U.S. FOOD & DRUG ADMINISTRATION

A Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS

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Executive Summary

The Food and Drug Administration (FDA) approves prescribing information for drugs, including information that health care providers (HCPs) can use to counsel patients about the indication to be treated and about the dosing, efficacy, and safety of the drug. For certain prescription drugs with serious risks, additional risk management steps are required to ensure that the benefits of using the drug outweigh the risks. These steps or activities can include risk communications, patient–provider agreements, and the use of other patient counseling tools. These requirements, which are designed to address a specific serious risk, may be approved by FDA as part of a Risk Evaluation and Mitigation Strategy, or REMS. When considering the use of a drug with a REMS, it is incumbent upon HCPs and patients to be aware that these drugs may warrant a higher level of understanding of the risks, a greater degree of vigilance, and/or the need to undertake a set of activities to ensure the benefits outweigh the risks. By using these approved risk mitigation strategies, HCPs and patients will help ensure that drugs with REMS are used safely.

FDA has developed a Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS to support HCPs who are considering prescribing, or are already treating patients with drugs that require a REMS. Development of the framework was guided by input from stakeholders and experts, who provided insights into the current state of patient counseling and risk communication. The framework outlines principles, best practices, and examples that help underscore the importance of taking an individualized and collaborative counseling approach when prescribing drugs with REMS, one that engages the patient, helps ensure a balanced conversation about both potential benefits and risks of a drug, and reinforces the patient's role in mitigating the risks when using such drugs.

The framework organizes best practices for effective counseling into four key domains: Evaluate, Educate, Engage, and Ensure. These domains (the 4 Es) are summarized here and discussed in greater depth in Section III D. A tool that can be used to help support their implementation is also provided in Appendix 6.

1. **Evaluate** (and continuously re-evaluate): Assess each patient initially and on an on-going basis to determine his/her individualized health profile, treatment goals, and counseling needs. Important factors to consider include those that could affect the potential benefits and risks of the drug to the patient and the patient's understanding and ability to adhere to the REMS requirements.
2. **Educate:** Inform each patient about his/her need for treatment and treatment options, including the potential risks and benefits of each, and the importance of understanding and adhering to REMS requirements. Tailor this discussion to the specific patient's individual health profile, treatment goals, and counseling needs.
3. **Engage:** Encourage and support the patient to be an active participant in his/her health care decisions, thereby enhancing the patient's level of involvement, understanding, and commitment to ensuring safe drug use. Activities can include discussing the treatment options in relation to the patient's goals and values, encouraging the patient to provide input and ask questions, and asking the patient to demonstrate his/her understanding.

4. **Ensure:** In the event that a drug with a REMS is prescribed, monitor and counsel the patient to reinforce key risk information and the steps required to help mitigate the risks in order to help those patients who may experience challenges adhering to the REMS.

While developing the framework, FDA recognized that benefit-risk counseling for drugs with REMS will be most effective if counseling methods can be learned and implemented consistently across all health care settings. Thus, the framework has been designed to provide broad educational considerations when developing and/or implementing benefit-risk counseling. The framework should also prove useful for HCPs who are counseling patients taking drugs that do not have a REMS.

It should be noted that the framework described herein, which is intended to support HCPs when counseling patients who are considering or taking drugs with a REMS, is separate from and should not be confused with FDA's draft "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making"[1]. The latter describes the framework used by FDA to support its regulatory benefit-risk assessments of drug products under review.

1 https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm329758.pdf

Introduction

An effective treatment outcome is the result, in part, of the patient's understanding of the basis for the treatment decision and his or her commitment and ability to properly follow the course of treatment, including using any prescribed drug safely. FDA recognizes that effectively counseling patients about the potential benefits and risks of a drug can help inform decisions about whether a patient should start or continue with a particular treatment. Counseling also enhances a patient's understanding of his or her role in the safe use of a drug.

Generally, patient counseling is the domain of the health care delivery system. Drug labeling includes prescribing information approved by FDA that health care providers (HCPs) can use for counseling patients on the safe and effective use of the specific drug. However, for certain drugs with specific serious risks, FDA may also require a Risk Evaluation and Mitigation Strategy (REMS).[2] Most REMS programs include communicating with and/or educating prescribers, dispensers, and/or patients about the serious risk(s) and the safe use conditions that should be maintained when using such a drug. Some REMS programs include tools that specifically support HCPs in providing this counseling.

At its core, effective patient counseling on drugs that have a REMS has the same goals as other counseling aimed at helping HCPs and patients select appropriate treatments and use them properly. However, when counseling about drugs with a REMS, effective counseling requires even greater emphasis, so that the serious risks are carefully considered and can be effectively managed.

Many HCPs already employ counseling techniques that reflect the need to effectively educate patients about how to safely use drugs with REMS. However, FDA and other stakeholders have recognized the need for more effective counseling to improve patient understanding of the balance of potential risks relative to benefits and to enhance patient adherence with REMS program requirements that ensure safe use.

The Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS, presented in this report, was developed to support implementation of more effective counseling practices by HCPs as they counsel patients on drugs that have a REMS. Through the framework described here, FDA hopes to help HCPs evaluate (and continuously re-evaluate) their patients' treatment and counseling needs; educate their patients about their medical condition and treatment options; appropriately engage their patients in the treatment decision-making process; and help to ensure their patients' safe drug use with respect to drugs that have a REMS. Following an overview of REMS, this report sets the background and context for developing the framework, then describes the framework itself and approaches to enhance its implementation.

I. Background On REMS And The REMS Benefit-Risk Counseling Initiative

When considering the use of a drug with a REMS, it is incumbent upon HCPs and patients to be aware that such drugs may warrant a higher level of understanding of the risks, a greater degree of vigilance, and/or the need to undertake a set of activities to ensure that a drug is used safely. The rationale for these

2 See section 505-1 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355-1.
https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/default.htm

additional steps is discussed here, followed by a description of the REMS benefit-risk counseling initiative and the development of the framework.

A. What is a REMS?

FDA can require a REMS to ensure that the benefits of certain drugs outweigh their risks; that is, without a REMS, the risks of such drugs would otherwise exceed their benefits.

A REMS is a safety program, comprising interventions that supplement approved product labeling, including prescribing information, that FDA may require to mitigate a known or potential serious risk associated with a drug or a class of drugs (see Appendix 1). REMS generally include goals that describe the overall, safety-related health outcome(s) that the REMS is designed to achieve, and other requirements for drug manufacturers and REMS participants. REMS participants are the stakeholders who have a role in the drug use[3] and distribution process and can include HCPs who prescribe, patients (their guardians or caregivers), health care settings, practitioners, pharmacies, and wholesalers/distributors. The REMS requirements may include communications to HCPs, training requirements for HCPs who prescribe or dispense the drug, limitations on drug prescribing and use, dispensing and distribution restrictions, and/or monitoring requirements or other conditions of safe use.

REMS communication materials may be used to help convey information about the serious risk(s), inform prescribing decisions, support patient counseling, and help HCPs establish and reinforce safe use conditions and behaviors. A comprehensive discussion of REMS and examples of various REMS requirements, can be found in Appendix 1.

B. What a Drug With a REMS Means for HCPs and Patients

A REMS is not intended to provide general information about a drug—that information is already described in the FDA-approved prescribing information. Additionally, a REMS may not address the complete safety profile of the drug. Instead, a REMS is designed to convey focused information about a drug's particular serious risk(s). A drug with a REMS may have adverse reactions that are addressed in the prescribing information, but are not the focus of the REMS.

REMS can vary in their design because each REMS has specific safety measures intended to address the serious safety risks associated with a particular drug or class of drugs. Although all REMS communicate information about a drug's serious risk(s), certain REMS have additional requirements included to help assure safe use conditions and decrease the frequency or severity of the serious adverse event that the REMS is intended to mitigate. For example, a REMS program might require that the patient and HCP use a Patient–Provider Agreement before beginning treatment to formally document safe use conditions and ensure that both understand the specific serious risk(s) the REMS is addressing. Other REMS may require verification that training has been completed by the HCP, or that certain conditions of safe use, such as required laboratory monitoring, are in place before a prescription for the drug can be filled or refilled.

