

RADARS® SYSTEM  
DENVER HEALTH AND HOSPITAL AUTHORITY

**Evaluation of Risk Evaluation and Mitigation Strategy (REMS) Programs**  
**Comments for Docket No. FDA-2009-N-0143**

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## Evaluation of Opioid Risk Evaluation and Mitigation Systems

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The purpose of a Risk Evaluation and Mitigation Strategy (REMS) is to reduce the risks associated with specific medications. In the case of drugs that are misused, abused or diverted (MAD), REMS should reduce evidence of MAD while simultaneously allowing appropriate access to these medications by patients.<sup>1</sup>

### Goals of Opioid REMS

- To ensure that the benefits of a opioid product achieves appropriate balance with the risks through:
  - Proper patient selection
  - Minimizing the risk of overdose, both accidental and intentional
  - Minimizing the risk of abuse
- To ensure that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products

### Proposed Opioid REMS Elements

FDAAA allows for the following components of REMS.

- Elements to Assure Safe Use (ETASU)
  - Prescriber training and certification (possibly through demonstration)
  - Expanded/modified medication guide
  - Prescriber-patient written agreements
  - Pharmacist registration
- Implementation system
- Evaluation
  - Timetable for submission of assessments
    - Section 505-1 Evaluation required from the date of REMS approval:
    - At least by 18 months, 3 years, 7 years

### **RADARS<sup>®</sup> System**

The Researched Abuse, Diversion and Addiction Related Surveillance (RADARS<sup>®</sup>) System was initiated in 2002. The System offers continuous surveillance of the misuse, abuse and diversion of opioids and stimulants throughout the United States ([www.RADARS.org](http://www.RADARS.org)). The System is composed of multiple components, each representing a different perspective on misuse, abuse and diversion: Drug Diversion (DD), Key Informants (KI), Poison Centers (PC), Opioid Treatment Programs (OTP), Impaired Health Care Workers (IHCW), College Survey (CS), Survey of Key Informants' Patients (SKIP). It is owned and operated by the Denver Health and Hospital Authority.

### **PRINCIPLES OF REMS ASSESSMENT**

The assessment of opioid REMS must follow basic principles of surveillance and public health as defined below. We propose an evaluation framework that is designed to monitor both the intended consequences (reduction in the unintended consequences of outpatient opioid use) and potential unintended consequences of the proposed opioid REMS.

### **Nine guiding principles form the basis for the evaluation of opioid REMS:**

1. Evaluation should include the effects of opioid REMS on misuse, abuse, addiction, diversion and overdose

2. All types of opioid products must be included: branded and generic as well as extended-release and immediate-release. Furthermore, illicitly manufactured opioids (e.g., heroin) should be included.
3. The risks unique to specific formulations of prescription opioids must be measured separately (e.g. patch, tamper resistant, etc).
4. The evaluation should be comprehensive, including both the benefits and risks.
  - a. Access to opioid medications by existing pain patients and appropriate potential candidates for opioid treatment must be evaluated.
  - b. The prescribing of alternative forms of analgesic therapies and their attendant adverse events must be included (reinforcing the need to monitor immediate-release formulations).
  - c. Quality-of-life and functioning must be measured in patients already receiving opioid pharmacotherapy; these factors must also be measured in patients with degenerative painful conditions who would have received extended-release or long-acting opioids in the absence of the proposed REMS (i.e., the counterfactual model of determining causality in epidemiology).
5. Multiple perspectives on the natural history of substance use disorders are needed to assess the proposed opioid REMS, measured separately but in parallel.
6. The impact of the opioid REMS on opioid treatment programs must be evaluated.
7. Assessments of opioid REMS must be conducted on pre-scheduled basis (required by Section 505-1).
8. Outcomes in specific populations must be monitored (e.g., young children, adolescents, etc.). The effects of opioid REMS on patients *and* non-patients (e.g., abuse) must be included.
9. Evaluation must assess whether existing disparities in access to opioid pain medications by vulnerable minorities is not exacerbated.

