. MORRATO: I just wanted to build upon what Dr. Parker was saying in terms of coordination and alignment. I think harmonizing with a blueprint is also in a way going to help to harmonize likely with other state or association efforts because they also are going to be likely turning to the blueprint as sort of a plan to work against. So I think that's important.

I think two things related to that. I anticipate, though, or I suspect that it might be problematic in trying to do that because we're trying to merge label type of information that the companies care about, that may be different across some of their products, et cetera, the drug-specific information, versus the CDC's is probably more like a treatment guideline type of

information, which may have greater latitude, if you will, in terms of on-label, off-label kinds of considerations.

So I just hope, in the goal of trying to achieve a common national public health message, it doesn't get bogged down in some of those details. And that may be, given the importance of this and the feedback that we heard from the committee as well as the public that this is really important, we'll be able to work through that.

Having said that, I think a lot of times, things like a blueprint or just labeling may become static over time, and the only way they change is when you have a meeting like this or there's a big event where someone is going through a regulatory submission process.

So I hope that part of what can be built in is a bit of nimbleness that these sorts of things can be changing, and adapting, and not requiring all these meetings to help force that process along, and that given the importance of this public health problem, that the FDA has that latitude to

be working forward.

DR. WINTERSTEIN: Dr. Hertz?

DR. HERTZ: Thank you. Sharon Hertz. I'm hearing some really interesting ideas and, as I hear an idea, I'm already thinking about how it could potentially be operationalized, not that I know what we're going to operationalize yet, but with each possible suggestion, I try and envision that.

So I'm hearing a lot about taking out drug-specific information and putting in pain management. I'd like to hear, when folks have that sort of suggestion about what should go in, how do you see that fitting into a REMS blueprint in this sort of context?

DR. BUCKENMAIER: May I respond to that?

DR. WINTERSTEIN: Yes.

DR. BUCKENMAIER: I think it was Osler that said that the only victor in war is medicine. And so for 15 years, we've been in conflict. And this issue came to us, I think, sooner than it came to the civilian sector. And so there's been work

done, particularly by the VA.

They have a stepped care model, which is a very ordered way to approach, from a primary care standpoint, a pain patient. And so you can use some of those tools that already exist and other tools that the DoD and the VA have been collaborating on not just for a month or two, but at this point, literally years.

We have an entire pain task force that we went through together that preceded the IoM report, and we have a national pain strategy also.

One other comment I would like to make is, I'm a fan of the CDC guidelines because they're guidelines that can fit in this framework. But they are not good enough on their own, and, in fact, the evidence, by their own admission, supporting those guidelines is extremely weak. But we all understand why it was done that way.

I liken it to, if you just focus on the CDC guidelines as an approach or an answer, it's sort of like treating cholera in the modern era, and only treating cholera patients, and never bothering

to check the water source.

The driver -- and I'll say it again -- it's three times, and we have to do that in the military; that means it's important -- if you separate the issue of opioids from the driver, which is pain, you will fail.

So I think it's an excellent suggestion and we already have tools that we can either adopt or look at as examples to begin that process of an effective REMS that would incorporate good pain care, and that doesn't start with opioids.

If you look at the stepped approach, the first answer is not opioids. It's a lot of other things. And you begin to change the culture because that's what we're talking about, a cultural change.

That's why this has been such a challenge in the DoD, because we are 230 years not hampered by progress, and it's very difficult to get things to move in a certain direction. And that's what you're attempting to do, but that's what this REMS process could do if you expanded it beyond just

what I think is a relatively myopic focus, though I still support it because it did demonstrate success.

DR. WINTERSTEIN: Dr. Gerhard?

DR. GERHARD: I completely second the last comment. I think it's critically important, and I think the perspective provided in the public comment session of just putting the utilization rates for opioids, including the IR opioids in an international perspective, gives you some idea of how off the charts we are in this country.

So there is clearly use that is maybe initiated too early, as was just mentioned. It should not be the first step in pain treatment. There is likely a lot of use for indications where the evidence base for the effectiveness of opioids is very weak.

So I think, to strengthen that type of information in the blueprint is critical. And when that is done together with an emphasis on the risks, I think it's pretty clear that everybody exposed to opiates is exposed to -- that hopefully

would lead to a situation that only the patients that are likely to benefit from opiates and that have exhausted less risky alternatives, that only those patients will receive the opioids, and that we get away from situations where we have patients that aren't likely to benefit from the opioids but are at the risk for all the adverse outcomes that we've been discussing.

So both of these issues could be incorporated, an emphasis on the risks and a clear emphasis on alternative treatment strategies, on areas where there is a clear lack of effectiveness of opioids, they probably don't have a role that's anywhere close to the size that these drugs have in their current practice.

DR. WINTERSTEIN: Dr. Raghunathan?

DR. RAGHUNATHAN: I thought you could fit it in within the context of appropriate and inappropriate use of opioids. So if you take the pain management as a crux of the matter, then appropriate/inappropriate use can be framed, and then that gives you a way to really measure the

outcome as well.

DR. WINTERSTEIN: Dr. Brown?

DR. BILKER: One comment, addressing directly to Dr. Hertz's question, and that is that I don't really think that the content of the blueprint needs to be absolutely perfect. There's no perfection in either the choice of medications that we choose for individual pain patients, nor in the other alternatives.

But what does have to be perfect is that we have to offer folks alternatives if we're suggesting that opioids are, what some people have said, not safe to be used under all circumstances. And the blueprint has to suggest that the information that we're giving people can be presented in a way that adult learners can digest because if we give them a Sears and Roebuck catalog and expect that, that is going to have an impact on their behavior, the Sears and Roebuck catalog is not going to be utilized.

So I think that this is something that can be done. We can operationalize this if we put our

minds to it.

DR. WINTERSTEIN: Dr. Krasnow?

DR. KRASNOW: I don't want to go off on a tangent, but the only times I've gotten upset during this meeting is when I hear about our comparison to other countries in the world. As an oncologist, I've read quite a bit about the pain problem in cancer patients around the world, and I'm well aware that there's no access in most countries other than perhaps western Europe to modern pain control.

So I would not hold up our international neighbors as paragons of virtue. We can still agree that there's too much opioid prescribing in the U.S.

DR. WINTERSTEIN: Dr. Hoffman?

DR. HOFFMAN: So I think, while we don't want to focus on detailed descriptions of medicine, as a person who thinks about safety, I also think about there are certain medications where it's critically important that providers who are prescribing an opiate know about issues like need

to monitor, QT interval, and drug interactions like a patient on methadone.

So I think you can't completely take medications out of the education. I just think we need to think about extremely high-risk situations to help mitigate that risk, and then put systems in place hopefully. And I think this will not need to be done at the FDA level, but at the institutional level where you're sort of reminded, hey, idiot, you haven't checked an EKG on this person who you're about to prescribe this medication to. But I think you need some information about medication when it comes to risk reduction.

DR. WINTERSTEIN: I think the committee agrees that the blueprint is very important for two purposes, one, to ensure that the appropriate information is covered; second, to produce a standardized framework for the education. And in this context, it was emphasized that coordination needs to occur with all the other programs that are happening to have one clear message that gets conveyed.

