REMS Logic Model: A Framework to Link Program Design With Assessment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2024
Safety - Issues, Errors, and Problems

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REMS Logic Model: A Framework to Link Program Design With Assessment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to describe FDA's risk evaluation and mitigation strategy (REMS) logic model. The REMS logic model is a framework that FDA recommends, which provides applicants[2] with a systematic, structured approach to the design, implementation, and evaluation of a REMS. The aim of applying the REMS logic model is to develop clear goals, objectives, and strategies that align with the intended outcomes and to help applicants incorporate the REMS assessment planning into the design of the REMS.[3] The principles in this guidance apply to designing a REMS, developing a REMS assessment, and modifying a REMS.

This guidance is not intended to clarify how risk management or a REMS factors into the benefit-risk[4] assessment of a drug.[5] Although this guidance does not directly address how the Agency determines when a REMS is necessary to ensure that the benefits of the drug outweigh

[1] This guidance has been prepared by Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research in cooperation with other offices within CDER and the Center for Biologics Evaluation and Research at the Food and Drug Administration.
[2] For the purposes of this guidance, the term *applicant* refers to sponsors of investigational new drug applications and applicants of new drug applications (NDAs), biologics license applications (BLAs), and abbreviated new drug applications (ANDAs).
[3] This guidance is one of several documents FDA is issuing to fulfill the performance goals under the sixth reauthorization of the Prescription Drug User Fee Act (PDUFA VII), available at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027.
[4] See the guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[5] Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) applies to applications for prescription drugs submitted or approved under subsections 505(b) (i.e., NDAs) or (j) (i.e., ANDAs) of the FD&C Act and to applications submitted or licensed under section 351 (i.e., BLAs) of the Public Health Service Act (42 U.S.C. 262). For the purposes of this document, unless otherwise specified, the term *drugs* refers to human prescription drugs, including those that are licensed as biological products.

its risks,[6,7] the concepts discussed in this guidance may be relevant to consider when determining if risk mitigation strategies beyond labeling are necessary.

The Glossary defines many terms for the purposes of this guidance. Terms that appear in ***bold italic*** type upon first use are defined in the Glossary.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. REMS Authority

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) authorizes FDA to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. FDA can require a REMS before initial approval of a new drug or, should FDA become aware of new safety information[8] 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.[9]

A REMS is a required risk management strategy that can include one or more elements to ensure that the benefits of a drug outweigh its risks. If FDA determines that a REMS is necessary,[7] FDA may require one or more REMS elements, which could include a Medication Guide or a communication plan.[10] For drugs that pose a serious risk of abuse[11] or overdose, the Agency may require certain packaging or a safe disposal system as part of a REMS.[12] FDA may also require elements to assure safe use (ETASU) as part of a REMS.[13] FDA may require ETASU if the drug has been shown to be effective but is associated with a specific serious risk, and the drug can be approved only if, or would be withdrawn unless, such ETASU are required as part of a strategy to mitigate a specific serious risk or risks listed in the labeling of the drug. In addition, in the postmarketing setting, FDA may require ETASU for drugs initially approved without ETASU

[6] See the guidance for industry *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (April 2019).
[7] In general, the purpose of a REMS under section 505-1 of the FD&C Act is related to serious risks. The term *serious risk* is defined for purposes of section 505-1 as a "risk of a serious adverse drug experience."
[8] Section 505-1(b)(3) of the FD&C Act.
[9] See section 505-1(a)(2) of the FD&C Act.
[10] See section 505-1(e)(2)–(3) of the FD&C Act.
[11] Consistent with section 505-1(b)(1)(C) of the FD&C Act, this guidance uses the term *abuse*. As used in this guidance, the term *abuse* refers to the intentional, nontherapeutic use of a drug for its desirable psychological or physiological effects. The term *abuse* is used in this document to describe a specific behavior that confers a risk of adverse health outcomes. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.
[12] See section 505-1(e)(4) of the FD&C Act.
[13] See section 505-1(f) of the FD&C Act.

when other elements are not sufficient to mitigate a serious risk. Specifically, ETASU may include one or any combination of the following requirements:[14]

- Health care providers who prescribe the drug have particular training or experience, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug be dispensed to patients only in certain health care settings, such as hospitals
- The drug be dispensed to patients 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

If a REMS includes certain ETASU, the REMS may also include an implementation system to enable the applicant to monitor, evaluate, and improve the implementation of the element(s) (e.g., development of a REMS-specific website or call center to facilitate enrollment; establishment of electronic databases of certified health care settings).[15]

All REMS should include one or more goals. If the REMS has ETASU, the REMS must include one or more goals to mitigate a specific serious risk listed in the labeling of the drug and for which the ETASU are required.[16]

Finally, a REMS generally must include a timetable for submission of assessments of the REMS.[17] The timetable for submission of assessments of the REMS must include an assessment by the dates that are 18 months and 3 years after the REMS is initially approved and an assessment in the seventh year after the REMS is approved, or at another frequency specified in the REMS.[18]

Section 505-1(g)(3) of the FD&C Act specifies that a REMS assessment shall include, with respect to each goal in the strategy, an assessment of the extent to which the approved strategy, including the elements, is meeting the goal or whether the goal or elements should be modified. The FD&C Act does not specifically describe how an applicant should conduct this assessment.

[14] See section 505-1(f)(3) of the FD&C Act.
[15] See section 505-1(f)(4) of the FD&C Act.
[16] See section 505-1(f)(3) of the FD& C Act.
[17] See section 505-1(d). NDAs and BLAs must include a timetable for submission of assessments. ANDAs are not subject to the requirement for a timetable for submission of assessments (section 505-1(i) of the FD&C Act), but FDA can require any applicant, including ANDA applicants, to submit REMS assessments under section 505-1(g)(2)(C) of the FD&C Act.
[18] Section 505-1(d) of the FD&C Act; see also 505-1(g)(2) of the FD&C Act.