3 For the purpose of the document, the drug use process involves clinical assessment, prescribing, dispensing, administration, and monitoring.

FDA has the authority to require a responsible person, which may include a drug manufacturer, to design and implement a REMS to mitigate a serious risk associated with a drug. However, the effectiveness of the REMS may ultimately depend on HCPs adopting and incorporating the REMS into clinical practice. To perform to their fullest effectiveness, REMS may depend on HCPs to carry out the functions of the REMS and support the patient in understanding and mitigating the risk(s) that the REMS is designed to mitigate.

C. Patient Counseling as Part of REMS

The HCP plays a pivotal role in supporting the patient in (1) understanding the risks of a drug and the associated REMS program, (2) assessing and explaining a drug's potential risks in the context of its potential benefits to the patient, and (3) fulfilling REMS program requirements and reinforcing patient understanding and adherence to maintaining safe use conditions.

REMS programs use a variety of counseling tools[4] to help HCPs communicate with and educate patients about serious drug risk(s) (see Appendix 2). These tools are intended for use during HCP–patient interactions to help support understanding of the specific risk(s) that the REMS is intended to mitigate. Key topics addressed by REMS program patient counseling can include the drug's indication, the serious drug risk(s) being addressed by the REMS, the signs and symptoms of the serious adverse reaction, instructions for safe use, and any necessary monitoring requirements under the REMS program. As noted, REMS counseling tools may not provide comprehensive information about the overall safety profile of a drug, and, apart from the approved indication, they do not discuss the potential benefits of a drug. As such, existing REMS counseling tools may not, on their own, provide a means to ensure that a comprehensive discussion between the HCP and patient about a drug's benefits and risks occurs.

However, recognizing the importance of discussing both benefit information and safety information about treatment options in helping to make an informed treatment decision, the Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS presented here is intended to support HCPs in engaging with their patients in a more comprehensive tailored counseling conversation about drug benefits, safety, and any REMS requirements.

D. The Benefit-Risk Counseling in REMS Initiative

This initiative was the result of FDA's Prescription Drug User Fee Act reauthorization of 2012 (PDUFA V) commitments and the goal of evaluating and improving FDA's implementation of its REMS authorities.[5] In July 2013, FDA held a public meeting, Standardizing and Evaluation of Risk Evaluation and Mitigation Strategies, to seek feedback from stakeholders on potential projects that could help to standardize REMS and better integrate them into the health care system.[6] Based on stakeholder input, FDA developed a preliminary work plan for providing benefit and risk information through counseling to patients as part of a REMS.

4 For purposes of this document, the term REMS tool is used to describe any materials, processes or system designed to operationalize one or more REMS requirements.

5 PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017. http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

6 Meeting materials are available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm351029.htm.

The work plan was presented to FDA's Risk Communication Advisory Committee in December 2013 to seek their feedback on existing and potential new approaches to counseling patients about drugs' risks and benefits in REMS.

In September 2014, FDA released its report, Standardizing and Evaluating Risk Evaluation and Mitigation Strategies, which described in depth four priority projects as part of the REMS Integration Initiative, including the Benefit-Risk Counseling Framework project.[7] This project included a literature review of published research on effective health care counseling practices to begin developing an evidence-based framework of desired outcomes, principles, and best practices to support effective counseling. Using previous risk communications research and publications as a foundation,[8] FDA evaluated subsequent literature, concentrating on findings from systematic reviews and meta-analyses. The Brookings Institution, in collaboration with FDA, developed a white paper[9] synthesizing the literature review and identifying gaps in knowledge.

In July 2015, FDA participated in an expert workshop held at The Brookings Institution to obtain feedback on effective counseling processes, practices, techniques, and tools.[10] FDA synthesized the information from this workshop, conducted subsequent outreach calls, and participated in a follow-up meeting held at the Duke-Margolis Center for Health Policy with an extended set of health care stakeholders in April 2016 to refine and validate the counseling framework.[11]

II. Setting The Context For Benefit-Risk Counseling

The Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS focuses on supporting HCPs when they are counseling patients who are being considered for, or who are being treated with, a drug with a REMS. The serious risks of these drugs may necessitate additional communications by the HCP to help support a higher level of patient understanding about the potential benefits and risks of different treatment options, as well as reinforcement of the need for greater vigilance to emerging symptoms of a serious adverse event and the importance of adherence to REMS requirements. A more active patient role may be required when making treatment decisions, and additional steps may be needed to make sure patients understand how to use a drug safely.

In the context of this framework:

- Counseling encompasses the broad range of interactions between a patient and his or her HCP that occur beginning with educating the patient about his or her condition and selecting treatment options and continuing throughout the duration of the patient's use of the selected treatment and/or other treatment options.

7 Draft report: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS), available at http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm415751.pdf.
8 Fischhoff B, Brewer NT, Downs JS, Eds. 2011. Communicating Risks and Benefits: An Evidence-Based User's Guide, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM268069.pdf.
9 Risk Evaluation and Mitigation Strategies (REMS): Building a Framework for Effective Patient Counseling on Medication Risks and Benefits, available at https://www.brookings.edu/wp-content/uploads/2015/08/REMS-BenefitRisk-communication-white-paper.pdf.
10 Meeting materials are available at https://www.brookings.edu/events/risk-evaluation-and-mitigation-strategies-rems-building-a-framework-for-effective-patient-counseling-on-medication-risks-and-benefits/.
11 Meeting materials are available at https://healthpolicy.duke.edu/events/risk-evaluation-and-mitigation-strategies-improving-benefit-risk-counseling-between-providers.

- Treatment decision-making encompasses consideration of the range of possible options in the course of managing a condition, which may include whether to initiate, maintain, modify or stop treatment, based on patient response.
- Patient, in this context, refers to any individual who is contemplating medical treatment to treat or prevent a condition. The term may also extend to include caregivers, as appropriate (e.g., a parent involved in decisions about treatment for a child).
- HCP includes any individual involved in the treatment of patients (e.g., physician, nurse, pharmacist) who may have a role in counseling a patient on his or her treatment needs, options, drug risks, and safe drug use.

The following scenarios were envisioned during the development of this framework. They provide three examples of situations involving making treatment decisions that include a drug with a REMS, when an enhanced counseling approach could be undertaken.

Scenario 1: A patient newly diagnosed with a progressive chronic condition, such as multiple sclerosis or pulmonary hypertension, has been referred to a specialist.

Based on this HCP's assessment of the patient's history and current disease state, the HCP believes that a drug with a REMS may be the best treatment for this patient, but the HCP would consider alternative treatment option(s) for this patient based on the patient's treatment goals, their understanding of, and their ability to participate in the REMS.

Scenario 2: A patient with a symptomatic condition that is not life-threatening, such as severe acne, has been treated by his or her general HCP for over a year and has tried multiple therapies.

The patient feels that the symptoms have not been adequately controlled and would like to consider other treatments. Alternative products that have a REMS are approved to treat this condition. The HCP has not previously considered alternative therapy for this patient, but is now willing to discuss the benefits and risks of treatment using a drug with a REMS as one possible treatment option.

Scenario 3: A patient is currently being treated with a drug with a REMS, but is having difficulty keeping appointments for scheduled laboratory testing.