With respect to the information on the blueprint and the content of the educational intervention, the committee recommends more emphasis on pain management rather than individual opioids -- now I said it the fourth time -- more emphasis on risk and enhanced discussion; how to reduce opioid use; more emphasis on alternative or opioid-sparing treatment strategies; consideration of the CDC guidelines; lack of efficacy in chronic non-cancer pain and the idea that opioids may not always be the right choice; more concrete guidance on what is appropriate and inappropriate use for physicians; to include immediate-release products, to include special populations such as pediatrics, especially when immediate-release products are included; deemphasize drug-specific information, but retain key issues that are drug specific, the key safety risk issues that are drug specific.

There were several comments on the structure. Perhaps several separate hours rather than one session might be more effective; a broader portfolio of formats to accommodate different

learning styles; core and specialty-specific segments such as a pediatric-specific segment or an emergency doctor-specific section.

There was a recommendation to ensure maintenance of the blueprint so that new information, as it becomes available, gets incorporated and case-based education that focuses on management of pain as opposed to just the drugs themselves. Then lastly, there was the recommendation to think about a blueprint for patient education.

Moving on, question 6, discuss whether the current medication guide and patient counseling document are sufficient. If not, what should be added or deleted? Ms. Shaw Phillips?

MS. SHAW PHILLIPS: Until we get started, I would like to start by saying I think these documents are both very good, and we can't lose sight of the major problem, which is they're not being used. So most physicians are not using the counseling guide when they're talking to their patients, and even though a lot of times they're

getting stuffed in the bag with the product at the pharmacy, the patients may be aware of them but don't even look at them.

So I think getting uptake of actually reading in use and practice is really important, and it needs to be part of the strategy. So that's where public outreach to communication to the patients is important. Public health announcements are important. Web-based and other media things are important.

But I do want to commend the FDA and the folks that put this together. I think one page, or one page back and front medication guide, is really, really good. They're a lot better than most of the medication guides that I've seen.

They really do highlight some of the key messages that I heard some of our other speakers talk about and say that they would like to see in there, which is, this is because other modalities have not treated your pain well enough where you couldn't control or you weren't able to tolerate them; and even if you take this correctly, you're

at a risk for addiction, abuse, and misuse that can lead to death.

So I think those messages are right up front, but it is put in the context of, this is something that your doctor feels that you need, but here's some things to think about. So I do think a lot of the necessity is around increased uptake abuse of these documents rather than a whole-scale rewrite of them.

DR. WINTERSTEIN: Dr. Galinkin?

DR. GALINKIN: So being from Colorado, I really think that you need to have some focus on not co-administering marijuana and opiates. In Colorado, from our data, the number one reason people got medical marijuana cards before things went legal was severe pain. And 94 percent of marijuana cards, in I think it was, 2012, were for medical marijuana cards, and that was nearly 107,000 prescriptions for medical marijuana cards.

I'm sure that's true across all states. Now that we're legal, we have somewhere between 5 to 10 percent of people using marijuana on a daily

basis. So putting our head in the sand and saying these are not co-administered can't go on. So we really do need to have some advocacy for people not co-administering these drugs.

DR. WINTERSTEIN: Dr. Fry?

DR. FRY: As far as the medication guide goes, working in a retail pharmacy, Oregon is a mandatory counsel state. So I do try to hit the big points every time someone gets it. On refills, we don't counsel. We always offer. It does get stuffed in the bag, and you will see that even more in your big-box pharmacies, where they're understaffed and busy.

I think it should be something that prescribers should be mentioning, but it does also fall on the pharmacist to do that. And I know it's not always going to be done, but I think pharmacy agencies or boards should also stress that with a pharmacist. We also have mandatory pain CE in Oregon to do also, so something like that should be stressed more than it actually is.

DR. WINTERSTEIN: Dr. Stander?

DR. STANDER: I think the content is one piece, and I would echo that, for the most part, it's quite good; I think some of the expansion around mental illness, other medication, the risks. But really, the key is -- and again, it's more about quality improvement effort -- how do you actually effectively use it?

I think, as we've heard, the primary care physicians are incredibly overburdened. They may have 15 minutes with patients. They're not going to likely effectively do the counseling. And I really think, beyond just the content, we have to look at what's really the most effective way to make sure patients hear this message, whether that involves the rest of the team? Have we talked about the nurses?

Maybe the oncologists could offer us some suggestions. I know that in their offices, a lot of the nurses are doing some of the education about chemotherapy; the role of the pharmacist at the dispensing end, and whether we should really look at the patient signing or acknowledging they have

received this counseling and education in some format.

Again, I think we're looking at ways to impress upon them the seriousness of the medication they're about to receive rather than just, sure, here's some oxycodone.

DR. WINTERSTEIN: Dr. Tyler?

DR. TYLER: Thank you. I agree with Dr. Shaw Phillips in that I was really impressed with the medication guide and patient counseling document. I think we do need to take this opportunity to see how it coordinates with naloxone, whether it's having a med guide for naloxone. But that's something that's changed since it has been written.

DR. WINTERSTEIN: Dr. Kaye?

DR. KAYE: I just want to build on what Dr. Stander said. The average patient does not -- I think if they understood clearly the risks versus benefits of opiates, such as shutting down your endogenous opiate production, hormonal changes, suppression of natural killer cells that

can lead to propagation of infection or cancer, and the psych issues, that may make the average person, in layman terms, not in high-tech science terms, think that maybe they don't want to be on these for the rest of their life.

So I think that some better mechanism would be useful in our epidemic.

DR. WINTERSTEIN: Dr. Parker?

DR. PARKER: So I was focusing specifically also on the patient counseling document. And I was stepping back, saying, what is it that everybody really should be doing in that interaction, and is this document going to guide the person prescribing it through it?

I think the ordering of the content really needs to reflect the priorities. And I think that document could be made better very specifically. I do think a key message up front is that you're being prescribed a narcotic, which is addictive, what that means, why this counseling is happening, and really reflect that rather than the dos, read the medication guide.

We already know most people don't read them. That's a problem. We're telling people to read them. But what are the absolute critical messages here, a way to make this more interactive and to say here are two or three questions you should be asking your provider; to engage and to look for ways to have the person receiving it interact with the person who's actually prescribing it for them.

So I think there could be some focused attention that could improve that. It does need to be a standard document. It needs to be the same across, and it needs to become a conversation that you are very facile with and move through very quickly that reflects the priorities and is in a language. I think it's a good start, but it could be made better.

The med guide, same thing. I think there's always room for improvement on some of those. And there again, the ordering needs to really reflect the most important messages.

One other comment I wanted to make about the patient counseling, there's nothing on here about

use of alcohol in addition to the marijuana, other substances, those being very important, and just being very sure that those key messages are right there.

DR. WINTERSTEIN: Dr. Hoffman?

DR. HOFFMAN: I think some of the things that everybody is talking about, again, the VA has a pretty nice med guide that goes through some of these issues that I'd be happy to share with you. And we have also done some of the how do you get this to patients.

So patients did have to sign informed consent in Pittsburgh. We had a year to get it done. We tried it multiple ways, so initially providers were given this task to do alone, and we weren't very effective at doing it.

So then we did pre-mailings to patients to let them read the guide before they came to clinic, so that they could have a discussion with us at the time they came to clinic. Our boss actually created a YouTube video that goes through the guide.

So there are a number of different ways that I think it can be done, and I'm happy to share that with you so that you don't have to reinvent the wheel.

