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Risk Evaluation and Mitigation Strategies (REMS)

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Risk Evaluation and Mitigation Strategies (REMS)

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LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. Define risk evaluation and mitigation strategies (REMS) and their purpose.
2. Identify at least 3 internet sites that provide timely information about REMS medications and requirements.
3. Identify the challenges and benefits REMS present health system pharmacy departments.
4. Explain practical approaches such as including the Pharmacy and Therapeutics (P&T) committee to enhance REMS implementation in health systems.

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Meet the Author

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Risk Evaluation and Mitigation Strategies (REMS)

A Culture of Safety

Risk Evaluation and Mitigation Strategies (REMS) are intended to lead the way to a much safer medication use system than we have currently. Before describing the REMS program, a short discussion about medication safety and also about adverse drug reactions is in order. A recent study, "Temporal trends in rates of patient harm resulting from medical care," published in 2010 in the New England Journal of Medicine[1] found no improvement in patient safety more than 10 years after the Institute of Medicine's report "To err is human" published in 1999[2] raised the profile of medical errors for practitioners, the public, and our government. The New England Journal retrospective study of ten North Carolina hospitals measured the occurrence of adverse events and applied an internationally recognized scale to assess these adverse events for harm caused. This assessment for harm was confirmed by two reviewers. It was expected that the advances in automation put in place over the ten plus years since 1999 including computer prescribing, implementing evidence based care, and restricting the hours of medical residents would lead to a measurably safer health system. In this study, more than 2,300 patient cases were reviewed and harm was identified 25 times for every one hundred admissions. After further analysis, the authors concluded there was no difference between the rates of harm in this 2010 study when compared to the Institute of Medicine 1999 report. The FDA was encouraged by a number of public health experts to take a more active role in supporting medication safety and the REMS programs were developed as a result of these concerns. As healthcare providers, as patients, or as family members, we cannot continue to tolerate this lack of progress. Clearly it is about time we do something effective to improve medication safety.

The REMS programs can be viewed as part of an overall concept termed a "Culture of Safety." The Agency for Healthcare Research and Quality (AHRQ) considers a culture of safety the basis for a high reliability organization. "High reliability organizations maintain a commitment to safety at all levels, from frontline providers to managers and executives. This commitment establishes a culture of safety".[3] An organization working under a culture of safety recognizes the high risk nature of their business and is determined to reach a goal of having a consistently safe organization. An important component of a culture of safety is to establish a blame free organization where every employee can report unsafe practices without fear of reprimand. A highly reliable organization promotes collaboration between disciplines, for example, between physicians, nurses, pharmacists and pharmacy technicians; and also between ranks, for example, between managers, directors, executives and regular employees.

A blame free culture does not mean that clinicians and employees are not held accountable for their actions. Instead human error (mistakes) should be expected to happen and therefore systems should be put in place to recognize these errors before reaching a patient. For example, a computer order entry system that warns of potential medication errors caused by medication allergies, or the use of smart pumps to

prevent infusion errors, are system solutions to address the potential for human error. In a culture of safety sometimes referred to as a "Just Culture," risky behavior such as taking shortcuts which undercut safety controls is not accepted by colleagues and supervisors. Any clinician is held accountable for reckless behavior such as overriding a computer warning before investigating the validity of the warning. An organization would react to reckless behavior whether or not an error reached the patient. In a just culture, the pharmacy department that refused to dispense a dose of penicillin to a patient with an allergy to penicillin would be rewarded rather than reprimanded. The pharmacy department that did dispense the penicillin would face the reprimand. The culture of safety and the need for hospitals and clinics to operate as highly reliable organizations is part of the basis for the Risk Evaluation and Mitigation Strategies developed by the FDA.

Adverse Drug Reactions

The Food and Drug Administration (FDA) defines an adverse drug reaction (ADR) as any undesirable experience associated with the use of a medical product in a patient.[4] There are a number of methods available to categorize ADRs. As an example, dronedarone (Multaq®) is a new version of amiodarone used to help control the atrial (upper chambers of the heart) heart rate. A very common method used in most package inserts (PI) is to list ADRs by frequency of occurrence. The PI for Multaq® states that "Most common adverse reactions (≥ 2%) are diarrhea, nausea, abdominal pain, vomiting and asthenia (loss of strength)."[5] A frequency approach provides a listing of adverse effects seen in at least X% of patients. The frequency method helps the clinician to understand the rate of occurrence of adverse effects (AEs), and provides an idea of what effects to expect to see, but listing by frequency also promotes memorization, and there are far too many possible side effects to memorize. The frequency of occurrence approach is also a passive approach to understanding adverse effects. An approach that promotes an action to prevent an adverse effect would be desirable. Also, since serious adverse events are thankfully rare, they are often missing from lists based on frequency. **Table 1**: **Learning about Adverse Effects - Dronedarone** compares the official frequency listing of adverse effects to the REMS requirements for dronedarone.

Methods of Classi cation

There are also pharmacologic methods of classification. These methods help clinicians to understand the cause of an adverse effect and, at least for pharmacologic effects, does not require memorization. There are a number of classification schemes to use but these four classifications serve as a good starting point.

1. ***Pharmacologic:*** These adverse effects are seen with larger doses and represent an exaggerated pharmacologic effect of the drug. For example, a hypoglycemic event (low blood sugar) following an excessive dose of insulin; or symptomatic hypotension following an excessive dose of an antihypertensive medication.
2. ***Intolerance:*** Refers to exaggerated pharmacologic ef-

Table 1. Learning about Adverse Effects - Dronedarone

Current Method[5]	**Proposed Risk and Evaluation Mitigation Strategy[8]**
Package insert lists the most common adverse reactions: (≥2%) diarrhea, nausea, abdominal pain, vomiting, asthenia. *is method (referring to a listing of adverse reactions) requires memorization and is a passive approach.*	The goals of the MULTAQ REMS are: [2] To prevent MULTAQ use in patients with NYHA Class IV heart failure or NYHA Class II–III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic by educating prescribers about increased mortality when MULTAQ is used in this patient population [2] To inform health care professionals and patients about the serious risks of MULTAQ, including: ▪ Increased mortality in patients with severe unstable heart failure ▪ Signs and symptoms of liver injury and hepatic failure *is method is a proactive approach.*

fects seen at low doses of a medication. For example, drowsiness following a very low dose of morphine; or dizziness from a low dose of diphenhydramine (Benadryl®).

3. ***Idiosyncratic:*** Reactions that are not predictable and not related to dose or pharmacology. For example, muscle pain with cholesterol lowering medications known as statins (atorvastatin/Lipitor®; simvastatin/Zocor®; rosuvastatin/Crestor® and many others).
4. ***Allergic:*** Medication allergies are most commonly seen with antibiotics and are immune mediated reactions, such as hives, rashes of other types, and bronchospasm (congested breathing tubes).