### **Expansion of Principles**

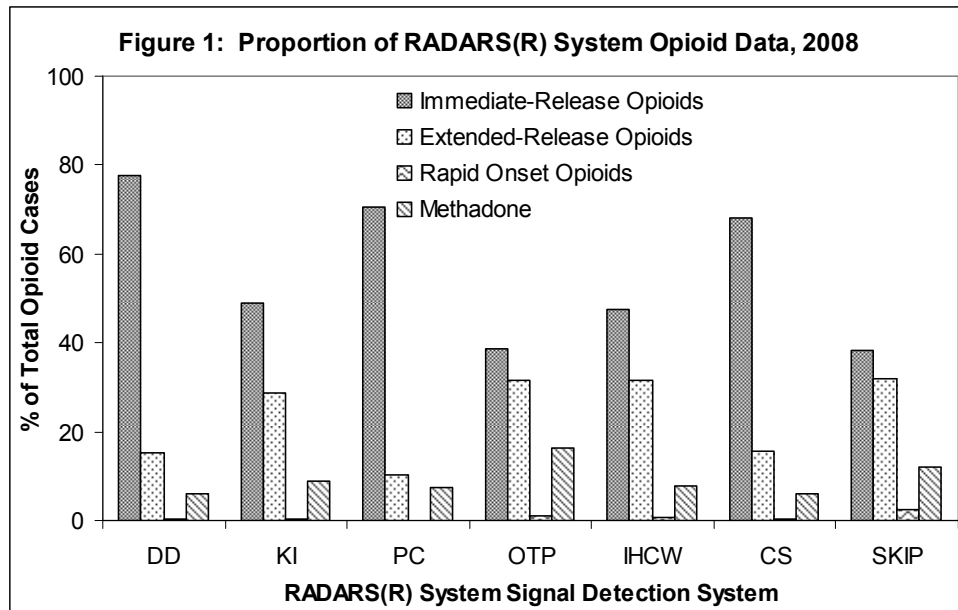
1. **Evaluation should include the effects of opioid REMS on misuse, abuse, addiction, diversion and overdose**  
 As indicated by FDA, some of the major goals of REMS are to reduce misuse, abuse, addiction, diversion and overdose, thereby improving the risk-benefit assessment. While diversion is a responsibility of the US Drug Enforcement Administration (DEA), FDA views diversion as an indicator of drug abuse.<sup>2</sup> These outcomes must be measured in parallel because supply side reductions in opioid availability will affect each outcome differently. While the five outcomes are related through a common exposure, there are many other factors on the causal pathway which lead to the outcome. As discussed directly below, REMS has limited scope to affect the causal intermediates which result in the five outcomes of interest.
2. **All types of opioid products must be included: branded and generic as well as extended-release and immediate-release. Furthermore, illicitly manufactured opioids (e.g., heroin) should be included.**
3. **The risks unique to specific formulations of prescription opioids must be measured separately (e.g. patch, tamper resistant, etc).**  
 The inclusion of immediate-release formulations as a comparison group is of utmost importance. The number of unique individuals filling a prescription for immediate-release opioids is nearly 30,000,000 each quarter, whereas extended-release opioids have less than a tenth of the number of recipients (unpublished data, RADARS<sup>®</sup> System).

It is well documented that the abuse, misuse, addiction, diversion and overdose problems associated with opioids are not limited to the extended-release opioids. If the proposed REMS is targeted only at the extended-release and long-acting formulations, we can expect to see a shift to the use of immediate-release opioids (and heroin), resulting in separate and overlapping adverse health outcomes, and possibly lesser harms in some cases than with the nonmedical use of extended-release opioids. Many of these shifts would be expected to involve generic products.