DR. WINTERSTEIN: I think, on large, the committee likes the medication guide that is available. The primary emphasis was placed not so much on the content than the delivery of the medication guide. Several suggestions were made, one including larger involvement of the pharmacist in going over the guide and ensuring that patients know what they're getting in terms of information that is important.

The second was to perhaps add a mechanism to the REMS that would require patients to sign that they received the medication guide or to sign the medication guide itself, similar to some type of consent form. That of course could either happen in the pharmacy or it could also use these patient-provider contracts that have been suggested to initiate opioid-based pain therapy. In terms of content, two specific issues were mentioned that

involved concurrent use with medical marijuana in those states where it's available and alcohol.

Does that summarize it?

Moving on to 7, discuss whether a REMS for immediate-release opioid analgesics should be required to ensure the benefits outweigh the risks? Ms. Shaw Phillips?

MS. SHAW PHILLIPS: I don't think, after our discussion, the next few days, we have to say much more than yes. Right? Because I think there's general agreement about that. But I think that's where a key part there is going to be that medication guide for the patient is another piece of paper, yes, but getting that initial communication in the patient's hand and that initial discussion both at the provider level and at the pharmacist level, at the dispensing level, that this is something significant, not to be taken lightly.

Even if you're taking it for an acute pain episode, there's still a lot of things you need to think about, both to use it safely, to avoid

addiction or other behaviors, and to prevent diversion of the product.

DR. WINTERSTEIN: Dr. Floyd?

DR. FLOYD: Just to second that, I hope the answer is a unanimous yes. And I think the focus is not on any one high-risk product. It's on the chronic use of opiates for chronic pain and the various safety risks and concerns. And that really is the focus and not the product.

Just to second previous comments, I think the CDC guidelines are a great template and starting place. Of course, there are other elements that could be included, but that reflects our best assessment of the very limited evidence we have and the best recommendations.

So I think that is a starting point, and that clearly involves all kinds of opiates, primarily with an emphasis on chronic use.

DR. WINTERSTEIN: Dr. Choudhry?

DR. CHOUDHRY: I obviously agree as well. The one minor wrinkle is, of course, that there are lots of different state regulations on the use of

short-acting immediate-release products for acute pain, and they vary from state to state. So the Massachusetts legislation is quite different than the ones in New York, different from Arizona, and so on and so forth.

So to the extent that there is, they're included, but there needs to be an acknowledgment of the variability, which may be greater and could create confusion if it's just blanket saying, here's what the CDC says.

DR. WINTERSTEIN: Dr. Craig?

DR. CRAIG: Thank you. I just want to echo that this actually was a recommendation on original REMS discussion in, I think, 2011, and I remember saying the same thing I'm going to say now, that all opioids should be included in any particular REMS educational program because if you look at death data, it's impossible to look at the ER versus IR formulations. Then, if you're going to prescribe opioids, it's probably worthwhile that you know how to use this tool and use it safely, hopefully.

So just to a little bit of déjà vu, we should probably include all opioids as we originally recommended.

DR. WINTERSTEIN: Dr. Morrato?

DR. MORRATO: Just to add to that, the boxed warnings have already been expanded in order to be more similar to the ER/LA, so by not having a REMS function with immediate release, you'd have to be explaining why. Why have a warning that's similar but not have the risk management similar?

DR. WINTERSTEIN: I don't think there's a need to summarize that. Three times, yes. Mr. O'Brien?

MR. O'BRIEN: I summarize by saying yes, but I did want to emphasize, in terms of counseling, it adds even a more difficult issue because it's tough enough when a patient comes in. First of all, they only retain 10 percent of what they have anyways. I think we have to be really creative and think about methodologies. And I think the VA source that's mentioned may be good because just to sign something -- if you're in acute pain, and you're

sitting there, and you really just want to get something to relieve, you only hear 10 percent anyways, you don't hear. You sign anything. You already asked to sign nine different forms anyway. You have no idea what they say.

Unfortunately, the patient is desensitized right now because if you want whipped cream, it has a label that's this big, and tells you you're going to die of this and that, and this and that, never mind when you get into an opioid.

So I think we have to think about, really, what's the environment and what's the reality; what makes us feel good, but really what is effective in terms of delivering that message to that particularly the first time opioid user?

DR. WINTERSTEIN: Moving on to question 8, discuss whether prescriber education should be required in order to prescribe an ER/LA and/or IR opioid analgesic? If so, consider any burden on the healthcare delivery system and patient access. Discuss mandatory prescriber education by a restrictive closed-system REMS or some other

mechanism by which education should be required, for example via DEA registration and renewal process, state licensing and renewal process.

Dr. Galinkin?

DR. GALINKIN: I think the easiest way to actually get everybody, if you're going to make this mandatory, is to tie it to DEA registration. You'd have everybody registered within three years. The pharmacist would not need to check anything except the DEA registration, so it would not be an undue burden on pharmacists beyond what they already do.

So I think that would probably be the most straightforward and easy way to do it as long as the FDA could cooperate with the DEA on that.

DR. WINTERSTEIN: Yes. I was reminded that the FDA actually wanted to clarify something in this regard and, of course, I forgot about it.

DR. THROCKMORTON: Yes. Thanks. This is Doug Throckmorton. I just wanted to help frame this discussion because it's been a discussion that people have commented on for the last couple of

days.

The major thing that we need your feedback on here is mandatory versus available but not mandatory prescription provision of the educational materials. There are a variety of programs that one could think about that might support a mandatory prescriber education. The DEA is one of the things that's been mentioned already. That would be an authority under the Controlled Substances Act. That's the DEA. They're not here in the room to defend themselves.

That would be one mechanism that people have talked about, including the stated White House interest in providing that. There is interest in an authority under the Food, Drug, and Cosmetics Act that the FDA might use to require mandatory prescriber education. That would link to the provision of the education through the manufacturers. So our authority is over the manufacturers. That would be a provision of the mandatory prescription education in that way.

There are programs that exist, for instance,

in the Indian Health Service and the NHHS that require certain groups of prescribers, federal prescribers, to take education on pain management and the use of opioids. And then there are a variety of state activities that have required the receipt of education around the use of opioids under one authority or the other.

Any or all of those might be something that we would contemplate, but for today, the most important thing for us is to have you think about mandatory versus non-mandatory provision of education, especially I will say, given the answer you just made to the last question.

So if your interest is in a very broad set of opioids and educating about them, now we need to really make sure that we're talking openly about the impact of that kind of a choice and, again, mandatory versus non-mandatory provision of the education. Thanks.

DR. WINTERSTEIN: If I may comment on this, I think the impact somehow cannot disconnect it from the implementation. And I think that was made

very clear by Dr. Auth earlier when she exemplified the numbers of checks that pharmacies may have to do if there were really a program that would be similar to the current REMS that are organized through the manufacturer, basically some third-party entity that registers, where the prescribers have registered and so on.

So I'm not sure it's easy for the committee to discern those two, but we can certainly have two separate discussions. One is, are we in favor of a mandatory program if there had to be a check for every single prescription by a pharmacy versus a mandatory program where that would not be the case because the pharmacy would be able to imply that, if they see a controlled substance prescription, that this person is certified in terms of the training.

Would that make sense to have those two separate discussions? Because knowing how my committee fellows feel, I think they are separate discussions.