Pharmacological Adverse E ects

There are a few more examples of pharmacologic adverse effects to review. Medications such as warfarin (Coumadin®), dabigatran (Pradaxa®), heparin and low molecular weight heparins (enoxaparin/Lovenox®; dalteparin/Fragmin®) act to prevent blood from clotting. If too large a dose is administered then bleeding is an expected pharmacologic adverse effect. Medications such as clopidogrel (Plavix®) and prasugrel (Effient®) inhibit platelet aggregation. Platelet aggregation is part of a sequence of physiologic steps which leads to the formation of a blood clot. Once again, if too large a dose is administered, then bleeding is an expected pharmacologic adverse effect.

Pharmacologic adverse effects, while undoubtedly unpleasant, are predictable (because they are based upon the mechanism of action of the medication) and easy to reverse (by stopping the medication or lowering the dose). Many times there is an antidote specifically for pharmacologic effects. For example, clinicians use vitamin K as an antidote for excessive warfarin, protamine for heparin, or administration of blood for heparin or for enoxaparin. Clinicians often monitor (look for evidence) for these adverse effects and catch them early. Some examples are to recheck blood pressure coinciding with the peak effect of an antihypertensive medication, or to check creatinine (a laboratory value that measures kidney function) for drugs that can affect the kidney. It is very common to recheck blood sugar at the time of the peak effect for insulin.

Intolerance and Allergies

Some patients experience diarrhea after taking antibiotics such as amoxicillin. Diarrhea associated with amoxicillin is an example of intolerance. On the other hand, if a patient experiences hives, itching, etc. after taking amoxicillin, this is most likely an example of an allergic adverse reaction. These adverse effects while unpleasant, and for allergies sometimes dangerous, are also predictable and clinicians often monitor for these effects in order to catch them early. It is important to record these events in a patient's medication history to help prevent future events of intolerance or allergic reactions. It is also extremely important for patients to update their own history to protect against repeat adverse reactions. Unlike pharmacologic adverse events, intolerance and allergic reactions are not dose related and often do not have an antidote.

Idiosyncratic Drug Reactions

Idiosyncratic drug reactions are adverse effects that cannot be explained by the known mechanisms of action of the medication (hence are not pharmacologic), are not seen at any dose in most patients (thus not an example of intolerance), but instead are seen unpredictably and only in susceptible patients. There are very few antidotes for idiosyncratic reactions. Idiosyncratic reactions are important to understand because most severe and or life-threatening adverse effects as well as many other reactions requiring discontinuation of treatment are idiosyncratic in nature. These reactions are often a result of patient differences in metabolism of medications which result in accumulation of a toxic compound.[6] The REMS approach to improving medication safety tends to focus on these idiosyncratic (unpredictable yet severe) reactions.

Recognizing the Type of Adverse Drug Reaction

It is hard to tell if a person is having an adverse reaction to medication or if the noted symptoms are caused by a disorder or worsening of their condition. The symptoms caused by adverse reactions to some medications can be the same as the disease symptoms. One of the symptoms of an aspirin overdose is headache! There are methods to relate some symptoms to medications. An adverse drug reaction usually is related to the initiation of a treatment and symptoms frequently begin to improve once treatment is stopped. It is clear the event is an adverse drug reaction if administration of an antidote provides a dramatic improvement in symptoms. This is seen when naloxone is used to reverse excessive effects of an opioid such as morphine or hydromorphone. An adverse drug reaction is often related to the mechanism of action of the medication or is one of a series of known examples of intolerance or idiosyncratic reactions. Sometimes there is laboratory confirmation of the adverse drug reaction (for example elevated blood levels of the medication) and at times the patient may describe a similar reaction to this medication in the past.[4] See **Table 2: Identifying Adverse**

Table 2. Identifying Adverse Drug Reactions
Was the reaction previously reported?
Did the reaction appear after starting the medication?
Did the reaction improve after the medication was stopped?
Did the reaction return if the medication was re-started?
Are there other causes for this reaction?
Was there a similar reaction to other medications in this pharmacologic class?

Drug Reactions for a checklist to assess if a symptom is an adverse drug reaction.

Identifying Risk

Any one of us can identify patients at risk for serious ADRs by reviewing the contraindications, warnings, black box warnings, and precautions sections of the package insert. "The contraindications section lists in a bulleted format situations in which a medication should absolutely NOT be used. The Warnings and Precautions section is a summary of the most clinically significant adverse reactions and what to do about them. This section also presents information about the monitoring parameters (how to look for them) for these side effects."[7] A boxed warning may also be present in the highlights section. The boxed warning is a shortened version of the contraindications section and is placed very prominently in the package insert, so that the boxed warning is almost impossible to overlook. The REMS developed by the FDA adds a formal and regulated process to this identification of risk and initiates a series of requirements designed to minimize patient use in these hazardous situations.

Risk Evaluation and Mitigation Strategies Approach

Table 1 compares the PI frequency approach described to a classification of adverse events using a REMS approach. This example is taken from the REMS statement for dronedarone: There is a risk evaluation and mitigation strategy in place for dronedarone.[8]

Goals of the Dronedarone Risk Evaluation and Mitigation Strategy

- To **prevent** MULTAQ use in patients with NYHA Class IV heart failure or Class II-III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart failure clinic by educating prescribers about increased mortality when MULTAQ is used in this patient population.
- To **inform** healthcare professionals and patients about the serious risks of MULTAQ, including: increased mortality in patients with severe unstable heart failure and signs and symptoms of liver injury and hepatic failure.

The REMS approach is focused on prevention. Notice that increased mortality is an unusual event which is not even mentioned in the frequency listing of adverse effects for dronedarone. By following a REMS protocol we are able to identify patients at risk of serious adverse drug reactions and implement a strategy to reduce this risk. In this particular case clinicians should not use dronedarone in patients with advanced types of heart failure (the risk of harm is greater than the benefit) and should evaluate liver function in all patients taking dronedarone. Compared to the traditional frequency approach, the REMS approach promotes understanding and identification of risk factors (advanced heart failure, liver injury) rather than memorization and offers an active method to prevent serious adverse drug reactions.

Risk Evaluation and Mitigation Strategies Background

The basic purpose of the REMS program is to ensure that the benefits of a drug or biological product outweigh its risks. A REMS is unique to a medication and is a result of a negotiation between the FDA and pharmaceutical manufacturer. The REMS is based on occurrence of serious adverse events in clinical trials or observed post marketing. Clinical trials in this case are the studies that a drug manufacturer is required to conduct in order to secure FDA approval of their medication. Post-marketing refers to information gathered about a medication after it is approved by the FDA. Traditionally these situations where it is expected that the risks outweigh the benefits are labeled as contraindications. If prescribers do not react to warnings of contraindications, often a black box warning is added to the labeling. Under a REMS system many of these contraindications will be spelled out under the REMS. The REMS goal for FDA is to permit approval of a new medication in the situation where it is unclear if the drug benefits outweigh the risks, and for the pharmaceutical industry to ensure a faster FDA approval, broader indications, less restrictive warnings, etc. It makes sense that a medication would have unique REMS as drugs have different side effects and different mechanisms of action, therefore resulting in different risks. For example, a REMS for a cardiovascular medication needs to be different from a REMS for a pain reliever.

