NCCN Oncology Risk Evaluation and Mitigation Strategies White Paper: Recommendations for Stakeholders

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Key Words
REMS, risk, oncology, safety

Abstract
REMS are a particularly important issue for oncology and the National Comprehensive Cancer Network (NCCN). A disproportionate number of drugs with complex REMS are used in patients with cancer or hematologic disorders. REMS policies and processes within oncology may act as a model for other clinical areas. A breadth of experience and access to a wide knowledge base exists within oncology that will ensure appropriate development and consideration of the practical implications of REMS. NCCN is uniquely positioned to assume a leadership role in this process given its status as the arbiter of high-quality cancer care based on its world-leading institutions and clinicians. Notwithstanding the potential benefits, the successful design, implementation, and analysis of the FDA’s recent requirement for REMS for some high-risk drugs and biologics will present significant challenges for stakeholders, including patients, providers, cancer centers, manufacturers, payors, health information technology vendors, and regulatory agencies. To provide guidance to these stakeholders regarding REMS challenges, the NCCN assembled a work group comprised of thought leaders from NCCN Member Institutions and other outside experts. The Work Group identified challenges across the REMS spectrum, including the areas of standardization, development and assessment of REMS programs, medication guides, provider knowledge and impact on prescribing, provider burden and compensation, and incorporation of REMS into clinical practice. (JNCCN 2010;8[Suppl 7]:S7–S27)

Executive Summary
Managing drug safety and developing drug safety systems is an ongoing, critically important challenge for all involved in manufacturing drugs, regulating drug use, prescribing drugs, dispensing drugs, and consuming drugs. Risk Evaluation and Mitigation Strategies (REMS) are the newest tool of the FDA to help manage and ensure safe drug use. The FDA may require manufacturers to develop REMS for both existing drugs and those in development when it determines that special action is needed to ensure that the benefits of a drug outweigh its risks. It is recognized that REMS can facilitate the FDA approval of drugs with a high-risk potential that would not otherwise be approved, or allow a drug to stay on the market. REMS are a particularly important issue for oncology and the NCCN. A disproportionate number of drugs with complex REMS are used in patients with cancer or hematologic disorders. REMS policies and process within oncology may act as a model for other clinical areas. A breadth of experience and access to a wide knowledge base exists within oncology that will ensure appropriate development and consideration of the practical implications of REMS. NCCN is uniquely positioned to assume a leadership role in this process given its status as the arbiter of high-quality cancer care.
based on its world-leading institutions, clinicians, and pharmacists and its past record of developing the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), widely accepted as the standard for clinical policy in oncology in the United States. Additionally, the NCCN Drugs & Biologics Compendium (NCCN Compendium) is recognized by the Centers for Medicare & Medicaid Services as a mandated reference for oncology coverage policy.

Notwithstanding the potential benefits, the successful design, implementation, and analysis of the FDA’s recent requirement for REMS for some high-risk drugs and biologics will present significant challenges for stakeholders, including patients, providers, cancer centers, manufacturers, payors, health information technology vendors, and regulatory agencies. To provide guidance to these stakeholders regarding REMS challenges, NCCN assembled a work group comprised of thought leaders from NCCN Member Institutions and other outside experts. These multidisciplinary thought leaders represented providers (physicians, pharmacists, and nurses), patients, manufacturers, payors, and government/regulatory organizations.

The NCCN REMS Work Group convened on March 13, 2010, during the NCCN 15th Annual Conference: Clinical Practice Guidelines & Quality Cancer Care in Hollywood, Florida. The Work Group identified challenges across the REMS spectrum, including the areas of standardization, development and assessment of REMS programs, Medication Guides, provider knowledge and impact on prescribing, provider burden and compensation, and incorporation of REMS into clinical practice. The Work Group provided recommendations for all of the challenges, some that could be foreseen being implemented in the near future and others that would require collaboration across stakeholder groups and a longer amount of time to implement. Additionally, the Work Group identified metrics that should be collected to assess the impact of REMS on clinical practice, and subsequently developed a survey that was administered through the NCCN Trends Surveys & Data program and through the Oncology Nursing Society (ONS). These recommendations and survey data were presented at the NCCN Oncology Summit: Recommendations for REMS Stakeholders on May 7, 2010, in Washington, DC.

Overview

REMS have emerged as a priority topic for numerous stakeholders, including patients, providers (including physicians, other prescribers, and pharmacists), specialty pharmacies, industry, and government organizations. The FDA has authority to require manufacturers to develop REMS for both existing drugs and drugs in development when it determines special action is needed to ensure that the benefits of a drug outweigh its risks.

REMS are designed by the manufacturer to track
and protect patients from specific risks of drug therapy. Based on draft guidance from the FDA, REMS may even facilitate access to medications by allowing some drugs with safety concerns to be FDA-approved that otherwise may not be approved without a REMS program. Some REMS are relatively simple (e.g., only require provision of a medication guide), whereas others have numerous components and require actions by prescribers, pharmacists, pharmacies, and patients. When used appropriately, REMS can ensure safe use of prescribed drugs, including appropriate patient selection, monitoring, and education. However, as the number and complexity of REMS programs increase, the challenges associated with prescribing and dispensing also increase. Thus, REMS may add significant workload to prescribers and dispensers of drugs with REMS, making it potentially less likely for a drug with a complex REMS to be used. Therefore, complex REMS must be designed so that they do not impose an inappropriate burden on patients, physicians, pharmacists, other health care providers, and practice centers. The application of REMS must balance feasibility for providers and pharmacists with the FDA’s goal of mitigating the risks of a drug.

Although the law that authorizes REMS went into effect in early 2008, REMS have received broader attention as the number and scope of REMS have increased over the past year. In particular, the recently announced erythropoiesis stimulating agent REMS and recent action by the FDA to develop a class-wide REMS to ensure the safe use of long-acting and extended-release opioids have brought REMS to the forefront. The FDA has already received more than 2000 comments on the proposed opioid REMS from pain specialists and others. The FDA is taking a careful approach to developing this class-wide REMS by allowing comments through October 19, 2010.