DR. THROCKMORTON: I'd agree that impact

can't be completely severed from the potential routes of implementation, and I do think Dr. Auth's presentation is very useful in that context. I think what we'd like to do is make sure that we understand the rationale for a recommendation to make it a requirement to get education.

So in the last couple of days, there has been discussion about potentially how a requirement might change prescriber willingness and interest in education and things like that. So just understanding whether that requirement changes the value, the impact, the outcomes that we all want to have as a consequence of the education sufficient that it's important to do, that would be an important first question for us.

Then the impact is the second question, and you're absolutely right. That can't really be separated entirely from the mechanisms that we might use. I don't want us to get wrapped up in questions entirely focused on the mechanisms because, one, we can't predict exactly the nature of them, so it's going to be a little bit

challenging to have a granular discussion; but second, it's beyond the full scope of what we'll be able to discuss today.

DR. WINTERSTEIN: Dr. Higgins?

DR. HIGGINS: I concur that it should be a restricted system. I think we've seen through the REMS data that we've been looking over the last two days that a voluntary approach really yields some inconsistency with respect to saturation and quality, I believe.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: To Mr. Throckmorton's point, I think that most physicians are at this juncture entirely used to specific requirements for continuing medical education so that it's not going to be a circumstance where we're going from zero to infinity.

The Commonwealth of Kentucky requires that every two years, we have 4 hours training concerning HIV/AIDS, and I don't think anybody has thrown themselves off the roof for that. I agree with everybody that has said that unless we make

this mandatory, then we're never going to know whether or not we had the potential to infiltrate and inculcate education into the broadest possible population of healthcare providers.

I seriously doubt that any kind of voluntary program is going to be able to be effective.

DR. WINTERSTEIN: Dr. Morrato?

DR. MORRATO: I just wanted to add to that. So I was on the 2010 committee as well that was reviewing this, and I was in the minority and voted in favor of voluntary.

At the time, I was concerned about the potential burden at my place, but also the precedent-setting nature that, if we can't make voluntary work in this kind of setting, does that mean all future prescriber education needs to be mandatory?

So it seemed like this might be an environment in which voluntary might work. There was a clear need on the importance of this. And I was concerned around a simple solution like linkage with the DEA licensure might take too long.

However, I think what we've seen -- I was also anticipating that there would be strong marketing and a lot of concerted effort around getting the voluntary program, and we haven't seen that. We haven't seen results like we saw in New Mexico or heard about.

So just like what Dr. Brown was saying, I've come to the resolution that it really does need to be mandatory. But I think as we're debating the mechanism of mandatory, I would hate for us to take our foot off the pedal on the existing voluntary program so that we are at least trying to move that forward and we're not in a limbo waiting for a decision around another kind of solution.

DR. WINTERSTEIN: Dr. Floyd?

DR. FLOYD: I agree with what's been said. I think, of all the different elements involved, this is just one. And it may not be the most effective one, but I do think it has the potential to be effective with encouraging safe prescribing. And for it to have any chance of being effective, it must be mandatory, whatever the mechanisms. I

want to be clear about that, voter recommendation.

Secondarily, of course it would be much easier if you could link to DEA, so a strong encouragement to try to work it out with the other agencies. But even if that's not possible, I do still think that this needs to be a mandatory education component.

DR. WINTERSTEIN: Dr. Craig?

DR. CRAIG: I'll take just a little bit of an oppositional view here. I don't think it should be mandatory. Actually, at the time when we had the original meeting, I thought it should be. And if I've heard anything from the past day, it's that the education is not working, and the education won't work.

The REMS is to try to reduce abuse and overdoses. We know that majority of people who abuse opioids are not patients prescribed opioids, so targeting prescribers so as to get at that problem won't work.

Number two, targeting overdoses, again, the majority of patients who die from opiate overdoses

were not prescribed those drugs. So opiate REMS will have no effect on those two in my personal opinion. So mandating more education -- and I think pain education is a wonderful idea and I think that mandating pain education, I think, makes more sense. I think mandatory opioid education in my opinion doesn't make any sense.

DR. WINTERSTEIN: Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: I had a couple of comments, but I'll try to comment on that one, too. I was not here in 2010, and I sure don't want any of my comments to -- I'm not critical, and I'm not using the retrospect scope, but I think we learn from history and we learn from process that came before.

Now, just to be open to the committee, having come into the end of the two days, I reflect on the feedback we've received. And we spent a good part of yesterday hearing from the pharmaceutical industry and the continuing education industry And of course, we heard from the FDA and other experts.

We spent only two hours hearing from public comments today. So I feel like, one, I'm supportive of mandatory, and for the record, we can't disconnect those. And I'm sorry, FDA, we cannot disconnect the mechanism.

Bureaucracy has to be challenged. We are responsible to do the right thing and we can't use bureaucracy as an excuse to not do something. So mechanism must be addressed. It must be addressed aggressively, and the DEA option should be explored.

So having said that, I think -- and my other reservation is I am worried that we could be back here again getting more feedback from the pharmaceutical industry and the continuing education industry, and that's going to be guiding our decisions. And that is a major concern for me because I'm already feeling that I spent a lot of time hearing from groups that are wonderful groups, a lot of hard work, but I'm just really confused as to how those groups became the driving source of data and dialogue about a risk reduction program

related to products that they produce in an industry that was educating us about them.

DR. WINTERSTEIN: Dr. Raghunathan?

DR. RAGHUNATHAN: Since with the modification of REMS that includes some information about pain management, I feel comfortable in adding the IR, feel comfortable that it should be mandatory in order to make an effect on the an appropriate and proper use of the opioid for pain management.

But I also think that there is a middle ground where you can develop a mandatory system, but there are some placement exams built in where they can pass that exam and they don't have to go through that mandatory CME.

So for example, we do give that kind of exam to the people who want or are taking biostatistics courses. So we give placement exams. And if they pass, then they don't take any biostats courses.

So maybe there could be a common ground where you can provide some legitimate exemption for this process if this is going to be burdensome for

healthcare delivery.

DR. WINTERSTEIN: Dr. Tyler?

DR. TYLER: Thank you. I want to build on Dr. Garcia-Bunuel's comments. It strikes me, if you ask the fundamental question, do we have a public health crisis or not, I think all of us in this room would say, yes, we do. Then how do we create the urgency that we would around any other public health crisis?

So to your point, the frustration that you're hearing coming out in different ways today is each of the agencies are using the tools that they have available to them to try to address it, but here we are. Each of the agencies by themselves will not be able to create the urgency in terms of what we need to do.

I think this is where it's like a square peg in a round hole in terms of REMS doesn't all by itself solve it. And if we're trying to do the education in the constructs of the REMS, then I think that's where we're going to have some difficulty.

So when we start talking about mandatory education, it's about how we solve some of the other how do we manage pain in the United States and the opioids that go along with it. So when you talk about education like that, much like what the New Mexico model was, which I was very impressed with, then we start realizing that we can't really do it in the constructs of the REMS.

REMS by their very nature involve industry very closely, and having industry drive this agenda does not make sense for a variety of reasons that are already stated or already discussed.

So I think it's very important that we think about how we pull together the agencies that are involved that can help make a difference, both at the federal level within Health and Human Services and with the DEA and Department of Justice.