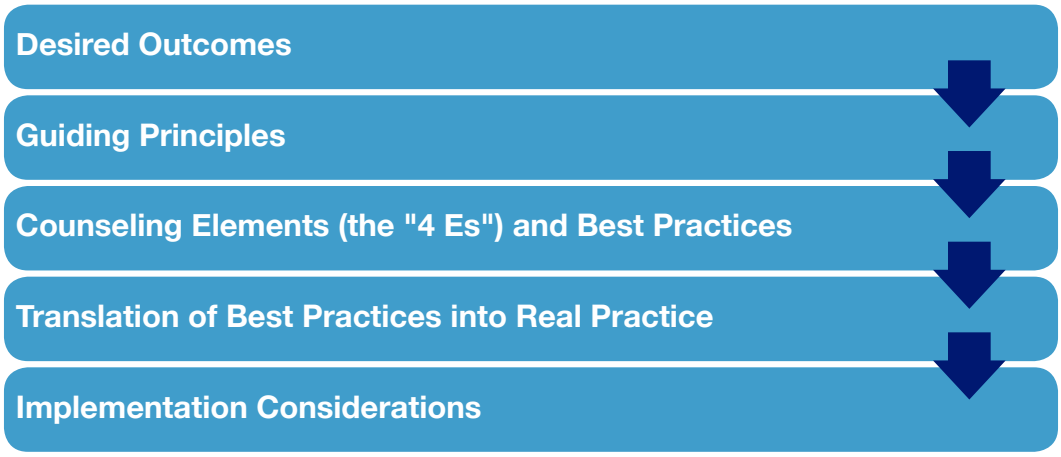
The HCP, seeing the patient for a scheduled follow-up appointment, reassesses both the benefits of the drug and the reasons behind the patient's noncompliance. The HCP discusses other possible treatment options with the patient and counsels him or her about those treatment options.

III. A Framework For Benefit-Risk Counseling

A. Elements of the Framework

FDA developed this framework for counseling patients about potential benefits and risks when the treatment option being considered, started, or maintained includes a drug that has a REMS. The framework (see Figure 1) describes a set of desired outcomes from the implementation of effective counseling by various stakeholders and guiding principles and best practices for achieving those outcomes. The framework recognizes and introduces potential approaches to translating the framework for incorporation into the treatment process, as well as other implementation considerations.

Figure 1: A Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS



B. Desired Outcomes

FDA began developing the framework by first identifying a set of potential desired outcomes, or aspirational results, of counseling about the benefits, risks, and requirements of drugs with a REMS. These desired outcomes are organized and described below by the groups—most notably patients and HCPs—who have a stake in the outcomes of implementing effective counseling practices. FDA also considered potential desired outcomes (both direct and indirect) of health care systems with a stake in effective counseling. Desired outcomes were shared and then refined during discussions at public workshops with stakeholders.

Desired Outcomes for Patients

- The patient feels that he or she is able to participate in and contribute to the treatment decision-making process.
- The patient feels sufficiently informed about why treatment is needed and what he or she may expect in terms of the potential benefits relative to the serious risk of a drug that the REMS is intended to mitigate, as well as the benefits and risks of alternative treatment options (including no treatment), taking into account his or her individual health profile, values, and preferences.
- The patient understands the treatment decisions (including the initial treatment decision and any subsequent treatment decisions) while taking a drug with a REMS and feels the decisions are right for him or her.

- The patient knows what to do while on treatment and is confident that he or she will be able to do what is necessary to minimize the risks and realize the benefits of a drug with a REMS.
- In the event that the patient takes a drug with a REMS, the patient understands the need to periodically re-assess his or her treatment experience (including his/her individual benefits and risks) with the HCP to help make informed decisions about continuing or adjusting treatment.

Desired Outcomes for HCPs (e.g., those providing counseling; including prescribers, nurses, physician's assistants, pharmacists, care coordinators, counselors)

- The HCP is able to elicit the individual patient information he or she needs (including patient's values) to assess and effectively counsel each patient on the potential benefits and risks of the recommended and alternative treatment options for that patient.
- The HCP is confident that the patient (1) understands the risks and benefits of the recommended and alternative treatments; (2) understands instructions, precautions, and steps needed to take the drug appropriately; and (3) is able to adhere to the safe use conditions established in the REMS.
- The HCP is confident that treatment decisions are appropriate for the patient.
- The HCP is able to obtain the reliable patient feedback needed to reassess the patient's benefit-risk profile while on treatment (e.g., treatment response, adverse events) to be able to make appropriate treatment adjustments and to effectively counsel the patient.

Desired Outcomes for Health Care Systems

- The health care system's standards of providing high-quality patient care throughout the duration of treatment are supported by maintaining consistent standards of counseling practice across all HCPs.
- HCPs and patients are supported with processes, support systems, information, tools, and technologies that assist them in using drugs with REMS safely.

C. Guiding Principles

With these desired outcomes in mind, FDA next identified five guiding principles, or standards, that served as the basis for developing the framework. The guiding principles highlight the importance of establishing an early and ongoing dialogue between the HCP and patient, the need to tailor counseling to the individual patient, and the importance of active patient involvement in the process of treatment decision-making and ongoing monitoring. These principles are summarized here and discussed further in Appendix 3.

A Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS: Guiding Principles

Principle 1: Counseling is a necessary activity. It is essential for counseling discussions to take place between a HCP and patient about potential benefits and risks when a drug that has a potential serious risk requiring a REMS is a treatment option and patient understanding or actions are needed to ensure safe use.

Principle 2: Counseling should be ongoing. Effective counseling is a dynamic process that starts with the initial assessment of the patient and should be reinforced at subsequent patient-HCP interactions.

Principle 3: Counseling should support collaborative informed decision-making. It should support making informed treatment decisions by a patient and HCP and follow a process of active patient engagement and participation. It should be based on potential benefits and risks, as well as a mutual understanding of patient and HCP obligations under the REMS for appropriate and safe use.

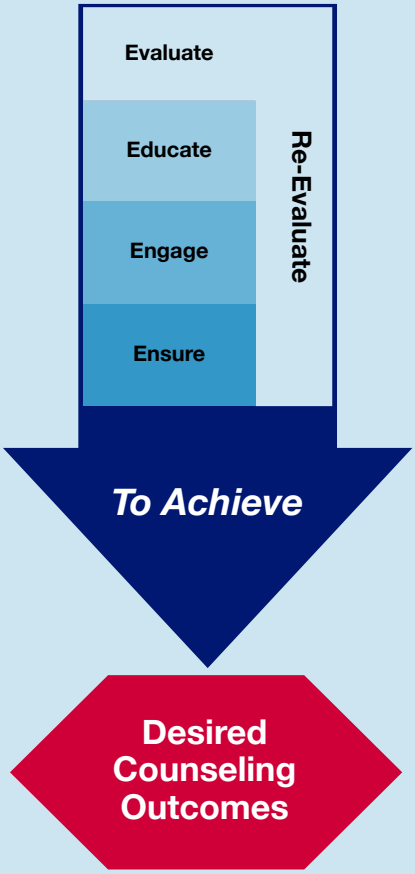
Principle 4: Counseling should be individualized. The counseling discussion about the potential benefits relative to risks of different treatments should be individualized to the patient's profile, considering their needs and preferences.

Principle 5: Counseling should reflect evidence-based and/or best practices and tools. Counseling about drugs with REMS should incorporate techniques, decision support tools, and other resources for effective risk communication and health care counseling.

D. Counseling Best Practices: Evaluate, Educate, Engage, and Ensure (The 4 Es)

Consistent with these desired outcomes (Section III B, above) and guiding principles, the framework identifies best practices for counseling about potential benefits and risks of drugs with REMS. These have been organized into four domains, or elements of effective benefit-risk counseling, that HCPs should consider undertaking whenever they are counseling patients who are either considering or taking drugs with REMS. Figure 2 is a schematic of the four elements of effective benefit-risk counseling for drugs with REMS (4 Es).

Figure 2: The 4 Es for a Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS



The 4 E's for a Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS

Evaluate the patient's health profile, potential treatment options, and counseling needs. Continuously re-evaluate against desired outcomes.

Educate the patient on his or her health condition and treatment options – their benefits, risks, and steps needed to minimize risks (safe use conditions).

Engage and support the patient in the treatment decision-making process to the extent that is possible and to the extent that he or she desires.

Help to **Ensure** that the patient understands and is able to adhere to the REMS requirements. If a drug with a REMS is prescribed, re-evaluate at follow-up the patient's experience with treatment and REMS requirements.