4. **The evaluation should be comprehensive, including both the benefits and risks.**
  - a. **Access to opioid medications by existing pain patients and appropriate potential candidates for opioid treatment must be evaluated.**
  - b. **The prescribing of alternative forms of analgesic therapies and their attendant adverse events must be included (reinforcing the need to monitor immediate-release formulations).**
  - c. **Quality-of-life and functioning must be measured in patients already receiving opioid pharmacotherapy; these factors must also be measured in patients with degenerative painful conditions who would have received extended-release or long-acting opioids in the absence of the proposed REMS (i.e., the counterfactual model of determining causality in epidemiology).**

The evaluation of the proposed REMS must also focus on the “benefit” side of the societal risk:benefit balance that the Agency is attempting to alter; it is not sufficient to reduce the “risk” side of the ratio if the “benefit” side suffers greatly. Therefore evaluation must actively monitor for the unintended consequences of enacting the proposed opioid REMS.

5. **Multiple perspectives on the natural history of substance use disorders are needed to assess the proposed opioid REMS, measured separately but in parallel.**

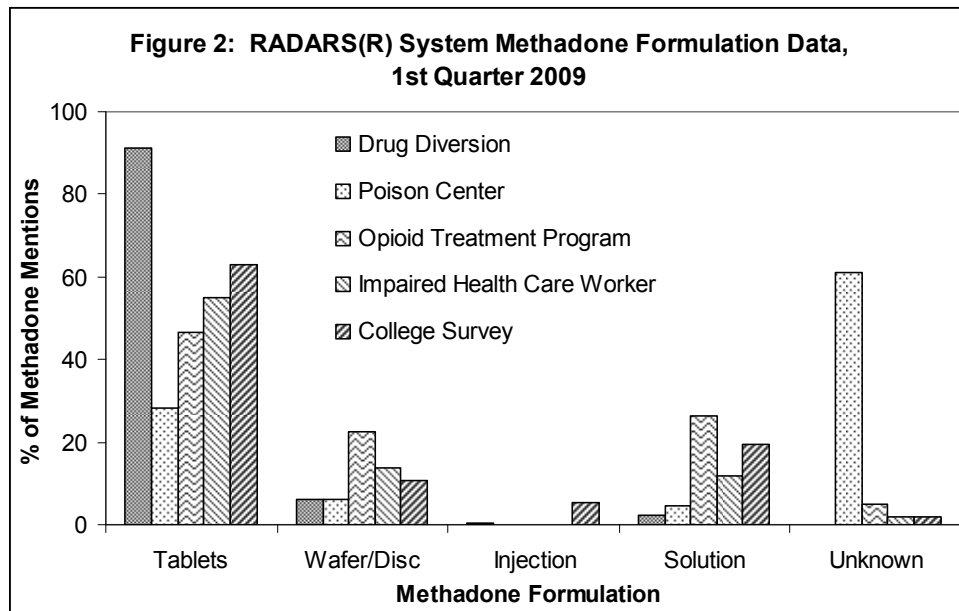


Abbreviations: Drug Diversion (DD), Key Informants (KI), Poison Centers (PC), Opioid Treatment Programs (OTP), Impaired Health Care Workers (IHCW), College Survey (CS), Survey of Key Informants' Patients (SKIP).

- Our experience with the RADARS® System has been that immediate-release and extended-release opioid formulations appear in different proportions in each Signal Detection System, reflecting marked preferences for specific formulations during different points in time over the course of opioid use disorders.
- Acute events reported to poison centers and reports of diversion from law enforcement are predominantly for immediate-release opioids, whereas those seeking and entering drug treatment programs are more likely to report nonmedical use of extended-release opioids.
- Furthermore, specific product results often vary substantially depending on the type of user/abuse, giving rise to the need to understand the subpopulations exposed, as discussed in Principle 6, below.
- It is likely that the effects of REMS will be different depending on the system used to measure. Therefore, a complete picture can only be obtained through multiple perspectives.