Several drugs within oncology, including several supportive care medications, currently have associated REMS. A disproportionate number of drugs with complex REMS are used in patients with cancer or hematologic disorders. Availability of and access to these appropriate drugs are essential for patients with serious and life-threatening terminal illness. In addition, the proposed class-wide REMS for long-acting and extended-release opioids is particularly relevant to cancer care. The use of REMS is expected to grow substantially in the future, especially for oncology-related therapies. As the new REMS paradigm develops, the practical implications of the policies and process must be carefully considered so that REMS are implemented in a feasible manner that allows patients to have access to innovative drugs and biologics.

### Background

Signed into law on September 27, 2007, and effective on March 25, 2008, the FDA Amendments Act of 2007 (FDAAA) gave the FDA “enhanced authorities regarding postmarket safety of drugs.” Among other regulations, this authority allows the FDA to require a REMS for drugs or biologics that the agency determines to have a high risk potential. As stated by the FDAAA, one purpose of REMS is to “[provide] safe access for patients to drugs with risks that would otherwise be unavailable.” These types of risk mitigation strategies, which traditionally fell under the jurisdiction of private sponsors, drug manufacturers, and health care providers, are now coming to drug manufacturers and health care providers in the form of unfunded mandates through FDA regulations and guidance. Before REMS, risk minimization action plans (RiskMAPs) were required for a few medications. The goals of RiskMAPs were very similar to those of REMS. The FDA has deemed that several drug and biologic products approved before the effective date of Title IX of FDAAA have in effect an approved REMS. These medications include lenalidomide and thalidomide.

REMS are issued by the FDA for certain drugs and biologics that the agency believes require a mechanism to ensure that the benefits outweigh the risks for patients. This applies mainly to new drug applications, but can be applied retroactively to existing approved medicines. Manufacturers for which REMS are mandated are asked to create systematic plans that can be used both to educate patients and health care providers about risks associated with particular medications and to simultaneously work to minimize those risks through various strategies, for example requiring strict monitoring and restricting access to the drug through a closed distribution system.

A REMS program can have 3 components: 1) a medication guide or a patient package insert; 2) a communication plan for health care providers; and 3) elements to assure safe use (ETASUs). A drug’s REMS program may not require the provision of all 3 components, because the specific components of a REMS program will vary based on the severity of the risks, the popu-
lation likely to be exposed, and other factors. In fact, the most common REMS only require the provision of a medication guide. However, all REMS programs must state specific risk mitigation goals, and have a timetable for assessing the mitigation strategy. Manufacturers must measure the effectiveness of their REMS programs 18 and 36 months after implementation. They may also be required to evaluate effectiveness after 7 years, depending on the measured success at 36 months.

Although manufacturers are responsible for developing effective REMS programs, they do not have authority over providers to ensure they are complying with REMS requirements. Furthermore, the FDA has the authority to fine manufacturers and even prevent the sale of a drug if it finds a manufacturer has failed to comply with REMS requirements.

The most complex REMS, which are those with an ETASU component, are the most challenging to health care providers, patients, drug manufacturers, and other stakeholders. Considered the “highest level” of a REMS regulation, ETASUs would require documentation and assurance of all or some of the following: 1) the prescriber of the drug has particular training, experience, or specialty credentials; 2) the dispenser of the drug is specially certified; or 3) the drug is dispensed to patients in certain health care settings. Additionally, patients may be required to enroll in a registry that facilitates periodic monitoring (i.e., of laboratory tests) and provides documentation of “safe-use” conditions (i.e., ensuring that patients who are taking the drug meet specific criteria). ETASUs are the latest step in an evolution of risk mitigation strategies that started with RiskMAPs that were used to minimize the known severe risks to patients before drug approval. Examples of drugs that used a RiskMAP include clozapine, thalidomide, and lenalidomide (many of these RiskMAPs are now deemed REMS).

The FDA recognizes the potential to disrupt the provision of care and reduce access to a drug if the REMS program is overly cumbersome. Therefore, the FDA has been open to seeking input from providers and others on how to balance systems for mitigating the risks of a drug while minimizing the burden to providers. The FDA continued to seek input by holding a 2-day public meeting in July 2010 for all interested stakeholders to make comments.

**REMS in Oncology: Is it Different?**

REMS serve a useful purpose in identifying, monitoring, and minimizing serious known and unknown risks of certain drugs. The regulation was conceived to create a formal process through which the FDA can collect risk information, communicate these risks, and restrict the distribution of a drug or biologic if necessary. This additional step was necessary to implement after serious safety concerns were identified with specific agents.

On the surface, it makes sense to apply REMS toward drugs and biologics in the oncology setting. After all, many of these agents have serious and sometimes life-threatening toxicities. However, the concept of REMS did not arise because certain agents simply have serious associated risks. Instead, REMS were developed because of an increasing sentiment in the 1990s that relying on black box warnings and labeling information was not adequate for mitigating risks of specific medications. During this time of heightened focus on drug safety, there was a realization that labeling recommendations and black box warnings were being overlooked, and that certain medications were being used in ways that increased risk to patients.

The oncology realm is different, however, because the practice within oncology involves much more collaborative interaction among multiple types of health care practitioners (e.g., physicians, nurses, pharmacists) than other therapeutic areas. Oncolytic therapy historically has been designed to kill human cells and has known risks that must be closely managed. Therefore, specific processes already exist to minimize risk from medications. For example, when dispensing and administering a chemotherapy regimen to a patient, the current practice uses a system of double-checks by a nurse or pharmacist. These double-checks include evaluating the clinical appropriateness and monitoring laboratory values and clinical signs and symptoms for toxicity. Patients are typically educated regarding the expectations and adverse reactions from the medications. Furthermore, proactive supportive care measures are commonly used to mitigate serious known toxicities, such as anaphylaxis, infections, and neutropenia. Additionally, clinicians practicing within the oncology realm are usually highly specialized, having obtained additional education, training, and certification to care for these patients. In this particular example, the oncology subspecialty has taken the responsibility of playing an active role in mitigating the risks associated with these agents, particularly because the adverse effects are generally more severe than those of medications for other diseases.
The cancer treatment paradigm is shifting toward an increased use of oral agents. A recent NCCN Task Force Report reported that an estimated 25% of antineoplastic agents in the research pipeline are administered orally. Most of these agents are classified as “targeted therapy,” and have a different side effect profile than traditional cytotoxic chemotherapy, some of which may be life-threatening (e.g., nilotinib may cause QT interval prolongation). Additionally, the use of oral agents tends to bypass the aforementioned rigorous process of double-checks for infusional chemotherapy, although patient education may still be provided.