Desired outcomes for the PATIENT:

- Able to contribute to the treatment decision-making process
- Informed about treatment needs and treatment options
- Confident in ability to adhere to the REMS requirements
- Feels that decisions are right for him or her
- Understands the need to reassess his or her treatment experience over time

Desired outcomes for the HEALTH CARE PROVIDER:

- Able to elicit information needed to effectively assess options and counsel
- Confident that the patient understands treatment options and can adhere to the REMS requirements
- Feels that decisions are appropriate for the patient
- Able to make informed decisions about continuing or adjusting treatment

HCP use of these four counseling elements is intended to be flexible and individualized. The relative emphasis of the elements and the sequence of their use should be tailored to each patient's needs and the relevant treatment scenario. For example, some aspects of evaluation may precede education, while other aspects, such as evaluating patient understanding may also be appropriate following education.

Each of the four counseling elements is described in further detail here. A tool for tracking progress, with potential examples and techniques to consider applying as best practices, is provided in Appendix 6.

Four Elements of the REMS Benefit-Risk Counseling Framework

REMS Benefit Risk-Counseling Framework: The 4 Elements

✔ Evaluate ✔ Educate ✔ Engage ✔ Ensure

1. **Evaluate** – when considering or prescribing a drug with a REMS, each patient should be assessed initially and on an ongoing basis. This assessment should encompass factors that could affect the potential benefits and risks to the patient, the treatment decision, and the patient's understanding and ability to adhere to the REMS requirements.

   The HCP should consider conducting the following assessments as part of the ongoing counseling process:

   - Identify potential benefit(s) and risks of different treatment options and patient-related factors that may affect patient outcomes
   - Identify non-clinical and/or practical factors that could affect the treatment decision
   - Assess the patient's level of understanding
   - Identify areas where the patient could benefit from additional counseling
   - Assess the patient's treatment goals

2. **Educate** – when considering or prescribing a drug with a REMS, inform the patient about all treatment options, potential benefits and risks of each treatment option, and any REMS requirements. Tailor education to each individual to maximize patient understanding.

   The individualized counseling discussion should include the following, based on approved product labeling, the patient's profile and REMS obligations:

   - Potential drug benefits for the patient
   - Potential harms of the drug
   - Any important uncertainties
   - Considerations on how to determine if the potential benefits are expected to outweigh the risks for the individual patient
   - Steps or actions the patient needs to take to reduce the risk(s)

Counseling should also educate the patient about the REMS program, including:

- The purpose of a REMS
- Key risk messages from the REMS about the adverse event(s) of concern
- The elements of the specific REMS program for the prescribed drug and the patient's role in maintaining safe use conditions
- REMS tools that are available to the patient to support their education, understanding, and compliance

3. **Engage** – Counseling patients about drugs with serious risks and REMS requirements will be most effective if the HCP both encourages and supports the patient to become an active participant in treatment decision-making, thereby enhancing the patient's level of ownership, understanding, and commitment to ensuring safe drug use. The scope of engaging the patient can include discussing patient goals and values, encouraging the patient to share information and ask questions, checking and asking the patient to demonstrate understanding, and having the patient assume an active role in the process.

   One approach to engaging the patients and enhancing their role, particularly relevant when the HCP does not recommend any one particular treatment option, is to use a shared decision-making (SDM) approach.

Shared decision-making (SDM) is when a HCP and a patient work together to make a health care decision that is best for the patient.

The optimal decision takes into account evidence-based information about available options, the provider's knowledge and experience, and the patient's values and preferences. [12]

FDA both reviewed the SDM literature and discussed with stakeholders which SDM techniques could potentially be readily adopted by HCPs while minimally impacting their practice workflow. Among various SDM approaches, a practical step-wise approach has been described, [13,14] in which the HCP and patient undertake a collaborative process of sharing evidence and then the HCP supports the patient in considering options and making an informed choice.

When encouraging active patient participation and/or SDM, the HCP should:

- Explicitly convey to the patient that a treatment decision will need to be made and, when appropriate, the HCP's desire for active patient participation in the decision-making process.
- Encourage questions and give patients the opportunity to describe themselves, to express their communication needs, values, and desired outcomes and to identify areas of patient interest, concern, and/or sensitivities.
- Assist the patient in determining which treatment options are most concordant with the patient's own goals and values.
- Understand the patient's initial assessment of treatment options and preferred treatment choice, once the patient has reviewed relevant aspects of the drug with a REMS and possible alternatives.
- Check to actively confirm patient understanding; provide opportunities for the patient to express to the HCP his or her own understanding of the information.
- Formulate an overall assessment and recommendation(s) of treatment, and the basis for that recommendation, ideally relating this assessment and recommendation to the patient's goals, values, and preferences.

12 SHARE Approach Workshop. Content last reviewed September 2016. Agency for Healthcare Research and Quality, Rockville, MD., available at http://www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/workshop/index.html.

13 Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, Cording E, Tomson D, Dodd C, Rollnick S, Edwards A, Barry M. Shared decision making: a model for clinical practice. J Gen Intern Med. 2012 Oct;27(10):1361-7. Epub 2012 May 23. Review.

14 Elwyn G, Lloyd A, May C, van der Weijden T, Stiggelbout A, Edwards A, Frosch DL, Rapley T, Barr P, Walsh T, Grande SW, Montori V, Epstein R. Collaborative deliberation: a model for patient care. Patient Educ Couns. 2014 Nov;97(2):158-64. doi: 10.1016/j.pec.2014.07.027. Epub 2014 Aug 13.

- Determine and consider the patient's level of comfort with the recommendation, their role in mitigating risks, including the patient's ability to administer the drug, follow instructions around safe use, and maintain adherence to the regimen and safe use conditions, given the patient's understanding of his or her health profile, treatment goals, values, and preferences.
- Confirm the treatment decision or the decision to defer treatment.
- Help the patient identify and overcome potential or actual REMS burdens.
- In some cases, further information or consultation with other HCPs, the patient's family, etc. may be required before a decision can be made. In such cases, the HCP should explicitly acknowledge that the decision will be deferred until a follow-up visit, when more information has been gathered.

4. **Ensure** – At follow up visits, the HCP should counsel patients taking drugs with REMS to reinforce key risk messages, REMS information, and the need for patient actions to help effectively mitigate the risks. This may include recommunicating and supporting patients' understanding of the following:
   - Key risk messages from the REMS.
   - Signs and symptoms of the serious adverse events of concern that may emerge and that need to be reported to the HCP.
   - The patient's role in adhering to their obligations under the REMS program requirements.
   - Any next steps towards fulfilling previous or ongoing REMS program requirements, if applicable.
   - Specific aspects of the patient's reported benefits and risks while on treatment (e.g., improvements in functioning, tolerability issues) that could affect the HCP's assessment and warrant adjustments to the treatment regimen.
   - The treatment decision and any recommended changes based on the patient's reported burdens and/or barriers to complying with the REMS and their ability to address them.
   - Offering relevant materials and/or additional instructions the patient can refer to at home.
   - Creating opportunities for reviewing prior decisions at follow-up appointments, as patient circumstances, values, and preferences may change over time.
   - Seeking out additional areas of interest, any misunderstandings and/or concerns from the patient about serious adverse event risks and the REMS program.

IV. Implementing the Framework

A. Translating the Framework into Practice

An important component of the framework is demonstrating how the best practice elements identified in the conceptual framework could be translated into the real world practice of HCP counseling within the clinical setting. Based on the scenarios presented in Section III, two examples illustrating potential tools that could help HCPs implement the Benefit-Risk Counseling Framework were developed:

- The first example (Appendix 4) is an overall counseling guide illustrating the types of assessments, topics, and questions that could be addressed using the framework.
- The second example (Appendix 5) is a mock discussion guide illustrating questions the HCP may find useful during the process of counseling to help ensure patient adherence to the REMS.

These examples are, by design, high-level and not specific to any particular drug or REMS program. FDA envisions that these examples, or others, could be adapted by educators, counseling tool developers, and/or health care systems administrators. They can be used to develop processes, support systems, and/or more targeted tools that, in turn, can help support counseling by HCPs, within the context of specific drugs or REMS programs, patient populations, or health care systems.

