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Margolis-FDA Convening: Reconsidering Mandatory Opioid Prescriber Education Through a Risk Evaluation and Mitigation Strategy (REMS) in an Evolving Crisis

Virtual Public Meeting
October 13, 2021 | 1:00-5:00 p.m. ET
October 14, 2021 | 1:00-4:05 p.m. ET

Background and Landscape Analysis

Trends in Opioid Prescribing and Overdose Deaths

The nature of the opioid and substance use crisis has changed significantly since the early 2000s, though opioid-related drug overdose deaths have been steadily rising throughout the entire period. The Centers for Disease Control and Prevention (CDC) describes the crisis as being composed of three distinct, though overlapping, waves of overdose deaths: first, a rise in overdose deaths driven by prescription opioid analgesics beginning in 1999; second, a shift toward overdose deaths related to heroin beginning in 2010; and third, a spike in overdose deaths related to illicitly manufactured synthetic opioids, including fentanyl, beginning in 2013. This last wave continues to be a main driver of rising opioid-related overdose deaths, while overdose deaths involving prescription opioids and heroin have plateaued. Polysubstance use, or the use of other (often illicit) substances, especially stimulants like methamphetamines, has become more common in recent years and has been characterized by some experts as a fourth wave.

The initial wave of overdose deaths from prescription opioids correlated closely with prescribing practices – from 1999 to 2010, prescribing rates for opioid analgesics quadrupled, which correlated with the quadrupling of the prescription opioid driven overdose death rate. This first wave was met accordingly with a variety of public and private interventions intended to promote safe and appropriate prescribing practices to reduce the risks of opioid-related overdose and other adverse consequences. As one example of interventions intended to improve the safety of opioid prescribing, CVS identified "outlier" prescribers responsible for a disproportionate number of prescriptions and requested justifications for those practices as a condition for continuing to fill their prescriptions. Medicare also tested the efficacy of warning letters to providers writing an unusually high number of prescriptions relative to their peers alerting them to their outlier status. Researchers studied the effects of sending prescribers a notification when a current or former patient to whom they had prescribed opioid analgesics experienced an overdose. Understanding the true impact of these types of interventions on outcomes, like overdose mortality, is challenging given the number of confounding factors and other policies being put into effect at the state and federal levels.

One influential intervention, cited by many providers and state policymakers, was the 2016 release of CDC's "Guideline for Prescribing Opioids for Chronic Pain," which recommended prescribers avoid opioid analgesics when possible and, when prescribing them, to limit the dosage and duration of prescriptions to reduce the risk of dependence and addiction. The guideline set forth morphine milligram equivalent (MME) thresholds providers should avoid crossing without careful reassessment of individual patients' benefits and risks, and emphasized that unnecessarily lengthy opioid prescriptions for acute pain can lead to longer-term use. In response to concerns that misapplication of the CDC Guidelines were resulting in denial of appropriate care for patients with chronic pain, the CDC has clarified that the guidelines were not intended to "deny any patients who suffer with chronic pain from opioid therapy as an option" and recommends that providers exercise clinical judgement in weighing the risks and benefits of all treatment options.

The combined effect of many of these interventions was to reduce the frequency with which providers prescribe opioid analgesics to patients, with many providers and patients raising concerns that patients are being inappropriately denied access to adequate pain care. Despite reductions in the frequency of opioid prescribing, prescription opioids were still involved in more than 16,000 fatal overdoses in 2020, higher than the number seen at the peak of opioid analgesic dispensing in 2012. And despite a trend toward more overdose deaths involving illicit substances, many users of illicit opioids are initially exposed to opioids through nonmedical use of prescription opioids. Providers can still play a crucial role in combating the crisis, both through mitigating the potential harms of opioid prescribing and in supporting evidence-based interventions for individuals with substance use disorders. However, as the substance use crisis continues to shift, future policy interventions must consider how providers can most effectively support positive change in this evolving context.

