Risk Evaluation and Mitigation Strategies (REMS): Building a Framework for Effective Patient Counseling on Medication Risks and Benefits

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Meeting Summary

Introduction

The Food and Drug Administration Amendments Act (FDAAA) of 2007 expanded the ability of the U.S. Food and Drug Administration (FDA) to ensure the safety of drugs and biologics on the market. Among the new authorities granted to the agency was the power to require sponsors to develop Risk Evaluation and Mitigation Strategies (REMS) for drugs or biologics that carry serious potential or known risks. The REMS program has since become an important tool in ensuring that the benefits of a given medical product outweigh its risks and has enabled the agency to approve a number of products that otherwise might not have been made available for patient use. Since the implementation of the REMS program, however, concerns have been raised regarding the effectiveness of the program, its potential to unnecessarily limit patient access to products, and the burden associated with its implementation.[1] In response to these concerns—and as part of FDA's commitments under the Prescription Drug User Fee Act of 2012 (PDUFA V)—FDA has undertaken efforts to standardize and reform the way REMS are designed, implemented, and evaluated, and to better integrate REMS programs into existing health care systems.

Following extensive consultation with a range of stakeholders, in September 2014 the agency outlined four priority projects that it will pursue, one of which focuses on improving provider-patient benefit-risk counseling for drugs that have a REMS. Through this project, FDA aims to support the standardization of effective benefit-risk counseling between providers and patients, encourage providers to systemically educate patients about the benefits and risks of drugs that have a REMS, and improve patient involvement in decisions regarding the initiation, management, and termination of the use of such drugs. To this end, and under a cooperative agreement with FDA, Brookings is working with the agency to develop an evidence-based framework of principles and best practices that can be used to support effective counseling and may help inform the development and use of REMS tools.

Risk Evaluation and Mitigation Strategies

Beyond the standard labeling and safety surveillance requirements that apply to all medical products on the market, FDA has a number of additional tools at its disposal to mitigate safety risks. Prior to the passage of FDAAA in 2007, FDA employed Risk Minimization Action Plans (RiskMAPs) for drugs that required safety measures above and beyond the approved labeling and routine reporting requirements.[2,3] Many of the principles used to develop RiskMAPs would subsequently inform the development and implementation of REMS.

FDA can require a REMS for a particular drug prior to its initial approval or following approval if new information comes to light regarding the risk of serious adverse events associated with that drug. The drug's sponsor (i.e., its manufacturer) is responsible for designing, implementing, and evaluating the REMS. Sponsors develop and submit a proposed REMS plan for their product, which is then reviewed and adapted in consultation with FDA. A given REMS program can include one or more elements as well as a diverse set of materials and processes (collectively referred to as 'tools') to help mitigate the risks of a particular drug:

1) Medication Guide or Patient Package Insert (PPI)
    - FDA-approved patient labeling.
2) Communication Plan
    - Risk communications (e.g., Dear Health Care Provider letters) to health care providers, such as physicians, pharmacists, nurses, and physician assistants.
3) Elements to Assure Safe Use (ETASU)
    - Prescribers have specific training/experience or special certifications;
    - Pharmacies, practitioners, or health care settings that dispense the drug be specially certified;
    - Drug be dispensed only in certain health care settings (e.g., infusion settings, hospitals);
    - Drug be dispensed with evidence of safe-use conditions such as laboratory test results;
    - Each patient using the drug be subject to monitoring; and
    - Each patient using the drug be enrolled in a registry.
4) Implementation system
    - System to monitor and evaluate implementation of ETASU.

Sponsors may be required to provide a range of resources as part of a REMS, including handouts or online resources for both patients and providers as well as other support services. Sponsors are required to specify goals and objectives against which the REMS program can be evaluated, and an assessment must be conducted at a minimum of 18 months, 3 years, and 7 years after the program has been approved. Drug sponsors can submit additional assessments outside of that timeline and may also request a modification or removal of the REMS at any point. FDA may also decide to alter or discontinue the REMS altogether if assessments show that the REMS is not achieving its intended outcome or if new safety information comes to light that indicates the REMS is no longer necessary.

Patient Counseling as a Part of REMS

Many REMS programs also include an element of patient counseling, which may take a variety of forms depending on the nature of the drug's risks, the design of the REMS, the provider(s) and processes of care, and the timing and tools needed to support the counseling. However, the counseling goals are largely the same: to help providers educate the patient about the drug's risk and its associated REMS requirements, and to help ensure the patient uses the drug safely.