We have a network of public health systems with our state partners, and I think we can coordinate some stuff with our states that would create an incredibly strong program in addition to the resources that are already in our federal

services healthcare system.

DR. WINTERSTEIN: Dr. Choudhry?

DR. CHOUDHRY: On balance, I'd probably favor a mandatory approach, but I see some of the pragmatic problems with this, and I shared some of Dr. Craig's concerns about its ultimate effectiveness.

There are perhaps two middle grounds, and these are two sort of disparate concepts. But one is about, maybe it's not for all prescribers, but it's for some. And there are ways for us to define using routinely available data that's basically available in real time prescribers who actually prescribe to lots of patients appropriately or otherwise, who prescribe a many-days supply, who prescribe lots of pills, who prescribe on average a high total or maybe cumulative total morphine equivalents.

So one middle ground might be to actually think about who this is then mandated for. In a similar vein that we require certification for performance of procedures for those who actually

performed the procedures, this is kind of in that same vein.

The second middle ground is just more of an operational thing in terms of how this could be mandated or Dr. Raghunathan was talking about passing out of a qualifying in a biostat kind of course. But we write recertification exams. And while the cycle may be too long, it's certainly something to think about.

So every 10 years, those of us who are internists here do this. I suspect the anesthesiologists and the pediatricians have their own cycle. So to the extent that those exams are supposed to reflect what we're supposed to know in order to practice, it seems, to some extent, duplicative to then create entirely parallel systems.

So I think I would encourage a different type of collaboration. We've talked about regulatory collaboration, but there's also state medical boards or specialty societies that have a lot do with this process as well.

DR. WINTERSTEIN: Dr. Parker?

DR. PARKER: You give me pause. I appreciate your saying that. But I do feel like, all in all, the mandatory I think needs to be there. I do underscore -- I know the agency has since 2011 been in favor of working with the DEA registration and requiring that all DEA registration for controlled substances have to be trained on responsible opioid prescribing as a pre-condition for that registration.

That makes sense to me, and I know it hasn't happened. And I know that it's a complicated story, but I still think it's the right thing. So I just say that as part of the record like many others.

I think the other thing to really underscore is industry-sponsored REMS as part of mandatory training. Does it make sense? I don't think -- and I think, if you go with REMS or restrictive REMS, and it's industry sponsored, I think that's still going to lead to some problems.

So I do think the industry sponsorship is

something that needs specific attention for this, and were it linked to the DEA registration or whatever other mechanism, that needs to be very carefully thought through. There could still be sponsorship, but it could be at arm's length from what actually ends up happening in the training sessions.

There may be a way to pay for it but be at arm's length and not really linked to the bottom line of the manufacturers who are actually producing the products. I have some concern with that.

DR. WINTERSTEIN: Dr. Israel?

DR. ISRAEL: I would support what Dr. Parker just said, that I think that mandatory education is necessary. And we're in the middle of a public health crisis. I would like to see something happen in an easier, if there is such a thing, way to make this happen.

We all have to go through CME to get licensed every time our license needs to be renewed. Part of those hours could be 3 hours,

5 hours, whatever it is, of opioid education every 2 years, so it gets reinforced without having to go back and create a whole new system to try to figure out how to track all this stuff. And I do think it needs to be separated from industry, at least at arm's length.

DR. WINTERSTEIN: Mr. O'Brien?

MR. O'BRIEN: I wasn't here in 2010 anyways, but I had taken history to be that it wasn't funding. I thought it was industry funded, not industry sponsored, so I'm not clear about the independence issue, but independent to me is important.

But to the issue of mandatory, the perspective, which I reflected earlier or yesterday, was looking from a patient perspective, I think there's a quandary. And I would support mandatory; not that I like mandatory programs, but to the issue -- my understanding is in Massachusetts, for example, it's now mandatory for education. We have other states, as was mentioned, so we've got this quandary.

Well, from quality of care, if that's going to be a standard of care, then from my mind, this shouldn't be a different standard of care because someone is educated in Massachusetts but they're not educated in whatever other state that may be. We should have a standard that exists throughout all.

So from that perspective, from a patient's perspective, I would support a mandatory education. Now, obviously, we have the two arms, and I cannot separate impact because if that means that people can't get the medication they need, well, that's a whole different story.

But absent of tying the two together, then I think from a standard-of-care perspective, I would be in favor of all mandatory. Everybody should be educated to understand the risk and benefits of this condition or this medication.

DR. WINTERSTEIN: Dr. Fry?

DR. FRY: I just wanted to add that when they think about the mandatory training, linking to the DEA is probably the smartest way. Part of REMS

is patient access; 67,000 plus pharmacies in the country, all of us had to get licensed also, and then go through special certifications to fill. And every time a prescription comes in, go through that, it would really limit patient access.

DR. WINTERSTEIN: Dr. Stander?

DR. STANDER: I think the only thing you can say about mandatory education -- I'll take a little issue with Dr. Craig when he said it doesn't work or we see education doesn't work -- I think the best we can say is, nobody expects that education alone can work to fix this problem or to make people better.

I think the best you can say is that it will increase the likelihood that people will use these medications more wisely with greater competence. So I think, on balance, I would favor mandatory education.

I think there are ways to build on rather than creating a whole new separate system. I like Dr. Israel's comment about, virtually every state has mandatory CME. If you can document that

X number of hours every cycle of your license is built in.

could link it to some of the board certification, although nobody has ever shown that board certification necessarily guarantees that people practice well, and those are often separated by 10 years at a time. But you could opt out of -- have certain specialties, whether it's pain specialists, anesthesia, who have trained in this and might be able to opt out just by maintenance of their certification.

So for the rationale, I think, on balance, you would say that educating people about the use of very dangerous medications intuitively would increase the likelihood that they do things more correctly.

I'm not quite sure that you opt out -- only educate the high-volume users. So I'll take a little issue with Dr. Choudhry because it may be that those people -- again, if you believe in the volume, quality relationship, it's maybe the people who are barely using it once or twice a year or

cavalierly, I think they need the training more.

The other unintended consequence of this, which may be a good thing if you link it to DEA registration, may be the people who will opt out of the training and the people who really don't want to prescribe this, or don't want to deal with this, or don't want to get the training, maybe we don't want them to be prescribing anyway.

So I mean, I don't know if we know that will happen or not, but for those reasons, I think I would favor the mandatory. If we keep it voluntary, we're never going to get very many people trained.

DR. WINTERSTEIN: Dr. Krasnow?

DR. KRASNOW: A follow-up to some of the comments here raised, in my mind, the model of the CITI bioethics course, which many of you may have had to take. I have to take every three years as an investigator and IRB member.

When you go to that exam for your recertification, you don't have to go through the whole course material. You can flip through and

take the exam questions. And if you pass the exam, you're done. I can do that in well under an hour, having done it so many times. That would be one way to make it less painful for people who are well trained and experienced in their field.

The other thing about the CITI course is that it has expandable modules. There's a core curriculum that everybody is tested on, but then, if people are interested and want more information, you can expand the modules and get more, but that part is optional.

So there are ways to do this that I think would be relatively painless.

DR. WINTERSTEIN: Dr. Buckenmaier?

DR. BUCKENMAIER: After 26 years in the Army, mandatory doesn't bother me, so maybe I'm not the right person to comment on this.

(Laughter.)