Timeline of FDA's Opioid Analgesic REMS

Provider education, particularly for prescribers of opioids, is another form of intervention implemented alongside many of those discussed in the previous section. In 2012, FDA approved the Extended-Release and Long-Acting Opioid Analgesic Risk Evaluation and Mitigation Strategy ("ER/LA REMS"). The goal of the REMS was to "reduce serious adverse outcomes" like addiction, overdose, and death resulting from "inappropriate prescribing, misuse, and abuse" of ER and LA opioid analgesics, while maintaining patient access to necessary medications. The REMS required the manufacturers of ER and LA opioid analgesics to make training available to prescribers of ER/LA opioid analgesics. The manufacturers met this training requirement by providing educational grants to accredited continuing education (CE) providers who offered the training based on the FDA Blueprint, which consisted of a high-level outline of core educational messaging, including general and product-specific information about the ER/LA opioid analgesics; information on proper patient selection for use of these drugs; guidance for safely initiating therapy, modifying dosing, and discontinuing use of ER/LA opioid analgesics; guidance for monitoring patients; and information for counseling patients and caregivers about the safe use of these drugs. Prescribers' participation in these CE programs was on a voluntary basis.

In 2016, the FDA held a joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee to discuss whether the REMS was meeting its goals and whether any modifications of the ER/LA Opioid Analgesics REMS program were necessary. The committee members recommended that FDA should modify the REMS program by expanding the REMS requirements to include immediate-release (IR) opioid analgesics, that the education cover broader information about appropriate pain management, including alternatives to opioids for the treatment of pain, and offering education to other health care providers who participate in the management of patients with pain. In addition, committee members agreed that education for prescribers should be mandatory and preferred education to be provided through mechanisms other than a REMS. There was additional discussion on improving REMS assessment and evaluation of CE effectiveness.

In 2017, FDA sent letters to all the opioid analgesic manufacturers informing them that the IR opioid analgesics would be subject to the same REMS requirements as ER/LA opioid analgesics. FDA also published an example of the notification letter online. This document included an updated FDA Blueprint that contained educational messaging on pain management. FDA sought public comment on draft revisions to the Blueprint.

In September 2018, FDA approved an expanded Opioid Analgesic REMS (OA REMS) that applied to manufacturers of most opioid analgesics and made training available to all health care providers who are involved in the management of patients with pain, including physicians, nurse practitioners,

physician assistants, and pharmacists. Furthermore, the updated Blueprint includes a primer on addiction medicine that outlined the basic elements of addiction and the treatment of Opioid Use Disorder (OUD). Specifically, the document mentioned that HCPs should be familiar with the neurobiology of OUD, the use of tools to identify patients at risk for addiction, pharmacologic and nonpharmacologic treatments and when to refer a patient to an addiction medicine specialist. The Blueprint does not include principles for managing opioid use disorder, including treatment with buprenorphine. Provider participation in OA REMS CE remains voluntary.