B. Applying a Framework for REMS Design, Implementation, and Evaluation

Frameworks have been used in public health program design, implementation, and evaluation (see Ridde et al. 2020). Frameworks provide a systematic, structured approach to identify the ***program goal***, explain the relationship between a program's ***activities*** and intended ***outcomes***, improve adoption (the research-to-practice gap), and determine what is important to measure.

In 2018, FDA assessed the feasibility and utility of applying commonly used and validated scientific frameworks to REMS assessments (Toyserkani et al. 2020; Huynh et al. 2021). FDA used a repository of commonly cited dissemination and implementation frameworks to select three eligible frameworks that are U.S.-based, include multilevel interventions, and are in the field of public health.[19] The three eligible frameworks included RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) from implementation science; PRECEDE-PROCEED (Predisposing, Reinforcing, and Enabling Constructs in Educational Diagnosis and Evaluation — Policy, Regulatory, and Organizational Constructs in Educational and Environmental Development) from health program planning and evaluation, and CFIR (Consolidated Framework for Implementation Research) from clinical quality improvement.

FDA concluded that frameworks provide a logical, structured approach for determining what outcomes should be measured, when the outcomes should be measured, and the process and health impact ***indicators*** for facilitating these measurements (Toyserkani et al. 2020; Huynh et al. 2021). The application of these frameworks also identified areas for strengthening and improving REMS assessments, including the following:

- Explicitly linking program design assumptions with ***program evaluation*** metrics to validate the assumptions, allow for necessary modifications, and improve program performance

- Improving and increasing outcomes and health ***impact*** measures

- Identifying measures to assess integration and sustainability of REMS into the health care system and clinical practice to inform on whether the REMS requirements can be eliminated

- Identifying a primary outcome measure to determine whether the REMS goal is being met

However, none of the frameworks evaluated provided a single unifying framework that could be applied to the design, implementation, and evaluation of a REMS. Therefore, FDA adapted another commonly used framework, a ***logic model***, to the REMS program design and evaluation. Logic models are often used to guide program development by providing a road map of the steps needed to achieve program goals and the desired outcome. A logic model provides a clear and concise way of presenting the key elements of a program and how they relate to each other. Through creating a visual representation of the relationships between program ***inputs***, activities,

[19] See the Dissemination & Implementation Models in Health web tool, available at https://dissemination-implementation.org/.

outputs, and outcomes, a logic model makes explicit the scientific evidence, assumptions, and underlying logic that support the program and the various processes behind it.

Logic models are also commonly used in program evaluation. Logic models have been developed and used by other U.S. Department of Health and Human Services agencies. For example, the Centers for Disease Control and Prevention (CDC) use logic models in public health and health prevention initiatives, such as the CDC Overdose Data to Action which helps implementers and evaluators see how their activities and initiatives are similar or different from the ones presented in the model.[20,21,22]

Existing health care program frameworks, logic model principles, and FDA's research informed the development of FDA's ***REMS logic model***.

III. FDA'S REMS LOGIC MODEL

FDA's REMS logic model provides a recommended framework to help applicants design, implement, and evaluate a REMS (**Figure 1**).

- The first and second rows in **Figure 1** outline the three phases of a REMS life cycle: design (planning), implementation (process), and evaluation (outcomes).

- The third row in **Figure 1** reflects the various steps of the REMS logic model within each phase.

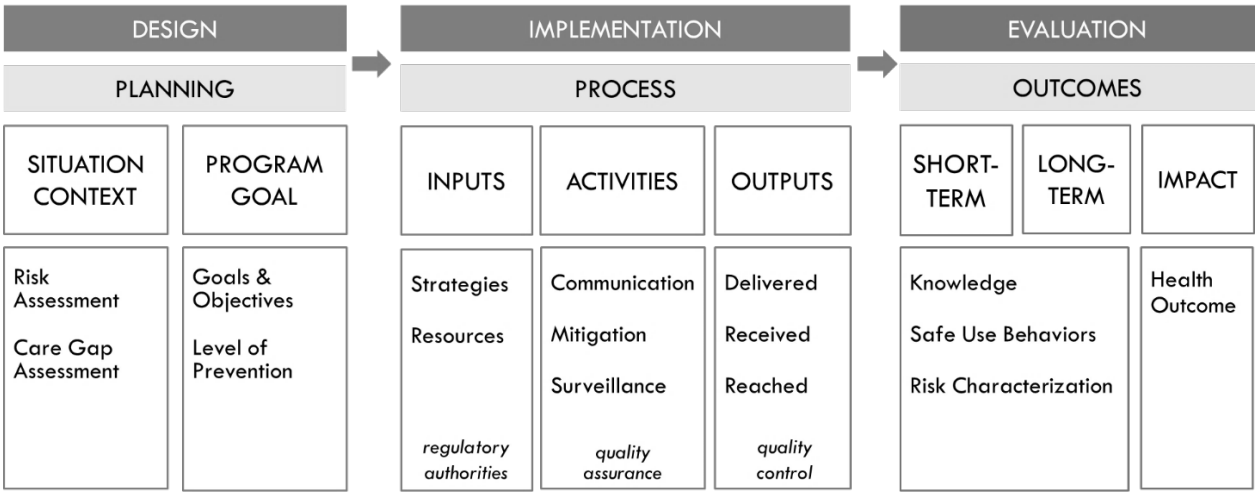
  — Under the design phase, the left two columns reflect assessing a situation context and establishing a REMS program goal.

  — Under the implementation phase, the middle three columns reflect determining the inputs, activities, and outputs for the REMS.

  — Under the evaluation phase, the last two columns reflect the evaluation of short-term and long-term outcomes and the impact of a REMS.

[20] See the CDC, Office of Policy, Performance, and Evaluation web page on CDC's Analytical Framework, available at https://www.cdc.gov/policy/paeo/process/analysis.html.
[21] See the CDC, Office of Policy, Performance, and Evaluation, web page on Framework for Program Evaluation, available at https://www.cdc.gov/evaluation/framework/index.htm.
[22] See the CDC, National Center for Injury Prevention and Control web page on Drug Overdose Data to Action, available at https://www.cdc.gov/drugoverdose/od2a/evaluation.html.