**6. The impact of the opioid REMS on opioid treatment programs must be evaluated.**

- The potential of methadone being a pilot program, as proposed by the Industry Working Group, highlights specific considerations in terms of evaluation. Since different formulations of methadone are used for analgesia and management of opioid dependence disorders, the measurement of formulation-specific results is required. For example, while there is a separate ICD-10 code used to designate methadone poisoning mortality, the coding schema does not differentiate between methadone formulations. If the overall number of deaths involving methadone does not decrease, but there is a shift in the type of methadone implicated, how will this be interpreted in the scope of REMS evaluation?
- Further, methadone could theoretically have greater widespread use if the REMS is implemented successfully (including exposures in previously understudied populations).



**7. Assessments of opioid REMS must be conducted on pre-scheduled basis**  
Required by Section 505-1

**8. Outcomes in specific populations must be monitored:**

- a. Patients and non-patients
- b. Young children
- c. Adolescents
- d. Patients in substance abuse treatment
- e. Elderly

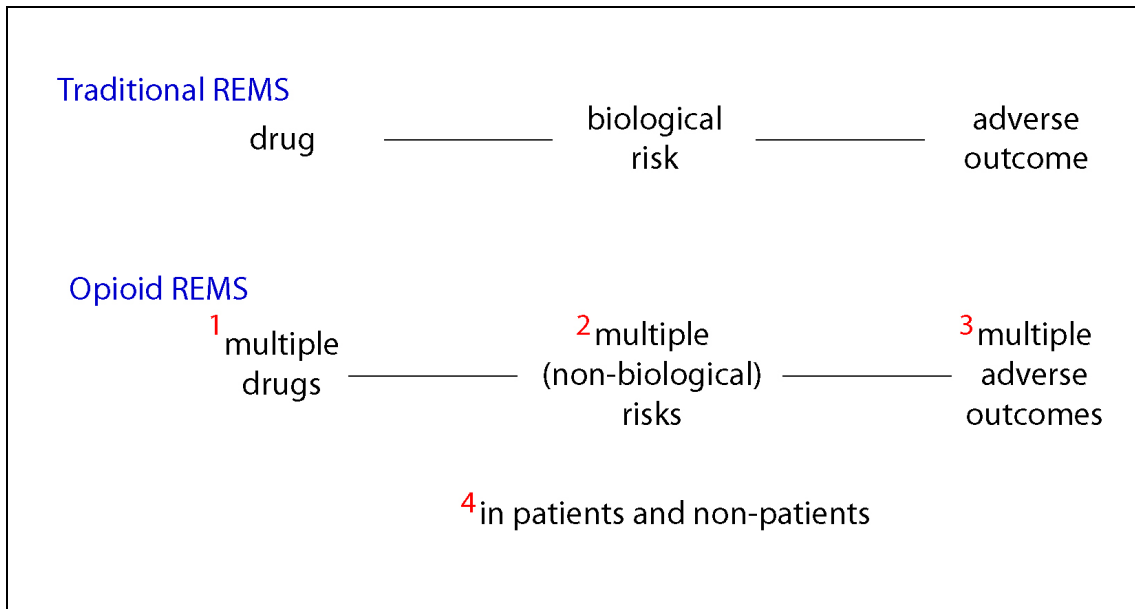
There are obvious reasons to expect that the effect of REMS may vary by age. Changes required by REMS may increase or decrease poisoning in children. Another example is that REMS could cause a product to be unavailable to a specific group.

**9. Evaluation must assess whether existing disparities in access to opioid pain medications by vulnerable minorities is not exacerbated.**

Some groups already experience serious challenges in appropriately obtaining prescription opioid products. REMS could create additional unintended barriers and must be monitored during REMS evaluation.

**THE UNIQUE CASE OF OPIOID REMS**

The proposed opioid REMS differ from REMS for products not regulated as controlled substances in four specific ways that have direct consequence on evaluation.



1. Opioid REMS attempts to mitigate risks from a class of drugs, instead of one specific product. Since each drug has a different profile and specific risks, data collection systems should strive to evaluate each drug formulation individually, while being able to aggregate for the entire covered class of drugs. With methadone as a potential pilot program, the importance of drug specificity in data collection systems is more pressing, since most federally-sponsored national cross-sectional studies do not provide drug-specific (let alone formulation-specific) information.