Oncology is also different from other therapeutic areas in that the patient population is generally more engaged in the delivery of their care. As active participants in the decision-making process, individuals with cancer tend to contribute to the risk-versus-benefit discussion. Therefore, imposing a REMS so that specific risks must be discussed may be considered a duplicative process. Additionally, REMS may complicate patient involvement and communication with clinicians because the risk/benefit discussion in medication guides only focuses on the toxicities of a drug, not the benefits.

Off-label prescribing practices have also been charged with contributing to unnecessary toxicities. However, appropriate off-label use must be distinguished from inappropriate off-label use. In the case of appropriate off-label use, the efficacy of a medication has been demonstrated through evidence and possibly expert judgment. However, inappropriate off-label use has not been shown to provide benefits. Therefore, patients for whom these uses are prescribed may be unnecessarily exposed to the toxicity of the agent. In the oncology setting, the FDA-approved indications for anticancer drugs tend to be narrowly focused in more recent years, reflecting the inclusion criteria and trial design of the pivotal trials that were submitted to obtain FDA approval. However, the FDA label does not always reflect the most current evidence regarding the appropriate use of certain medications. Instead, compendia can provide guidance to the appropriateness of off-label uses of cancer medications. For example, the NCCN Compendium is derived directly from the recommendations in the NCCN Guidelines and is recognized by Medicare and many private payors as a source for off-label cancer medication coverage policy.

Despite these differences and safety guards already in place, REMS requiring ETASUs seem to have disproportionately affected individuals with cancer or hematologic disorders. According to the list of FDA-approved REMS, 19 drugs require an ETASU (Table 1). More than half of this list of drugs (n = 10) could potentially be prescribed by oncologists and hematologists for supportive care treatment. Furthermore, as the FDA considers a class-wide REMS for opioids, individuals with cancer pain likely will be impacted.

**Challenges of REMS in Oncology**

The challenges of designing a REMS program and implementing it in clinical practice is an important issue to all stakeholders across broad disease specialties. However, some challenges are specific to the oncology setting. Most of the agents used in the active treatment of cancer and for supportive care management are associated with serious associated risks, potentially setting the stage for the imposition of a REMS on these drugs. However, the Work Group also recognized that REMS may facilitate the FDA approval of drugs with a high-risk potential that would not otherwise be ap-

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<th>Table 1 FDA-Approved Drugs Requiring Elements to Assure Safe Use</th>
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<td>Buprenorphine transdermal system</td>
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*Drugs that have the potential to be prescribed by oncologists and hematologists.*
proved without a REMS in place, or allow a drug that did not previously have a REMS to stay on the market. Additionally, the Work Group believed that REMS has the potential to improve patient safety; the question is at what cost? Although most REMS require only a medication guide, the Work Group identified many challenges with their development, particularly those requiring elements to assure safe use. Although not necessarily specific to the oncology setting, some of these challenges are as follows:

- REMS are relatively new and the requirements are not mature. Therefore, clinician knowledge of REMS regulations and requirements is suboptimal.
- For complex REMS, such as those with ETA-SUs, requirements such as certification/recertification and training/enrollment are specific to each. Complex REMS are not standardized or centralized, which creates inefficiencies in the administrative process of registering and enrolling in REMS programs that require this step.
- Institutions, practices, and clinicians are not compensated for the increased patient interaction and administrative time required to meet REMS requirements.
- In an already overburdened system, REMS requirements create additional administrative tasks that reduce the time allotted for providing patient care and, in some cases, ignore the obvious expertise of providers and institutions.
- REMS may influence prescribing practices. Prescriber practices could be altered so that access to some drugs with REMS is limited, and disparities in care could result.
- Providers and prescribers are skeptical regarding the benefits of REMS. If data show that REMS will significantly improve patient safety, then providers likely will embrace REMS.
- The documents that must be provided to patients (e.g., medication guides, acknowledgment/consent forms) do not necessarily take into account the issues related to patient health literacy or specific patient populations.
- The current process for developing and approving a REMS program is inefficient and the FDA does not routinely solicit and incorporate provider feedback into the final REMS. This may result in a delay of access to medications, suboptimal uptake and delayed adoption of an innovative therapy after it reaches the market, and the inability of providers to integrate REMS procedures that are contrary to the clinical and operational aspects of existing oncology practice.
- Manufacturers face many challenges when developing REMS programs, most notably: 1) communication with FDA and other stakeholders regarding the development of these programs, 2) methods to assess a successful implementation, and 3) the inability to hold providers accountable for following REMS requirements.

These challenges and the Work Group’s resulting recommendations are discussed later.

**NCCN REMS Work Group**

To offer recommendations and guidance about REMS in oncology to relevant stakeholders, NCCN convened a Work Group composed of physicians, pharmacists, nurses, and hospital administrators, along with representation from different stakeholder groups, such as patient advocates, specialty pharmacy, biopharmaceutical industry, and government. The Work Group included individuals who were internal (i.e., from NCCN Member Institutions) and external to NCCN, with the community and academic settings also represented. The Work Group meeting was held on March 13, 2010, as part of the 15th NCCN Annual Conference in Hollywood, Florida.

The goals of the meeting were to develop near-, medium-, and long-term recommendations related to the design and implementation of REMS in oncology that would be relevant to all stakeholders, including the FDA. Additionally, the Work Group realized the need to collect data regarding provider knowledge, opinions, and current practices surrounding REMS. Subsequently, the Work Group developed a survey that was administered through the NCCN Trends program and the ONS. The recommendations and data from the survey were presented at the NCCN Oncology Summit on May 7, 2010 in Washington, DC. This document encapsulates the discussion during the Work Group meeting and at the NCCN Oncology Summit, interspersed with an analysis of the data obtained from the NCCN Trends survey that focused on REMS.