Figure 1. REMS Logic Model



Each phase of the REMS logic model is described in more detail below. The REMS logic model, although visually linear, is intended to be an iterative process that involves moving back and forth or toggling between steps to address uncertainties, validate assumptions, incorporate new information, and refine the REMS program. In addition, toggling assists with continually verifying the relationship between the goal, ***objectives***, strategies, and intended outcomes of a REMS.

A. Design Phase

Application of the REMS logic model begins with the design phase, which consists of assessing the situation context and establishing a goal for the REMS (**Figure 2**). The purpose of this phase is to identify the ***problem***(s) associated with a serious risk that a REMS may be able to address and to determine what the REMS aims to achieve.

Figure 2. Design Phase

1. Situation Context

The first step of the design phase begins with assessing the ***situation context***, which consists of conducting a risk assessment and care gap assessment. In addition to the clinical trial data, the situation context may be informed by literature, ethnographic studies, and input from relevant stakeholders. Review of drugs with similar indications, risks, or postmarketing experience in the United States or foreign countries may also be helpful, if available.

a. Risk assessment

Risk assessment in the context of the REMS logic model is an in-depth assessment of the serious risk(s) identified that may require mitigation beyond labeling. The applicant should base the risk assessment on evidence from preclinical and clinical development, literature evaluation, postmarket clinical trials, epidemiologic studies, and real-world data, as applicable.

For example, the applicant should describe the following in the risk assessment and identify what are unknowns, assumptions, and uncertainties of the risk:

- Level of evidence (e.g., observed in humans, animals, or theoretical; identified in clinical trials or case reports)
- Severity and probability of occurrence (e.g., severity of adverse event and clinical outcomes, incidence, frequency, comparison to expected background incidence)
- Temporality (i.e., time to onset of serious adverse event after drug exposure)
- Detectability (i.e., ability to screen for, monitor, or identify the serious adverse event)
- Preventability (i.e., ability to avoid the serious adverse event)
- Reversibility (i.e., whether the serious adverse event is permanent or can be treated)
- Drug-related factors (e.g., dose, route of administration, pharmacokinetic and pharmacodynamic properties)
- Patient-related factors (e.g., differences in risk across patient subpopulations, age, comorbid conditions, other factors that may enhance or reduce probability or severity of an adverse event)

Applicants should consider how clinical trial protocols mitigated the risk of interest and how those mitigation strategies may or may not translate to clinical practice.

b. Care gap assessment

As part of the assessment of the situation context, applicants should understand and anticipate the potential ***care gaps*** in the health care system, including those that arise at patient, provider, and setting levels.

A care gap assessment involves identifying the discrepancies in risk mitigation between clinical trial protocols, best practices, and the actual care that is provided or anticipated to be provided in clinical practice. In the context of the REMS logic model, the care gap assessment should further focus on the care gaps that could be addressed by a REMS. As part of the care gap assessment, applicants should describe the proposed indication, intended patient population, the likely prescribing population, and the anticipated ***medication use process*** including drug procurement, distributing, prescribing, order processing, dispensing, administering, and monitoring (Institute for Safe Medication Practices 2023). Mapping out the medication use process can assist applicants with identifying care gaps within the existing health care delivery system and where additional support to effectively mitigate the risk may be particularly useful. Mapping can highlight key differences in the real-world setting compared to clinical trial setting and how this could impact safe use.

As part of the care gap assessment, applicants should also consider care gaps that may arise from the baseline knowledge, attitude, and beliefs of patients and/or health care providers about the risk and safe-use behaviors; ***self-efficacy*** and readiness for change; and the ***capacity for safe use***, including the available resources within the health care system. Applicants can assess these through qualitative research methods such as focus groups and individual patient and health care provider interviews and/or through literature review. Further, applicants should apply various theories related to behavior, health behavior, and health communication to the design of REMS because they give insight into why patients and health care providers might not engage in certain safe-use behaviors (Ajzen 2006; Mobley and Sandoval 2008; National Institutes of Health 2020). Applicants can use this insight when making decisions on how a REMS may be designed to achieve its intended outcomes (e.g., for REMS to address embryo-fetal toxicity, patients' and providers' attitudes and beliefs about contraceptive methods may impact the program design and outcome).

Applicants should evaluate the influence of system-level impacts—such as from clinical practice guidelines, Federal and State laws and regulations, accrediting organizations' standards, medical institutional guidelines, and insurance coverage decisions—on the situation context for the drug. These considerations can also assist with discussions related to the extent of support that may be required to mitigate the risk (e.g., educational programs, processes to document or verify that laboratory monitoring was completed).

Putting together the risk assessment and care gap assessment in the context of the medication use process should help identify the specific gaps in care (hereafter referred to as the *problems*), if any, that strategies beyond labeling may be able to address to ensure the benefits of a drug outweigh its risks.

2. Program Goal

The second step in the design phase is to identify what a program is intending to accomplish by developing a clear program goal[23] and objectives.

A program goal is a broad statement about the expectation of what the program intends to achieve. A well-defined goal statement should establish the "overall direction and focus for the program, define what the program will achieve and serve as the foundation for developing program strategies and objectives" (Family and Youth Services Bureau 2012). Objectives should be specific statements that describe intended results that are measurable to help monitor progress toward the program goal.

A REMS goal and objectives should be drug-specific and align with mitigating a serious risk listed in labeling.[16,23] Applying the principles of disease prevention (adapted from Beaglehole et al. 1993) to risk prevention for drugs can help applicants develop the REMS goal and objectives (**Table 1**). The levels of prevention consist of ***primary prevention*** (prevent the serious adverse event before it occurs), ***secondary prevention*** (screen or monitor for the serious adverse event to allow early identification to prevent worsening), or ***tertiary prevention*** (manage the serious adverse event once it occurs to reduce severity and long-term negative impact).

Table 1. Levels of Prevention and REMS Considerations*

Level of Prevention	Questions to Consider
Primary prevention	Can a REMS prevent the serious adverse event from occurring?
Secondary prevention	Can a REMS screen for or detect the serious adverse event to allow early identification to prevent worsening?
Tertiary prevention	If the serious adverse event develops, is it possible to treat, reduce the severity, or reverse the negative consequences and long-term negative impact?