2. The intermediate risk factors that are on the causal pathway between opioid exposure and the outcomes of interest are complex and directly influenced by phenomena outside the control of REMS, including (but not limited to) the social environment, genetics, social networks, and access to emergency medical and drug treatment services. These causal intermediaries are not measured in traditional pharmacovigilance. Many evaluations of REMS are likely to rely on ecological time-series analyses, before and after implementation of REMS. In addition to influences on the individual, broader policy changes may also directly affect the outcomes of interest.

At a minimum, a centralized database (a “policy bank”) of regional, state and local programs and policies needs to be created and maintained to document factors extrinsic to the REMS which will affect the outcomes. For example, increased substitution treatment has led to decreases in opioid overdose deaths in Norway and France, the targeted UNITE intervention in Kentucky appears have decreased consequences of the nonmedical use of opioids, other federal agencies continue to deploy primary prevention programs, and legislation has been introduced in the US Congress to provide major funding to overdose prevention programs. These efforts will have direct impact on the outcomes of interest, and the failure to account for the effects of national and sub-national initiatives would be scientifically dishonest. A centralized policy bank should be made accessible to all researchers who will conduct evaluations.

3. In contrast to existing REMS, the proposed opioid REMS is intended to reduce the incidence and prevalence of multiple outcomes including abuse, diversion, addiction, misuse and overdose. It has been articulated that the theoretical way to impact all of these outcomes is through decreased supply, since the Agency and industry has very limited authority and control over the causal intermediates which connect exposure to outcome. Further complicating the issue is that in certain cases, the outcomes are dependent on each other. For example, the physiological dependence engendered in addiction is protective against overdose, as documented by decades of research on heroin users. Perturbing prescription painreliever supply in opioid dependent non-patients, in the absence of expanded and low barrier access to substitution therapy, has been linked to an *increase* in overdose deaths in specific examples in the United States. It is therefore of utmost importance to measure the different outcomes separately but in parallel, using multiple standardized information sources. Since the outcomes are interdependent, and limiting supply of only extended-release and long-acting opioids is of dubious utility in the continued presence of alternative opioid preparations in the United States, the outcomes of interest for the REMS must also be evaluated for exposure to immediate-release opioids and heroin.
4. Opioid REMS attempts to simultaneously control behaviors and risks in patients and non-patients. It is likely that the REMS will have a significant impact on non-patients and former patients, as well as current and future patients. The Agency also has the public health responsibility of measuring the impact of REMS among non-patients, specifically with regard to the increased use of immediate-release opioids and heroin, and health consequences associated with nonmedical use of these drugs (e.g., talc-related injection complications, HIV, hepatitis, etc.). Similarly, there are unintended consequences of REMS within the patient population. The use of immediate-release combination products for the management of chronic pain may be associated with increased hepatic and gastrointestinal injury. While AERS and pharmacovigilance has been traditionally used to measure these outcomes, it is unclear what case detection bias may be present in spontaneous reporting after implementation of REMS for a separate class of products

In addition to the four design considerations above, the proposed opioid REMS potentially includes more patients (and non-patients) than all other REMS and risk management plans to date. The vastly expanded scope of the opioid REMS is likely to introduce additional challenges and opportunities for evaluation, which will become evident as plans are finalized for the methadone pilot or other initial steps. With the large number of individuals potentially affected by opioid REMS, there are likely to be unanticipated consequences which will also need to be measured. In this way, the evaluation plan will also need to be iterative and take advantage of new, electronically-based health information.

### **Data Collection for Evaluation of Opioid REMS**

Each Element to Assure Safe Use must be aligned with the goals of opioid REMS and evaluated in such a context. At this moment, it appears that the ETASU are intended to function through: 1) reductions in the prescribing and dispensing of extended-release opioids, and 2) improvements in knowledge among patients, prescribers and dispensers.