**NCCN Trends and ONS Surveys**

As part of the initial meeting, the Work Group affirmed the need for more data regarding the knowledge and perceptions of REMS and how REMS
will affect practice habits. To obtain near-term results, the Work Group developed a survey related to these issues. The survey was sent to registrants of www.NCCN.org via NCCN Trends and to nurse practitioner members of the ONS. The survey was administered between March and April of 2010. A convenience sample of 601 people from the United States responded to the survey.

NCCN Trends is an analytic tool that surveys how clinicians across the United States and around the globe are delivering cancer care on a monthly basis, and how they view practice and policy issues. The respondent pool includes more than 96,000 clinicians (United States and International), including oncology physicians, pharmacists, and nurses. A 5-question survey is sent each month, and the analyses from resulting data can help determine trends and patterns according to practice setting, practice size, specialty, or region. Although the survey was administered internationally, the results described in this report only include the United States population.

The roles of survey respondents in the management of patients with cancer are depicted in Table 2. Most survey respondents were practicing physicians in an oncology specialty (37%). An additional 34% were advanced practitioners or nurses in oncology, and 14% were pharmacists specializing in oncology. The remainder consisted of either nonclinicians, clinicians no longer practicing, or other types of clinicians in a nononcology specialty. Respondents who are nonclinicians and clinicians no longer practicing were excluded from the following descriptive analysis of the survey. Respondents who are clinicians but not specializing in an oncology specialty are reported as “other practicing clinician.”

The survey first asked participants to rate their familiarity with the REMS regulation (Figure 1). Overall, approximately half of the respondents reported that they were either not familiar (20%) or somewhat familiar (32%) with REMS. The other half of the respondents were either moderately (26%) or very familiar (22%) with REMS. When analyzing familiarity according to provider type, the proportion of physicians specializing in cancer who said they were not familiar with REMS slightly increased to 24%, and physicians who were very familiar slightly decreased to 18%. Advanced practitioners and nurses as a whole seemed to be a bit more familiar; 38% responded that they were somewhat familiar with REMS. Pharmacists proportionally seemed to be the most familiar with REMS, with 40% responding that they were moderately familiar and 34% that they were very familiar.

As a proxy for assessing provider burden, respondents were asked to estimate the amount of time they spend per week meeting REMS requirements (Figure 2). A proportion of responders ($n = 84; 14\%$) were unaware of the time it takes for meeting REMS requirements because others handle this responsibility, and still more do not prescribe, dispense, or administer the drugs with REMS requirements ($n = 117; 19\%$). Proportionally more clinicians not specializing in cancer responded that they do not use drugs with REMS (44%), whereas a small percentage of pharmacists state that they do not use drugs with REMS (3%). This is understandable because other types of clinicians (e.g., case managers) may not be directly involved in the medication use process, and physicians not specializing in cancer have the flexibility to choose the agents they prescribe. They can choose to avoid using drugs with REMS if they prefer. Pharmacists, however, interface with many different prescribers in their daily practice, thus increasing the chance that they will need to dispense a drug with REMS.

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their perceptions regarding whether REMS will achieve these goals (Figure 3). Most respondents were optimistic that REMS will better inform patients about drug safety risks, with 61% agreeing or strongly agreeing with this statement. A small percentage (19%) disagreed or strongly disagreed that REMS will better inform patients regarding drug safety risks, most likely representing some concerns and challenges with the medication guide. During the Work Group meeting, these challenges with the medication guide were discussed, and recommendations for improvement are offered within this report.

When asked to provide an estimate regarding how much time per week is spent dealing with REMS, 31% of participants reported that they spend less than 1 hour per week and 37% reported spending 1 to 4 hours per week handling REMS requirements. Small percentages reported spending 4 to 8 hours (5%) and more than 8 hours per week (4%) on REMS. When analyzed according to provider type, the responsibility of REMS seems to fall on advanced practitioners, nurses, and pharmacists. Compared with 40% of physicians, 27% of advanced practitioners/nurses and 25% of pharmacists spend less than 1 hour per week on these responsibilities. Instead, 41% of advanced practitioners/nurses and 56% of pharmacists spend between 1 and 4 hours per week on REMS, compared with 32% of physicians. The proportion of pharmacists spending more than 8 hours per week on REMS was 11%, compared with 3% for advanced practitioners/nurses and for physicians each.

The major goals of REMS are to enhance patient safety and to better inform patients regarding drug safety risks. The survey asked participants about their perceptions regarding whether REMS will achieve these goals (Figure 3). Most respondents were optimistic that REMS will better inform patients about drug safety risks, with 61% agreeing or strongly agreeing with this statement. A small percentage (19%) disagreed or strongly disagreed that REMS will better inform patients regarding drug safety risks, most likely representing some concerns and challenges with the medication guide. During the Work Group meeting, these challenges with the medication guide were discussed, and recommendations for improvement are offered within this report.

However, the respondents also perceived challenges with REMS. Higher percentages of respondents agreed or strongly agreed that REMS will interfere with the provision of patient care, drive use toward drugs without REMS, and create or increase disparities in care (55%, 60%, and 53%, respectively) compared with those who disagreed or strongly disagreed with those statements (16%, 13%, and 15%, respectively; Figure 4). Agreement with these statements was also analyzed according to who self-
reported that they are very familiar with REMS versus those who responded they are not familiar with REMS (Figure 5). The percent of those agreeing or strongly agreeing with the aforementioned statements seemed to increase with familiarity of REMS, whereas the percent of those disagreeing or strongly disagreeing were largely similar. Those who were very familiar with REMS seem to have less of a neutral position and more of an opinion on these statements.

Overall, the respondents also believed that REMS will not expedite FDA-approval of drugs. More people disagreed or strongly disagreed with the statement that REMS will allow drugs to be more easily and quickly FDA-approved (52%) than those who agreed or strongly agreed (12%).

Additionally, the Work Group had the goal of collecting information on the practice patterns of drugs requiring REMS. Respondents were asked to self-report their participation in REMS programs requiring ETASUs. Specifically, the Work Group asked about the drugs thalidomide, lenalidomide, romiplostim, eltrombopag, epoetin/darbepoetin, and the fentanyl buccal soluble film (Figure 6).