A number of different REMS tools have been used to support provider counseling of patients about the risks of REMS drugs. (See Table 1 below) These have included Medication Guides (MedGuides), a patient counseling document (developed in particular for the extended-release and long-acting opioid analgesic REMS), prescriber-directed counseling support tools, patient-prescriber agreements, and patient treatment continuation forms. A REMS may include one or more of these counseling support tools.

Table 1: Available REMS Tools to support Counseling of Patients on Risks

REMS TOOL	REMS TOOL DESCRIPTION
Medication Guide (MedGuide)	- Part of a drug's approved labeling - Describes all of the major risks of that drug, along with information on how to use it safely
Patient Counseling Document	- Single-page document developed for the extended-release/long-acting opioid analgesic REMS - Provides key points of information from the REMS MedGuide in summary form - Includes a blank space for a provider to write in information that is specific to his or her patient
Prescriber-Directed Counseling Tools	- Directed to the prescriber to help them prepare to counsel patients - Most frequently used for drugs that carry teratogenic risk; provides information on pregnancy prevention counseling
Patient- Prescriber Agreement	- Used to verify that counseling has taken place between a provider and patient and that certain required topics were discussed - May include patient-specific health information as part of the screening process to identify whether the treatment would be appropriate for a particular patient - Signed by both the patient and their health care provider before the initiation of treatment
Patient Treatment Continuation Form	- Must be signed by both the patient and provider to verify that the patient has benefited from the treatment and will continue to do so - May or may not require additional benefit-risk counseling to take place before the form is signed

Though these tools are designed to help patients make better-informed decisions, evidence of their effectiveness is lacking. Concerns have also been raised about the fact that these tools have historically focused solely on the risks of a given treatment rather than supporting patient understanding and the ability to balance both risks and benefits. Furthermore, most REMS tools focus only on the specific serious risk(s) targeted by the REMS rather than all of the risks associated with the drug. Others have noted that, with the exception of the patient treatment

continuation form, these tools are largely designed to be used primarily at the initiation of a treatment and have less of a role in decisions about maintaining or discontinuing a treatment. In some cases, providers are also required to document and verify that counseling took place, which may discourage providers from prescribing that drug.

The REMS Benefit-Risk Counseling Initiative

In response to these and other concerns related to the REMS program, FDA created the REMS Integration Initiative in 2011. Under this Initiative, FDA intends to standardize and improve the way that REMS are developed, evaluated, and implemented within the health care system. When PDUFA was re-authorized under the Food and Drug Administration Safety and Innovation Act of 2012, the REMS Integration Initiative was folded into FDA's PDUFA V commitments. As part of this, FDA pledged to continue its work to evaluate and standardize REMS processes and to work with stakeholders to integrate REMS into the current health care system.

In pursuit of this broader goal, the agency also agreed to undertake projects within each of four priority areas, one of which is focused on improving the communication of benefit-risk information to patients. Stakeholder feedback to FDA indicated that patients would value receiving information that would help them to better understand both the benefits and the serious risks involved with taking a drug with a REMS. Ideally, this information would be communicated to patients via their health care provider, and it would allow them to better participate in shared decision making about initiating, maintaining, and/or discontinuing that drug. This is particularly important with drugs that have potential or known risks that are serious enough to require a REMS, and both stakeholders and FDA saw opportunities to standardize and improve the techniques, procedures, and tools providers use to counsel patients about initiating and safely using these products.

Through this project, FDA hopes to achieve four major goals:
- Support the standardization of effective health care provider to patient counseling to help improve informed therapeutic decision-making and risk management.
- Encourage health care providers to systematically discuss and educate patients about risks of medications with a REMS and how those risks should be weighed against the potential benefits of the drug, using initial and follow-up counseling sessions both before prescribing and during treatment.
- Enhance patient involvement, knowledge, and understanding of the risks of products with REMS and how to manage them.
- Provide a basis for designing and demonstrating the impact of effective counseling instructions, techniques, and tools as part of risk mitigation programs.

In support of these broader goals, and under a cooperative agreement with the agency, Brookings worked with FDA to obtain literature-based evidence as well as practical expert insights into effective processes, techniques, practices, and language to support effective counseling and shared decision-making between providers and patients. This input will be used

to develop a framework for effective benefit risk counseling for medications with REMS, which can help support health care providers, patients and/or sponsors.