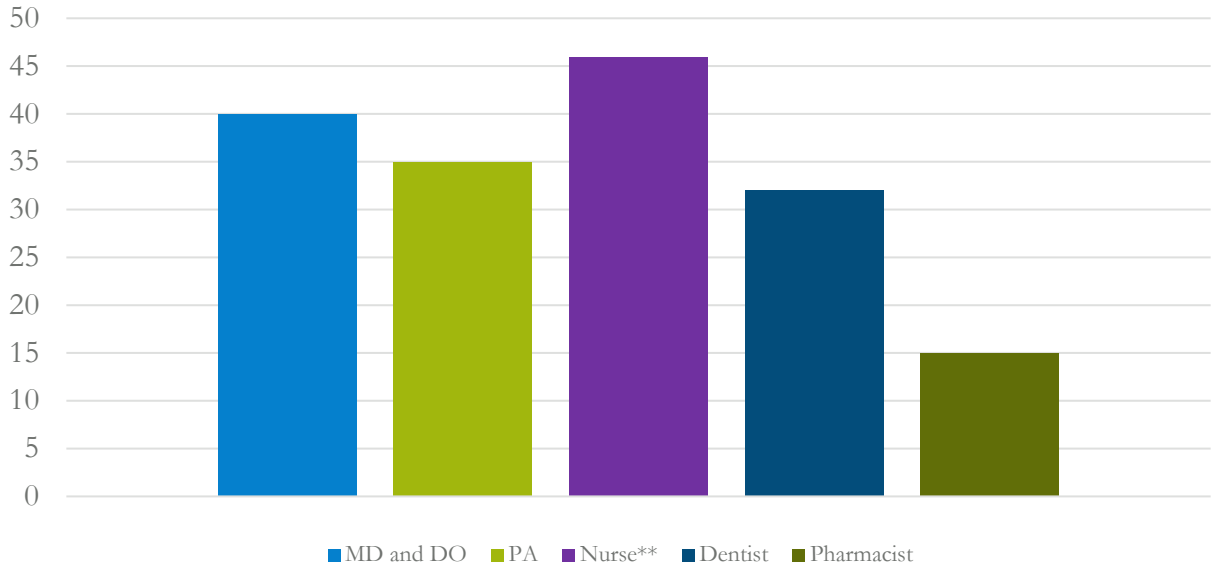
A 2020 HHS OIG report recommended mandating education through the Opioid Analgesics REMS program for prescribers to improve the effectiveness of the program. The report also concluded that the FDA had difficulty in measuring the effectiveness of the ER/LA REMS program for promoting safe use of opioids. In its response to these recommendations, FDA acknowledged the challenges in measuring the effectiveness of the REMS program and described initiatives underway to improve the REMS assessment process. FDA also stated it "has supported education of all prescribers of opioid analgesics but believes that mandating it through a REMS is not the best, or even a practical, method to implement mandatory training." FDA cited suggestions for alternative mechanisms to implement mandatory training, such as linkage between prescriber education and DEA registration for the purpose of controlled substance prescribing. While there have been expansions to the Opioid Analgesics REMS program and an inclusion of pain management core educational messaging, considerations for the future role and impact of REMS in addressing the opioid crisis have to deal with the question of educational requirements. While FDA recognizes the substantial practical and logistical challenges to implementing mandatory prescriber education through the REMS program, including the burden on the practitioners and patients, the Agency believes that it is possible that given technological advances in the intervening years, including broader implementation of e-prescribing for controlled substances, there might be ways to lessen the burden associated with a restricted distribution system. Although these logistical issues are not the subject of today's meeting, they will be the subject of a future public meeting. Despite substantial declines in dispensed opioid analgesic prescriptions annually since 2012, annual deaths involving prescription opioids have not similarly declined. Thus, the Agency is reconsidering whether there is a role for mandatory prescriber education in mitigating the risks of opioids in the current environment.

State-Level Prescriber Continuing Education Requirements

As detailed in a previous Duke-Margolis landscape analysis, many states have developed their own laws and regulations intended to mitigate the harmful effects of the opioid crisis. These measures include implementing prescribing guidelines, operating prescription drug monitoring programs (PDMPs), promoting access to overdose reversal drugs like naloxone, drug take-back days, public information campaigns, and rules on electronic prescribing of controlled substances designed to prevent drug diversion. A variety of state laws and regulations also set forth limits on quantities and dosages of opioids dispensed.

CE requirements have been another major policy intervention intended to mitigate the opioid crisis at the state level. State medical boards, along with the boards that govern licensure for many other types of healthcare practitioners (HCPs) have implemented varying CE requirements as conditions of licensure. In some cases, this was done at the direction of state lawmakers, but in many cases, governing boards developed CE requirements independently. Figure 1 shows the number of states with CE requirements related to pain management or opioid prescribing as a condition of licensure for different categories of HCPs, per a landscape analysis conducted by the REMS Program Companies in 2019.

