EXECUTIVE SUMMARY

Tufts HealthCare Institute Program on Opioid Risk Management

Meeting on

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

July 2009

Tufts Health Care Institute Program on Opioid Risk Management Summit Meeting
July 23 and 24, 2009
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List of Abbreviations:

FDAAA	Food and Drug Administration Amendments Act
POA	Prescription opioid abuse
REMS	Risk Evaluation and Mitigation Strategies
RCA	Root cause analysis

Introduction: The FDAAA (2007) authorizes the FDA to require drug companies to continue post-market monitoring of certain prescription drugs, and to ensure that the benefits of using these drugs outweigh the risks. Companies must do this by developing Risk Evaluation and Mitigation Strategies (REMS), which may include mandatory certification of patients, prescribers and pharmacists, and an outcome assessment for each REMS solution. The FDA has provided little specific guidance to date on how to develop a REMS that incorporates a rational intervention for preventing prescription opioid abuse (POA) while still maintaining adequate patient access to these powerful analgesics. In July 2009, Tufts Health Care Institute, as part of its Opioid Risk Management Program, organized a meeting to discuss REMS solutions; *the focus of this meeting was to offer a context within which reviewers can evaluate proposed REMS for specific opioids. Participants generally agreed that articulating a root cause analysis for POA, setting clear REMS goals, emphasizing behavior change rather than knowledge transfer in REMS-related educational programs, and mandating outcome evaluation, are essential elements for all successful REMS program.*

For prescription opioids, a number of risk management plans are already in use, yet the numbers of overdoses dues to POA continue to climb. A number of industries (e.g., airline, nuclear power, chemical power) use RCAs to understand the reasons underlying serious accidents, and to reduce risks of future mishaps. Attendees recognized the need for developing similar, comprehensive analyses of the causes of POA, but acknowledged that such an endeavor would need considerable time, effort and resources; however, they also agreed that the need to address the problems of overdose fatalities, accidental pediatric exposures, injection-related disease, and the very large numbers of individuals who meet DSM-IV criteria for addiction to prescription opioids, is urgent and immediate. All of these factors strongly motivate a REMS approach that deals with developing an RCA for POA, and at the same time implements specific interventions and evaluates the effectiveness of these interventions in relation to reducing known POA-associated risks. For this meeting, the outcome of interest was overdose death, and interventions were aimed at training aimed at altering target behaviors for three major stakeholders: prescribers, patients, and pharmacists.

Designing a Rational REMS Solution for POA: An effective solution should have the following ingredients:

- *A coherent and data-driven RCA*, even though it may be a provisional one.
- *Proposed systemic changes linked to the RCA***,** with a focus on altering specific behaviors on the part of prescribers, pharmacists, and patients; changes should be set within the framework of commonly used methods for setting performance improvement objectives. Targeted behaviors should be within the critical paths of RCA, and tactics for altering such behaviors should encompass workflow solutions, based on an awareness of how the system works.
- *A credible evaluation of program elements and of the overall program***,** encompassing technical (what does the program do, what it is supposed to do), performance (do doctors order adequate urine tests, do patients lock up their medications), and clinical (do overdose deaths decrease) aspects of the REMS solution.

A preliminary RCA of Opioid-Related Fatalities: Three levels of response can be considered when analyzing a serious accident with the intent of reducing the probability of recurrence: Level 1 considers the only the *Events or Accident Mechanism*, which are the physical events that lead to the disaster, though they are not necessarily the root cause; Level 2 refers to the *Workplace Conditions*; Level 3 encompasses *Systemic Factors*, which address broader issues such as how much feedback exists in the system and how comfortable employees (including managers) are about speaking up about possible risks without feeling

embarrassed. RCA asserts that essential change must occur at Level 3 in order to radically alter risk recurrence.