As an initial step, Brookings partnered with FDA to conduct a scan of the existing literature on benefit-risk counseling and shared decision-making between providers and patients. The resulting white paper can be found here. The major takeaways are summarized in the tables below.

SUMMARY TABLE OF BEST PRACTICES IDENTIFIED IN THE LITERATURE

Benefit and Risk Communication
- Use plain language and provide numeric data to support counseling.
- Exercise caution in applying evaluative labels such as 'low risk' or 'high chance'.
- Consider placing the targeted risks in context by comparing them to the risk of other outcomes, but exercise caution in comparing an individual patient's risk to the risk faced by an 'average' person.
- When communicating changes in numeric outcomes, use absolute risk rather than relative risk, and avoid using number needed to treat.
- When using natural frequencies or event rates, clearly define the denominator and keep it constant across different risks.
    - Event rates may be preferable when presenting the chance of a single event or the occurrence of two or more *independent* events.
    - Natural frequencies may be preferable when comparing the chance of occurrence of two or more *dependent* events.
- Keep time frames constant, and reinforce them repeatedly when describing risk over time.
- Use visual aids to support the communication of quantitative risk information.
    - When feasible, visual aids should depict the baseline risk separately from the treatment risk,
    - Bar graphs and pictographs are perceived more accurately and easily and may be preferable.
- Provide a summary table that lists benefits and risks of the intervention together so as to offset bias related to framing and ordering.
- Focus communication on key messages, and exclude non-critical information
- Providers should work with patients to identify and prioritize which decisions are appropriate for SDM.
- Providers should inform patients that a decision needs to be made, and elicit their preferred level of involvement in that decision.
- Providers should use the best-available evidence and apply the principles of evidence-based medicine to the SDM process.

Best Practices (Con't)
Shared Decision-Making

- The SDM process should be interactive; for example, providers should ask patients to explain how they themselves frame the decision, and use the teach-back technique to ensure that the patient has understood the information presented.
- Providers should elicit their patient's values and preferences, and avoid making assumptions regarding them.
- Providers should acquire the necessary knowledge and skills before using a decision aid in their practice, including:
    - The relevant clinical knowledge,
    - Effective communication and consultation skills, particularly in regard to eliciting a patient's values and preferences,
    - Effective numeracy skills,
    - Ability to effectively explain the tradeoff between a treatment's risks and benefits.
- Organizations should consider supporting training and education of providers in developing the skills and expertise needed to use decision aids effectively, and should consider prioritizing and disseminating the decision aids needed by their target patient population to all relevant health care providers and stakeholder groups.
- Providers should read and understand the content of a decision aid before using it with their patients.
- Providers should not use a decision aid to replace face-to-face discussions between providers and patients.
- Providers should ensure that decision aids have followed a robust and transparent development process (such as the process outlined by International Patient Decision Aid Standards Collaboration and the Ottawa Hospital Research Institute).
- Providers need to recognize that it may take more than one interaction with a patient to ensure that they can make an informed decision.
- Patients should be given the opportunity to review their decision at a follow-up appointment as their circumstances, values, and preferences may change over time.

SUMMARY TABLE OF KNOWLEDGE GAPS IDENTIFIED IN THE LITERATURE

Benefit and Risk Communication

- The impact of benefit-risk communication approaches delivered by other members of the health care team (e.g., nurses, social workers, pharmacists).
- Evidence to support the design and delivery of tailored risk information.
- How best to communicate changes in risk and benefit outcomes over time.
- How best to communicate uncertainty about risk estimates at the population and individual level.
- Whether and under what circumstances to include comparative risk information.
- Developing visual aids that support the presentation of complex multidimensional quantitative data.
- How best to communicate the *benefits* related to a medication (as opposed to simply communicating about a medication's risks) in an objective and non-promotional manner.
- How to practically provide absolute risk reduction tailored to the individual's clinical risks.
- How to narrow down the number of options/outcomes/risks to discuss (to avoid information overload).
- How best to account for/harness affect and emotion in communicating risks and benefits.