On the other hand, because each REMS is different, there is a great deal of time consuming administrative work placed on practitioners in order to keep track of all of the different requirements and operational rules. A portion of these additional administrative and clerical costs needed to maintain a REMS fall on the health system. These costs are not reimbursed. In addition each REMS is not static and can be changed at any time. For example, the REMS that was initiated for dabigatran was released by the FDA after only a few months. Therefore every pharmacy will have to prepare a special procedure section for all of the medications that have REMS so that all staff can stay up to date on both technical and procedural information. The REMS process opens up opportunities for pharmacy technicians, especially those with good organizational and communication skills, to play a key role in keeping the pharmacy department REMS guide and staff up to date.

Why REMS?

Failure of Warnings

Why has FDA developed a REMS process? This is partially due to the failure of Dear Doctor/Dear Pharmacist letters or black box warnings in the PI to discourage risky prescribing. Pharmacists and other clinicians routinely receive mailings from drug manufacturers about changes in the warnings section of the PI. Often these warnings are discussed to some extent in educational programs, but all of this information is provided after the fact. Think about some of the warnings that were recently communicated. Many of these warnings needed to be sent on multiple occasions and later the medication still had to be removed from the market.

Some examples of medications subject to national warnings include increased mortality in heart failure patients and liver failure with dronedarone (Multaq®); and cardiovascular warnings associated with rofecoxib (Vioxx®). There was major media coverage when antidepressants were found to influence suicide risk particularly when used in children. Recently smoking cessation agents were linked to violent behavior or even suicide risk; and rosiglitazone (Avandia®) and its severe cardiac adverse events are all current and serious examples. There are more than 500 medications that have a black box warning, often meaning that earlier boxed warnings likely did not change prescribing in the face of known risk factors for adverse events. Between 1995 and 2007 there were 174 products approved. The FDA instituted actions 82 times on 41 of these products.[9] A REMS is intended to help clinicians become aware of these warnings before they prescribe or advise a prescriber to order a medication for a patient. Perhaps many serious adverse events could be avoided simply by adopting a REMS approach.

Limitations of Research Protocols

There are other reasons to develop a REMS process. Drug research protocols due to their design have limited ability to detect rare yet serious adverse effects. Some design factors include the small numbers of patients receiving a study medication, the short duration of these clinical trials, and inclusion/ exclusion criteria that can result in only studying the healthiest of eligible patients. These groups of included study patients often are not representative of the actual people that will receive the medication once it enters the market.[10] Another way of putting this is that research studies are designed to see if the medication *can* show benefit under optimal conditions. These research studies try to answer the question: *Can this drug work*?[11] A study with many less exclusions would be needed in order to show benefit and safety under usual conditions. While not a topic for this paper, this discussion is the basis for the development of comparative effectiveness studies that you might have heard about. Comparative effectiveness studies try to answer the question: *Does this drug work*?[11] Of course, the FDA could have required more extensive clinical trials for drug approval, but this option would require the enrollment of many more patients and investigators for longer periods of time. This would be expensive and would likely delay product availability.[10] REMS through a focus on prevention and safety offer a different approach that is likely to gain the same benefits without the added costs of additional research and lengthy study durations.

O -Label Use

There are other limitations of drug research protocols. As stated, these studies often have narrow criteria for including patients in the study. The narrow indications seen in these research studies are the basis for FDA approval and these indications are often referred to as the labeled indications (as in labeled by the FDA). Once a drug is approved by the FDA, a prescriber can always use the medication for different purposes and at different doses than those described in the study. These different purposes and doses are referred to as off-label uses. Often when a safety warning is issued for a newly approved medication the warning refers to off-label use.[12,13] A safety specification study compares the frequency of reported adverse events between patients receiving a medication for labeled indications to the adverse events seen when the medication is used off-label. This information provides an early warning about types of patients or situations that are at-risk.[10] Safety specification studies might also warn

about drug-drug and or drug-food interactions, special risks for female patients, children, elderly or other types of patients that are often excluded from clinical trials. Comparative effectiveness and safety specification type studies offer new research opportunities for pharmacy.

Pharmacovigilance

Pharmacovigilance refers to medication research related to the detection, assessment, understanding, and prevention of adverse effects.[10] The rationale for the REMS program is that carefully planned pharmacovigilance, particularly addressing new drugs, might lower the risk of drug toxicity and increase overall health benefit. Safety data obtained in this manner could also help prevent effective drugs being taken off market, as use in patients at high risk for adverse effects could be avoided.[10]

In 2005, the FDA announced a plan to incorporate pharmacovigilance into their drug approval process. The plan was named Risk Minimization Action Plans, often referred to as RiskMAPs. A RiskMAP could be recommended for a particular medication because of the type or frequency of known risks when compared to expected benefits (for example, higher risks of adverse effects might be acceptable for an anticancer agent, particularly when failure to treat might be fatal); or because the type of patient being treated is at high risk of adverse events (elderly, children, or patients with renal failure); or because of the availability for alternative treatments (a higher risk of side effects might be accepted for a drug that is the only option to treat a serious condition); and finally because of the ability to prevent or reverse an adverse event. For example, vitamin K can be used to reverse the effects of warfarin. The tools adopted for RiskMAPs are very similar to the tools later installed for REMS- education, reminders, and restricted-access systems.

In 2007, the Food and Drug Administration Amendments Act (FDAA) was signed into law. Title IX enacted in 2008 provides the FDA with the authority to place requirements on drug manufacturers with respect to medication safety. REMS and RiskMAPs are very similar. RiskMAPs essentially evolved into REMS. However, under REMS, the FDA has the authority to include fines as an enforcement mechanism. Most products do not require a REMS or a RiskMAP; it is not required as part of submission for approval to the FDA (although many applications do include a REMS); these strategies are thought to be necessary to ensure that a drug's benefits outweigh risks of serious adverse effects; and a requirement for either can be identified after a medication is placed on the market.

Risk Evaluation and Mitigation Strategies Examples

Consider your work experiences. If, for example, your pharmacy fills prescriptions for dofetilide, you already have experience with a REMS that requires a medication guide, elements to assure safe use (ETASU), and an implementation system that provides education for pharmacists and prescribers. You commonly verify that the prescriber is on a registry of approved prescribers. REMS programs are very similar to procedures used for following medications like dofetilide, clozapine, and thalidomide. The success of the programs for these three drugs at preventing severe adverse effects may have influenced the FDA to expand this method to other medications.

REMS programs have three components with any combination of these possibly being required:[14]

1. **Level 1: Medication Guides and Patient Education.** A medication guide (MedGuide) is a pamphlet written to help patients to understand the risks of adverse effects associated with a particular medication.
2. **Level 2: Active Communication of Risk to Prescribers.** This might include letters, information provided at professional meetings or other continuing education.
3. **Level 3: Elements to Assure Safe Use (ETASUs).** Any combination of the following may be a requirement:
   - Health care providers who prescribe the drug are required to have particular training or experience or are specially certified.
   - Pharmacies, practitioners, or health care settings that dispense the drug need to complete safety training and are specially certified.
   - The drug is dispensed to patients only in certain health care settings, such as hospitals.
   - The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results, or patient consents.
   - Each patient using the drug is subject to certain defined monitoring.
   - Each patient using the drug is enrolled in a registry.