A pattern for participation in REMS programs was seen for the clinicians who use these medications. For thalidomide, lenalidomide, and the erythropoietin-stimulating agents, most are currently registered (or planning to register) in the respective programs. Only approximately 6% of respondents reported not registering and having no plans to register for each of these drugs because of administrative burden. However, the current and potential participation in programs for romiplostim, eltrombopag, and the fentanyl buccal soluble film was lower, and more reported not being registered and not having plans to register because of administrative burden. The Work Group surmised that the availability of other options for treating pain influenced whether clinicians were willing participate in the fentanyl buccal soluble film REMS program. Clinicians may choose the “path of least resistance” because options are available that do not have these administrative requirements. Furthermore, the Work Group was concerned that REMS requirements may decrease the rate of uptake...
of novel and innovative agents, such as with romiplostim and eltrombopag.

Lastly, to assess potential practice patterns, the respondents were also asked to consider different levels of REMS requirements and their willingness to use a drug with these requirements (Figure 7). Survey participants could respond that they would use a drug with the REMS requirements, use a different drug without the requirements, or refer to a different provider for scenarios of different REMS complexity. These scenarios escalated in the complexity of REMS requirements, starting with single REMS requirements, such as only provision of a medication guide, documenting a safety discussion, and completing education/training. The complex scenarios included situations in which 1) the provider must provide education/training, enroll patients in a registry, and complete data collection forms, and 2) the drug uses a restricted distribution system. For physicians, the proportion willing to use a drug with the single REMS requirement was 69%, with only approximately 23% reporting that they would use a different drug instead. A minority of respondents would refer to other providers who use the drug with those REMS requirements (approximately 7%). However, when considering the more complex scenarios, the proportion of physicians willing to use the drug decreased and the proportion of physicians reporting they would refer to another provider slightly increased.

Figure 3 Perceived impact of REMS on patient safety.

Figure 4 Perceived impact of REMS on the provision of patient care and access to medications.
This information seems to coincide with the thinking of the Work Group that there is a “breaking point” at which providers will consider other options when a drug has complex REMS requirements. This could be problematic if these other options are not as well established (based on evidence) as the drug that has the REMS requirements.

Because this survey represents a convenience sample of clinicians, those with more familiarity and experience with REMS were more likely to respond. However, the information provides useful insights into the workload burden associated with REMS and clinician perception of how REMS will impact clinical practice. This near-term information from the survey coincides with the Work Group’s assessment of the challenges of REMS in oncology, and provides the impetus to conduct future objective assessment of how REMS impact practice patterns, provider burden, and the cost of providing care.

**Work Group Recommendations**

The Work Group recommendations are separated into 9 sections, with the key area listed first, followed by the recommendations and a discussion of identified challenges and recommendations.

### Standardization of REMS Processes to Allow for the Provision of Efficient Care

#### Recommendations:

- Develop a system of standard risk categories and corresponding standard REMS requirements
- Manufacturers should work together to develop common procedures for certification, training, and enrollment in REMS programs
- Convene a summit with all stakeholders to develop common definitions and procedures for centralization and standardization of REMS registries
- Work with health information technology companies to develop a central clearing-house or Web portal for REMS
- Work with electronic health record companies and other stakeholders to integrate REMS into electronic health records
Figure 6 Overall participation in REMS programs for specific drugs with ETASU.

- Currently registered: 82%, 78%, 54%, 46%, 40%, 19%
- Not registered, but plan to register soon: 5%, 7%, 20%, 23%, 43%, 22%
- Not registered and no plans to register because of administrative burden: 5%, 6%, 15%, 18%, 6%, 37%
- Not required to register to use this drug: 8%, 9%, 10%, 13%, 11%, 22%

Figure 7 Perceived impact of physicians on prescribing based on REMS requirements.

- Will use a drug with this REMS requirement: 69%, 61%, 59%, 39%, 42%
- Will use a drug WITHOUT this REMS requirement, ONLY if equivalent effectiveness or toxicity: 19%, 27%, 25%, 33%, 33%
- Will use a drug WITHOUT this REMS requirement, even if lower effectiveness or higher toxicity: 4%, 6%, 7%, 10%, 9%
- Will refer to a different provider that uses a drug with this REMS requirement: 7%, 7%, 9%, 19%, 16%
One major area of concern for the Work Group was the lack of standardization in several areas within REMS. A main concern is the lack of standardization regarding how a specific risk mitigation strategy is chosen for a specific risk associated with a medication. Currently, risk mitigation programs for drugs with similar risks (e.g., teratogenicity) may differ in the requirements that providers and patients must fulfill. Therefore, this lack of standardization causes confusion when navigating the drug prescribing and dispensing process. The Work Group affirmed that specific risk mitigation strategies should be standardized and based on sound scientific methods, and the FDA should lead this process. For example, a table of specific risks (e.g., teratogenicity, anaphylaxis, overdose/diversion, sudden cardiac death, irreversible end-organ damage) should be provided, along with preferred strategies for mitigating that type of risk. Ideally, the recommended mitigation strategy would have been validated by scientific methods showing effectiveness in decreasing harm to patients. This validation can then be readily used for future drugs with the same type of risk.

Additionally, providers, whether they are physicians, nurse practitioners, or pharmacists, must visit different Web sites and navigate different registration systems to meet the REMS requirements for the multitude of drugs they prescribe or dispense. The lack of standardization creates inefficiencies in the administrative process of registering and enrolling in REMS programs. Standardization is especially important for the more complex REMS with ETASU, because they typically have program-specific requirements and vary in the frequency of interfaces, the types of certifications, and whether a registration-type component is necessary. Providers would greatly benefit from having access to a central clearinghouse or Web portal that would allow them to gather information, register, enroll, complete certification, and renew certification in a single location. Manufacturers must work together to develop common procedures for certification, training, and enrollment in REMS programs to make access to this source as efficient as possible.

In addition to increasing provider burden, these issues related to lack of standardization can lead to delays in getting a drug to market, which subsequently can delay patient access to important medications and may lead to suboptimal uptake and delayed adoption of an innovative therapy.