B. Other Implementation Considerations

FDA recognizes that counseling will be most effective if it can be readily implemented and reinforced consistently across various health care delivery settings by different HCPs. However, HCPs may face potential challenges when counseling patients who are being considered for, or treated with, a drug with a REMS. Likewise, patients may face challenges in understanding and implementing the counseling recommendations. To support consistent implementation, stakeholders and organizations, including HCPs, health systems, associations, and medical groups, should consider strategies that can help anticipate and overcome some of these challenges.

Stakeholders have suggested potential approaches that could be useful, including:

- Anticipate and mitigate HCPs' time and resource constraints
  - » Consider using other HCPs in the health care practice setting to support benefit-risk counseling efforts
  - » Stage counseling discussions to take place over one or more treatment visits
  - » Develop and use ancillary resources, counseling tools, and REMS materials to support and reinforce counseling messages
- Adapt processes and systems to help facilitate ease of use of REMS counseling messages and materials within the patient care process workflow
  - » Use electronic medical record technology platforms to cue counseling messages, scripts, and REMS program requirements at the point of care when patients are being prescribed drugs with REMS

- Foster the development of effective REMS counseling skills and techniques to help address and support the learning needs of less experienced HCPs
  - » Develop and provide reading materials, training videos, and other counseling support resources
  - » Provide additional education and training opportunities for HCPs to develop and refine their counseling skills and expertise, including applying the process of SDM
- Provide incentives for HCPs to undertake the necessary steps to become more proficient at providing benefit and risk counseling
  - » Establish health care quality indicators around REMS benefit and risk counseling to help incentivize adoption and implementation of counseling processes
  - » Make continuing education training programs available to encourage HCPs to develop skills and adopt more effective counseling methods
  - » Establish metrics and measurement systems to assess the effectiveness of REMS counseling, identify gaps, and encourage continuous improvement
- Encourage patient interest and active participation in the REMS counseling process
  - » Develop educational materials to help explain REMS and the importance of patient participation in REMS counseling
  - » Provide information, materials and other resources to support patient understanding and involvement in SDM

Appendix 6 is a tool that includes potential examples and techniques that could be used to support counseling implementation

Conclusion

This document describes a basic framework for counseling patients who are being considered for, or are being treated with, a drug with a REMS. The counseling framework is based on a flexible, individualizable, collaborative approach. HCPs can use this framework, examples, and tools to help ensure that their patients receive the information they need about potential benefits and risks; are well-informed; and are able to make, understand, and comply with decisions about their drugs with REMS and use them safely.

Counseling will be most effective if it can be readily implemented and consistently reinforced across various health care delivery setting by different HCPs. Because of its flexible design, the framework is intended to support various stakeholders (e.g., health care systems, educators, others) to develop and implement processes, support systems, and/or counseling tools for HCPs and patients.

Appendix 1: REMS Description

The Food and Drug Administration Amendments Act of 2007 (FDAAA) created section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which authorizes FDA to require a REMS for certain drugs if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks.

FDA can require a REMS before initial approval of a new drug application or, should FDA become aware of new safety information about a drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks, after the drug has been approved.

All approved REMS include one or more risk mitigation goals and include the necessary requirements to help ensure that the benefits of a drug outweigh the risks as determined by FDA.

Responsible persons, which may include sponsors and drug manufacturers, develop a REMS program based on requirements specified by FDA, which can include one or more of the following elements: :

- A Medication Guide or a Patient Package Insert
- A communication plan directed towards health care providers (HCPs)[15]
- Elements to assure safe use (ETASU),
- An implementation system to monitor and evaluate implementation

All REMS are required to include:

- A timetable for submission of assessments.[16] REMS assessments are conducted by the responsible person and reviewed by FDA.

REMS with ETASU may require that HCPs, patients, or other stakeholders take certain actions before prescribing, dispensing, administering, or receiving a particular drug. The ETASU can include one or more of the following:

- HCPs who prescribe the drug have specific training/experience or be specially certified
- Pharmacists, practitioners, or health care settings that dispense the drug be specially certified
- Drug be dispensed only in certain health care settings (e.g., infusion centers, hospitals)
- Drug be dispensed with evidence or other documentation of safe-use conditions such as laboratory test results
- Each patient using the drug be subject to monitoring
- Each patient using the drug be enrolled in a registry

FDA recognizes that REMS, particularly REMS with ETASU, may impose additional steps on the health care delivery system and could affect patient access. Consistent with the statute, FDA works to minimize the burden on patient access and the health care delivery system to the extent practicable.[17]

15 Abbreviated new drug applications (ANDAs) are not required to have communication plans.

16 ANDAs are generally not required to have a timetable for submission of assessments.

17 See section 505-1(f)(2) of the FD&C Act

Appendix 2: REMS Counseling Tools

Medication Guide

A Medication Guide is patient labeling provided to the patient at the time of dispensing and is approved as part of a product's labeling. FDA can require a Medication Guide if FDA determines one or more of the following:

- The drug product is one for which patient labeling could help prevent serious adverse effects.
- The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
- The drug product is important to health and patient adherence to directions for use is crucial to drug's effectiveness.[18]

A Medication Guide may be included as an element of a REMS if FDA determines it is necessary to ensure that the benefits outweigh the risks. The Medication Guide is designed to communicate the drug's most important information, including any boxed warnings or warnings and precautions associated with the drug and how to use the drug safely.

Unlike other patient educational materials in REMS, Medication Guides typically include information on a drug's major risks—not just the risks that are being addressed by the REMS.

Typically, a Medication Guide is given to a patient at the time the drug is dispensed; however, if a REMS includes a Medication Guide as an element of the strategy, the REMS program may require prescribers to review the Medication Guide with patients at the start of therapy to ensure patients are aware of the information provided in the Medication Guide.

Patient Counseling Document

A patient counseling document is intended to provide an HCP with a counseling tool that can facilitate an interactive dialogue with the patient at the start of therapy about the serious risk the REMS program intends to mitigate. A patient counseling document includes the key information about the risk addressed by the REMS found in the labeling that should be communicated to patients and may include a blank area for inclusion of information specific to the individual patient. For ease of use, the counseling document is often limited to one page; however, this may not always be the case, depending on the number and types of key messages that should be conveyed to a patient. A counseling document generally does not include benefit information or a comprehensive description of the known risk profile of the drug.

Prescriber-Directed Counseling Tool

A prescriber-directed counseling tool provides an HCP with the key messages about the serious risk the REMS program intends to mitigate. Although this tool includes information in patient-friendly language, it is intended to help the HCP prepare for effective patient counseling at the start of therapy. The prescriber-directed counseling tool may be a stand-alone tool, or included as a tool in the educational materials for

18 Medication Guides, http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm.

HCP. Like many of the other counseling tools, a prescriber-directed counseling tool generally does not include benefit information or a comprehensive description of the known risk profile of the drug.

Prescriber–Patient Agreement

A prescriber–patient agreement documents that patient counseling was provided by the prescriber to the patient and captures the minimally necessary topics a prescriber must convey to a patient. Documentation of counseling is captured by a signature from both the prescriber and patient at the start of therapy and often requires the prescriber to provide a copy to the patient and/or maintenance of the completed document in the patient's medical records. Additionally, a prescriber–patient agreement may include questions specific to the patient's medical history or health status to assist the prescriber in the screening of appropriate patients and/or the approved indication(s) for the drug. Like many of the other counseling tools, a prescriber–patient agreement generally does not include a comprehensive description of the known risk profile of the drug.

Patient Treatment Continuation Form

A patient treatment continuation form is intended to document that a prescriber has determined that the benefits of the drug continue to outweigh the risks the REMS is designed to mitigate for an individual patient. The form is generally completed on an ongoing basis after the start of therapy to ensure continued monitoring of the patient's clinical status. Some patient treatment continuation forms may also require the prescriber to provide ongoing counseling to make sure the patient is adequately informed throughout the duration of treatment. Like many of the other counseling tools, a patient treatment continuation form generally does not include benefit information or a comprehensive description of the known risk profile of the drug.