In a drug class implementation all medications in the drug class are included in the REMS, rather than just a single medication. Drug class REMS will soon be implemented for extended release and long acting opioids and for long acting beta adrenergic agonists (LABAs). See **Table 3: List of Long-Acting and Extended-Release Opioid Products Required to have an Opioid REMS**[15] for a listing of opioids scheduled for inclusion in this drug class REMS. The components of the opioid class REMS will include prescriber training,

Table 3. List of Long-Acting and Extended-Release Opioid Products Required to Have an Opioid REMS[15]

BRAND NAME PRODUCTS		
TRADE NAME	**GENERIC NAME**	***PHARMACEUTICAL MANUFACTURER***
Duragesic®	Fentanyl transdermal system	Ortho-McNeil-Janssen
Palladone®*	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma
Dolophine®	Methadone hydrochloride tablets	Roxane
Avinza®	Morphine sulfate extended-release capsules	King Pharmaceuticals, Inc.
Kadian Capsules®	Morphine sulfate extended-release capsules	Actavis
MS Contin®	Morphine sulfate controlled-release tablets	Purdue Pharma
Oramorph®	Morphine sulfate sustained-release tablets	Xanodyne Pharmaceuticals, Inc. King
Embeda®*	Morphine sulfate and naltrexone extended-release capsules	Pharmaceuticals, Inc.
OxyContin®	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma
Opana ER®	Oxycodone hydrochloride extended-release tablets	Endo Pharmaceuticals
Exalgo®	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt, Inc.
Butrans®	Buprenorphine transdermal system	Purdue Pharma

** No longer being marketed but still approved*

medication guides, participation in an assessment plan, and completion of additional and defined administrative requirements. The training for pharmacies, prescribers and others is available by outline form.[16] Although only available in outline form this document does provide information about the extent and type of training that will be available. "A REMS focused on prescriber education is intended to reduce the potential for serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of long-acting and extended-release opioids, while ensuring that patients with legitimate need for these drugs continue to have appropriate access to them."[17]

The other components of the opioid class REMS are not finalized. A drug class REMS was implemented this year for erythrocyte stimulating agents (ESA) - these are medications like Procrit®, Epogen® and Aranesp®. Prepare a bookmark to the FDA website[8] and check this site often to stay informed about expected new developments.

Three Levels of REMS

How does the FDA determine if a drug's benefits outweigh the risk of serious adverse events? The FDA reviews a number of issues including: the number of patients likely to be treated with this medication (a rare serious event in a large population would be a concern); the seriousness of the condition under treatment (serious side effects for a treatment of a mild condition would be a concern); the duration of treatment; and the seriousness of adverse events. There are three levels to a REMS. These levels are: a medication guide, ETASU, and/or a communication plan.

The responsibility for the implementation, communication to clinicians, monitoring, and record keeping of REMS is assigned to the pharmaceutical manufacturer. Finally, there is also a timetable for submission of REMS assessments. Unless otherwise stated these assessments are due at eighteen months, three years and at seven years.[14]

Medication Guide

A medication guide (MedGuide) is required by the FDA when: 1) patient labeling could help to prevent serious adverse effects (patient labeling refers to the medication guide in this example; official labeling refers to the PI); 2) the medi-

Table 4. REMS by Required Components

Adapted from www.fda.gov/Drugs/DrugSafety

NUMBER OF DRUGS	REQUIRED COMPONENTS
150	Medication Guide
12	Communication Plan
31	Medication Guide Communication Plan
11	Medication Guide Communication Plan Elements to Assure Safe Use Implementation System
5	Medication Guide Elements to Assure Safe Use
14	Medication Guide Elements to Assure Safe Use Implementation System

Table 5. Statement for Medication Guides

Example provided from Northwestern Memorial Hospital Department of Pharmacy, Chicago, IL

Pharmacists - Please use the following template to guide your discussions about Medication Guides.

As you know, all medicines have side effects. When a medication is brand new, we don't always know what side effects to expect. Keep in mind that one day you may have serious side effects if you do not treat your illness.

I have a pamphlet for you to read. This pamphlet was written by the company that sells this medication. It lists some of the conditions which might increase a person's chance of having a side effect. Most people do not have one of these conditions, and even if you do, there is nothing to be alarmed about.

Please look these over and tell your doctor if you or any family member has ever had one of the conditions that are listed. If you do, your doctor will explain why this medication is necessary for you. Your doctor is expecting to have this conversation with you so please do not hesitate to discuss your concerns with her (him). If you are not sure how or what to discuss with your doctor, please let me know and I will ask one of our pharmacists to help you.

cation has serious risks which patients might choose to avoid if patients knew about these risks; or 3) it is important for patients to closely follow use directions for the medication to be effective.

Patients being cared for in a hospital and receiving a drug having a REMS which requires a MedGuide, should receive a MedGuide if: 1) the patient is given or dispensed the drug to take home; 2) the drug is dispensed from a hospital based outpatient pharmacy for patient self-care/self-administration; or 3) the REMS documentation requires a MedGuide to be provided at specific points in the patient care process.[8] An outpatient pharmacy or community pharmacy should provide a MedGuide for any medication having a REMS which requires a MedGuide.

A MedGuide is different from a patient package insert (PPI). Remember, the purpose of a MedGuide is to help patients to prevent serious adverse events and to make informed decisions. Since the focus is on safety, reading a MedGuide can be a scary experience for patients. Spending a few minutes clarifying this information could help put a patient at ease. Reminders that all medicines have side effects, that not treating your illness will also have adverse effects, and helping patients to clearly communicate their concerns are important roles for the pharmacists in your work place. Reminding the patient that the pamphlet was prepared by the company that makes the medication can be reassuring. Sometimes the simple act of helping a patient to formulate questions to ask their own physician can be especially helpful. See **Table 5: Statement for Medication Guides** for guidelines from Northwestern Memorial Hospital for communicating MedGuide information to patients. Check with your pharmacy manager to see if these guidelines might be helpful for your workplace.

Elements to Assure Safe Use (ETASU)/ Restricted Drug Distribution Systems (RDDS)

Elements to assure safe use (ETASU) are implemented when serious risks may not be avoided by only providing educational materials to patients and prescribers. An ETASU may require that prescribers have specific training or certification; that pharmacies and healthcare settings are certified; that medications are only provided in defined health care settings; that medication is only dispensed when documentation of safe use conditions is provided; each patient is subject to defined monitoring; or each patient is enrolled in a registry. See **Table 4: REMS by Required Components** for a summary. Implementation systems often require certification of a distributer to ensure compliance with REMS and ETASU regulations.