* REMS = risk evaluation and mitigation strategy.

Applicants should identify and, subsequently, design a program to target the earliest achievable stage of prevention. In some situations when primary, secondary, and tertiary preventions are not feasible or practical, the REMS may aim to ensure ***informed benefit-risk decision-making*** (i.e., the patient's and prescriber's decisions are based on appropriate information). A program may include a combination of prevention levels, which applicants may complement by incorporating informed benefit-risk decision-making.

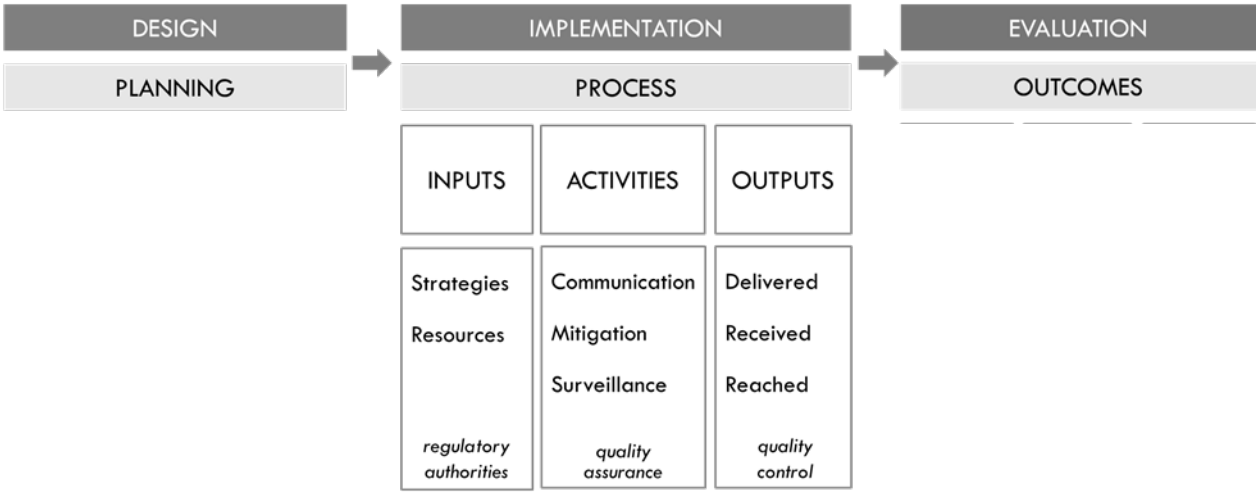
Applicants should consider, as they develop the program goal and objectives, how they will inform the development of the inputs (see section III.B.1). At this point in the design phase of the logic model process, applicants should begin to develop the critical program outcome indicator (i.e., ***key performance indicator***) for determining whether the REMS goals are being met (see section III.C.1).

[23] In some instances, a program may have more than one risk and/or goal.

B. Implementation Phase

The second phase of the REMS logic model is the implementation phase, which consists of the development of inputs, activities, and outputs (**Figure 3**) of the REMS. The purpose of this phase is for the applicant to develop the program that will be implemented and begin to consider the data necessary to evaluate if the program is being implemented as intended. Evaluating the actual effectiveness of the program occurs during the last phase, the evaluation phase (see section III.C).

Figure 3. Implementation Phase



1. Inputs

The first step of the implementation phase involves identifying the inputs. Inputs are what an applicant needs to operate a program. In the context of REMS, inputs consist of two components: (1) the ***strategies*** and (2) ***resources***.[24]

As recommended by FDA, the REMS logic model organizes the strategies into three categories: (1) those that are intended to affect knowledge (communication strategies), (2) those that are intended to affect ***safe-use behavior*** (mitigation strategies), and (3) those that are intended to inform ***risk characterization/mitigation*** (***surveillance strategies***). The substrategies are based on FDA's regulatory authorities.[25] **Table 2** depicts strategies and corresponding substrategies that an applicant should consider when designing and implementing a REMS.

[24] See the guidance for industry *Format and Content of a REMS Document* (January 2023).
[25] See section 505-1 of the FD&C Act.

Table 2. Strategies and Substrategies Related to REMS*

Strategy	Substrategy
To affect **knowledge**	• Medication Guide • Communication plan • Training (e.g., prescriber, pharmacy, health care setting) • Certification (e.g., prescriber, pharmacy, health care setting, patient)
To affect **safe-use behaviors**	• Health care setting requirements necessary for dispensing (e.g., equipment, personnel) • Documentation of safe-use behaviors (e.g., verify completion of laboratory testing) • Monitoring the patient (e.g., observation, assessing results of laboratory testing) • Packaging (e.g., unit dose, limited supply, package warnings) • Disposal systems (e.g., mail back envelopes)
To inform **risk characterization/mitigation**	• Patient Registry

* REMS = risk evaluation and mitigation strategy.

Applicants should select strategies that align with the identified problems from the situation context assessment and the program's goal and objectives. When selecting which strategies to implement, applicants should consider a variety of factors and the available evidence, including, but not limited to, the following:

- The effectiveness of the proposed strategy in mitigating the risk (e.g., results from pretesting of risk messaging and educational formats with stakeholders, effectiveness demonstrated during clinical trials or from the published literature, findings from human factors studies, previous experience with similar REMS). Often REMS will incorporate, at a minimum, a strategy to affect knowledge. However, it is important to consider that knowledge does not necessarily translate to behavior.

- The feasibility and practicality of implementing the proposed strategies for each affected stakeholder and health care system. Applicants should evaluate if the REMS can be designed to be compatible with established clinical assessment, prescribing, dispensing, administering, and monitoring as well as the procurement and distribution processes. Applicants should also evaluate the potential ***burden*** of the proposed mitigation strategies on the health care delivery system and the intended patient population. For example, strategies that directly affect safe-use behavior (e.g., monitoring requirements) may be more effective but may also be more burdensome than knowledge-based strategies.