Post-marketing surveillance and data from existing and novel federally-sponsored studies must be used in conjunction to assess opioid REMS. While the overall goal of opioid REMS is to reduce the unintended consequences of opioid availability, it will be difficult to make causal inferences about the effectiveness of opioid REMS based solely on post-marketing surveillance data and national cross-sectional studies. Specific elements of opioid REMS need to be assessed and linked with post-marketing surveillance data in order to perform a comprehensive evaluation as required under Section 505-1.

One of the key difficulties will be assessing whether individuals recorded in post-marketing surveillance and federally-sponsored studies have been “exposed” to the REMS. While all individuals receiving the opioids in question (e.g., analgesic methadone in the pilot) should have received the relevant information, it is not guaranteed that they did or that their physician or pharmacist was properly registered. The underlying assumption in using most of the data sources will be that the implementation of the REMS is uniform and universal. Since this is unlikely to be the case, the use of all these data sources must be done with caution, and causal inference must be accorded time and methodological rigor to be achieved properly.

Data collection to evaluate REMS programs will often involve a combination of prospective phase 4 clinical trial data and post-marketing data. Post-marketing surveillance data are of use for several reasons:

- Post-marketing data may be the only source because some patient populations are unwilling to participate in prospective studies (e.g., diversion-related activities)
- Post-marketing data are more generalizable to the actual risks incurred during routine medical use than clinical trial data because both patient and non-patient populations are included
- Postmarketing research avoids some of the limitations inherent to prospective research
  - Allows evaluation of circumstances such as accidental or intentional overdose that cannot be studied ethically studied in a prospective manner.
  - Rare events can be detected because sample size is much larger
    - Unusual methods of abuse or diversion
    - Allergic reactions
    - Unusual drug combinations (e.g. malignant hyperthermia)
    - Various types of illegal activity

- The post-marketing setting offers the opportunity to conduct small randomized trials to test and modify different components of the REMS before they are implemented. This is especially important if methadone is to be the pilot drug.
  - Impact of physician training course on prescribing behavior
  - Patient knowledge retention and behavior change based on the Med Guide
  - Burden of ETASU on pharmacists

### **Requirements of Post-marketing Data Collection Systems**

The following are requirements for surveillance systems:

- Geographic specificity (at least at 3-digit ZIP code level) to guide further investigation and evaluate effects of simultaneous non-REMS interventions
- Product and formulation specificity (immediate- vs. extended-release, tamper deterrence, etc.)
- Timely reporting of data to allow improvement of REMS as early as possible in the process
- Multiple perspectives from different points over the course of the natural history of drug use/dependence (e.g., treatment seeking, non-dependent community-dwelling, diversion, etc.)
- Include a measure of drug availability in the community. Studies have found repeatedly that much of the drug available for abuse and diversion arises directly or indirectly from a licensed prescriber of controlled substances
- Appropriate quality control to assure that data are collected appropriately, managed cleanly and reported accurately without sacrificing time. A quality assurance program is needed to address quality issues and assure that the system consistently improves itself
- Representative national coverage

## ***APPLICATION OF PRINCIPLES OF REMS ASSESSMENT***

### **Measurements**

Specifying *a priori* metrics and outcomes of interest is critical to provide objective evaluations of opioid REMS. More than a decade of opioid risk management indicates that both intended and unintended consequences of a REMS should be included.

Intended Consequences of a REMS Program:

- Monitored drug is not prescribed to inappropriate patient (i.e. high potency opioid to opioid naïve patient)
- Monitored drug is not involved in poisonings to young children out of proportion to other opioid products
- High potency opioid product is not used by new initiates to prescription opioid abuse out of proportion to other opioid products
- Diversion of prescription opioid is not out of proportion to other opioid products

Unintended Consequences of a REMS Program:

- Access to prescription opioids to legitimate pain patients is not substantially decreased by the REMS
- A clinically undesirable shift in prescribing. For example, potential for increased prescribing of immediate-release opioid products for cancer patients following institution of REMS for extended-release products.