There are a number of drugs approved under a REMS that require restricted drug distribution through certified pharmacies. A RDDS is a type of ETASU. In a RDDS, the hospital, the patient, the prescriber, or the pharmacy may be required to enroll and qualify in an identified program. These programs can require training and special record keeping. Some RDDS have already identified a limited listing of approved suppliers and or pharmacies. This list may not include the pharmacy where you work. As you can see, these programs can become very complicated for pharmacies to manage.

Examples of ETASU

One of the first measures adopted as a formal REMS was for epoetin alfa. If you provide epoetin alfa for cancer patients you also have experience with a REMS/ETASU. If you work in a hospital, a representative of the hospital and also prescribers must enroll and complete the APPRISE oncology program training module. This hospital representative must verify enrollment of prescribers and patients, and patients must receive a MedGuide. Epoetin alfa acts to increase the production of red blood cells and is used in chronic kidney disease and also in some types of cancer patients. However in other kinds of cancers this medication actually reduces the chances of survival and may also act to stimulate new cancers. Other patients might be at risk for serious blood clots leading to stroke or heart attack. This REMS and ETASU was set up so that epoetin alfa would remain available for patients in need while not available for those at risk of severe adverse effects.

Romiplostim (Nplate®) is another example of a medication with an ETASU. Romiplostim acts to increase the production of platelets and is used to treat chronic idiopathic thrombocytopenic purpura (ITP) a condition that reduces platelets. The drug is available exclusively through a restricted distribution program (the Nplate NEXUS Program) set up by the company under the REMS process of the FDA. There are usually a limited and defined number of physicians who are enrolled and recognized as Healthcare Providers in the NEXUS Program. Your work place must also be enrolled and recognized as an institution that can obtain the drug for a patient enrolled by one of these physicians. The complete NEXUS Program details, patient enrollment forms, and ordering process for instituions can be found on the internet.[18] Romiplostim is associated with a number of serious and sometimes fatal adverse effects. There is a risk of changes in bone marrow; a risk for blood clot complications, and for cancers of the blood elements. On the other hand when a patient has ITP, their blood does not clot properly. This is due to a low number of blood cell elements called platelets. Bleeding occurs inside the body and also in the skin. Some types of bleeding are serious and can be life threatening. By setting up a REMS with an ETASU a process is in place to provide a medication for life saving situations where the risks of serious adverse effects are justified. Without a REMS process in place, it is very possible that romiplostim would not be on the market and available to patients.

Communication Plan

A communication plan might consist of the Dear Doctor/ Dear Pharmacist letters described earlier in this module, or this information might be scheduled for presentation at professional meetings, Internet Broadcasts, and other educational venues.

Risk Evaluation and Mitigation Strategies Resources

ASHP

The American Society of Health-System Pharmacists (ASHP) maintains an excellent internet site for REMS information. The REMS Resource Center (http://www.ashp.org/REMS) is a comprehensive and easy to use reference for detailed information about REMS programs. Use the practice and policy tab to access an alphabetical listing of resource centers. Once inside the REMS resource center detailed information about individual medications is listed alphabetically by generic name. Each monograph follows a standard format and includes internet links to websites containing detailed information. The monograph begins with an explanation of why a REMS is required and a description of the identified risks. This explanation is an excellent starting point for understanding the purpose of a specific REMS and should be understood by everyone in the pharmacy. The next section of the monograph summarizes the requirements for the health care organization, the pharmacy, prescribers and suppliers. The need for a MedGuide is identified, and often the link to a MedGuide is provided. Other information about required training and available continuing education credits is also provided. See **Table 6: REMS Information for Epoetin alfa** for an example of the epoetin alfa monograph taken from the ASHP site.[19] The REMS Resource Center also has internet links to a number of summary documents in addition to the individual medication monographs.

FDA

The FDA has very helpful information under Drugs; Drug Safety and Availability; Post Market Drug Safety Information; Approved Risk Evaluation and Mitigation Strategies (REMS) at http://www.fda.gov/.[20] This table lists medications

Table 6. REMS Information for Epoetin alfa (Procrit®, Epogen®)[10]

Why is this medication required to have a REMS?
To ensure the benefits outweigh the risks of shortened overall survival and/or increased tumor progression or recurrence.

Do I or my hospital/pharmacy have to enroll in a certain program?
Yes - APPRISE Oncology Program Training Module for Hospital Designees at Hospitals that Dispense ESAs for Patients with Cancer *

Does the prescriber have to enroll in a certain program?
Yes - ESA APPRISE for Healthcare Providers who prescribe/dispense **

Do I have to verify that the patient and/or prescriber are enrolled?
Yes - the hospital designee is responsible for establishing or overseeing and maintaining paperwork ***

Do I have to dispense a Med Guide or any other material to the patient?
Yes - Procrit Med Guide - Epogen Med Guide

What do I have to document?
Evidence of compliance with the ESA APPRISE Oncology Program, including:
- List of HCP that prescribe epoetin alfa for cancer patients and documentation (enrollment ID#) of enrollment in APPRISE
- Healthcare Professional Acknowledgment Form for each cancer patient for whom an epoetin alfa prescription was filled and documentation of the risk: benefit discussion between certified prescriber and patient

Am I required to complete CEs?
No

Are there restrictions on amount of this medication (i.e., quantity dispensed, re lls)?
No

Am I or my pharmacy subject to an audit by the manufacturer/FDA/3rd party?
Yes

** The ESA APPRISE Oncology Program applies only to the use of epoetin alfa in oncology patients. This requirement does not apply to its use in anemia associated chronic kidney disease or other non-oncology uses.) If your hospital dispenses epoetin alfa for use in oncology patients, the hospital must be certified through the hospital site level enrollment in the ESA APPRISE Oncology Program. This requirement does not apply to epoetin alfa used for anemia associated with chronic kidney disease or other non-oncology uses. Each hospital must select a hospital designee who will assume responsibility for ensuring the hospital's compliance with the program. They must complete and sign the ESA APPRISE Oncology Program Enrollment Form for Hospitals and the ESA APPRISE Oncology Training Module before enrolling the hospital in the program. Individual pharmacists are not required to enroll in the ESA APPRISE program.*
*** Physicians who prescribe or administer Epoetin alfa specifically for use in oncology patients must be trained and certified through the ESA APPRISE Oncology Program. This requirement does not apply to Epoetin alfa used for anemia associated with chronic kidney disease or other non-oncology uses.*
**** The establishment of a system, order sets, protocols, or other measures to ensure that the healthcare provider who prescribed Epoetin alfa for patients with cancer has enrolled in the ESA APPRISE Oncology Program and that the discussion between the patient and ESA APPRISE Oncology Program-enrolled prescriber on the risks of Epoetin alfa therapy is documented by patient and prescriber signatures on the ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgement Form prior to initiation of each new course of Epoetin alfa therapy.*

Table 7. Changes to Committee Practices

Example provided from Northwestern Memorial Hospital Department of Pharmacy, Chicago, IL