**Development of REMS Programs**

**Recommendations:**

- REMS applicants should include providers and patient advocates as part of the discussion while in the development phase
- Manufacturers and the FDA must communicate early in the clinical development process regarding risk strategy
- A manufacturers’ work group should be convened to provide input and help finalize future FDA REMS guidance
- A public–private advisory committee should be developed that includes clinical professional and patient advocacy societies to guide the development of REMS programs
- Using scientific methods, the methodology behind implementing risk mitigation strategies should be refined

Development of REMS programs is a complicated and sometimes lengthy process for manufacturers and the FDA. The Work Group recognized that manufacturers face many challenges when developing their REMS programs, and identified 3 primary challenges: communication with the FDA and other stakeholders, the lack of available methods to assess a successful REMS implementation, and the inability to hold providers accountable for meeting REMS requirements.

Manufacturers must communicate early and often with a multitude of stakeholder groups to ensure development of an easy-to-use and effective REMS. The FDA and manufacturers should discuss risk strategy early in the clinical development process to make the development process more efficient. If training or certification is required for providers, manufacturers must engage health care providers (through professional organizations) during the development process. Providers should be consulted during development to ensure that they will be able to accommodate and comply with REMS requirements. This could also be a prospective means through which provider burden is minimized.

In the long term, development of a public–private advisory committee that includes clinical professional and patient advocacy societies will help guide the development of REMS programs that can be implemented and will improve patient safety.
This could also be done on an individual basis in which a manufacturer with the help of a third party could convene an advisory committee for each drug they anticipate needing a REMS.

**Assessment of REMS Programs**

**Recommendations:**
- The FDA must define success so that manufacturers can develop appropriate REMS programs and measurement tools
- The FDA should standardize core survey questions
- Conduct a comprehensive survey of providers and qualitatively assess the perceived impact of REMS on patient safety
- Perform a long-term study that assesses whether adherence to REMS requirements improve patient outcomes (safety)

Although development and implementation of risk mitigation strategies are of great importance, so is the ability to evaluate and assess the impact these strategies have on actual patient safety, cost, and patient access. In the past, the FDA has not invested in important social sciences such as risk communication and risk mitigation. However, the success of REMS programs depends on this ability to assess and evaluate the programs. A first step would be for the FDA to define success. Is success defined as better patient understanding or better safety outcomes? What percentage of improvement is considered successful? These ideals must be defined before the impact of REMS programs can truly be evaluated. Once success is defined, some of the risk management strategies may be found to be so onerous and costly that the risk mitigation achieved is not effective relative to the costs imposed on the system.

Surveys of patient and physician understanding of risks are one of the primary assessment methods of REMS. Currently, the FDA offers little guidance on survey design, construction, methodology, or recruitment. Results from surveys can vary depending on who provides the medication guide, how much assistance is provided to understand the medication guide, and the disease state of the individual, among other variables. The Work Group recommended the FDA standardize core survey questions so that assessment of these programs can in turn be standardized.

The Work Group recommended performing long-term studies that assess whether a specific risk mitigation strategy improves patient safety and outcomes. These studies, which would not be needed for all drugs and their corresponding REMS, can elucidate which mitigation tools have achieved an optimal level of risk minimization for what specific risk. These studies are of utmost importance to implementing new REMS programs and ensuring they have the best REMS from the outset and that the best mitigation tools are being matched with the understood risks.

**Improvement of the REMS-Associated Medication Guide and Overall Health Literacy**

**Recommendations:**
- Develop medication guides that contain language at a level patients can understand and that are available in multiple languages to ensure patient comprehension
- Reformat medication guide to address benefit and risk
- Pretest medication guides before use to gauge comprehension and literacy
- Perform an assessment of public health literacy comprehension
- Use Web and social media to communicate REMS requirements to patients
- If desired, allow providers to customize the medication guide to reflect specific risks pertinent to the population being treated
- Develop partnerships with patient advocacy groups to ensure patients receive accurate and comprehensible information regarding REMS
- Conduct a longitudinal study as to how REMS will affect patients in underserved populations

Medication guides are the most commonly required element of REMS and are the primary mode of communication to patients under a REMS. Medication guides contain technical language at a level many patients cannot understand, and language and cultural barriers may also prevent full comprehension. The Work Group stresses the importance of having medication guides written at the proper reading level. This observation was corroborated by many attendees at the NCCN Oncology Summit.

Medication guides are required to address the risks deemed relevant by the FDA. Emphasis on these risks can improperly influence patients, resulting in patients choosing to abstain from taking a medication that may in fact be beneficial. For patients to make an informed risk/benefit analysis, medication
guides should be reformatted to address and balance risks and benefits of medications.

Furthermore, the discussion during the NCCN Oncology Summit highlighted the concern that medication guides and other documents for patients do not necessarily take into account the issues related to patient health literacy. The Work Group recommends that manufacturers and the FDA consider performing an assessment of public health literacy comprehension to ensure that understandable medication guides are developed. Medication guides should also be pretested for comprehension before release.

The Work Group also discussed that medication guides tend to address specific risks that may vary in importance to the patients prescribed the medication. In oncology, often the benefits outweigh the risks because of the life-threatening nature of the disease. The relevance of the toxicity emphasized in the medication guide will vary according to individual treatment situation. The Work Group agreed that providers or institutions should have the ability to customize the medication guide (within reason) to address specific patient populations, which would likely entail providing additional patient education materials. This is a service provided in many of the larger medical centers, but not in smaller and more rural communities.

A final area for improvement is the communication of REMS requirements to patients. Patients must understand the requirements they and their providers must meet. The Work Group provided 2 recommendations for this problem: 1) partnerships should be developed between patient advocacy groups and manufacturers to ensure patients receive accurate and comprehensible information regarding REMS, and 2) these partnerships in turn should use social and Web media to communicate REMS requirements to patients.