Appendix 3: Key Principles of Benefit-Risk Counseling for Drugs with a REMS

Appendix 3 describes FDA's perspectives on certain key principles that helped guide the development of this framework, including the identification and selection of best practices, materials, tools, and training that will support effective HCP patient counseling about benefits and risks of drugs with REMS.

Principle 1: It is essential for counseling discussions to take place between an HCP and patient about potential benefits and risks when a drug that has a potential serious risk requiring a REMS is a treatment option.

Counseling about potential benefits and risks should take place regardless of whether there is a specific REMS tool or a requirement for counseling as a formal component of the REMS program. This counseling about the benefits and risks of different treatment options is essential when one of the treatment options has a serious risk requiring a REMS and patient understanding or actions are needed ensure safe use.

Principle 2: Effective counseling is a dynamic process that starts with the initial assessment of the patient and should be reinforced at subsequent patient-HCP interactions.

The counseling process begins with an interactive discussion between the HCP and the patient to both assess the patient and make a shared treatment decision. The assessment and decision are based on potential benefits and risks as they pertain to each patient, the patient's values and preferences, and the patient's understanding of the drug with a REMS and alternative treatment options.

Counseling to educate and reinforce patient understanding of a drug with a REMS should continue and be reinforced while the patient is on treatment, including when adjusting or discontinuing the drug and REMS. However, as treatment progresses and some uncertainties about potential benefits and risks are clarified or eliminated, the nature of counseling should evolve accordingly.

Principle 3: Counseling should support making informed treatment decisions by a patient and HCP, following a process of active patient engagement and participation. It should be based on potential benefits and risks, as well as a mutual understanding of patient obligations and need for adherence with the REMS to support appropriate and safe use.

This approach for engaging the patient is encouraged to maximize patient participation, as both patient understanding and adherence to REMS requirements are essential to establishing and maintaining safe use conditions.

When there is not one clinically preferred treatment option, the HCP may want to undertake a shared decision-making approach. Shared decision-making is a process whereby an HCP and patient determine that a decision is required and share best available evidence for risks and benefits of each alternative option while considering both the HCP's guidance and the patient's preferences and values. An informed decision is an outcome that has been reached once a patient understands the risks and benefits, has considered his or her preferences, and has participated in the decision to the level desired.

In some cases, a more directive counseling approach may be required, for example, when counseling is needed to address REMS program non-compliance to reinforce the importance of maintaining conditions of safe use.

Principle 4: The counseling discussion about the potential benefits relative to risks of different treatments should be individualized to the patient's profile, considering their needs and preferences.

Counseling should be based on each patient's individual potential treatment benefits and the risk factors for adverse events from the drug with a REMS as well as alternative options. Of particular importance, the patient's individual values, treatment goals, and preferences should be elicited, rather than assumed. Furthermore, patient understanding of, and their capacity to maintain, safe use conditions must be considered, as well as any prior experience the patient has had from any of the treatments being considered.

HCPs are encouraged to discuss and counsel on a spectrum of counseling topics, using techniques, best practices, and tools that have shown evidence of effectiveness in optimizing patient understanding, promoting patient involvement in decision-making, and fostering adherence to the selected treatments and/or activities needed to ensure safe use of drugs.

As appropriate, REMS materials should be used by HCPs to communicate with or educate patients about the REMS-related serious risk information and REMS program requirements. However, since REMS materials do not include information about the potential benefits of the drug or about benefits and risks of other treatment options, these should also be discussed.

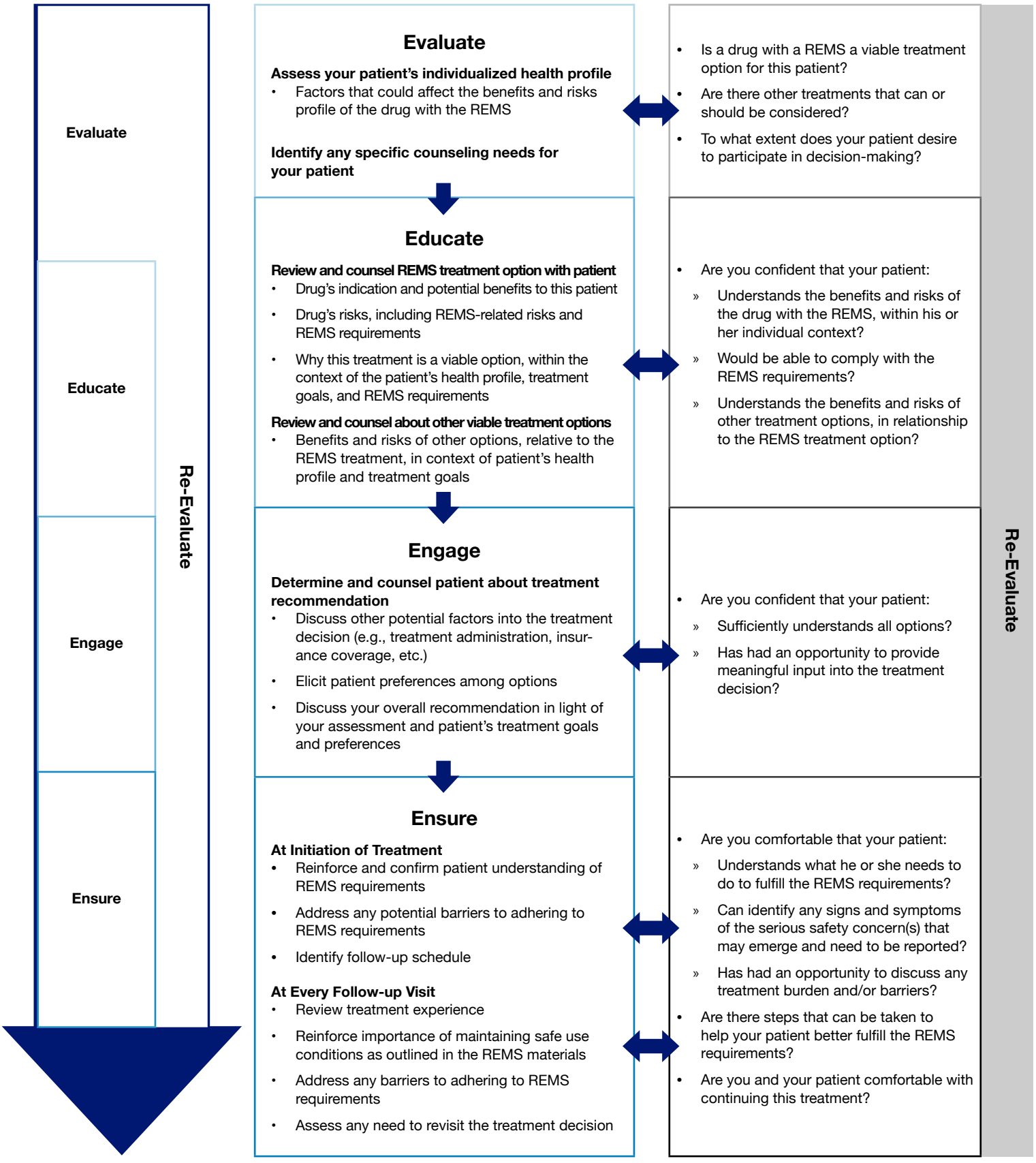
Principle 5: Counseling about drugs with REMS should incorporate techniques, decision support tools, and other resources for effective risk communication and health care counseling.

For counseling to be effective, counseling practices should be adopted and tools used that encourage patient participation in decision-making, support and confirm patient understanding, and reinforce the importance of patients undertaking actions that are consistent with safe use behaviors and the achievement of the REMS goals and objectives.

Because such counseling may go beyond the education routinely provided at the time of prescribing other drugs, the HCP may need to undertake training in patient-appropriate communications, counseling techniques, alternative communication vehicles, and support tools, including the use of visual/graphical depictions that have supporting evidence that may aid in patient understanding and shared decision-making.