REMS/ETASU included in:
- Formulary Request
- Formulary Monograph
- Formulary Recommendation
- Online Formulary
- Pharmacists to sponsor formulary action for newly invoked REMS/ETASU/RDDS

Table 8. Formulary Request Form - Tolvaptan

Example provided from Northwestern Memorial Hospital Department of Pharmacy, Chicago, IL

There are 5 steps to add a medication to the Formulary

1. Disclosure of potential conflicts of interest with Otsuka, the manufacturer of tolvaptan (Samsca®).
2. Submit a protocol for the use of this medication on patients at Northwestern Memorial Hospital. Your protocol should summarize the evidence supporting your recommendation and also include the indications, patient selection, status (first line, alternative agent, etc.), and precautions that you recommend. A typical protocol is 1-2 paragraphs in length.
3. Describe the REMS and plan for compliance for tolvaptan. A REMS is enacted because of increased risks associated with overly rapid correction of serum sodium leading to osmotic demyelination. Each patient is to receive a FDA-approved Med Guide.
4. Identify inferior and/or superfluous medications replaced by tolvaptan that should be removed from the Formulary.
5. Attend the P&T Committee to defend your proposal.

by their trade names, provides the effective date, and summarizes the components of the REMS and any elements to assure safe use. There are approximately 200 listed medications. A MedGuide alone is required for approximately 150 medications. A combination of MedGuide, communication plan, implementation plan and other elements to assure safe use is required for approximately 70 medications. See **Table 4: REMS by Required Components** for a summary of the various REMS and ETASU in place as of September 29, 2011. On the FDA web site the link provided under the medication brand name takes you to a PDF file that has a very comprehensive listing of every component of the REMS. This part of the site would be helpful for preparing a detailed search of specific information in a REMS assigned to a medication. REMS requirements will change frequently. To remain up to date on this topic, insert a bookmark on your internet browser for the ASHP and FDA internet sites under your favorites tab for continuing reference about REMS.

Manufacturers

The package insert of a medication will provide information on required REMS. In most cases, package inserts are also available online through the manufacturer.

Practical Experiences

One approach for health-systems is to develop an internal process to assess the REMS and ETASU components within the Formulary system which is approved by a Pharmacy and Therapeutics (P&T) Committee. A P&T Committee is a medical staff advisory group which determines all matters pertaining to the use of medications in an institution or organization. One primary function is to review medications for inclusion in the formulary (medications stocked or permitted) for use by the institution or organization. At Northwestern Memorial Hospital (NMH) in Chicago, Illinois, information about a REMS is included in the form for a Formulary Request. See **Table 7: Changes to Committee Practices**. If a requested drug has a REMS, the REMS and the reasons for the REMS are described in that form. See **Table 8: Formulary Request Form - Tolvaptan**. The Formulary monograph also explains why there is a REMS and what the various elements of that REMS consist of. See **Table 9: P&T Committee Monograph for Tolvaptan**.

A Formulary monograph is a balanced summary of the advantages and disadvantages of a medication under Formulary consideration. This monograph is prepared by the pharmacy department and provided to P&T Committee members to assist in decision making. The advocate for a Formulary request must describe how they plan to comply with the REMS. When possible, information about the REMS is built into the computer prescriber order entry system. Many prescribers and vendors are unaware of the REMS process. See **Table 10: Recent Experiences at NMH.** In our experience, only two of seven advocates of Formulary additions were even aware of the existence of a REMS for the medication in question. The two prescribers who were aware of the REMS did not have correct information thinking the REMS was optional. The goal of our P&T Committee is to establish collaborative and proactive best-practice-type approaches to manage the implementation of REMS programs in our organization, to assess the hazard risk in our health-system, and to work with professional organizations to educate colleagues in medicine, nursing and pharmacy about the entire process.

Northwestern Memorial Hospital REMS Study

A formal process was developed at Northwestern Memorial Hospital for identifying practical mitigation possibilities of medications assigned to a REMS.[21] The FDA and ASHP REMS listings were consulted to review medications for inclusion in this study. Data from a six-month retrospective review of use, purchasing, formulary status, and mitigation possibilities were used to narrow the list of drugs resulting in six study medications. A parameter that could be addressed by the pharmacist, such as ordering a laboratory test for liver enzyme elevations, electrolytes, or contraindications was considered to be a mitigation possibility. The medications studied were: bosentan (Tracleer®); dronedarone (Multaq®); exenatide (Byetta®); quinine sulfate (Qualaquin®); teriparatide rDNA origin (Forteo®); and tolvaptan (Samsca®). Mitigation parameters included pregnancy for bosentan, dronedarone, and exenatide; evaluation of liver function for bosentan and dronedarone; and specific indication for quinine. See **Table 11: Medications in REMS Study at NMH** for a full listing of the mitigation parameters. Medication orders in 6 of 50 assessments were changed. See **Table 12: Results in REMS Study at NMH**. Liver function was not assessed and was the most common (3) of the pharmacist changed orders for dronedarone. These results found a low rate of risky prescribing and they did show that NMH is meeting goals for safe prescribing and proper monitoring. On the other hand, none of the physicians contacted were aware of the specific REMS or even knew anything about REMS. This study demonstrated that clinicians working at an academic medical center are not yet familiar with REMS or with REMS requirements.

An example of a medication with both a REMS and a restricted drug distribution system is bosentan (Tracleer®). Bosen-

Table 9. Pharmacy and Therapeutics (P&T) Committee Monograph for Tolvaptan*

Example provided from Northwestern Memorial Hospital Department of Pharmacy, Chicago, IL

ITEM	FINDING/URL
Product dedicated website	http://www.samsca.com
FDA News Item	FDA Approves Samsca to Treat Hyponatremia (May 22, 2009) http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm161945.htm
REMS A Risk Evaluation and Mitigation Strategy (REMS) is intended to manage a known or potential serious risk associated with a drug or biological product. A REMS will be required of the sponsor if the FDA believes it necessary to ensure that in use, the benefits of the drug or biological product outweighs its risks. A REMS can include a Medication Guide, Patient Package Insert, a communication plan, elements to assure safe use, and an implementation system, and must include a timetable for assessment of the REMS. List of other drugs with REMS: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm	The company was required to implement a REMS by the FDA. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm187491.pdf The REMS is required in order to lessen the potential risk of osmotic demyelination syndrome (ODS) by: • Educating healthcare providers on the risk of overly rapid correction of serum sodium associated with tolvaptan and the need for initiating tolvaptan in a hospital to ensure proper titration and monitoring • Informing patients of the serious risk associated with the use of tolvaptan, particularly the risk of osmotic demyelination syndrome Elements of REMS include: • Medication Guide • Communication Plan to Healthcare Professionals - involved in the prescribing, purchasing, dispensing or administration for both inpatient and outpatient setting at time of launch.