DR. BUCKENMAIER: But I hate HIPAA, can't stand it, hate the information, don't want to have anything to do with it. And despite my best efforts, I know an awful lot about HIPAA because I

have to do it every year. In fact, this is my birth month. I'll be doing it here, and it takes me no time. But there is occasionally a question that trips me up because something has changed. And despite my best efforts, I know stuff about HIPAA that the government wants me to know, and I can't stop it.

The fact is that, for this training, it's so fundamental to what we do as physicians, particularly the pain management aspect of it, why wouldn't we want to do that on a routine annual or semi-annual basis to make sure that we have that information down pat, and that as things change that we may not be aware of, these were not in a training situation anymore, we're getting that information.

You don't have to like pain, but you're not going to be able to do medicine unless you're a pathologist and not deal with it. So why not make this mandatory for everybody since we already do that for some other critical issues like HIPAA.

DR. WINTERSTEIN: Dr. Kaye?

DR. KAYE: Just to dovetail, I was reminded from what you just said that I have to renew my ACLS card --

(Laughter.)

DR. KAYE: -- if I want to practice in my hospital, so amen to that.

DR. WINTERSTEIN: All right. I think there is fairly overwhelming, not complete, but overwhelming agreements that this should be a mandatory educational system. I think everybody is doubting how much of an impact it has, but it also is, I think, very clear that everybody agrees that proper prescribing practices should be available and should be given to every opiate prescriber.

I think everybody favors that if there were a mandatory program, checking off, complying with that mandate would be tied to something that would not need to be checked by pharmacies. So that would be, I think, favorably either DEA registration or licensure.

Many arguments why mandatory were provided. The biggest ones were, providers are used to

required CME. It can be part of the overall CME anyways. There's an increasing number of states that require pain CME now. Why not? It's not different from HIPAA, and so on.

The mechanism should be addressed. And I just mentioned this, -- sorry -- the evaluation should be addressed of the programs. I think there was some discussion to deemphasize the industry impacts in administering those programs if it becomes a mandate.

I think most panel members agree that there should be some process that would allow prescribers with clearly adequate knowledge such as pain specialists to opt out or take some type of prior exam that would allow them not to take the CE essentially.

Does that cover it?

(No response.)

DR. WINTERSTEIN: All right, which brings us to voting. So considering all available information, which one of the following options do you recommend FDA pursue regarding the ER/LA opioid

analgesic REMS?

We have three options, continue, eliminate, or modify? Then after the vote, we would all get the opportunity to explain what we meant with our vote. So after the vote, please describe the rationale for your recommended option. And if we voted for modify, please discuss your rationale and provide specific recommendations for how you would want it modified.

Any clarifying questions?

DR. KAYE: Are we voting [inaudible -- off mic].

DR. WINTERSTEIN: So if you look at your voting, there's not only yes or no. There's also A, B, C underneath. So you just select attend, yes or no, equals A, B, C.

Clarifying question?

DR. SHOBEN: Was this modified like in any way modify or modify in ways that we haven't previously discussed?

DR. WINTERSTEIN: In any way modify, yes. I see nodding. However you want it modified, if you

want it modified in any way, hit C.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. In this case, we want you to state the reason. We will continue in this same manner until all questions have been answered or discussed.

If there are no questions or comments concerning the wording of the question -- everybody

knows how the buttons work? Not yet. They say hold on, not yet.

DR. STANDER: The Army brat over here suggested we just vote the old-fashioned way, either by paper or just go around the table and say what we think.

DR. BUCKENMAIER: I'm not understanding what we're gaining by silently voting if we're going to say what we're voting anyway around the table. We could just get started.

DR. WINTERSTEIN: I think the idea is that we should not get influenced by each other when we vote. It's probably more relevant when there are yes/no votes.

(Laughter.)

DR. WINTERSTEIN: You were not supposed to influence anyone during the discussion, even though you might have.

Are we good? Okay. So we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 minutes -- seconds,

sorry.

(Laughter.)

DR. WINTERSTEIN: That was really not planned; 20 seconds to vote. Please press the button firmly. After you have made your selection, the light might continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

LCDR BEGANSKY: The vote was, A, zero, continue without modifications, B, zero, eliminate the REMS, and C, 30, modify the REMS.

DR. WINTERSTEIN: We will start with Dr. Floyd and Dr. Parker giving us their recommendations because they have to catch a flight, and then we will just go around the table.

Dr. Floyd?

DR. FLOYD: So sorry, the car is already here waiting, I think.

DR. WINTERSTEIN: Well, state your name.

DR. FLOYD: James Floyd. I voted C. Just

to very briefly reiterate comments over the last two days, I think education is just one element of what's needed in this REMS. I think it ought to be mandatory and to reflect the best available guidelines as a starting point, which are the CDC guidelines.

I also want to mention other parts of restrictive REMS, which we really have not had any robust discussion about, but I think ought to be considered. These could include things like for certain patients on high doses or with long-term use being in a registry or needing monitoring.

I don't think I can make a recommendation because we have not really had a discussion to consider this. I don't think that this should be outright discarded because even though existing restrictive REMS like iPLEDGE and TIF have been seen as burdensome, you can take or leave out certain elements and adapt a restrictive REMS.

So my recommendation would be to have more discussion about some of the other restrictive elements, but I don't think that we can make a

recommendation on those parts today. Thank you.

DR. WINTERSTEIN: Dr. Parker?

DR. PARKER: Yes. I would support. Everybody voted the same. I do think changes are needed, and I think we've covered many of those, the immediate-release certainly being a part of that, looking at how the REMS, if they are restrictive; how the industry support for them is disarticulated from the immediate use of the REMS products.

That's got to be carefully looked at and understood, but I think there's a need and we've gotten into that some. So I really underscore that as one of the needs that needs to be addressed, the patient counseling document being a part of that, that I think we can really improve on as well as some of the medication guides, looking very carefully at content, flow, and what exactly we're looking for in those. Thank you.

DR. WINTERSTEIN: Start with Dr. Krasnow.

DR. KRASNOW: I'll be quick because I think you're going to hear the same thing a lot. I think

the scope of the current REMS is too restrictive, and I think the addition of other elements like immediate-release drugs and other pain management modalities may actually have a positive benefit on the use of the current REMS products.

There is clearly, from the data provided, no assessment data, no outcome data that could be analyzed, and I think that the modifications suggested would address that, and part of that being it should be mandatory. I also think that the length of the education should be very closely looked at and restricted to make it palatable, and I think those are the major elements. Thank you.

DR. WINTERSTEIN: Could you state your name and your vote for the record? We have to vote into the record, so just state your name and what you voted.

DR. KRASNOW: Steve Krasnow, and I voted for modification.

DR. BOHNERT: Amy Bohnert. I voted for modification. The main factors for me were to be able to add the immediate-release, short-acting.

Like others, I am in favor of mandatory, but do recognize that there are some real challenges to that. I think the content that's required within the blueprint needs some updating, particularly around new information that has come out since it was originally written.

Then I think something we've discussed less but that I also think is equally important is that I think it needs to be tailored to learner types and incorporate other best practices around this type of education.

DR. HOFFMAN: My name is Erika Hoffman. I voted to modify as well, and I agree with everything else that's already been said. The one thing that I will add is I think it's really important to improve upon the patient education piece because I think if we do a better job at educating the patient on alternative means of pain control, along with risk-benefit ratio, number needed to treat, number needed to harm, there are people that we will end up not treating with opiates.