However, given that such counseling should be implemented consistently and regularly reinforced for drugs with REMS, it is critical that HCPs choose counseling practices, tools, and training that can easily be implemented and used in clinical practice. To that end, the practices, tools, and trainings presented in this framework should be considered, and HCPs may identify additional examples for their use. In all cases, however, practices, tools, and trainings should be chosen that can be evaluated for their effectiveness.

Appendix 4: Example Tool for Patient Counseling



Appendix 5: Example Counseling Discussions When Ensuring REMS Adherence

Background:

Consider a 22 year old female with a symptomatic condition that is not life-threatening, such as moderate nodular acne. The patient began treatment with a specialist over a year ago and tried multiple first line therapies. Three months ago, the patient and HCP discussed the patient's desire for a more efficacious treatment, and the HCP prescribed a treatment that has REMS requirements, including documented blood tests before the initial prescription and each monthly refill can be dispensed. The patient adequately adhered to all REMS requirements for the initial treatment. However, the patient did not adequately adhere to the requirements for the first and second monthly refills, and the dispensing pharmacist denied treatment. The HCP is now seeing the patient for a scheduled follow-up appointment to evaluate the patient's treatment experience and assess the reasons behind the patient's non-adherence.

Mock counseling during follow-up session:

Thank you for coming in today. I see that you were able to start on the treatment that we prescribed, but that you have been having some difficulty in meeting the necessary testing requirements, and therefore you were not able to access your treatment for the last two months. I understand that your current treatment requires a significant commitment to monitor your drug, but I do have to emphasize that this is a necessary step to help minimize the potential for certain side effects to occur during treatment.

The following is sample text that could support this counseling discussion, organized in two sections. This discussion will vary depending on the patient's responses to questions assessing the patient's root cause of noncompliance with the REMS requirements and experience on treatment.

Section 1. Assessing root cause(s) of patient's noncompliance with the REMS requirements

Let's talk about the challenges you face in complying with the REMS requirements. What has made this most difficult for you?

After discussion, if the HCP does not have a solution to the patient's challenges with adherence, or if the HCP believes that the patient may continue to experience non-adherence, they may need to reassess the decision of prescribing this drug as an appropriate treatment for this patient. See Section 2.

Sample Root Cause(s) of Patient's Noncompliance	Sample Talking Points
The patient is having difficulty making sense of all of the REMS requirements	Let's discuss and clarify these requirements. We'll start by reviewing why this treatment has a risk evaluation and mitigation strategy, or REMS. Then let's review the specific testing requirements for your current treatment. We also have some additional take home materials that you might find useful.
The patient is having difficulty accessing the lab (such as location of lab, labs opening hours, etc.)	That's a common challenge. Let's see if there is a lab facility with acceptable hours closer to you. Would that help you keep your testing appointments?
After seeing limited improvements or bothersome side effects in the first month, patient questions whether the treatment is worth the time and resources needed to comply with the REMS requirements.	Thank you for explaining your reasoning. I want to learn more about your experiences on this treatment. We discussed your goals for treatment during our initial consultation, but we may need to reevaluate them to see if this treatment really is right for you. (See sample text in Section 2.)

Section 2. Evaluating the patient's experience with the drug and reassessing the treatment options for this patient

Let's start by discussing what, if any, improvements you saw in your symptoms and what, if any, side effects you have experienced. Keep in mind, treatments for your condition often take a few months to see the full benefits. We discussed your goals for treatment during our initial consultation, but we may need to reevaluate them to see if this treatment really is right for you. This reconsideration is even more important if you are now having trouble following the REMS requirements for your current treatment.

Assess the patient's experience, confirm your understanding of the patient's treatment goals and determine whether alternate treatments should be considered.

If you determine that alternate treatments should be considered:

As we discussed during our initial consultation, based on your medical history and your goals for treatment, we do have another potential treatment, Treatment B. Treatment B may result in some improvements for you. It may also have fewer side effects for you. There are no monthly monitoring requirements for Treatment B and so it may be a more suitable option for you at this time.

Review the expected benefits and potential side effects of Treatment B (relative to the benefits and side effects of the current REMS treatment) within the context of patient's health profile and treatment goals. Discuss other potential factors affecting the treatment decision (e.g., treatment administration, insurance coverage, etc.).

At this point, I'd like to hear your thoughts about whether you think it best to try to continue on your current treatment, or if you'd like to try this alternative treatment. Please let me know if you have any questions.

Discuss your overall recommendation in light of your assessment and patient's treatment goals and preferences. If your recommendation deviates from the patient's preference, clearly articulate your reasoning and discuss further with the goal of ensuring your and the patient's comfort with the final decision. Confirm treatment decision.

If you and the patient decide that it is appropriate to continue the drug with the REMS:

Stress once more the importance of complying with the REMS requirements and confirm any strategies discussed to help improve compliance. Identify the next follow-up appointment and discuss that the patient's experience with the drug and the requirements will be carefully re-evaluated.

Appendix 6: The Four Elements of the Benefit-Risk Counseling Framework

Evaluate – when considering or prescribing a drug with a REMS, each patient should be assessed initially and on an ongoing basis. This assessment should encompass factors that could affect the potential benefits and risks to the patient, the treatment decision, and the patient's understanding and ability to adhere to the REMS requirements.

The HCP should consider conducting the following assessments as part of the ongoing counseling process:

- Identify potential benefit(s) and risks of different treatment options and factors that may affect the patient's benefits or risks of experiencing a serious adverse reaction to the different treatment options (e.g., response to prior treatment, factors that may put patient in different categories of risks and/or benefits, etc) in the process of making a treatment decision.
- Identify non-clinicaland/or practical factors that could affect the treatment decision (e.g., administration of drug, insurance, formulary availability, compliance barriers, as well as questions or concerns the patient may have that affect the treatment decision).
- Assess the patient's level of understanding of:
  - » His/her risk of experiencing the (serious) adverse event of concern.
  - » The purpose of a REMS and the specific REMS for the drug being prescribed.
  - » His/her responsibilities for achieving effective risk mitigation.
- Identify areas where the patient could benefit from additional counseling.
  - » Any other factors that may affect (impair or enhance) the patient's ability to adhere to REMS program requirements.
  - » A patient's understanding of the treatment options and any preferences he or she may have among the different treatment options.
- Assess the patient's treatment goals

Techniques to consider when evaluating patients include:

- Use open-ended questions to learn about the patient's medical condition, treatment goals, counseling needs and concerns.
- Use the *teach back* method to assess what the patient has learned and how he/she would implement safe use practices. Ask each patient to teach the HCP about what he/she have heard using his/her own words, to confirm their understanding.

Educate – when considering or prescribing a drug with a REMS, inform the patient about all treatment options, potential risks and benefits of each treatment option, and any REMS requirements. Tailor education to each individual to maximize patient understanding.

- The individualized counseling discussion should include the following, based on approved product labeling, the patient's profile and REMS obligations:
  - » Potential drug benefits for the patient, including factors that lead to a greater or a lesser benefit for the patient and how the drug benefits may change over time.
  - » Potential harms of the drug, including a discussion of the key drug risk(s) addressed by the REMS and any other safety concerns, and how those risks could change over time.
  - » Any important uncertainties (e.g. limited number of patients studied under controlled clinical trial conditions).
  - » Considerations on how to determine if the potential benefits are expected to outweigh the risks for the individual patient, including the patient's prior experience on the drug (if applicable).
    - ◊ Any secondary issues (unrelated to drug benefits and harms) that may factor into the HCP's or patient's decision-making (e.g., dosing regimen, need for ongoing testing or monitoring, other side effects, insurance coverage, other cost considerations, anticipated burdens, etc.).
  - » Steps or actions the patient needs to take to reduce the risk(s), including REMS requirement(s) (as directed by REMS materials) for the patient and confirming patient understanding and addressing patient concerns, with adhering to these requirements.
- Counseling should also educate the patient about the REMS program, including:
  - » The purpose of a REMS.
  - » Key risk messages from the REMS about the adverse event(s) of concern.
  - » The elements of the specific REMS program for the prescribed drug and the patient's role in maintaining safe use conditions.
  - » REMS tools that are available to the patient to support their education, understanding, and compliance.
    - ◊ REMS tools inform and educate about certain specific serious risk(s), presenting key risk messages and risk mitigation requirements of the REMS; however, they do not convey benefit information beyond the approved indication or overall drug safety information.