* *is example is a small component of a full monograph for tolvaptan at NMH*

Table 10. Recent Experiences at NMH

Example provided from Northwestern Memorial Hospital Department of Pharmacy, Chicago, IL

MEDICATION	REMS	FORMULARY SPONSOR	ACTION
Tolvaptan / Samsca® *Otsuka*	Medication Guide	Unaware of REMS	Added to restricted formulary
Alvimopan / Enterg® *Adolor*	E.A.S.E. Program (ETASU)	Unaware of REMS	Rejected
Romiplostim / Nplate® *Amgen*	NEXUS (ETASU)	Aware but voluntary	Proposal withdrawn
Deferasirox / Exjade® *Novartis*	RDDS rather than REMS EPASS Care System	Unaware of REMS	Proposal for off-label use tabled
Epoetin Alfa / Epogen® *Amgen*	APPRISE (ETASU)	Aware but assumed inpatients were exempt	Restricted use for oncology patients
Dabigatran* / Pradaxa® *Boehringer Ingelheim*	Medication Guide	Unaware of REMS	Added to restricted formulary
Liraglutide / Victoza® *Novo Nordisk*	Medication Guide	Unaware of REMS	Added to restricted formulary

**REMS for Pradaxa® was later released.*

Table 11. Medications in REMS Study at NMH

Example provided from Northwestern Memorial Hospital Department of Pharmacy, Chicago, IL

MEDICATION	MITIGATION PARAMETER
Bosentan (Tracleer®)	Pregnancy, increased LFTs
Dronedarone (Multaq®)	Pregnancy, SCr, LFTs ordered, Heart Failure
Exenatide (Byetta®)	Pregnancy, CrCl less than 30 ml/min, Pancreatitis
Quinine Sulfate (Qualaquin®)	FDA indication, CBC ordered, PLT less than 100
Teriparatide rDNA origin (Forteo®)	Medication use greater than 2 years increased risk for osteosarcoma
Tolvaptan (Samsca®)	Na/K ordered BID, Rate of Na correction, Discontinuing fluid restriction

LFTs = liver function tests; SCr = serum creatinine ; CrCl = creatine clearance; CBC = complete blood count; PLT = platelets; Na = sodium; K = potassium

Table 12. Results in REMS Study at NMH

Example provided from Northwestern Memorial Hospital Department of Pharmacy, Chicago, IL

MEDICATION	# OF PATIENTS	
Bosentan (Tracleer®)	7	
Dronedarone (Multaq®)	31	*(3/31 were interventions)*
Exenatide (Byetta®)	6	
Quinine Sulfate (Qualaquin®)	1	
Teriparatide rDNA origin (Forteo®)	2	*(2/2 were interventions)*
Tolvaptan (Samsca®)	3	*(1/3 was an intervention)*

Total: 6 interventions / 50 assessments

Mitigation rate: 12%

tan is used to treat pulmonary artery hypertension. The pulmonary arteries carry blood from the heart to the lungs to pick up oxygen. Elevated pressure in the pulmonary artery can weaken the heart. Adverse effects from bosentan on the other hand are frequent and some can be serious. Liver toxicity, birth defects if the patient is pregnant, and serious drug-drug interactions are some of the complications of therapy. Bosentan is only available to prescribers and pharmacies enrolled in the Tracleer Access Program (T.A.P.). Patients must also enroll and meet every requirement of the program. This medication is only available from select specialty pharmacies and is not dispensed through retail pharmacies. Specialty pharmacies are chosen to help ensure that required monthly liver function and pregnancy testing has occurred. The specialty pharmacies deliver the medication to patients every month and notify the prescriber if the patient does not confirm having the monthly tests or becomes pregnant.[22] A copy of a medication guide for patients and a guide for prescribers is available at http://www.tracleer.com/Hcp-prescribing-Tracleer-Tracleer-Access-Program. Of course, a medication guide and other documentation is a requirement. Prescibers are required to review the prescriber's guide, to review and document the patient medication guide with every enrollment and follow up visit, and also document liver function and pregnancy testing. Prescribers are required to submit all adverse effects to the Tracleer Access Program. Bosentan clearly is another example of a medication that might not be available to patients if establishing a REMS program was not an option.

Quinine is another example. Quinine is approved for use to treat malaria. There are a number of very serious concerns about the safety of quinine. Quinine has adverse effects on platelets, the kidney and the heart. However, as malaria is a life threatening illness, the benefit of quinine in malaria is thought to outweigh the risk for these adverse effects. Quinine is sometimes prescribed off-label to relieve painful leg cramps. There is very little evidence to support any benefits of quinine to relieve leg cramps, so for this off-label condition the risk of hazard far outweighs any benefits. The FDA REMS program for quinine requires that a medication guide be provided with every prescription for quinine in order to help patients understand the purpose of this medication and the risk of serious injury for a use (treatment of leg cramps) that is often unnecessary.[20]

Teriparatide is a parathyroid hormone used to improve bone strength. Unfortunately, with prolonged use of teriparatide, the risk of contracting a bone cancer increases. A REMS is in place so that healthcare providers are more aware of

Table 13. Advantages and Disadvantages of REMS

Advantages	Disadvantages
² Improve the safety of selected newly approved medications	² Lack of standardization
² Enhance the capability to react to safety concerns raised by recent studies	² Confusing for healthcare providers
² Help patients play a more active role in medical decisions	² May be time-consuming
² Collect observational data about the safety of selected medications	² Practitioners did not have a great deal of input
	² A new process has to be developed and implemented for each medication that requires a REMS

the two-year maximum lifetime duration of treatment with teriparatide. There is a voluntary support group for patients at Forteo® Connect.[23] Patients receive a small reimbursement for registering and they also receive safety information written in patient friendly language. In the NMH study, a patient was identified who had reached her lifetime maximum of teriparatide.[21] This took many hours of pharmacist and pharmacy student time to confirm the starting date and identify the community pharmacy and convince the pharmacist to review patient records. However, an unnecessary risk of cancer was avoided because of these extra efforts. Pharmacy technicians can certainly help to verify the duration of treatment with teriparatide and help to make medication use safer for these patients.

Tolvaptan is used to treat clinically significant hyponatremia (diminished sodium in the blood). Tolvaptan should be reserved for patients who do not respond to conservative measures like fluid restriction. Tolvaptan has not been compared to other treatments and has not shown benefit for long term outcomes such as frequency of hospitalizations or even mortality. Since this medication basically only improves short term symptoms and laboratory values, clinicians and patients should be less willing to accept serious adverse effects. Tolvaptan is one of the few medications where the REMS spells out that all patients should receive the medication guide before receiving their first dose. A REMS is in place because of increased risks associated with overly rapid correction of serum sodium leading to nervous system damage. Since the benefits are short term, the purpose of the REMS is to promote safe use. At NMH, the P&T Committee made the decision to restrict tolvaptan to the treatment of patients with clinically significant hyponatremia which is symptomatic and has resisted correction with fluid restriction. Treatment must be initiated or re-initiated only in hospitalized patients with close monitoring of serum sodium and only if: The patient is able to sense and appropriately respond to thirst; has sufficient kidney function; and is not taking other medications which interact with the metabolism of tolvaptan.