- The potential impact of the proposed strategies on ***patient access*** to the drug. For example, applicants should evaluate the impact of the REMS on patient access across a

variety of factors that can lead to health care disparities such as socioeconomic status, age, rural and medically underserved areas, language, gender, disability status, and sexual identity and orientation. In addition, applicants should also evaluate the impact of the REMS on coordination and transition of care (e.g., transition from inpatient to outpatient, transition between providers and/or facilities) for patients.

The second component of inputs is resources. Resources refer to the people, materials, and technologies that are needed to support the REMS, such as but not limited to the following:[26]

- People include anyone involved in implementing and participating in the REMS (e.g., patients, applicant, vendors, prescribers, health care providers who manage and monitor the patient, pharmacists, wholesalers-distributors, and/or call center staff).

- Materials include, but are not limited to, educational brochures, wallet cards, enrollment forms, medications that must be available or dispensed to the patient, and equipment necessary to administer the medication and/or monitor for and manage adverse events.

- Technologies include, but are not limited to, websites/portals, authorization systems, text messaging, databases, phone, and fax.

Applicants should think broadly about how the possible resources and strategies can be used throughout the medication use process. Applicants may need to toggle back to the design phase of the REMS logic model (see section III.A.1) and consider how compatible the identified resources and strategies are with established clinical care of a patient, prescribing, dispensing, administering, and patient monitoring as well as the procurement and distribution processes.

2. Activities

The second step of the implementation phase involves selecting the REMS activities. Activities are defined as the actions completed by the participants, as well as the applicant(s), to achieve the program's goal and objectives. Activities support the strategies that were selected, and each strategy will have one or more corresponding activities. The REMS logic model organizes activities as they relate to supporting communication-related strategies (to affect knowledge), mitigation-related strategies (to affect safe-use behavior), and/or surveillance-related strategies (to inform risk characterization/mitigation).

In the context of a REMS, activities are the same as *REMS requirements*, or the actions applicants and different participants complete to comply with a REMS, as described in the ***REMS Document***.[27]

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[26]Examples of typical resources and materials can be found in the guidance for industry *Format and Content of a REMS Document* and the associated technical specifications document *REMS Document Technical Conformance Guide* (January 2023) also available on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. These examples are not all inclusive.

[27] For a list of the most common required activities (or REMS requirements), see the guidance for industry *Format and Content of a REMS Document* and the associated technical specifications document *REMS Document Technical Conformance Guide*.

As part of this step, applicants should consider and proactively establish ***quality assurance*** plans related to the activities. Quality assurance includes the proactive plans, protocols, and procedures to ensure the applicant is implementing the required activities as intended. Some examples of activities related to quality assurance include establishing and maintaining noncompliance plans, audit plans, and registry protocols.

3. Outputs

The third step of the implementation phase focuses on identifying and developing the program outputs. These outputs begin to form the basis of the assessment. Outputs are the direct results of the activities and inform how the REMS is operating.

Outputs can provide insight into whether the program's strategies or activities are being implemented as intended (e.g., delivered, received, reached). For example, output data on the number of letters delivered and to whom (e.g., reached) should provide insight into whether the applicant distributed the communication materials as required.

Outputs can also provide insight about whether the design assumptions are valid. For example, if most enrollments are expected to be completed online, outputs can inform the validity of that assumption. Outputs can also identify implementation barriers or access issues. For example, if enrollment is not occurring online and is only occurring by phone, additional analysis (e.g., root cause analysis) may identify why the design assumptions are not valid. If patient demographic data are not aligned with the expected patient population, these data could indicate a variety of issues that would require further analysis to determine why the patient population is different from expected and if there is a patient access issue that needs to be addressed. If data indicate that there are no certified prescribers in certain geographic regions, these data could indicate additional analysis is needed to determine why prescribers from a particular geographic region are under-represented, which could contribute to a patient access issue.

Applicants should measure outputs by developing indicators to determine if the program is being implemented as intended and whether the program is expected to achieve its outcomes. Indicators can be qualitative (e.g., health care providers' attitudes about the risk and safe-use interventions) or quantitative (e.g., number of health care providers trained on the risk and safe-use interventions). Indicators can provide signals about a change (e.g., when a change occurred, what changes are happening over time) but may not explain the reasons why a change occurred. Examples of information that can be obtained that inform why a change occurred could be gathered from performing root cause analysis, failure mode effects analysis, and/or stakeholder outreach.

Indicators can be categorized as ***process indicators*** or ***outcome indicators***.

- Process indicators determine how well a program is being implemented and operated by measuring the implementation activities and outputs. These can include measuring outputs on the REMS administrator side (i.e., applicant(s)) and the recipient side (i.e., ***REMS participants***). Process indicators should include measures of outputs that inform

about burden as well as patient access to medications. Other process indicators include measuring the extent to which the REMS materials reach the intended stakeholders, which intended stakeholders are participating in the program, and how effectively the REMS is being implemented along with compliance with the requirements.

Process indicators also provide important data to assess REMS from a ***quality control*** perspective, verifying that REMS activities have occurred or been fulfilled. Quality control is a retrospective process to determine if the REMS is being implemented as intended and to identify areas that may need improvement. In contrast to quality assurance, which are the plans that are put in place to ensure ***fidelity***, quality control is the manner of evaluating fidelity.

- Outcome indicators determine if a program is achieving its intended results, and applicants can subdivide outcome indicators into *program outcomes* and *health impact*. Outcome indicators are described in more detail in section III.C.

A REMS often generates a considerable amount of data regarding how the program is operating (e.g., enrollment data, call center data, website metrics, audit reports). Applicants should evaluate the full scope of available data and then determine which data will gauge the program's fidelity to implementation, program improvement (or need for improvement), drug access, and program burden. The applicants should regularly assess all output data and, at specified intervals, provide a comprehensive analysis to FDA that includes the applicants' interpretation of the data.[17]

C. Evaluation Phase

The third phase of the REMS logic model is the evaluation phase, which consists of short- and long-term outcomes and impact (**Figure 4**). The evaluation of REMS is essential to ensure program effectiveness. In this phase of the logic model, outcomes are further defined, and the outcome indicators, methods, data sources, and expected availability of data to inform on the success of the program are determined.