There are many risks involved in the use of prescription opioid medications:

- Adverse events, particularly from inappropriate patient selection (i.e., prescribing of high dose opioid medications to opioid naïve patients)
- Accidental overdose (children, elderly patients)
- Intentional overdose (self-harm)
- Intentional misuse to increase the therapeutic effect of a drug
- Abuse and diversion
- Withdrawal from improper discontinuation of medication
- Acetaminophen and NSAID toxicity from increased use of immediate-release combination opioids

The appended Table presents specific measurements and data collection systems that can be used to measure the intended and unintended consequences of the proposed opioid REMS, specifically linked to each ETASU that has the highest probability of being enacted. The table indicates whether the data collection mechanisms already exist, could be modified to address specific questions, or would need to be created.

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#### References

1. Hertz S: <http://www.fda.gov/cder/meeting/opioid/3Hertzsporsormeeting3-3-09.pdf>
2. Rappaport R. Statement at FDA meeting on Risk Evaluation and Mitigation Strategies, Rockville, Maryland, May 4-5, 2009

## Appendix. Framework for Evaluation of Opioid REMS

REMS Element and Objective	Subpopulations of Interest	Examples of Evaluation Data Sources	Examples of Measurements
<b>Prescriber training and registration</b>			
<i>Intended Outcomes</i>			
Improved knowledge of pain management and opioids prescribing among healthcare providers	HCP who previously did not prescribe (extended-release) opioids	Surveys of prescribers (REMS-specific)	Pre-/post-training, trained vs. non-trained, retention of knowledge
More appropriate patient selection for opioids		<ul style="list-style-type: none"> <li>Longitudinal cohort of potential and current pain patients</li> <li>Administrative medical care data/EMR</li> </ul>	
Utilization of support tools for better monitoring of patients	Patients with psych/substance use histories	<ul style="list-style-type: none"> <li>PMP Utilization</li> <li>Physician surveys</li> </ul>	Physician satisfaction, use of REMS tools
Reduced diversion		<ul style="list-style-type: none"> <li>RADARS System Drug Diversion</li> <li>Stolen medication reports from law enforcement</li> </ul>	Product-specific rates, minimal divertible units
Reduced nonmedical use (abuse)	School age children	<ul style="list-style-type: none"> <li>RADARS System Poison Centers abuse category</li> <li>RADARS System College Survey</li> <li>RADARS System Opioid Treatment Program and Survey of Key Informants' Patients</li> <li>DAWN and DAWN Live</li> </ul>	Rates of nonmedical use
Reduced overdose	Pediatric	<ul style="list-style-type: none"> <li>NPDS</li> <li>RADARS System Poison Centers</li> <li>DAWN Medial Examiner</li> <li>Vital statistics</li> </ul>	Rates of overdose in children
Reduced opioid dependence disorder (addiction)	Iatrogenic opioid dependence disorder Treatment seekers	<ul style="list-style-type: none"> <li>RADARS System Opioid Treatment Program and Survey of Key Informants' Patients</li> <li>RADARS System College Survey</li> </ul>	College Survey DAST scores Referrals to treatment for opioid dependence disorder

• NAVIPPRO

Reduced medication errors	General practitioners	Claims data	Appropriate starting doses, especially for methadone Combinations of CNS medications Prescribing in opioid tolerant patients
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<u>Unintended Consequences</u>			
Increased use of short-acting combination products for chronic pain, and consequences	Patients with pre-existing hepatic conditions	<ul style="list-style-type: none"> <li>• RADARS System Poison Centers</li> <li>• ED data</li> <li>• Mortality data</li> <li>• Commercial sales data</li> </ul>	Product-specific rates of acute hepatic injury, GI bleeds, etc.
Fewer HCP prescribing extended-release opioids	General practice Non-registered HCP	Commercial sales data	Number of prescribers
Decreased willingness to prescribe/dispense extended-release opioids	Immediate- vs. extended-release opioids	<ul style="list-style-type: none"> <li>• Prescriber and pharmacist attitude surveys</li> <li>• Prospective cohort of painful disease state-specific potential patients</li> </ul>	