Shared Decision Making and Decision Aids

- How to integrate shared decision making (SDM) into clinical practice, identifying practice models and characteristics of interventions that promote integration.
- How to measure and define good decision-making, particularly in cases where there is no 'best' option.
- The effect of SDM interventions on health care delivery, resource use, unwarranted variation, and clinical outcomes.
- How to ensure quality control of decision aids (DAs) in order to minimize bias and conflicts of interest in their development.
- How to develop tools that target and facilitate communication among patients and their health care providers in a way that reflects the inter-professional nature of health care delivery.
- How best to tailor the health information being provided to a particular patient so as to reflect their clinical risks and information needs (both of which can change over time), preferences, and their level of health literacy.
- How different approaches to SDM impact its outcomes, and which approaches are most effective in supporting good decision-making.
- The cost-effectiveness of different SDM approaches including the use of decision aids.
- How to ensure that a patient understands the benefits, not just components, of knowledge.

These findings served as the starting point for subsequent discussion with external experts who were convened at an expert workshop on July 24, 2015. This workshop provided an opportunity for Brookings and FDA to develop the framework based on feedback from the assembled group of experts.

Meeting Objectives

Under a cooperative agreement with FDA, Brookings hosted an expert workshop on July 24, 2015 entitled, "Risk Evaluation and Mitigation Strategies (REMS): Building a Framework for Effective Patient Counseling on Medication Risks and Benefits." This workshop was intended to seek feedback on the findings from the literature review as well as solicit input into FDA's initial framework of principles and best practices that could be used to support effective counseling and may inform the development and use of REMS tools. Workshop participants included providers, decision aid developers, industry representatives, and academic experts in the fields of shared decision-making, health literacy, and benefit-risk communication. The full agenda and list of participating panelists are available here. A summary of the workshop discussion is outlined below.

Principles and Best Practices for Effective Patient Benefit-Risk Counseling and Shared Decision-making

Participants began the day's discussion by identifying a number of techniques, tools, and best practices regarding benefit-risk counseling, using the white paper as a starting point. Stakeholders also discussed a number of challenges that may hinder the adoption and implementation of these counseling strategies.

Communicating Risk

Much of the discussion focused on tactics regarding how best to communicate risks to patients. Participants agreed that a more fully grained and strategic approach to communication is

needed in order for benefit-risk counseling to be effective. Messages need to be communicated from multiple sources and in multiple ways over time in order for those messages to have an effect on a patient. Ideally, redundancy and interactivity should be built into the way benefit-risk messages are communicated. Several participants suggested that building a toolbox containing tools with different ways to communicate with patients over time and that reflect a patient's changing circumstances would be beneficial.

Participants also discussed the content of the communication apart from its format. There was broad agreement that the benefits as well as the risks of a drug needed to be included in counseling discussions, and that it will be necessary to find a way to balance the two. Participants noted that information on a drug's benefits often comes from the drug's label, so early patient engagement and patient-focused drug development upfront will be important for eventual conversations about a drug's benefits. Providers should also note that the patient may not experience any benefit from the drug at all and that the chances of a patient experiencing an adverse event with a drug may be uncertain. However, participants also noted that this would need to be done carefully given the possibility of "amplifying" people's risk aversion more than necessary. The question of what to communicate to the patient when there is only limited evidence of risks will also need to be addressed.

Stakeholders expressed additional concern that REMS regulations conflict with what is known about best practices for decision-making. Decision making should start with data, which becomes information, which then becomes knowledge. REMS tools are currently constructed to provide safety information to providers and patients, but this may not always be translated into the knowledge they need to decide to undertake and maintain behaviors consistent with safe use. When designing tools for REMS drugs, there will also need to be a clear explanation of where the threshold lies between discussing a drug's benefits and creating promotional materials for the drug. Translating real-world risks into understandable and useful information is daunting even in the absence of the regulatory challenges posed by REMS.

Decision Aids and Tools

Participants agreed that decision aids are an important tool in the benefit-risk counseling process but that several barriers exist to adapting them for drugs with a REMS. For example, most decision aids do not focus on one specific drug but instead encompass a range of options, which may not be applicable to discussions centered solely on a REMS drug. Drug sponsors do not currently play a role in the creation of most decision aids, but given the involvement sponsors play in the design and implementation of a drug's REMS program, they may need to take on the responsibility to help create decision aids around their products. Participants also discussed issues with implementing decision aids even if the decision aid itself is well designed. Additional work is needed to encourage providers to begin using decision aids and to keep using them consistently.

Participants also stressed that user testing is an essential part of the tool design process and suggested forming a standing panel of patients and providers to test and provide feedback on new tools.