Figure 1: Number of States* with State-Level Pain and Opioid CE Requirements, by HCP Type



Source: Continuing Education: Pain Management and Safe Opioid Prescribing, RKT Consulting, July 2019.

*Includes District of Columbia

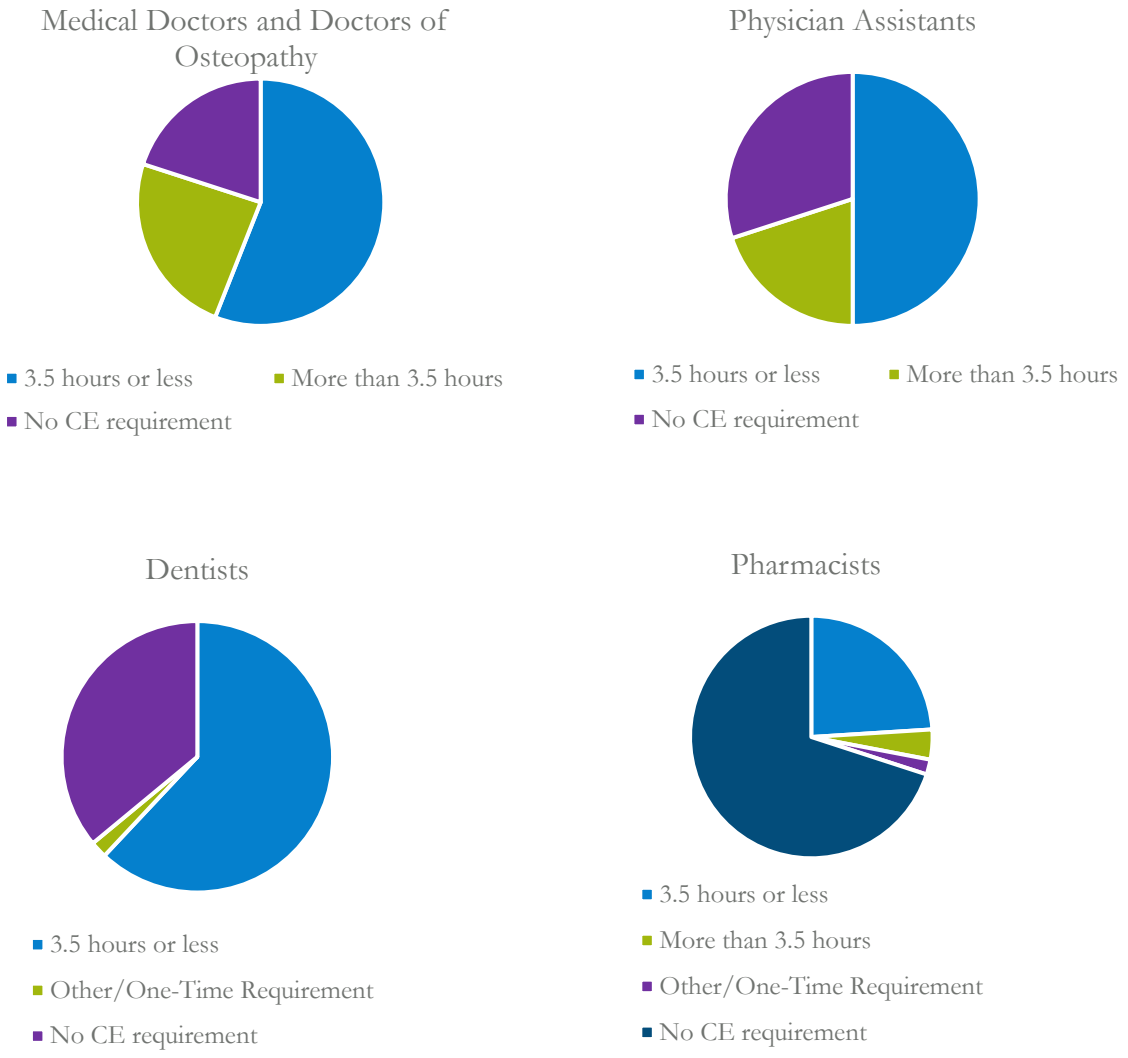
**Includes APRNs, NPs, CRNAs, and CNMs

Eighty percent of states have CE requirements for Medical Doctors (MDs) or Doctors of Osteopathy (DOs) on this subject (most of these states apply the same standards to both categories, with just six states detailing differing requirements). Seventy percent have requirements for Physician Assistants (PAs), and over 90% have a requirement for at least one category of nurse that is authorized to prescribe opioid analgesics, including Advanced Practice Registered Nurses (APRNs), Nurse Practitioners (NPs), Certified Registered Nurse Anesthetists (CRNAs), and Certified Nurse Midwives (CNMs). Although significantly fewer dentists are required to take CE on this subject, a majority of states do require it. Finally, pharmacists must meet requirements related to pain management and opioid prescribing in just 30% of states. Most requirements related to opioid prescribing apply only to those HCPs with a DEA Registration Number allowing them to prescribe controlled substances.

It should be noted that states without CE requirements tend to be less populous, such that coverage of current state requirements is often even greater than Figure 1 suggests. For example, while only 80% of states have CE requirements for MDs and DOs, over 93% of the population resides in a state with such requirements.

State-level CE requirements can be further analyzed in terms of the amount of CE required. Among the states that do require HCPs to complete CE as a condition of licensure, there is still significant variation – some CE requirements are much more extensive than others. Figure 2 illustrates these differences.

Figure 2: Proportion of States* Requiring Varying Amounts of CE per Licensure Cycle, by HCP Type



Source: Continuing Education: Pain Management and Safe Opioid Prescribing, RKT Consulting, July 2019.

*Includes District of Columbia

Across HCP types, most CE requirements on opioid prescribing or pain management are less than 3.5 hours per licensure cycle (licensure cycles generally require renewal every two years). Almost one in four states requires MDs and DOs to complete more than 3.5 hours per cycle, however, and one in five states requires more than 3.5 hours per cycle for PAs. While most states do require CE on opioid prescribing or pain management for dentists, no state requires more than 3.5 hours per cycle – dentists generally undergo less CE on the subject than MDs. The majority of states require no CE for pharmacists on the subject, though there are two states where pharmacists must complete more than 3.5 hours each cycle.

In some states, there is further variation in requirements by specialty or scope of practice. For example, in Ohio, MDs and DOs who own or operate pain management clinics must complete 20 hours of CE on pain medicine every two years, including at least one course "addressing the potential for addiction."

In general, though, addiction and substance use disorders (SUD) are rarely a required part of CE even in states that do have CE requirements related to pain management. While 80% of states have CE requirements related to pain management more generally, only 20% of states offer educational content related to addiction and substance use disorders. Even in those states, education on the risks of SUD, how to identify it, and how to treat it is sometimes an optional focus alongside other content related to pain management and analgesic prescribing. For example, in Oklahoma, MDs must complete at least "one hour of education in pain management or one hour of education in opioid use or addiction" before renewing their license.

The extent of CE HCPs receive on opioid prescribing and OUD varies by HCP type, by state, and by area of practice. This variation exists in terms of frequency and amount of CE, but also in the content covered in these programs. Perhaps most notably, information on key issues like opioid tapering or MOUD is far from universally included in state CE requirements.

Health Professional Education and Training

Some experts have suggested that prescribing behaviors are strongly influenced by curricula and trainings provided by health professional education programs. A recent survey commissioned by the Association of American Medical Colleges (AAMC) found that 87% of 102 medical schools that responded taught their trainees about the nature of pain, pain assessment and risk for substance use disorder (SUD), management of pain including SUD treatment, and the context of pain and SUD. However, only 55% of the surveyed medical schools assessed their trainees on these topics. While a majority of programs utilized case-based learning, clinical experience, and lectures to teach students, there were 18 total teaching methods and eight assessment approaches captured by the survey, indicating significant variation.