Summary and Recommendations

There are several important goals of the REMS approach and I believe almost everyone in the pharmacy profession supports these goals. These goals are: To improve the safety of selected newly approved medications; to enhance the capability of health systems to react to safety concerns raised by recent studies; to help patients play a more active role in medical decisions; and to collect observational data about the safety of selected medications. Of course, there may be obstacles to implementing this process in your pharmacy. The REMS are not standardized; a new process has to be developed and explained to all members of the pharmacy; and the rules are new and many are confusing. See **Table 13: Advantages and Disadvantages of REMS** for a side by side comparison of the advantages and disadvantages of the REMS approach.

It is clear that a new approach is needed to improve the safety of our medication use system. Inserting a checking step at the end of a very complex process is not working. A highly reliable health system builds in quality at every step of the medication system. It is not known yet if REMS are the answer, and many questions remain. Are patients safer under REMS? Can pharmacies conduct these studies? This presents an opportunity for pharmacists and technicians to play a new role in patient safety. Are patient outcomes better under REMS? Does a REMS reduce prescribing in patients having known risk factors or instead have the same minimal impact as Dear Prescriber letters have now? Pharmacies might have enough information on hand to answer these questions. Do we know of the best practices developed all over the United States for REMS implementation? This may be a chance for your pharmacy to submit a best practice poster. You can help with this poster and help to build new roles for pharmacy technicians. Does your health-system have a mechanism to educate colleagues perhaps by using a case study approach to describe successes in implementation? The hope is that REMS will provide the balance needed between access to newly discovered medications and patient safety. There are several operational questions that

must also be considered. When will prescription software and/or computer prescriber entry systems include REMS? Right now a work-around the customary procedures is needed to meet the REMS requirements. Ideally computer software will provide the alerts, identify the need for and provide a medication guide, and assist prescribers and pharmacists so we don't have to memorize the various rules for each of the individual medication's REMS. It is important to communicate our concerns to software vendors. Nothing will change if we do not take the initiative. REMS are a new process, and of course everything does not always work smoothly in any new process. If we are proactive, we can work together to improve this process and help to bring about a safer health system.

At NMH, we plan to conduct post-Formulary approval use studies of clinical outcomes for REMS medications; we want to place our focus on medication use studies that address safety concerns. For patient education we must go beyond stapling a computer generated handout to a paper bag. We can help patients understand the purpose and the hazard of their medications. We can clarify and focus discussion with patients on their own key issues so that patients have better communication with their doctors.

Our patients and their families expect us to do our best to provide a safe medication use system for them. What are your plans to provide this care? ▪

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Risk Evaluation and Mitigation Strategies (REMS)
SELF-ASSESSMENT QUESTIONS 1 — 20

1. The best way for a pharmacy technician to help patients understand the risks and benefits of treatment is to:
- A. Staple the medication guide to a bag containing the filled prescription.
- B. Go through the medication guide with them and answer their questions.
- C. Tell the patient that you would be happy to ask a pharmacist to discuss the medication guide with them.
- D. Tell the patient to refer all questions to their doctor the next time they have an appointment.

2. Sometimes a beta blocker like metoprolol is used to slow the heart rate. If a patient receives a very high dose of a beta blocker their heart may beat too slowly. What type of adverse drug reaction is this?
- A. Pharmacologic
- B. Intolerance
- C. Allergic
- D. Idiosyncratic

3. If a patient receives a very low dose of beta blocker and their heart beats too slowly what type of adverse drug reaction is this?
- A. Pharmacologic
- B. Intolerance
- C. Allergic
- D. Idiosyncratic

4. If a patient breaks out in hives after receiving a beta blocker what type of adverse reaction is this?
- A. Pharmacologic
- B. Intolerance
- C. Allergic
- D. Idiosyncratic

5. Adverse drug reactions are often described by the frequency of occurrence. Which is the true statement?
- A. This is found in the package insert, helps clinicians determine what to expect, but tends to promote memorization
- B. Frequency of occurrence is the basis for REMS
- C. A frequency distribution will always capture the most serious reactions
- D. Side effects are only important for patients

6. A REMS approach to adverse effects:
- A. Has a focus on prevention
- B. Identifies factors that increase the risk of a serious adverse effect
- C. Is part of a collaboration between FDA and the drug manufacturer
- D. All of the above

7. New drugs are tested in clinical trials. What do these trials usually tell us?
- A. Everything we need to know about effectiveness and safety
- B. If a drug can work
- C. If a drug does work
- D. How much a new drug will cost

8. What are the three components of REMS programs?
- A. Socialized medicine, death panels, and direct to consumer advertising
- B. Patient package inserts, power of attorney, and release forms
- C. Patient education, clinician education and elements to assure safe use
- D. Pharmacologic, intolerance and idiosyncratic

9. Adverse drug reactions can be identified because:
- A. The patient is always complaining
- B. The patient read about side effects on the internet
- C. Medications do not cause adverse reactions
- D. The reaction appeared after starting the medication and the patient improved after stopping the medication

10. Which is the most commonly used component of REMS?
- A. Medication guides
- B. Communication plans
- C. Implementation systems
- D. Restricted drug distribution systems

11. A P&T Committee can address REMS via which mechanism?
- A. The formulary request
- B. The P&T monograph
- C. In the formulary recommendations
- D. All of the above

12. Credible and updated information about REMS is available on:
- A. Wikipedia
- B. Material Safety Data Sheets
- C. FDA website
- D. None of the above

13. Pharmacovigilance refers to medication research regarding adverse effects through all <u>except</u>:
- A. Detection
- B. Understanding
- C. Assessment
- D. Reversal

14. What is a disadvantage of REMS?
- A. Not approved by the FDA
- B. A lack of standardization
- C. Requires more memorization from pharmacists and pharmacy technicians
- D. Implies that new drugs are not safe

15. An implementation of a Class REMS means:
- A. All drugs that are 2 years on the market receive a REMS
- B. The most expensive drugs are assigned a REMS
- C. All drugs in the same pharmacologic class receive the same REMS
- D. REMS are reserved for terminal patients only

16. A restricted drug distribution system:
- A. Includes all hospitals
- B. Includes every pharmacy
- C. Is limited to designated providers
- D. Is a health rationing system

17. Off-label use refers to:
- A. Medications that have spilled out of the container
- B. Use outside of FDA approval
- C. When a technician forgets to put a label on a prescription
- D. Use of an antidote

18. A medication guide is intended to:
- A. Help patents understand the risks and benefits of a medication
- B. Promote off-label use of a medication
- C. Avoid implementation of a REMS
- D. Keep a record of side effects

19. What should patient counseling for medication guides do?
- A. Remind patients that all medications have side effects
- B. State that adverse effects can happen if you don't treat your illness
- C. Provide advice as to what to ask your doctor
- D. All of the above

20. Who is responsible to improve the safety of medication use?
- A. Manufacturers
- B. Physicians
- C. FDA
- D. Everyone in health care