Leveraging Existing Resources

Discussion also focused on how to bring other health care providers besides physicians into the counseling process and how to best leverage current tools and other pre-existing resources to support counseling. Participants agreed that more attention should be paid to the question of who is the best person to counsel a particular patient. Getting adequate time with a physician to talk through the benefits and risks of a drug can be difficult; other members of the health care team may be able to step in and fulfill this role. There was a general consensus that pharmacists and pharmacies in particular need to be included more and used more effectively in the counseling process, as they are often the last health care provider to have contact with a patient before they begin using a drug. It was also suggested that it may be possible to build a structural system that uses peers or family members to inform patients, guide them through the counseling process, and help them come to a decision.

Participants also suggested leveraging existing technologies to support counseling. One of the challenges in encouraging and improving benefit-risk counseling is how much autonomy providers have. While FDA cannot dictate to providers what they can or cannot say to their patients, it may be possible for electronic medical records (EMRs) to send automatic reminders to providers to talk with their patients about the benefits and risks of a drug their patients may be taking as a simple way to promote counseling. Other examples of existing technologies included the MAGIC app, which is a platform that helps turn health guidelines into decision aids and can be used by individuals to develop their own content. However, participants warned that just because such technologies are available does not mean they will be widely used, and suggested that a broader strategy to capture data on process, outcomes, and technology use is needed in order to effect behavioral and system changes.

White Paper Gaps and Clarifications

Participants agreed that the white paper provided a solid base regarding what is known about best practices for benefit-risk counseling but that there were several missing aspects. The paper did not go into detail about values clarification methods, even though clarifying a patient's values is an important part of the counseling process. Best practices for values clarification have been difficult to identify thus far, but an upcoming values clarification literature review may be able to provide additional information. Participants also noted that there is an updated version of the Cochrane review on decision aids that was heavily cited in the white paper, which will be published in the near future with more information about the effectiveness of decision aids in the counseling process.

Proposed Elements of a Benefit-Risk Counseling Framework

In the afternoon, a preliminary working draft of the benefit-risk counseling framework was presented as part of the day's proceedings, which laid out FDA's initial vision for a structured framework for developing benefit-risk counseling tools that can be used to support provider-patient counseling around drugs that have a REMS. The panel discussed desired outcomes for different stakeholder groups, potential guiding principles, and an initial set of best practices that were identified from the literature.

Translating Best Practices into a Benefit-Risk Counseling Framework: Key Challenges and Facilitators

Participants discussed a number of critical aspects of an effective counseling process that could be included in a FDA framework. Many participants cited a need to make the framework accessible to providers and patients rather than designing it only for use primarily by sponsors. As a part of this, several participants suggested that having the ability to tailor the language of the framework for specific diseases or conditions would be useful, though others warned that tailoring at the individual level may not be practical. Putting the framework online with an interactive website would give patients the opportunity to understand the context and basic concepts of benefit-risk counseling, and was suggested as another way to make the framework more patient-accessible. Other participants pointed out that the use of a "risk talk" curriculum—scripts and suggested language for providers to use with patients—has been successful in the past, and it may be beneficial to develop something similar as part of this framework.

Stakeholders agreed that building user testing into the framework itself as a part of how counseling tools are created will be vital to ensuring the quality and effectiveness of the tools that are subsequently developed. Allowing for periodic review and revision of the framework was also agreed to be of importance, as the data and understanding of how these tools work (or do not work) will change over time.

Participants also noted the many challenges that would need to be overcome in order for a framework to be implemented within the regulatory context of REMS. A number of these challenges stem from the manner in which elements of REMS programs are currently designed, as well as from the limits of FDA's authority under the statute. For example, a sponsor may not know that a REMS tool will be necessary until relatively late in the development and approval timeline, which may leave little time to develop and conduct end user testing of a decision aid before the drug is approved. In such cases, it may be necessary to develop and implement such tools in the post-market setting. Furthermore, it can be very challenging to ensure the uptake and effective use of REMS tools, as FDA does not regulate medical practice or provide formal training on effective counseling techniques. REMS programs also do not provide a comprehensive overview of a drug's benefit-risk profile; rather, they focus on specific risks associated with the drug that are considered more serious.

Participants also cited a need to better orient both providers and patients towards REMS at the start (i.e., to find a way to make it clear to both parties what a REMS is and why the counseling process is important). Participants also noted the challenge of communicating REMS benefit-risk information to other providers who may have contact with a patient besides the patient's prescribing physician. If a patient has an acute reaction to the drug, for example, they will likely go to an emergency room instead of their prescribing physician, and providers in the ER may not automatically have all of the relevant information about the risks of the REMS drug. There may be innovative ways to address this problem such as developing supporting tools like wallet cards that patients could carry with them to alert other providers that the patient is taking a high-risk drug.