Incorporation of REMS Into Institutional Clinical Practice

Recommendations:

- Supply chain considerations must be determined to minimize new costs and indirect impact on prescribing and patient access
- Specific to institutional practice, the institution’s formulary system should be proactively applied to oversee the implementation of drugs with REMS requirements
- Institutions should build triggers and alarms into their medication use system for compliance with REMS requirements and for quality control purposes
- Institutions should share best practices surrounding the implementation of REMS into clinical practice

Incorporating REMS into clinical practice will take the entire practice site’s assistance and efforts. Efficient incorporation will require strategic planning among different provider groups (e.g., physicians, nurses, pharmacists) and within these provider groups. This planning would coordinate the communication regarding whether REMS requirements were met before a drug can be dispensed or administered. For example, pharmacists working within an institution may need to verify that a prescriber is registered in a REMS program, and that the patient has enrolled in a registry before the drug can be dispensed. Similarly, a prescriber may need to coordinate with pharmacists about how to provide a drug to a hospitalized patient through a restricted distribution system. In turn, pharmacists would need to coordinate with each other regarding the process as shifts change and the responsibility of care is transferred.

The Work Group recommends that for most institutions, the formulary system be proactively applied to oversee the implementation of drugs with REMS requirements. The Pharmacy and Therapeutics Committees that oversee the formulary system have the ability to direct and standardize how drugs with REMS are introduced and used in their hospital systems through setting medication use policy. They can provide coordination and consistency to the rest of the health care system through writing, publishing, and communicating these policies to all providers within the institution.

Institutions can further monitor compliance with REMS requirements and improve patient care through building triggers and alarms for REMS compliance into their medication use system. This will allow institutions to identify problems and make changes that benefit the entire system and improve the care patients receive.

REMS and Off-Label Drug Use

Recommendations:

- The FDA must provide more guidance for manufacturers on issues regarding off-label drug use arising from REMS
- The FDA should consider allowing third parties under a REMS to provide complete information on off-label drug use to inform physician/patient
decision-making

There are many cases of appropriate off-label use for oncology drugs. REMS, in most cases, tend to limit use towards specific FDA-approved indications. These programs cannot address indications that are not FDA-approved because federal regulations mandate that all REMS components must be consistent with the drug’s approved labeling. Therefore, manufacturers are not able to provide risk information for patients using the medication in an off-label setting, even if this use is considered appropriate based on the evidence. The Work Group recommended that the FDA should provide more guidance on off-label drug issues related to REMS.

One suggestion to address this problem is to consider that third parties could provide complete information on off-label drug use to fully inform physician/patient decision-making under a REMS. Compendia already partially fulfill this need, and nonprofit organizations could undertake this responsibility.

Provider Knowledge and Acceptance of REMS

Recommendations:

• Survey clinician knowledge of REMS
• Survey clinicians regarding the perceived impact of REMS on prescribing patterns and access to medication
• Increase provision of REMS as a topic in continuing education programs
• Incorporate REMS into medical, pharmacy, and nursing school curricula
• Conduct a long-term assessment of the prescribing patterns of drugs with REMS requirements

The NCCN Trends data suggest that providers are largely unfamiliar with REMS. Currently, REMS programs are relatively immature, and knowledge of what is required with REMS has poorly penetrated clinician practices. This is concerning because providers may increase their acceptance and use of REMS if the benefits of REMS are better understood and demonstrated. The Work Group recommended increasing provision of REMS as a topic in continuing education programs to increase knowledge and acceptance in the short term while incorporating education on REMS into medical, pharmacy, and nursing schools’ curricula in the longer term.

REMS may influence prescribing practices because of the administrative burden of meeting some requirements and the availability of alternative treatment options without REMS requirements. Initial NCCN Trends data suggest that providers are less willing to participate in REMS programs with complex requirements because they tend to be time- and resource-intensive. For example, drugs requiring the use of a restricted distribution system may present extra steps in the procuring, preparing, and administering process, all without being monetarily compensated. Some providers may choose not to use (i.e., prescribe, dispense, or administer) drugs with REMS and instead might prescribe a different treatment option that may not be as safe or effective. Furthermore, providers may refer patients to other providers who will use a particular drug with the REMS. The Work Group discussed and was concerned about the possibility that these practice trends may ultimately lead to treatment disparities. For example, a particular drug with strict REMS requirements may only be used in urban areas compared with rural areas, because the urbanized areas tend to have more resources available to handle REMS requirements. The Work Group recommends conducting a long-term assessment of drugs with REMS requirements to identify the impact on prescribing patterns and how it translates into access for patients.

Ultimately, if REMS can be shown to not have a negative impact on patient access and to increase overall patient safety, providers may be more willing to assimilate REMS into the routine of daily patient care activities.

Minimization of Provider Burden

Recommendations:

• The FDA must establish a process to allow for provider feedback regarding future and emerging issues with REMS requirements and during REMS development
• A study must be conducted to benchmark the time and resources spent meeting REMS requirements
• An objective assessment of the cost impact of REMS must be performed

Providers practice in an already overburdened system in which they must deal with prior authorization requirements, patient assistance programs, and various payors with rules and policies that change constantly. Providers may see REMS as the breaking point of being able to practice medicine. To meet some REMS requirements, providers must spend additional time on administrative tasks such as registra-
tion, training and certification, and documentation, which may take away valuable time from patient care activities, including thoroughly presenting the risk/benefit ratio of proposed therapy.

As stated in the legislation, the FDA must consider the burden of REMS to providers, and can achieve this by establishing a process that allows provider feedback on future and emerging issues with REMS requirements and during REMS development.

Although the NCCN Trends data provided some preliminary information regarding the amount of time providers self-reported they devote toward meeting REMS requirements, a study must be conducted to precisely benchmark the time spent meeting REMS requirements. The time spent will continue to increase as the number of REMS programs increases, along with greater participation in REMS programs.

Along with examining time spent meeting REMS requirements, the cost impact of REMS must be considered. The monetary costs of meeting REMS requirements will need to be calculated, and how REMS will shift the workload of all types of providers will need to be considered. To meet REMS requirements, providers may need to shift some part of their work to others, or delay or not attempt other aspects of their jobs. The cost of this work-shifting is unknown and may negatively affect patient care, especially if patient care activities are deferred.