Figure 4. Evaluation Phase

1. Outcomes

The first step of the evaluation phase is determining the outcomes (short-term and long-term), which builds upon the outputs from the implementation phase. A program outcome is defined as the specific change the REMS is intended to achieve as a result of the program strategies and corresponding activities. A program outcome indicator should have the following key qualities: clearly defined and measurable, linked to the program goal and objectives, aligned with the strategies (inputs) selected, have baseline measures and/or ***thresholds*** established as a point of reference, and have outcome time frames determined (short-, intermediate-, and long-term outcomes).

There are three program outcome categories that align with the strategies:

- Outcomes that affect knowledge, evaluate awareness and/or understanding of risk messages and safe-use behaviors among REMS participants.

- Outcomes that affect safe-use behavior, evaluate changes in behavior observed in the REMS participants or adoption of safe-use behaviors such as appropriate patient selection, monitoring, and early recognition of a serious adverse event and appropriate intervention.

- Outcomes that inform risk characterization/mitigation, evaluate the incidence, severity, and frequency of the risk as well as appropriateness of the risk mitigation strategies (e.g., the appropriate duration of the observation period after a patient receives the drug). Within this outcome category, applicants could, for example, assess the number of new patients who develop the serious adverse event among all new patients (incidence), or all patients treated with the drug who experience the serious adverse event among the entire treatment population (prevalence), or factors that increase or decrease the risk. Outcomes may be needed in people for whom the drug was not prescribed but who were exposed to the drug either through diversion or accidental exposure.

The program outcomes categories that are selected to evaluate a program should align with the strategies. Different program designs present different challenges for evaluating the program outcomes. For example, often knowledge is assessed as a surrogate outcome when data on direct evidence of the safe-use behavior is not available or difficult to directly measure. Additionally, other factors may influence program outcomes, such as health care providers' and patients' beliefs, attitudes, and risk perceptions as well as external factors (e.g., insurance coverage, State laws); applicants should account for these factors when proposing a program outcome measure.

Because program outcome indicators should measure change (e.g., change in knowledge, change in safe-use behavior), FDA recommends that applicants establish a baseline and/or threshold for the program's outcome. This threshold is the target value that, if achieved, indicates that the REMS is performing as intended. For many drugs with REMS, FDA requires a REMS at the time of initial drug approval.[28] Therefore, in this scenario, program outcomes cannot be determined by comparing outcomes before and after REMS implementation. Nevertheless, the applicant should extrapolate from the clinical trial data, literature, and/or data from other drugs to identify the baseline and propose a threshold to which the program outcome indicator could be compared against to measure the program's success. The applicant can define the threshold relative to a corresponding value measured in a comparator group.

Time frames for outcomes assessment are relative and should be specified for each program. In general, short-term outcomes are achieved in year 1 through year 3 of the program; intermediate-term outcomes are achieved during year 4 through year 6 of the program; and long-term outcomes are achieved during year 7 through year 10 of the program (Knowlton and Phillips 2013). Optimal time frames may vary as they depend on a variety of factors, such as the risk, complexity of the program design, the evaluation methods, and data sources.

Key Performance Indicator

When developing program outcome indicators for REMS, applicants should prospectively identify the key performance indicator(s) that demonstrates if the REMS program is meeting its goal. A key performance indicator is similar to a primary (versus secondary) endpoint in a clinical trial. Applicants and FDA should agree on the key performance indicator(s) that provides insight into whether the program is having the intended effect.

2. Impact

Applicants should evaluate the long-term expectation of what the program intends to achieve. This is accomplished by measuring the program's impact. Impact tends to be a distal outcome measure, meaning it may take time to allow the result of the program to be observed, and the relationship between the program and result may not be direct. For a REMS, impact generally aligns with the health outcome or a serious adverse event the REMS intends to mitigate. Applicants should propose measures for assessing the impact of the REMS in mitigating the risk in the postmarketing setting. Applicants can assess this by comparing change in the incidence of the serious adverse event associated with the drug relative to a comparator. Additionally,

[28] See section 505-1(a)(1) of the FD&C Act.

applicants should identify evidence that demonstrates sustainment of knowledge and incorporation of safe-use behaviors into medical practice (e.g., clinical practice guidelines).

In some cases, it can be challenging to evaluate the impact of a REMS program on health outcomes. For example, orphan drugs that have a REMS with ETASU have patient populations that are relatively small,[29] limiting the statistical power to measure the impact of the program. Additionally, sometimes it can be difficult to interpret the specific contribution of a REMS to the overall observed outcome because REMS are often implemented alongside other factors that can confound the relationship of the REMS to the observed outcome, such as changes to the prescribing information, varied care delivery settings, payer interventions (e.g., payer reimbursement and formulary decisions) and other sources of drug-related risk information (e.g., FDA drug safety communications, medical journals, online resources, mainstream media). Despite these challenges, applicants should consider how additional real-world data or prospective studies with original data collection may be able to assist with assessing the health impact.

Table 3 depicts the relationship between REMS program outcome and health impact.

Table 3. Relationship Between REMS Program Outcome and Health Impact*

	Reassuring Health Impact	**Concerning Health Impact**
Program Outcome Met	• Indicators of health impact are reassuring • REMS program outcome (KPI) is met	• Indicators of health impact are concerning • REMS program outcome (KPI) is met
Program Outcome Not Met	• Indicators of health impact are reassuring • REMS program outcome (KPI) is <u>not</u> met	• Indicators of health impact are concerning • REMS program outcome (KPI) is <u>not</u> met

* REMS = risk evaluation and mitigation strategy; KPI = key performance indicator.

Program outcomes may or may not align with the desired health impact. With each of the four combinations of outcomes and health impact illustrated above, different decisions could be made about the REMS to improve the program and ensure better alignment between the program outcomes and desired health impact.