Developing a comprehensive RCA for overdose fatalities related to POA is difficult, since few publications exist in the literature on the causes of this many-faceted problem: Capturing such data is prerequisite for developing an effective REMS. Who are the people that are dying? Are they patients or non-patients? From where do they get their medication? Do they live in urban or rural areas? Have they seen a doctor in the past year, and if so what kind? What induced them to start taking the medication? For patients, was there a therapeutic error of some type? What were the individual-level risk factors for overdose? What were the environmental risk factors? However, drafting a preliminary RCA has great utility in helping to update our mental models of the problem, and to build collaborative relationships at the systemic level, so that people can learn together while continuing to collect data and analyze why trends go up or down. In this review, our focus is on overdose fatalities, but similar analyses can also be developed for other manifestations of POA (pediatric exposure, addiction, etc.). We consider the system to be a dynamic entity, constantly adapting (internally and externally) to new technologies, new people in the workforce, and new regulations; REMS can be viewed as a control strategy aimed at managing this very complex and adaptable system over time, based on a knowledge of the risks and the sources of these risks. REMS solutions for POA should thus be based on the analysis of causes that underlie opioid-related fatalities and addiction, and unraveling of causal pathways that lead to these problems is key to this analysis.

An etiologic assessment of POA involves looking at three aspects of the problem (how opioid use and abuse begins, why potentially fatal opioid exposures occur, and why these exposures become fatal) and two populations (those needing pain management, and non-patients in the community). While proximal causes of opioid use and overdose may be quite different for the two populations, downstream causes that lead from overdose to fatality are much less distinct.

Linking Proposed System Changes to the RCA: The preliminary RCA developed for overdose fatalities related to POA highlights a number of rational opportunities for deploying interventions, illustrative examples of root causes, target behaviors linked to these root causes, specific interventions for altering the behaviors, and ways to evaluate the efficacy of the interventions are listed for each of the principal stakeholders: prescribers, patients, pharmacists (see Figures and Tables in paper). Based on the experience in other industries, traditional reactive approaches of blaming individuals, hoping for change, making vague pronouncements about need for greater attention to “drug safety,” “medication errors,” or “patient non-compliance” are not likely to be helpful, and specific experience of the failure of some of these approaches in reducing POA already shows that different approaches are needed. A formal, data-driven, and quantitative RCA would no doubt lead to predictions of which interventions would have the greatest impact, and would suggest other interventions not obvious in the present superficial approach. And while FDA has been challenged to reduce POA through its REMS authority, the need to engage stakeholders over which the FDA has no direct authority creates new challenges and opportunities. The challenge lies in identifying the intervention opportunities in the RCA that can be addressed by pharmaceutical company activities, and are therefore in principle subject to FDA authority. The more difficult challenge will be to identify intervention opportunities in the RCA that can only be addressed by non-pharmaceutical company stakeholders, and to establish collaborations and provide leadership to those stakeholders so as to implement such interventions. Recent meetings held by FDA with multiple diverse stakeholders suggest that the FDA has recognized the need for cross-stakeholder collaboration and is moving in this direction.

Behavior Change through Effective Use of Pharmacy Systems: The vast majority of prescriptions (90%) in the US are transacted electronically, through a switching company that links pharmacies to payers for the purpose of insurance verification. The existence of this infrastructure provides a cost-effective opportunity to support behavior change for physicians, patients, and pharmacists in a manner that does not burden the health care system. Switching technology can be used to automatically verify whether a specific prescriber, or patient, or pharmacist, has completed training in safe opioid use as a "safe use condition" for dispensing the medication. And cash prescriptions, which have tended to remain outside the province of the switch providers, can be captured using a variety of approaches. Such technologies have the potential to meet the goals of REMS, at least with respect to supporting automated verification of stakeholder training at the point of dispensing.

In conclusion, meeting participants agreed that rational interventions to POA overdose death can be drafted based on a preliminary Root Cause Analysis, but that the need for interventions does not obviate the urgent need for a comprehensive RCA of POA overdose deaths; this should be considered a high priority by funding organizations interested in prescription drug abuse.