Engage – Counseling patients about drugs with serious risks and REMS requirements will be most effective if the HCP both encourages and supports the patient to become an active participant in treatment decision-making, thereby enhancing the patient's level of ownership, understanding, and commitment to ensuring safe drug use. The scope of engaging the patient can include discussing patient goals and values, encouraging the patient to share information and ask questions, checking and asking the patient to demonstrate understanding, and having the patient assume an active role in the process.

One approach to engaging patients and enhancing their role, particularly relevant when the HCP does not recommend any one particular treatment option, is to use a shared decision-making approach. Shared decision-making (SDM) is when a HCP and a patient work together to make a health care decision that is best for the patient. The optimal decision takes into account evidence-based information about available options, the provider's knowledge and experience, and the patient's values and preferences.

Techniques to consider when educating patients:

- Ask patients how they prefer to receive information (e.g., using numbers, words or pictures), and how much they wish to participate in decision making
- Use the best available scientific evidence
- Provide information to patients at a literacy level appropriate to supporting their understanding of their condition and their various therapeutic options
- Provide examples of written information (handouts, pamphlets, articles), relevant media programs (videos, podcast), and/or online sources of information
- Use plain language (not technical jargon)
- Convey simple, quantitative evidence of the probability of benefits and harms (e.g., round numbers and denominators, minimize computations, provide comparisons, timeframes, and uncertainties)
- Use tested visual depictions to support the communication of quantitative risk information to improve risk perception and understanding
- When feasible, tested visual aids should depict the underlying event risks separately from the risks related to treatment
- Pictographs, icon array, bar charts and/or graphs can be used depending on the differing types of messages being conveyed and graphical literacy
- Focus discussions on a limited number of key benefit and risk messages
- Attempt to translate the bottom line qualitative meaning or gist of risk information
- Link recommended treatment options to patient treatment goals
- Use the teach back method, asking each patient to teach the HCP about what they have heard using their own words, to confirm their understanding

FDA both reviewed the SDM literature and discussed with stakeholders which SDM techniques could potentially be readily adopted by HCPs while minimally impacting their practice workflow. Among various SDM approaches, a practical step-wise approach has been described, in which the HCP and patient undertake a collaborative process of sharing evidence and then the HCP supports the patient in considering options and making an informed choice.

When encouraging active patient participation and/or SDM, the HCP should:

- Explicitly convey to the patient that a treatment decision will need to be made and, when appropriate, the HCP's desire for active patient participation in the decision-making process.
- Encourage questions and give patients the opportunity to describe themselves, to express their communication needs, values, and desired outcomes and to identify areas of patient interest, concern, and/or sensitivities.
- Assist the patient in determining which treatment options are most concordant with the patient's own goals and values.
  - » The term values refers to the extent to which a particular decisional attribute matters to a patient. For example, one patient may value the possibility of slowing disease progression while another may value maintaining the ability to work or preserving quality of life while on treatment.
  - » Discuss factors patient may wish to consider between different treatment options (i.e., trade-offs).
- Understand the patient's initial assessment of treatment options and preferred treatment choice, once

the patient has reviewed relevant aspects of the drug with a REMS and possible alternatives.

- Check to actively confirm patient understanding; provide opportunities for the patient to express to the HCP his or her own understanding of the information.
- Formulate an overall assessment and recommendation(s) of treatment, and the basis for that recommendation, ideally relating this assessment and recommendation to the patient's goals, values, and preferences.
  - » For example, "I am recommending drug X because, if I understood correctly, it's important to you to avoid side effect Y. Drug X has lower rates of side effect Y than drug Z."
- Determine and consider the patient's level of comfort with the recommendation, their role in mitigating risks, including the patient's ability to administer the drug, follow instructions around safe use, and maintain adherence to the regimen and safe use conditions, given the patient's understanding of his or her health profile, treatment goals, values, and preferences.
  - » Any differences between the patient and HCP preferences or recommendations should be identified and if possible reconciled.
- Confirm the treatment decision or the decision to defer treatment.
- Help the patient identify and overcome potential or actual REMS burdens.
- In some cases, further information or consultation with other HCPs, the patient's family, etc., may be required before a decision can be made. In such cases, the HCP should explicitly acknowledge that the decision will be deferred until a follow-up visit, when more information has been gathered.

Techniques to consider when engaging patients to participate in REMS decision making:

- Open-ended questions help to learn about the patient, his or her condition, values, and concerns, as well as to establish or reinforce a relationship and to convey a desire to have the patient participate in the decision making process.
- Values clarification tools and techniques can help HCPs and patients clarify what aspects or features of different treatment strategies may be important to them.
- Decision aid tools can also elicit patient input.
- A blank summary table template can be filled out by the HCP to consolidate the potential benefits and risks of the intervention specific to the individual patient.
- Consider the example algorithm depicted in Appendix 4.

Ensure – At follow up visits, the HCP should counsel patients taking drugs with REMS to reinforce key risk messages, REMS information, and the need for patient actions to help effectively mitigate the risks. This can include recommunicating and supporting patients' understanding of the following:

- Key risk messages from the REMS
- Signs and symptoms of the serious adverse events of concern that may emerge and that need to be reported to the HCP
- The patient's role in adhering to their obligations under the REMS program, such as identifying and/or reporting adverse events, compliance with ongoing monitoring, etc.

- Any next steps towards fulfilling previous or ongoing REMS program requirements, if applicable
- Any follow-up assessments, such as specific aspects of the patient's treatment experience (e.g., improvements in functioning, tolerability issues) that the HCP will use to assess a patient's benefit-risk profile while on treatment and use to make possible adjustments to treatment regimen.
  - » Benefits and adverse events the patient has experienced on treatment.
  - » Patient's reported ability to comply with the REMS requirements once the drug has been prescribed, as well as actual benefits, risks and other experiences the patient has had with the REMS while on treatment.
  - » Patient's perspective on the burdens of meeting REMS requirements, barriers to compliance they may have had, the patient's ability to overcome these barriers to maintain overall compliance with the REMS requirements.
  - » Recommended approaches to addressing and overcoming any barriers to treatment or issues with compliance, if applicable.
- Review and provide relevant materials and/or instructions for the patient to refer to at home.
- Give the patient the opportunity to review and discuss their decisions at follow-up appointments, as patient circumstances, values, and preferences may change over time.
- Reviewing and reconsidering treatment decision based on patient's reported benefits and risks while on treatment, burdens, and barriers and the ability to address them.
- Repeatedly seek the patient's level of understanding and identify and answer additional areas of interest and concern to the patient about serious adverse event risks and the REMS program.

Techniques to consider when ensuring patient understanding and compliance:

- Set expectations with the patient up front that more than one counseling interaction may be needed to help him or her make informed decisions and to help them retain information about their role in mitigating risks.
- Repeatedly reinforce the importance of continuing to fulfill their REMS requirements, including repeating key counseling messages at follow up patient visits and reviewing any REMS tools that were previously used (e.g., signed Patient-Provider Agreement and re-confirming patient understanding, as needed).
- Reconfirm the patient's understanding of the serious adverse reaction the REMS requirements and the patient's role in recognizing and reporting such events to the HCP.
  - » Use the teach-back technique to assess the patient's attitudes on safe medication use and to identify any further potential barriers to compliance
  - » Have the patient demonstrate safe use practices and counsel based on observations
- Consider reviewing the case study example described in Appendix 5.
- Use enhanced techniques (e.g., motivational interviewing) to help patient's address non-compliance issues, if applicable.

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