The top left quadrant is considered a favorable state for a REMS and illustrates that both the intended program outcome and health impact are achieved. However, even under this circumstance, it does not negate the need to evaluate whether there are external factors that are driving the health impact, how much the REMS is contributing to the overall impact, whether

[29] The Orphan Drug Act defines a rare disease as a disease or condition that affects less than 200,000 people in the United States.

improvements are needed, and whether the strategies are being sustained within the health care system. Data or information that demonstrate that other factors within the health care system are sufficient to mitigate the risk and/or ensure that sustainment of the strategies independently of the REMS may support elimination of the program.

The bottom left quadrant illustrates the scenario where indicators of health impact are reassuring but the program outcomes (i.e., key performance indicator) of the REMS are not being met. In this scenario, one possibility may be that there are external factors that may be contributing to the impact and that the REMS may not be necessary. Another possibility may be that the REMS is not functioning as designed. Further modification to the REMS may be needed in this case, including potential elimination because the health outcome may be achieved without the REMS. Another possibility may be that the REMS is affecting the health impact, but the key performance indicators may not be the correct measures of the program outcomes.

The top right quadrant illustrates the scenario where the REMS program outcomes are being met but the health impact is concerning. In this case, data indicate that the REMS is functioning as designed, but it is not having the intended impact on the risk. Therefore, reevaluation of the program design may be necessary. Also, applicants may need to reconsider the indicators used to evaluate the health impact and to ensure that the indicators are valid. Applicants may also need to reconsider if the data are sufficient to make accurate determinations on the health impact. In this scenario, a reevaluation of the REMS is warranted, and a broad reanalysis may be warranted to determine what is necessary to ensure the benefits of the drug outweigh its risks.

The last quadrant in the bottom right illustrates an unfavorable scenario where both the program outcome is not being met and the health impact is concerning. In this scenario, a reevaluation of the REMS is warranted, and a broad reanalysis may be warranted to determine what is necessary to ensure the benefits of the drug outweigh its risks.

IV. CONSIDERATIONS FOR APPLYING FDA'S REMS LOGIC MODEL

The REMS logic model's systematic, structured approach is designed to guide thinking and discussion to link program design, implementation, and evaluation of a REMS. The REMS logic model can be helpful to identify the evidence, assumptions, and uncertainties about the risk and risk mitigation measures as well as map out what the REMS can and cannot accomplish. The model can also be helpful to applicants and the Agency to determine if the program was implemented with fidelity. The model can help in identifying what is important to measure to determine if the program is being implemented as intended and achieving the desired public health outcomes.

Applicants should use the REMS logic model to support their REMS design proposals and throughout the REMS' life cycle to support continuous evaluation and program improvement. Applicants should apply the REMS logic model when designing a new REMS, even in circumstances where there is a REMS for a similar drug or risk because the context may vary. Applicants should also apply the REMS logic model to evaluate and modify a REMS as needed. In addition, some of the logic model principles may be useful when evaluating whether risk

mitigation strategies beyond labeling are necessary. In this scenario, the focus may be limited to the design phase of the REMS logic model to help elucidate the benefits, feasibility, and challenges with requiring additional risk mitigation measures beyond labeling.

A mapping tool (see Appendix) may help applicants visualize how the identified problem, goal and objectives, strategies, and intended outcomes relate to one another and support the program evaluation and program improvement. Applying the model using a mapping tool could help applicants to think critically through the logic model phases for a specific drug. Using the REMS logic model could also facilitate communication throughout a REMS' life cycle between FDA staff and the applicant(s) by establishing a common framework. Widespread adoption of the REMS logic model would allow for consistent use of principles and terminology, which can also enhance efficiency during the review of the REMS proposal and REMS assessment reports.

Although the REMS logic model is a useful tool, its application does not guarantee that the resultant program will deliver the intended results. Furthermore, logic models are not static and should evolve based on new data and information that compel changes to the REMS. Lastly, the application of the REMS logic model also does not preclude the use of other theories or models. The REMS logic model is flexible and adaptive, and other theories and frameworks can be complementary and simultaneously incorporated into an applicant's decision-making process.

GLOSSARY[1]

Activities: The actions that occur to fulfill the program requirements. For a risk evaluation and mitigation strategy (REMS), the required activities are described in the REMS Document and are the same as the *REMS requirements,* which are the actions completed by the applicant(s) and the participants to comply with the REMS and achieve the program's goal and objectives.

Burden: Reflects the additional effort that health care providers and other stakeholders expend in complying with the REMS requirements beyond what is required for standard clinical care.

Capacity for safe use: Availability of resources on an individual, setting, or system level to complete the activities necessary for safe use of a drug.

Care gap: The discrepancy between best practices and the care that is provided or anticipated to be provided in clinical practice. For REMS, the discrepancy between the necessary care a patient needs for the benefits of the drug to outweigh its risks and the care that is actually (or anticipated to be) provided.

Fidelity: The degree to which an intervention or procedure is implemented according to plan. For REMS, the degree to which a program, or its specific strategies or activities, is implemented as intended.

Framework: A structure, overview, outline, system, or plan consisting of various descriptive categories and the relationships between them.

Impact: A distal measure of the program's effects. For REMS, impact should generally measure the program's effect on the health outcome or serious adverse event the REMS intends to mitigate.

Indicators: A measure of outputs and outcomes used to determine if the program is being implemented as expected and achieving its outcomes (categorized into process indicators and outcome indicators).

Informed benefit-risk decision-making: For REMS, this concept aims for discussion between health care providers and patients to reach a mutual decision about starting or continuing a treatment when it may not be feasible to prevent, screen, or manage the risk.

Inputs: The resources put into the program and are essential for the activities to occur. This can include people, organizations/settings, tools, technologies, and funding.

Key performance indicator: A quantifiable measure used to track and assess a company's or program's success at achieving its overall business and program objectives. For REMS, it is a specific outcome indicator developed a priori that can be measured to determine the progress toward assessing the REMS effectiveness.

[1] The definitions in this glossary are presented for the purposes of this guidance only.