The prevalence of opioid education and pain management in other clinician trainings has also been the subject of some research. A survey on opioid education in 88 physician assistant student training programs reported that about 56% of programs required opioid prescribing education while 36% had no mandatory education and 8% were unsure. Just over 50% of surveyed programs required opioid addiction education while about 39% of programs did not mandate this education. Another survey of 207 physician assistant student training programs found that 57% included pain medicine as a module in multiple courses, nearly 27% included it as module within one course, about 14% did not include it in the curriculum, and only about 3% included it as a separate course in the curriculum. At a 2016 White House event, 191 nursing schools and 54 pharmacy schools announced their commitment to general, mandatory prescriber education requirements for graduation and education on overdose interventions, respectively. Nursing student training dedicated to opioid education and pain management has been described as being limited in content, curricular hours, and access to faculty with pain management training.

There are many challenges to improving prescriber and provider education on opioids and pain management. Three distinct challenges emerged in the aforementioned 2017 AAMC survey: faculty and resident subject matter expertise, time within the curriculum, and assessment of the students' learning. A lack of time and faculty training were also cited as barriers to physician assistant student training on

opioid education as well as a lack of available resources. Several best practices emerged for teaching and assessing prescribers' and providers' knowledge on opioids and pain management. The 2017 AAMC survey mentioned five strategies: sharing and making use of existing resources, teaching inter-professionally and engaging community partners, integrating SUD and pain content throughout the curriculum, optimizing experiential methods such as case-based teaching, and building faculty capacity to teach evidence-based practices. A 2019 article in the *AMA Journal of Ethics* identified methods for improving education on opioid prescriptions including multilevel interventions, improving the quality of teaching, providing more experiences in addiction management, and incorporating longitudinal curricula.

Academic medical institutes have also adapted prescriber and provider education on opioids and pain management to meet the needs of their communities. A 2019 AAMC report spotlighted the best practices of academic medical institutes in seven areas of need compiled in Table # below.

Area of Emphasis	Number of Academic Medical Institutes Spotlighted for Applying the Area of Emphasis
Integrating Content Throughout Undergraduate Medical Education	27
Reinforcing Content in Residency Training	6
Educating Existing Providers and Enhancing Continuing Medical Education	7
Providing Clinical Care to Patients Experiencing Pain and/or Substance Use Disorders	16
Research into New Methods of Treating Pain and Substance Use Disorders	7
Partnerships with the Public and Private Sectors	4
Educating the Public	4

This is by no means an exhaustive list of educational efforts by academic medical institutes. The list does, however, reflect broader trends in educational resource development centering changes in medical education, patient care, and research. There are many similarities between the educational endeavors developed by academic medical institutes. The overwhelming majority of resources listed are dedicated to physician education. Academic medical institutes have the ability to share best practices and learn from one another by working with the AAMC and other organizations. The National Academy of Medicine's Action Collaborative on Countering the US Opioid Epidemic also features a Health Professional Education and Training Working Group. The Working Group prioritizes "creating a coordinated, interprofessional, patient-and family-centered framework" that facilitates health professional education on acute and chronic pain management and substance use.

Provider Perspectives

It is important to also consider that health care professionals form their viewpoints on opioids and pain management in part based on clinical experiences. These clinical experiences do not necessarily align with medical education including education under a REMS program. For example, a study by Boston University researchers, published in 2017, found that clinicians sought more knowledge on questions classified into five themes: safe alternatives to opioids, barriers that surface when implementing opioid prescribing guidelines, government enforcement of regulations, the role of marijuana in opioid

prescribing, and best practices for patient communication. These themes were considered to be divergent from the core educational messages presented in the October 2015 version of the FDA ER/LA REMS program Blueprint. The authors suggest that future updates to the Blueprint would benefit from soliciting feedback from providers in the development of more clinically aligned educational guidelines.

Assessment of training and knowledge of opioid prescribing across a wider range of health care provider professionals was also done in a survey published in 2021 in the Journal of the American Board of Family Medicine. Primary care physicians (89.5%) and nurse practitioners (85.5%) responded that they had been exposed to opioid educational information at a higher rate than specialists (71.9%) and physician assistants (78.8%). Across all professional disciplines, the three most common sources of opioid educational information were medical journals, online presentations or webinars, and hospital or conference presentations.

Academic Detailing

One more avenue for implementing prescriber education is academic detailing at the health system level. Academic detailing entails direct educational outreach to prescribers in the form of a one-on-one, in-office educational visit, often from another trained HCP who provides information on best practices and latest available evidence on a given topic. This strategy has been widely adopted by the Veterans Health Administration, Kaiser Permanente, and a number of other large healthcare systems. A 2007 Cochrane Collaboration literature review found that academic detailing changed self-reported prescriber behavior. A New York City Department of Health and Mental Hygiene pilot study conducted numerous one-to-one educational visits to health care providers in Staten Island. The Department shared a multitude of resources with providers including judicious opioid prescribing guidelines, borough-specific data on prescribing patterns, and patient information material. After the campaign, provider knowledge of safe prescribing patterns increased. While this initiative does demonstrate the potential for academic detailing campaigns, it can be difficult to isolate the real impact of academic detailing or other prescriber education efforts at the health system level, as prescriber education is often only one of many concurrent tools health systems use to promote safe opioid prescribing.

Conclusions and Outstanding Questions

Prescriber education is one of many policy interventions that legislators, regulators, and healthcare institutions have used as part of their broader efforts to mitigate the opioid and substance use crises. The landscape of required education for providers surrounding safe opioid analgesic prescribing, pain management, and OUD is complex and varies widely by state, health system, academic institute, and provider type. Education offered through the OA REMS covers the same topic areas and follows the same core messages based on the FDA Blueprint wherever it is offered, but given that it is voluntary, providers may or may not have received it. A recent update from the Accreditation Council for Continuing Medical Education found that as of May 2021, 185,854 learners had completed Opioid Analgesic REMS compliant CE activities. Twenty-five accredited providers reported 270 Opioid Analgesic REMS-compliant CE activities, with 208 held and 62 planned for the future.

Federally-required prescriber education through REMS could set a nationwide standard for education on opioid analgesic prescribing and related topics. But given the complexity of the current landscape of education activities and state-level requirements, related guidelines and training requirements for prescribing buprenorphine for OUD, and the dynamic opioid and substance use crisis, there are

numerous outstanding questions and considerations as to how such a federal requirement could most effectively improve appropriate opioid prescribing, pain management, and the treatment of OUD. A new federal CE requirement under a REMS would have to account for considerations like ensuring patient access to necessary medication, avoiding excessive provider and health system burden and redundant requirements, covering complex topics such as pain management, evaluation and treatment of OUD, and more. Feedback from a wide range of stakeholders is essential to shaping effective policy in this space and ensuring that prescriber education can most effectively address the opioid and substance use crisis.

Accordingly, the Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the FDA, is convening this public meeting to discuss the potential role of mandatory prescriber education in combating the opioid and substance use crisis. This workshop will explore topics and considerations related to:

- The evolution and current state of the opioid and substance use crisis, particularly in regard to the changing role of prescription opioids and the various actions taken by FDA and others in response to the evolving crisis.
- The landscape of opioid prescriber education at the federal, state, and health system levels, and how mandatory opioid prescriber education through REMS may improve appropriate opioid prescribing, pain management, and management of OUD and reduce the likelihood of adverse outcomes associated with the use of opioid analgesics and help mitigate the current crisis more broadly.
- Opportunities for expanding and improving opioid prescriber education, including a modified Opioid Analgesics REMS mandating completion of a standard educational program before prescribing opioids.

Funding for this workshop was made possible in part by a cooperative agreement from the U.S. Food and Drug Administration Center for Drug Evaluation and Research. The views expressed in written workshop materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.