DR. RAGHUNATHAN: Trivellore Raghunathan. I also voted for C, modify. Some of the reasons include the already-mentioned addition of IR, modification of REMS modules to increase the information about the pain management system, and also making this mandatory. And I also agree that there are some challenges, but there may be some middle ground that could come up.

Also, I think the REMS should be modified in terms of evaluation purposes. I think we need to rethink about how do we want to restructure the evaluation of the program and whether what we are doing is achieving the goals that we want to achieve. That needs to be thought out in the modification as well.

But I also want to say that why we are doing these modifications is, we want to also make sure that we don't stop what we are doing currently, at least reaching out to people, even on a voluntary basis, to a wider set of prescribers, should continue and not wait for these modifications to take place.

DR. McCANN: Hi. I'm Mary Ellen McCann, and I voted to modify the REMS, but I almost thought about voting for eliminating the REMS. And the reason for that is I think there has been very little evidence shown in the last two days that the present REMS has altered behavior by much at all.

The reason I voted to modify REMS is that I think my view of it is it's basically a manual on how to prescribe opioids, when it should be a manual or blueprint on how to treat pain, much like Dr. Buckenmaier has mentioned before. And I agree with everybody else on the panel that we need to streamline the process. There should be shortcuts for individuals who are already educated on this to take the exam or et cetera, et cetera, so that we make it the least burdensome possible for people.

DR. GERHARD: Tobias Gerhard. I voted for C, modify. I believe it should be mandatory. It should include the immediate-release forms as previously noted. It should focus on pain management broadly and the role of opiates within this rather than narrowly on opiate use as such,

really focus on the evidence-based use of opiates versus non-evidence-based use of opiates, and within that, emphasize clearly the risks of opiates.

Obviously, as this has been worked on and put together, it's important to not -- or to try as much as we can to not affect access for patients that really do need opiates because, obviously, there is a large group of patients where opiates have an important role in their pain management.

DR. HIGGINS: Jennifer Higgins. I voted to modify for the reasons that I previously mentioned.

MR. O'BRIEN: I'm Joe O'Brien, and I voted to modify for all of the things that have been said in terms of expanding scope, including the IR, improving outcome measurements and data collection, involving the entire healthcare team, making it mandatory so that we have a standard of care that applies to all, and particularly emphasizing -- and I would encourage in terms of not only just patient education, but empowering the patient, getting them involved in the entire process.

The one statement I would make is that the majority of patients -- based on the data we've seen, the majority of patients are in fact utilizing the drug in an appropriate manner. And I think, because there's a lot of stigma associated with it, that may misdirect them or cause angst within them. I think there needs to be a positive campaign as well as identifying the risks and benefits that go along with that.

DR. GARCIA-BUNUEL: My name is Martin Garcia-Bunuel. I voted C, to modify, also parenthetically considered the B to eliminate, and I will just specify on that. I think I've made my points fairly clear, but I do think we need to make an attempt at the mandatory inclusion of the ER/LA and the IR class.

Having said that, I also urge our government partners that if we are unable to navigate and make those changes, then I do think that's where the B, eliminate, would come in. If we are willing to take no for an answer because of bureaucratic inertia and other influences, I would make sure,

for the record, that we would not fall back to the current state.

DR. BILKER: Warren Bilker. I voted to modify, and the reasons are, I think there should be addition of IR. It should be made mandatory. And in terms of assessment of the modified version, I think the study design needs to be changed, and the change should include allowance for assessing appropriate and inappropriate use and also risk-benefit.

DR. CRAIG: David Craig. I voted C, to modify, predominantly on the inclusion of the IR opioids. That was my suggestion. I think some of the other things that have been brought up about modifying stratification for mental health and suicidality makes sense as far as opioid risk assessment. It also, I think, is an important inclusion.

I still take the original position that it should be voluntary. I think mandatory pain education undergraduately and post-graduately, I think, makes sense, but I don't think an opioid

REMS is the mechanism to make that happen.

DR. KAYE: Alan Kaye from LSU. I voted to modify. I think we should have mandatory with teeth. I think just one out-of-the-box ideas might be to have a drug czar of some type to interface with the FDA, the medical and state boards, interventional pain, pharmacy, and evolve best practices for pain management in this country. Thanks.

DR. ISRAEL: Heidi Israel. I voted to modify, inclusion of the IR, mandatory training, and also pain management.

DR. EMALA: Charles Emala. I voted to modify for five key points, addition of IR, extension of mandatory, extension to the whole healthcare team, pain management rather than just opioid management. And finally, I think it's critical to do better objective measures of the effectiveness.

DR. PERRONE: Jeanmarie Perrone. I voted to modify, all the points that Dr. Emala made, as well as we need to teach people to use these drugs

sparingly, and to eliminate the metrics that we've had in the past like patient satisfaction scores and pain scores pushed by other people, and to separate pharma from any of the education opportunities.

DR. WINTERSTEIN: Almut Winterstein. I voted for modification. I am concerned that education of either provider and/or patient won't have the impact that we hoped for, but it is the basic infrastructure that should be in place. I suggest that this involves both prescribers and pharmacists because I believe that pharmacists can play an important role in patient education.

I suggest mandatory education for both, and I suggest modification of the educational program, including IRs, obviously, as well as a stronger focus on pain management. I also recommend formal patient education. That, I think, would be best built into patient-prescriber agreements.

I very much recommend formally an evaluation) of REMS that integrates questions that allow us to understand inappropriate prescribing

practices and how and why patients migrate into addiction.

DR. BROWN: Rae Brown. And I voted to modify, and I agree with everything that our chairperson has said, with one addition, and that is that I think it's really important to give a comprehensive re-look at the blueprint for REMS and to include, as a very important part, starting today, the assessment of success versus failure of the program, including things like the number of people that are completing the REMS, what the outcomes are for them, if that changes the way that they manage patients, and if there's a difference in outcome.

I think that's got to be incorporated into this, and I see that as one of the weaknesses of the system that we have now.

DR. SHOBEN: I'm Abby Shoben. I also voted to modify for all the reasons previously said. Most notably, I think it should be mandatory and should include the IR opioids. The blueprint should be redone to include both the IR and other

pain management strategies. There is great need for clarity about this appropriate/inappropriate use of opioids.

DR. MORRATO: Elaine Morrato and I voted C for modifying the REMS. I'd like to thank the efforts of the FDA to address the opioid epidemic over the years, given the limits of their regulatory and statutory authority. This has often been challenging, but it's important that they continue to push the critical conversation forward with their FDA opioid action plan.

I recognize the unprecedented scale of the REMS, number of drugs, companies, number of patients and providers. And I agree with many that we should be cautious in introducing unwarranted burden or unintended consequences.

But for me, the misuse in prescription opioids remains a public health crisis, and, as others have said, we have to act accordingly, like a medical emergency. So for me, strengthening REMS sends a very clear message and FDA's actions do have a cascading effect.

So the modifications I recommended are like others for the reasons that have been mentioned, making the prescriber education mandatory and, importantly, routine and renewing so that it becomes institutionalized in the work process, not an add-on; expanding the mandatory education to include IR products, that the education blueprint include the broad concepts of pain management and are harmonized with other national public health guidelines or agencies.

One thing that we didn't mention but I think is important is the ongoing communication plan. We didn't talk at great length, but the information on the website, one-time letters that were done are one time and rather stagnant, some mentioned in the open forum, not necessarily using innovative 21st century marketing and advertising methods. And I think there should be ongoing effort to support from the companies this kind of educational activity as well.

So the last comment I want to make, I also got the opportunity to participate in the 2013

meeting, which was the vote on rescheduling Vicodin-like products. And at that time, we heard a very impassioned argument from the DEA in favor of rescheduling products like Vicodin and that we should be doing everything possible to address the crisis.

We also heard testimony that was impassioned from Senator Manchin from West Virginia, who not only talked about the situation in his own home state, but he shared with us the unanimous bipartisan consent of the Senate in favor of rescheduling.

So I'm hopeful that today, we might have the political will to actually, like others have said, challenge the process and find a new path forward in concert with other regulatory agencies.

DR. GALINKIN: Jeffrey Galinkin. I voted to modify for many of the reasons that have been stated before. I do think it should be a mandatory requirement. And I think we should be addressing the kinds of not only responsible opiate prescribing, but rational opiate prescribing.

I think that's the word that we really should be using. This needs to be from, really, I would urge, a rapid multi-agency coordinated response to this issue, particularly around some of the reasons we keep talking about, maybe partnering with the DEA or whatever.

But if we're talking about actually guidelines for pain management, it's going to have to be potentially a much more multi-group response. I also think we should be expanding the groups, as I mentioned, for pediatric patients and also for medical students and residence because I think that's going to be an essential group to train.

DR. BATEMAN: Brian Bateman. I voted to modify. So all the data we reviewed at the meeting did not provide clear evidence either supporting or refuting the effectiveness of REMS training. We know prescription opioids carry considerable risks and that inappropriate prescribing has contributed to the epidemic we're currently facing.

It thus stands to reason that providers will benefit from training regarding their appropriate

use and that this is therefore one potentially important piece in addressing the broader problem.

Like others, I think the program should be modified to include the IR formulations, the blueprint revised in a way that the material focuses more broadly on the treatment of pain, including non-opioid medications and non-pharmacologic modalities. The blueprint also needs to clearly articulate the risks of opioids and what's known or not known regarding the efficacy of opioids for chronic non-cancer pain, and then to be brought into alignment with the CDC guidelines.

Lastly, I'd favor making the training mandatory in some fashion, either linking it to DEA registrations, state licensure, or as a pre-condition of being a CMS provider.

DR. GUPTA: Anita Gupta. I voted to modify. I believe the REMS should be mandatory. It should be comprehensive, evidence based in content for both pain and opioid therapy for providers and patients, and that the delivery of information should be engaging, digestible by potentially using

innovative technological solutions.

This will ensure a firm definitive broad public health impact. Immediate-release should be absolutely included, given that all opioids contribute to the epidemic. The REMS program should be interoperable with all provider systems, pharmacists, nurse practitioners, physicians, all clinicians appropriate to the provider level, whether medical student or senior physician, the actual specialty. It should also be collaborative with all federal agencies and stakeholders to ensure a clear and concise message.

DR. FRY: Michael Fry. I voted C to modify basically for the reasons that we stated. IR should be included, mandatory to ensure that prescribers are following the guidelines and training, and just better education for patients through all aspects of healthcare, where there's nurses or pharmacists, trying to educate them, so they know the dangers that do exist.

DR. STANDER: Paul Stander. I voted to modify and, again, for virtually all the reasons

we've heard, including the IR, coordinating, I think, with the CDC and other government agencies so it's a unified message focused on the risk and focused on the decreased efficacy and any chronic pain scenarios.

I agree with expanding it to the whole team, although mandating it for that group may be even more difficult than for physicians, although I am in favor of the mandatory for physicians.

I'd like to echo Dr. Morrato and commend the FDA for their efforts. And I'd also just like to say this is the first FDA advisory panel I ever participated in, and I appreciate the opportunity.

I just want to commend the other panel members and the other presenters. Truly, I learned a lot, and I felt that everybody was really trying to do their best to confront a very serious problem. So I appreciate the opportunity and everybody else's efforts.

DR. BUCKENMAIER: Dr. Trip Buckenmaier. I voted C for two reasons. One, my last name is actually spelled N-M-A-I-E-R, so I gave the FDA a C

on that effort. But I give them an A on their institutional courage to actually address this national health crisis and being able to do so despite the fact that it is a bit of a morass and very difficult.

I also voted to modify because I think we need an opportunity to snap-link pain management to the opioid issue and provide that training to our providers at all levels. And I echo the many folks in this room that have called for improved medical education of all specialties, doctors, nurses, and allied professionals in this area, since they're going to be the ones taking care of us in too short a time.

DR. TYLER: Linda Tyler. I also voted C, modify the REMS. Like others, I believe in mandatory education for the entire healthcare team, adapted to the special needs of each discipline. I believe that the role of industry needs to be separated from the development of the education. That said, I too want to compliment the RPC for their role and leadership in addressing this and

hope they continue to play a leadership role in this public health crisis.

There's no question from the FDA standpoint, it will be a challenge to fit the REMS as we know it into this model of what we've described today. Nonetheless, the goals of REMS programs to address risk still applies. It's important that we coordinate with the other resources in our public health network to be able to address this crisis, both at the federal and state level as well as the local levels.

DR. CHOUDHRY: Niteesh Choudhry. I also voted to modify, again, for four main reasons for me. I think the format length and the one-time nature of the education needs to change its content, as we've discussed, focusing on pain; immediate-release agents being tailored to different sorts of providers, including those who are non-physicians.

I do broadly support a mandate for this sort of REMS education. But perhaps most important of all, we clearly need a better evaluation strategy

to figure out whether this is worth the money.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips. I also voted to modify, C. So much has been said, so I don't want to repeat all of these things. I do want to recognize that mandatory confirmation of specific knowledge could be really important and makes sense to be tied to DEA registration for those prescribers that prescribe Schedule IIs and IIIs. But I also agree, as Dr. Tyler said, that we really need to educate the whole healthcare team.

So there's room for a lot more education than just that that might be tied to either licensure or registration. But there really needs to be synergy among federal agencies for safe and effective use of opioids within the larger umbrella of a national pain strategy.

DR. WINTERSTEIN: We really won't have time to address question 10 anymore. I think that we have done a lot previously when we discussed REMS evaluations. The FDA is nodding. So I think we have probably provided enough, at least for this meeting. Does the FDA have concluding remarks they

would like to share?

DR. LaCIVITA: Yes, I do. I want to thank everyone for attending. I know it's difficult to take two days, probably more with travel, out of your busy schedules. These are very important issues as it pertains to patient care and safety, and even people that aren't patients. We're talking about when it's used inappropriately by people that weren't prescribed the drug.

You've provided very thoughtful consideration to a great number of questions that we asked you, and we really appreciate that. We need to go back and think about all the things that you have provided to us today. So thank you all.

Adjournment

DR. WINTERSTEIN: Thank you, everyone. You were a wonderful committee. That's the largest committee that I've ever chaired, and it went extremely well. So thank you, thank you. Safe travels home, and the meeting is adjourned.

(Whereupon, at 5:00 p.m., the meeting was adjourned.)