**Patient registration system  
Prescriber-patient written agreements**

<u>Intended Outcomes</u>			
Reduced diversion via doctor shopping		<ul style="list-style-type: none"> <li>• Multiple PMPs</li> <li>• Claims data from Medicaid and other third party payers</li> </ul>	Number of individuals filling prescriptions from large number of prescribers
Improved adherence to opioids among patients in chronic pain	Patients on long-term therapy with short-acting opioids	<ul style="list-style-type: none"> <li>• Claims data</li> <li>• Patient surveys or studies</li> </ul>	Number of timely refills, duration of therapy

Unintended

Consequences

Appropriately selected potential patients not being placed on opioid therapy	Minorities (racial, insurance status) Rural vs. urban Cancer vs. non-cancer pain	Prospective cohort of painful disease state-specific potential patients	Medications received instead of long-acting opioids, including immediate-release combination products
Policy changes affecting access to opioid medications	State Medicaid and major (Top 5) insurance and pharmacy benefit providers	Central database of state and regional policy changes which may result in fluctuation of opioid prescribing (Also needed to assess confounding in natural experiments for evaluation of REMS)	Restrictions on reimbursement and coverage by third party payers Prior authorization requirements
Patient perceptions and attitudes for accessing pain medications	Minorities (racial, insurance status) Rural vs. urban Cancer vs. non-cancer pain	Patient surveys	Perceived stigma, difficulty, quality of life
Increased use of heroin among nonmedical users	Injectors	<ul style="list-style-type: none"> <li>• RADARS System Drug Diversion</li> <li>• RADARS System Poison Center</li> <li>• RADARS System College Survey</li> <li>• RADARS System Survey of Key Informants' Patients</li> <li>• RADARS System Opioid Treatment Program</li> <li>• NSDUH</li> <li>• MTF</li> <li>• Qualitative studies</li> <li>• NAVIPPRO</li> <li>• TEDS</li> </ul>	HIV/hepatitis risks RADARS System Poison Center: moderate/serious/death intentional exposure calls RADARS System Drug Diversion: Street price Impact of introduction of tamper-deterrent formulations
Public perceptions of opioids and pain		Telephone-based polling	Awareness and attitudes of opioids

**Expanded/redeveloped medication guides**

Intended Outcomes

Increased patient awareness of risks	Non-English literate Illiterate Low cognitive ability	Prospective studies of pain patients	Pre-/post-reading knowledge, retention of knowledge over time, exposure to other sources of safety information
Changes in patient behavior to ensure proper use, storage and disposal	Patients with children in home	Prospective studies of pain patients	Behavioral change studies • RADARS System Poison Centers misuse category
Reduced adverse events	Opioid non-tolerant outpatients starting methadone/extended-release opioids	<ul style="list-style-type: none"> <li>• MedWatch/AERS</li> <li>• ED-linked claims data</li> <li>• RADARS System Poison Centers</li> <li>• Patient surveys</li> </ul>	Rates of respiratory depression, cardiac arrest, death during therapeutic use

Unintended Consequences

**Pharmacist Registration System**

Intended Outcomes

Increased pharmacist awareness and action on risks associated with long-acting opioids	Pharmacy techs	Pre- and post-REMS implementation surveys	Changes in knowledge of risks Changes in counseling and dispensing
Distribution of educational materials by pharmacists to patients	Small/independent pharmacies Pharmacy techs		

Unintended Consequences

Pharmacy unwillingness to stock extended-release opioids	Small/independent pharmacies	Pharmacy and pharmacist surveys	Perception of benefits and burdens of REMS Increased staff and storage costs associated with REMS
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