Logic model: A tool commonly used in program planning and evaluation. Hypothesized chain of effects leading to the program's desired outcome. Graphical *causal pathway* diagram of human processes and behaviors. It makes explicit the scientific evidence, assumptions, and underlying logic that support the program and the various processes behind it.

Medication use process: A multistep process from drug procurement, distributing, prescribing, order processing, dispensing, administering, and monitoring.

Objectives: Specific statements that describe intended results that are measurable to help monitor progress toward the program goal.

Outcome indicators: Used to determine whether the program is producing its intended results and can be subdivided into program outcomes and health impact.

Outcomes: Change in individuals or organizations participating in the program and often include specific changes in awareness, knowledge, skill, behavior, and adverse event. Can be parsed by time increments into short-, intermediate-, and long-term.

Outputs: The direct results obtained at the program or project level through the execution of the activities. Reflects the information needed to verify that the activities identified in the process reach the right stakeholders and are of the quality and quantity needed to produce the intended results.

Patient access: The extent to which those patients, for whom the expected benefits of the drug outweigh its risks, are able to receive the drug without unnecessary barriers, delays, or interruptions in treatment.

Primary prevention: Aims to prevent disease or injury before it occurs (e.g., immunization against infectious diseases). For REMS, primary prevention aims to prevent a serious adverse event from occurring.

Problem: The main issue(s) a program is designed to address. For REMS, the specific gaps in care identified from putting together the risk assessment and care gap assessment in the context of the medication use process that a REMS may address.

Process indicators: Used to determine how well a program is being implemented and operated by measuring the implementation activities and outputs. Include measures of implementation activities and outputs that inform about unintended consequences (access and burden). Also include measures of implementation activities and outputs on the applicant side and recipient side.

Program evaluation: A systematic method of collecting, analyzing, and using data to examine the effectiveness and efficiency of those programs and to inform continuous program improvement.

Program goal: A broad statement of the ultimate aim, intended accomplishments, or a long-term expectation of what the program is intended to achieve.

Quality assurance: The proactive plans, protocols, and procedures established to ensure the required activities are implemented as intended.

Quality control: The retroactive process of verifying that activities have occurred or been fulfilled.

REMS (risk evaluation and mitigation strategy): A REMS is a drug safety program that the Food and Drug Administration can require for certain drugs with serious risks to help ensure the benefits of the drug outweigh its risks as outlined in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

REMS Document: Part of a REMS that is required by the Food and Drug Administration and establishes the goal and required activities of the REMS.

REMS logic model: Program logic model with assumptions built on the theory of change that provides a systematic approach for the design, implementation, and evaluation of a REMS.

REMS participants: REMS participants are stakeholders who participate in the REMS based on their roles in clinical assessment, prescribing, dispensing, administering, or monitoring as well as the distribution process. They can include health care providers who prescribe the drug; patients who receive the drug; health care settings, other practitioners, and pharmacies that dispense the drug; and wholesalers-distributors that distribute the drug. In addition, for the REMS logic model, applicants and their vendors may also be considered REMS participants.

Resources: The people, materials, and technologies needed to support the program.

Risk characterization/mitigation: The incidence, severity, and frequency of the risk as well as effectiveness of the mitigation strategies.

Safe-use behaviors: Behavior and/or adoption of safe-use behaviors observed in REMS participants.

Secondary prevention: Aims to reduce the impact of a disease or injury by detection and early intervention (e.g., regular exams, screening tests). For REMS, this concept emphasizes early event detection and focuses on screening/monitoring the serious adverse event to prevent worsening.

Self-efficacy: Individual's belief in their ability to execute behaviors necessary to complete a task or achieve a goal. Self-efficacy reflects confidence in the ability to exert control over one's own motivation, behavior, and social environment.

Situation context: Assessing the current state of the health care system as it relates to the serious adverse event and anticipated medication use process for the drug to identify potential care gaps.

For REMS, the context assists in identifying the problem(s) that that may be addressed through a REMS.

Strategies: What approach(es) the REMS is leveraging (to impact knowledge, safe-use behaviors, risk characterization) to address a risk. The substrategies refer to the elements of a REMS as outlined in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

Surveillance strategies: The strategies (e.g., registry, serious adverse event reporting) to evaluate the incidence, severity, and frequency of the risk as well as effectiveness of the REMS.

Tertiary prevention: Aims to manage the impact of an ongoing illness or injury (e.g., administering an antidote). For REMS, this concept targets the clinical outcome stage of a serious adverse event to reduce severity and long-term negative impact.

Threshold: Target value for a specified indicator that is considered acceptable.

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APPENDIX: MAPPING TOOL

Risk:

Design		Implementation					Evaluation		
Situation Context	Program Goal	Inputs			Activity	Output	Outcome		Impact
							Short-term	Long-term	
Problem	Goal and Objectives	Strategy	Sub-strategy	Resources	REMS Requirement	Process Indicator	Outcome Indicator	Outcome Indicator	Outcome Indicator

*Additional rows may be added as needed to map out the program.
REMS = risk evaluation and mitigation strategy.

This mapping tool for a risk evaluation and mitigation strategy logic model is designed to show and help applicants visualize the relationship between the problem, goal and objectives, strategies, activities, outcome indicators, and intended outcomes. Applying the model using a mapping tool can help applicants critically think through the logic model phases for a specific drug and risk. The logic model itself, along with the mapping process, can assist in providing a structured approach to be more intentional about how the design, implementation, and evaluation all relate to one another.

The mapping tool is recommended to be completed by the applicant while the applicant is thinking through the logic model process—starting with identifying the problem (the left side) and working through the logic model steps, moving across toward the right side of the mapping tool. Although visually linear, mapping should be an iterative process that involves moving back and forth or toggling

between steps to address uncertainties, validate assumptions, incorporate new information, and refine the program. The completed mapping tool should include sufficient detail to explain the relationship between the different inputs, outputs, and outcomes of the program. For example, one problem may require multiple strategies and associated substrategies. Each strategy and substrategy should have corresponding activities and resources. Building upon each of the selected inputs and activities, applicants should identify corresponding outputs, outcomes, and outcome indicators including the key performance indicator.