Compensation for Complying with REMS Requirements

**Recommendations:**
- Payors and providers should consider an alternative coding system for drugs that require REMS
- Payors must consider how REMS will affect their formulary process
- Managed care organizations should consider minimizing the burdens placed on providers and patients when administering prior authorization requirements for drugs with REMS

As identified during the discussion at the NCCN Oncology Summit, many have termed REMS an unfunded mandate. The Work Group discussed that providers will need to spend additional time and effort to meet REMS requirements and will incur costs in meeting these requirements. Questions remain as to how and if providers will be compensated for their work. The Work Group have recommended that consideration be given to developing an alternative coding system for drugs that require REMS, which could allow providers to be reimbursed for the time and resources spent toward meeting REMS requirements.

Beyond costs to providers, payors and managed care organizations must examine how REMS will affect their processes, including formulary setup and prior authorization requirements. For drugs with ETASUs, some requirements may overlap with prior authorization requirements. Streamlining overlapping requirements when possible would benefit both providers and payors.

**Closing Statement**

The successful design, implementation, and analysis of the FDA's recent requirement of REMS for high-risk drugs and biologics will present significant challenges for stakeholders, including patients, providers, institutions, manufacturers, payors, health information technology vendors, and government agencies. To provide guidance to these stakeholders regarding these challenges, NCCN assembled a Work Group composed of thought leaders from NCCN Member Institutions and outside entities. These multidisciplinary thought leaders represented providers (physicians, pharmacists, and nurses), patients, manufacturers, payors, and government.

The challenges of designing a REMS program and implementing it in clinical practice are an issue of importance to all stakeholders across broad disease specialties. However, some challenges are specific to the oncology setting. In oncology, patient involvement in treatment decision-making is much more common and the care system is more collaborative and interactive. Clinicians practicing within the oncology realm are usually highly specialized, having obtained additional education, training, and certification to care for these patients. Most of the agents used in the active treatment of cancer and for supportive care management have serious associated risks, potentially setting the stage for the imposition of REMS on a wide swath of drugs used in oncology.

The Work Group identified challenges across the REMS spectrum, including the areas of standardization, development, and assessment of REMS programs and medication guides; provider knowledge; impact on prescribing; provider burden and compensation; and incorporation of REMS into clinical practice.
The Work Group provided recommendations for all of the challenges, including some that could be foreseen being implemented in the near future and others that would require cooperation across stakeholder groups and a longer amount of time to implement.

Although the recommendations of the Work Group are diverse and offer much for stakeholders to consider, they are all directed to the same set of objectives: REMS, while imposing minimal burden on providers, should improve patient care and safety while creating nominal drug access issues for patients. Appendix b provides a summary of the recommendations.

References


Appendix A: Disclosure of Affiliations and Significant Relationships

Mr. Johnson has disclosed that he has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Mr. Dahlman has disclosed that he has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Mr. Eng has disclosed that he has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Dr. Garg has disclosed that she has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity. She is an employee of Amgen Inc.

Dr. Gottlieb has disclosed that he has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Dr. Hoffman has disclosed no conflicts at the time of publication.

Ms. Howell has disclosed that she has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Dr. Jahanzeb has disclosed that he has financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity. He is a principal investigator for Oxigene. He is a consultant for Abraxis Bioscience, Inc.; Eli Lilly and Company; Genentech, Inc.; and Pfizer Inc.; and a speakers’ bureau member for Genentech, Inc., and sanofi-aventis U.S.

Ms. Johnson has disclosed that she has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Dr. Mackler has disclosed that she has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Mr. Rubino has disclosed no conflicts at the time of publication.

Ms. Sarokhan has disclosed that she has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Dr. Stewart has disclosed that he has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Dr. Tyler has disclosed that he has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.

Dr. Vose has disclosed that she has financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity. She is a principal investigator for Applied Medical Resources Corporation; Bristol-Myers Squibb Company; Celgene Corporation; Genentech, Inc.; Genzyme Corporation; GlaxoSmithKline; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Allos Therapeutics; AnorMed, Inc.; Astellas; Rigel; and Pharmacyclics.

Dr. Weinstein has disclosed that she has no financial interests, arrangements, or affiliations with the manufacturer of products and devices discussed in this report or who may financially support the educational activity.
### Appendix B Summary of Recommendations for Stakeholders

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<tr>
<th>Recommendation Area</th>
<th>Near-Term</th>
<th>Medium-Term</th>
<th>Long-Term</th>
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<tbody>
<tr>
<td>Provider knowledge about the purpose, benefits, and challenges of REMS</td>
<td>Clergy and faith leaders should provide training and support for implementation of REMS programs</td>
<td>Establish measures to improve the development of individual REMS programs</td>
<td>Provide compensation for complying with REMS regulations</td>
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<td>Standardize REMS-related processes to allow for the provision of efficient care</td>
<td>REMS applicants should include providers as part of the discussion of individual REMS programs</td>
<td>Establish the impact of REMS on prescribing patterns</td>
<td>Payors and providers should consider alternative coding systems for drugs that require REMS</td>
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<td>Workflow improvements for REMS, including clarification of REMS responsibilities and roles</td>
<td>RECS should provide training for healthcare providers on how to implement REMS programs</td>
<td>Utilize scientific methods to refine the methodology behind implementing risk mitigation strategies</td>
<td>Manage care organizations should consider minimizing the burden placed on providers and patients when administering prior authorization requirements for drugs with REMS</td>
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<td>Increase the provision of REMS as a topic in continuing education presentations</td>
<td>Manufacturers should work together to develop common procedures for certification, training, and enrollment in REMS programs (i.e., “best practices”)</td>
<td>Audit the impact of REMS on patient safety</td>
<td>Payors must consider how RECS will affect their financial process</td>
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<td>Survey clinicians regarding the perceived impact of RECS on prescribing patterns and access to medications</td>
<td>A “best practices” guide should be developed to provide input and help finalize future REMS guidance</td>
<td>Conduct a long-term assessment of the prescribing patterns of drugs with REMS</td>
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<tr>
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Providers/Clinicians
- Patients/Patient advocacy
- Manufacturers
- Payors
- FDA
- Multiple