Applying Best Practices to the Design and Implementation of a Benefit-Risk Counseling Support Tool(s) in REMS

Participants generally agreed that reconciling the specific risks of a drug with a REMS within the existing model for decision tools—which typically focus on a range of drugs rather than a single drug—will be challenging. However, they cited a number of areas where best practices could be incorporated when designing and implementing future counseling tools. For example, it may be possible to design a 'generic' REMS counseling tool that could then be modified and tailored to a specific REMS. There are existing DAs that could possibly be adapted to this purpose and then tested.

Participants emphasized the importance of taking into account the unique needs of patients who may have low literacy, numeracy, or graphical literacy when creating new tools. Using multiple different formats, such as videos with animations and audio in addition to paper handouts, may be particularly useful in ensuring that benefit-risk counseling tools are accessible to all types of patients. Other participants remarked that developing tools not only for use during benefit-risk counseling but that could also be used to prepare patients before they have that conversation with their provider would be useful. Having patients be more educated at the start of benefit-risk counseling could help them participate and make better informed decisions. Connecting patients with online support groups was also suggested as a possible method to improve patients' decision-making processes, though it was also noted that this should be done with caution as some support groups can be a source of misinformation.

Although shared decision-making was heavily discussed throughout the day for the potential value it may bring to benefit-risk counseling, several participants noted that it may be difficult to reconcile shared decision-making within the context of REMS and the regulations that govern them. Participants expressed some concern about mission creep; REMS materials are meant to be educational only and are not permitted to include any information that may be construed as persuading or promoting use of the REMS drug over other options. However, in talking about benefits as well as risks during the counseling process, it may be difficult to discern what is promotional content and what is not. Some participants suggested that it may instead be more

beneficial to focus on informed decision-making, whereby physicians and patients share information and come to an agreement on a preferred treatment option, or to concentrate simply on the idea of making counseling more interactive. Participants noted that it is possible to effectively communicate benefits and risks outside of the shared decision-making framework.

Participants also agreed that steps need to be taken to promote greater general awareness among providers about what REMS are and why they are important. This can help ensure that providers are properly equipped to talk to their patients about the benefits and risk of a drug with a REMS and to successfully help implement benefit-risk counseling tools. Increased standardization and automation of the process by which health care providers are reminded and encouraged to counsel their patients (by using pop-up reminders on EMRs, for example) will also help lead to smoother and more consistent implementation of benefit-risk counseling tools.

Next Steps

Moving forward, stakeholders requested FDA provide additional clarification on several issues. Participants agreed that further clarification is required on the role that a drug's sponsor may play, if any, in the creation and implementation of benefit-risk counseling tools for a drug with a REMS, and that FDA should clearly define where a sponsor's responsibilities in this regard begin and end. The role of shared decision-making in REMS programs also needs to be clarified further. Participants also stressed the need to have the specific goals of this initiative made clearer.

Many participants emphasized the need to bring additional stakeholders into the conversation. Patients in particular need to be brought into benefit-risk tool development to give feedback and help to ensure that the tools created meet their needs. Participants cited insurers as another stakeholder that could be incorporated into this work, perhaps by requiring patients to undergo education on the benefits and risks of a drug as a condition of using it. Some participants suggested that this project could be tied to Sentinel as part of that initiative's goal to, among other things, increase FDA's ability to monitor drug safety. Others noted that it may be beneficial to reach out to an organization such as the Patient-Centered Outcomes Research Institute and have them undertake a more rigorous study of this issue and how best to communicate benefits and risks to patients.

Overall, participants agreed that this issue, though complex, is an important one for FDA to address and were optimistic that with additional work this project can produce a useful framework for developing impactful benefit-risk counseling and tools.

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[1] Reinke, T. (2011). Stakeholders Say FDA Must Change REMS Program. *Managed Care.* Retrieved from http://www.managedcaremag.com/archives/1103/1103.medmgmt.html

[2] U.S. Department of Health and Human Services. (2005). *Guidance for Industry: Development and Use of Risk Minimization Action Plans.* Retrieved from http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf.

[3] U.S. Department of Health and Human Services. (2009). *Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications.* Retrieved from http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf.