Survey Methodologies to Assess REMS Goals That Relate to Knowledge

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 the approach 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

This guidance provides recommendations to industry on conducting risk evaluation and mitigation strategies (REMS) assessment surveys, used to evaluate respondent knowledge of REMS-related information. This guidance discusses general principles and recommendations related to conducting REMS assessment knowledge surveys, including study design, survey instrument development, survey data collection and processing, and data analysis.

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

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1), as added by the Food and Drug Administration Amendments Act of 2007 (FDAAA) and later amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), authorizes

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

FDA to require REMS for certain drugs[2] if FDA determines that a REMS is necessary to ensure the drug's benefits outweigh its risks.[3,4,5]

REMS may include a Medication Guide, a patient package insert, and/or a communication plan.[6] FDA also may require certain elements to assure safe use (ETASU) as part of a REMS for a drug.[7]

Every proposed REMS for a new drug application (NDA) or biologics license application (BLA) must have a timetable for submission of REMS assessments,[8] that:

- Includes assessments submitted to the FDA by the dates that are 1) 18 months, 2) 3 years after the strategy is initially approved, and 3) in the 7th year after the strategy is so approved; and
- Is at a frequency specified in the strategy, and can be increased or reduced in frequency under certain circumstances and eliminated under certain circumstances.

With limited exceptions, REMS assessments are also required when submitting a supplemental application for a new indication for use, when required by the strategy, and whenever FDA determines that an assessment is needed to evaluate whether the strategy should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the strategy.[9] In addition to the required assessments, an applicant may voluntarily submit an assessment of an approved REMS at any time.[10]

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.

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[2] For the purposes of this document, *drug* refers to a prescription drug or biological product for which there is a pending or approved application, including a new drug application (NDA), abbreviated new drug application (ANDA), or a biologics license application (BLA).

[3] Public Law 110-85, September 27, 2007, available at https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm.

[4] Public Law 112-144, July 9, 2012, available at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf.

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

[6] Sections 505-1(e)(2)-(3) of the FD&C Act.

[7] See Section 505-1(f)(1) of the FD&C Act.

[8] See Section 505-1(c)-(d) of the FD&C Act.

[9] See Section 505-1(g)(2) of the FD&C Act.

[10] See Section 505-1(g)(1) of the FD&C Act.

FDA reviews REMS Assessment Reports[11] to evaluate whether the REMS is meeting its goals. The Assessment Report is the document applicants submit that contains information generated from the analysis of the metrics outlined in the REMS Assessment Plan, which specifies how the applicant intends to assess the performance of the REMS program in meeting its risk mitigation goals and objectives[12].

Many REMS include a goal related to knowledge,[13] such as to inform or educate patients and healthcare providers (i.e., those who prescribe, dispense, or administer drugs) about the serious risks associated with and safe use of a drug. When such knowledge goals are part of a REMS, the REMS assessment plan generally includes, as appropriate, a survey to evaluate patients' and healthcare providers' understanding[14, 15] of the serious risks associated with, and safe use of, the drug.

The majority of applicants use surveys to evaluate patients' and healthcare providers' understanding of the serious risks associated with, and safe use of, their drugs to assess REMS knowledge goals. Though surveys are not the only means to assess these types of goals, this guidance describes best practices for the design, conduct, and data analysis of the results of REMS assessment knowledge surveys. It incorporates input obtained from the June 7, 2012, public workshop entitled "REMS Assessments: Social Science Methodologies to Assess Goals Related to Knowledge,"[16] and the comments regarding the public workshop and accompanying FDA issue paper, submitted to the docket opened in association with the workshop.

III. REMS ASSESSMENT KNOWLEDGE SURVEYS: DESIGN, CONDUCT, AND DATA ANALYSIS

When designing and conducting a REMS assessment knowledge survey, it is important to:

- state the objective of the survey and how it relates to assessing the REMS goal(s)

[11] For purposes of this guidance, the *REMS Assessment Report* is the document applicants submit that contains information generated from the analysis of the metrics outlined in the REMS Assessment Plan.

[12] For more information on the assessment of REMS see the draft guidance for industry *REMS Assessment: Planning and Reporting*, available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

[13] For purposes of this guidance, *knowledge* is defined as the fact or condition of knowing something with familiarity gained through experience or association; the fact or condition of being aware of something; the range of one's information or understanding.

[14] For purposes of this guidance, *understanding* means to know and comprehend the nature or meaning of; the power of comprehending; the power to make experience intelligible by applying concepts and categories.

[15] Some applicants have also included survey questions to assess the behavior changes and burden associated with the REMS program requirements in their REMS assessment knowledge surveys.

[16] The transcript from the June 7, 2012, public workshop is available at https://web.archive.org/web/20170211122735/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM310935.pdf

- identify the target population for the survey (e.g., patients, parents/caregivers, prescribers, pharmacists, other healthcare providers)

- identify the REMS key messages based on the REMS goals and objectives and other relevant REMS materials. These messages should be grouped into appropriate REMS key message domains for assessment, each of which might cover several related REMS key messages and can be assessed with multiple questions or items in the survey. For example, the REMS key messages for Drug X are (a) risk A, (b) risk B, and (c) the need for patient counseling. The proposed protocol might group these three REMS key messages into two domains, Risk A and Risk B, with the relevant patient counseling messages for risk A and risk B grouped into the domains of Risk A and Risk B, respectively.

- specify and provide a rationale for the survey design used to meet the survey objectives (e.g., participant selection and recruitment methods, survey administration modalities), and for the statistical analysis plan (including any stratification by important factors, sample size calculations, and response rate goals [i.e., the proportion of invited subjects who actually completed the survey]).

- construct a survey instrument and test for reliability and validity with regard to survey purposes

- prespecify which questions and items will be used to assess each REMS key message domain

- minimize factors that might contribute to a biased survey (e.g., unrepresentative sampling, faulty recruitment strategies, leading questions that bias the responses in a particular direction, missing data)

- develop strategies to minimize burden on respondents and maximize participation

A. Endpoints of Interest

The endpoints of interest are measurements of knowledge of the REMS key messages in a target population of interest (e.g., patients, prescribers, dispensers, or others, as appropriate). At the subject level, the knowledge endpoint is a binary outcome indicating whether the subject knows or does not know the key message. In a target population, the endpoint is the knowledge rate of a REMS key message. The knowledge rate is the proportion of subjects who know the key message out of all subjects; it is also the chance that a given subject in the target population knows the key message.

Assessing the knowledge of everyone in the target population through a census is not feasible in most cases. Therefore, we recommend in section III.B using a probability random sample selected from an appropriate sampling frame to estimate the target population knowledge rate. To assess a subject's knowledge of REMS key messages, we recommend in section III.F using a well-designed survey instrument with at least one item for each REMS key message. When

multiple questions or items are within a REMS key message domain, then a subject's knowledge of that REMS key message is a composite score based on the answers to those items. The study protocol should clearly specify how the endpoint for each REMS key message domain is calculated from the survey items.

It is important to identify the endpoints pertaining to the REMS key messages for the target population when developing the survey methodology and instruments. Consider, for example, a drug that has a REMS which includes mandatory prescriber training and a goal of informing prescribers about certain serious risks and safe use associated with the drug. The three REMS key messages conveyed in the prescriber educational materials are (1) the serious risk, (2) the dosing and administration considerations related to mitigating that risk, and (3) patient monitoring requirements. Thus, the endpoints of interest would be the following knowledge rates:

1. the proportion of prescribers who know about the serious risk

2. the proportion of prescribers who know the dosing and administration considerations

3. the proportion of prescribers who know the patient monitoring requirements

4. the proportions of prescribers who know only one, two, or all of the REMS key messages

Analyzing answers to questions about the three REMS key messages from a probability sample of prescribers provides estimates and confidence intervals of these endpoints.

A prescriber survey instrument could include questions to assess other endpoints of interest (e.g., the prescriber's knowledge of appropriate patient selection criteria, appropriate counseling recommendations, and instructions to provide to patients). A patient survey instrument could include questions to assess a patient's knowledge (e.g., of the serious risks, safe use, counseling instructions, monitoring requirements, and which symptoms would necessitate contacting the prescriber).

Before conducting a REMS assessment knowledge survey, it is important to propose and provide justification for a performance threshold in the study protocol. This threshold is the minimum knowledge rate that, if achieved, indicates the REMS met the goal of communicating the REMS key messages (i.e., if the surveyed sample's knowledge rates of the REMS key messages meet or exceed the threshold, then communicating this REMS key message would be considered successful). In addition, if the knowledge rates are below the prespecified threshold, it is important to propose steps to achieve the desired knowledge rates (e.g., by enhancing REMS educational materials or outreach activities).

The performance threshold for each survey should be determined on a case-by-case basis. The choice of the prespecified threshold should be informed by the public health implications of a lack of knowledge of a REMS key message, which in turn depends on the indication, the severity and prevalence of the safety concerns, and the target population. Although there is no standard

knowledge performance threshold that is generally accepted for all REMS programs, in most cases it should be 80 percent or higher for each REMS key message domain.

B. Sampling Considerations

Since it is rarely possible to survey the entire target population of those who take a drug, or those who prescribe or dispense a drug, sampling of the target population is more feasible. REMS assessment knowledge surveys should be based on the principle of statistical inference, which generalizes findings from a sample to a target population.[17] The generalizability of the survey results to the target population is based on how representative the sample is of the target population.

An initial step in designing the survey is identifying a sampling frame of the target population. That is, a list of those in the target population from which the sample can be selected. Examples of sampling frames for a REMS target population include individuals in a REMS-mandated patient registry, patient enrollment database, or prescriber or pharmacy enrollment database. When a REMS does not include mandatory databases, possible sampling frames of patients and healthcare providers could be chain pharmacies, voluntary patient registries, or other sources. It is important to provide the rationale for choosing the selected sampling frame that takes into consideration the representativeness of the sampling frame relative to the target population. Evaluating representativeness of a survey sample of the target population includes identifying the demographic and clinical characteristics of the sample and comparing them to known characteristics in the population.

To sample from the selected frame, we recommend using a probability random sample. Probability random sampling assumes every member of the sampling frame has a known and non-zero chance of selection into the sample and ensures the sample is representative of the frame with respect to all characteristics, known or unknown, measured or unmeasured. This ensures the sample is not subject to selection bias. Probability random sampling design does not protect against nonresponse bias; however, when a bias exists because of nonresponse, probability random sampling gives the ability to quantify the magnitude of this bias to assess its impact on the main findings.[18]

A simple random sample (SRS) is a probability random sample in which each member in the sampling frame has the same probability of selection into the sample. Stratified random samples, stratified random samples with oversampling, and cluster samples (with or without stratification) are more elaborate probability random samples, discussed in the remainder of this section. Although selecting an SRS from a frame may be easier than more elaborate sampling designs, a more elaborate design may have advantages over an SRS in ease of conduct.

1. Stratified Random Samples

[17] Altman 1997, p. 490.

[18] Levy and Lemeshow 2008, p. 18-19 and p. 35-36.

In a stratified random sample, the population is first divided into homogeneous strata (e.g., gender, ethnicity, or socioeconomic status), then a simple random sample is taken from each stratum.[19,20] This sampling design is useful when the expected variation in knowledge between strata is larger than the expected variation within each stratum. In that case, we expect the precision of the estimated overall population knowledge rate to be higher in a stratified design than in an SRS of the same size. Therefore, it is important to account for the stratified sampling design in the calculation of the overall knowledge estimates and their standard errors.[21]

2. Stratified Random Samples with Oversampling

Although the distribution of individuals with a particular characteristic (e.g., sex, race) in the SRS sample should be approximately proportional to the distribution in the target population, occasionally it may be of interest to have disproportionate samples with respect to certain characteristics to ensure adequate sample sizes upon which knowledge estimates are based. Oversampling some subgroups of interest in a stratified random sample design leads to more precise knowledge estimates in those subgroups. Examples of oversampling for subgroups of interest include:

- [Serious Risk] is associated with Drug X. People taking Drug X who live in a certain part of the country are more susceptible to [Serious Risk]. All patients who take Drug X are eligible for the survey assessment. Oversampling would be for the patients who live in that certain part of the country because that population is more susceptible to the risk.

- [Serious Risk] is associated with Drug Y. [Serious Risk] is more prevalent in people who are of a certain age category. All patients who take Drug Y are eligible for the survey assessment. Oversampling would be for the patients who are within that certain age category because that population is more susceptible to the risk.

- [Serious Risk] is associated with Drug Z. [Serious Risk] can happen to females of childbearing potential (females who can become pregnant). All healthcare providers who prescribe Drug Z are eligible for the survey assessment. Oversampling would be for the healthcare providers who treat females of childbearing potential with Drug Z, because that population of healthcare providers treats the population that is susceptible to the risk.

3. Cluster Samples (With or Without Stratification)

A cluster sample consists of all or a random sample of subjects from a random sample of clusters. Example of a cluster is a clinic or a hospital. A cluster survey typically requires a larger sample of subjects from a few clusters of entities, and requires a more complex sampling design and analysis than an SRS. However, conducting a survey using a cluster design may be

[19] Aday and Cornelius 2006, p. 131-132.

[20] Dillman et al. 2014, p. 76.

[21] Levy and Lemeshow, p. 121-142.

more feasible than conducting the survey with an SRS design.[22] For example, a two-stage cluster survey design of patients can consist of selecting clinics at random in the first stage then selecting patients at random within sampled clinics in the second stage. In the example, surveying more patients from a few clinics may be logistically easier than surveying a SRS sample which may have fewer patients but from many more clinics scattered across the country. However, results from cluster surveys are more complex to analyze than results from an SRS because in a cluster design, cluster size and correlations of knowledge among subjects in the same cluster should be taken into account in determining precision of estimates of knowledge. It is important to account for the cluster sampling in calculating precision of estimates.

If an applicant demonstrates that using a probability random sample is not feasible, then the applicant should discuss using other types of surveys to assess knowledge with the Agency.

C. Sample Size Considerations

In this section, *sample size* refers to the number of survey participants in a population of interest. The number of subjects invited to participate in a survey should be larger than the target sample size to account for nonresponse.

For a given target population, we recommend that the sample be large enough to precisely estimate the knowledge rate in that population. Sample size calculation considers two important elements: sampling design (see section III.B, above) and precision of the estimated knowledge rate. This guidance discusses three sampling designs: SRS, cluster sample, and stratified random sample.

Precision is a measure of sampling uncertainty. In this guidance, precision is the absolute difference of the sample estimate and the lower bound of the two-sided 95 percent confidence interval of this estimate. We recommend it be controlled at 5 percentage points or less in the sample size calculation. This 5 percentage points represents an absolute value and is not relative to the knowledge rate.

Other elements that may enter in the sample size calculation are the target population's size and assumed knowledge rate:

- *Target population size* refers to the number of individuals in the target population. The target population depends on the REMS goals and is usually one of three groups: all subjects who take the drug, all subjects who prescribe the drug, or all subjects who dispense the drug.

- *Assumed knowledge rate* used for the sample size calculation is the best guess or expected knowledge rate in the target population based on relevant published literature, similar surveys, or pilot studies. For a more conservative estimate of the sample size while keeping everything else the same, one might choose to use a 50 percent knowledge rate, which would yield the largest sample size estimate.

[22] Levy and Lemeshow, p. 223-230.

Determining the appropriate sample size is easier for an SRS survey than for a cluster sample or stratified random sample. Table 1 presents the estimated sample sizes with a target precision of 4 percent for different assumed knowledge rates and target population sizes. It also shows how the appropriate sample size for an SRS survey with 4 percent target precision increases as the assumed knowledge rate approaches 50 percent, and the appropriate sample size for an SRS survey decreases from large target population sizes to small target population sizes. For example, given a target precision of 4 percent, an assumed knowledge rate of 50 percent, and a large target population size, the appropriate sample size is 601.

Table 1: Estimated Sample Size for a Simple Random Sample with a Target Precision of 4% (Half-Width of 95% Confidence Interval) for Different Assumed Knowledge Rates and Different Target Population Sizes

Target Population Size	Sample Size When Assumed Knowledge Rate Is --				
	90%	80%	70%	60%	50%
50,000	217	385	505	577	601
5,000	208	357	459	517	536
500	151	218	252	268	273

For a clustered design, a stratified random sample, or other complex designs, the sample size to achieve a certain precision differs from the sample size in a SRS by the *design effect* factor.[23] The design effect of a survey design is the ratio of the variance of estimates from that design, divided by the variance of estimates from an SRS of the same size. For example, when the design effect is 2, the sample size should be twice as large as an SRS survey to achieve the same target precision. Conversely, when the design effect is 0.5, the sample size can be half the size of an SRS survey to achieve the same target precision.

The appropriate sample size to achieve a certain precision is higher in a cluster design than in an SRS by the design effect factor because the variance of estimates in the cluster design is higher than in an SRS (i.e., design effect factor > 1).[24] The design effect in a cluster design increases with the number of subjects in each cluster and with intra-cluster correlation coefficients (ICC)[25].

The appropriate sample size to achieve a certain precision is generally lower in a stratified design than in an SRS by the design effect factor because the variance of estimates in a stratified design is lower than for an SRS (i.e., design effect factor $\leq$ 1).[26] The variance in a stratified design takes into account within stratum variability and allocation proportions or weights for the strata.

[23] Aday and Cornelius, p. 175-178.

[24] Levy and Lemeshow, p. 223-230.

[25] The formula for design effect using ICC and cluster size (M) is 1+(ICC)*(M -1). The definition of ICC is the ratio of between cluster variance to the sum of between cluster variance and within cluster variance. ICC is a measure of how related two measurements are within each cluster compared to between clusters. ICC ranges from zero to one, with zero indicating no correlation of survey responses within a cluster and one indicating all survey responses within a cluster are identical.

[26] Levy and Lemeshow, p.121-142.

When there are multiple REMS key messages, presenting a 95 percent confidence interval for each REMS key risk message independently can give a false sense of precision, as the overall confidence level for all REMS key messages is much less than 95 percent due to multiplicity. Therefore, we recommend having as few REMS key message domains as possible. Any REMS key message domains should be constructed in a meaningful way.

D. Participant Recruitment

Recruiting participants for REMS assessment knowledge surveys can be challenging. There is no single best way to recruit participants for these surveys because of the variation in how drugs are prescribed and dispensed and in patient populations. In general, we recommend a multimodal approach be used to recruit participants (e.g., sending survey invitations via U.S. mail, email, and phone).[27]

A description of the recruitment sources and justification for selecting the recruitment sources should be provided in the survey protocol. Combining several sources of potential survey participants may ensure a broader cross section of the patient or healthcare provider population of interest in the sampling frame, provide a robust approach to lower nonresponse, meet the target sample size, and lower potential nonresponse bias. Survey participants should be made aware that taking part in the survey is voluntary.

1. Methods to Minimize Non-Response

Using multiple recruitment sources might still result in a low response rate unless additional recruitment methods are employed. Follow-up contact to nonrespondents using a different mode than what was used to make initial contact can increase response rates during recruiting.[28] Using social validation is especially useful in nonrespondent follow-up. For example, informing nonrespondents that others have completed the survey can encourage them to respond to the survey.[29]

Finally, cluster samples and multi-stage survey sampling can make reaching participants easier and increase response rates.

Using multimodal approaches and other study designs can not only reduce nonresponse rates, it can also reduce nonresponse bias, which is possible even in probability surveys because knowledge of key messages of subjects who chose to respond to a survey may be different from knowledge of those subjects who chose not to respond to a survey. Thus, high nonresponse threatens the validity of a survey. By increasing response rate, the survey and estimated knowledge rate are more generalizable to the target population.

[27] Dillman et al., p. 400 - 403.

[28] Dillman et al., p. 417 - 418.

[29] Dillman et al., p. 30.

E. Survey Conduct

1. Eligibility Criteria

It is important to consider appropriate inclusion and exclusion criteria for the target population participating in REMS assessment knowledge surveys and provide an appropriate explanation in the protocol for the criteria selected. The disposition of survey participants at various stages of inclusion or exclusion should be provided in the REMS assessment report.

In general, eligible *patient* participants should:

- be age 18 or older (or have a parent/caregiver respond for a patient who takes the drug and is under 18 years of age)
- be currently taking the drug with the approved REMS, or have taken the drug within a reasonable timeframe[30]
- not be currently participating in a clinical trial involving the drug
- not have participated in a previous REMS assessment survey for the same drug
- Not be currently employed by the applicant, FDA, or the third party conducting the REMS knowledge assessment survey, or have other conflicts of interest that might affect their answers

In general, eligible *prescriber* and *pharmacist* participants should:

- be certified and/or enrolled to prescribe or dispense the drug[31] ***or*** have prescribed or dispensed the drug within a reasonable timeframe
- not have participated in a previous REMS assessment survey for the same drug
- not be currently employed by the applicant, FDA, or the third party conducting the REMS knowledge assessment survey, or have other conflicts of interest that might affect their answers.

2. Survey Administration

It is important to inform potential survey participants that their participation is voluntary, they can cease their participation at any time in the course of taking the survey, and they can contact

[30] Determining eligibility based on how recently a patient has used a REMS drug might present a trade-off between recall and the ability to recruit adequate numbers of patients. You might wish to shorten this interval or even limit participation to current users if it will not interfere with recruitment. In any case, the criteria should be specified.

[31] Applicable if there is a REMS requirement for prescribers or pharmacists to be enrolled or certified to be able to prescribe or dispense the drug.

the study sponsor with questions or concerns about their participation. Potential participants should be informed that their answers will not affect their ability to prescribe, dispense, or receive the drug.

The purpose of the REMS knowledge assessment survey is to evaluate the target populations' knowledge retention about the serious risks and safe use of the drug, not to evaluate their ability to read and comprehend the educational materials at the time of the survey. Therefore, respondents should not be offered an opportunity to read or see the Medication Guide, prescribing information, or any other REMS-related educational materials as part of the survey process. To remind the survey respondents what these REMS-related educational materials are, respondents may be provided a text description of the Medication Guide and illegible rendition of these materials for relevant survey questions.

Two general methods should be considered to administer the survey and collect survey data, each with its own advantages and disadvantages: self-administration (mail or Internet survey) and use of a trained interviewer (e.g., individual or group interviews, in-person or telephone interviews) to ask the questions. Survey administration modality should be decided based on the study question and target population, as well as the following additional factors:

- potential response rate
- noncoverage and nonresponse bias[32]
- complexity of concepts and survey questions
- length of questionnaire and time needed to complete the survey
- special characteristics of the population of interest

Ideally, survey participants should be offered multiple survey administration modalities for completing REMS surveys (e.g., mail, telephone, Internet, in person). Offering multiple survey modalities may:

- reduce coverage error when a single mode cannot adequately cover the population of interest
- improve response rate, with the recognition that some people prefer certain modes and may not respond to others
- reduce nonresponse bias by obtaining responses from people who may be difficult to reach via certain modes

[32] Aday and Cornelius 2006, p. 112-113.

- reduce measurement error by offering modes to ask/answer questions in non-embarrassing ways or allowing adequate time for survey participants to read and answer questions at their own pace

- improve timeliness of survey completion by reaching the target sample size quickly[33]

F. Survey Questionnaire Development

The survey questionnaire should be designed to accurately capture respondents' understanding of the REMS key messages and optimize the validity of the information collected. Wording, question structure, and question sequences can significantly affect the validity and interpretability of the data collected. Experts in questionnaire design should be involved when designing the questionnaire. Applicants should ensure that the proposed survey instrument's reliability and validity are tested and the results are acceptable.

The following recommendations merit particular consideration when designing the survey questionnaire:

- Use audience-appropriate vocabulary and pretested questions.

- Use direct, specific, and unambiguous questions.

- Use a variety of question types, such as open-ended, close-ended, multiple-choice, and true/false.

- Design questions to ask about knowledge, not about opinions. Appropriate responses to true/false questions are not "agree" or "disagree."

- Frame questions in a positive way.

  Examples of positively worded questions (recommended format):

  - You should tell your healthcare provider about [Symptom] before taking Drug X. (True/False/I don't know)
  - [Serious Risk] is associated with the use of Drug X. (True/False/I don't know)

  Examples of negatively worded questions:

  - You should not tell your healthcare provider about [Symptom] before taking Drug X. (True/False/I don't know)
  - Treatment with Drug X does not cause [Serious Risk]. (True/False/I don't know)

- Include questions to test whether respondents can successfully apply knowledge they learned from the REMS education materials.

[33] Dillman et al., p. 400 - 403.

- Ensure questions are not biased or leading.

- Ensure each question has an "I don't know" option. When listing response categories for multiple-choice questions, "I don't know" provides respondents permission to admit they do not know and thus avoid guessing. It is also important that dichotomous questions—for example, yes/no questions about potential drug side effects—offer an "I don't know" option.

- Advise respondents to select "I don't know" rather than guess an answer.

- Develop lists of answer categories that include all reasonable possible answers.[34]

- Multiple-choice responses should be mutually exclusive and independent.

- Include foils or decoy answers (i.e., plausible incorrect answers) as possible answer options.

- Randomize the order of multiple-choice responses for each question.[35]

- Randomize correct responses between "true" and "false" and include an equal (or near equal) number of answers that are "true" as are "false."

- Include an instruction to "select all that apply," when appropriate.

- Do not include any information that educates or influences a respondent's ability to answer subsequent questions.

- Do not allow respondents the opportunity or ability to skip ahead or go back to previous questions in the survey.

- Offer education for incorrect and "I don't know" responses at the *end* of the survey, not after each question.

- Specify answer key for each question in the survey.

1. Questionnaire Design Considerations for Patient Surveys

Questionnaires for assessing patient knowledge should include questions about the specific risks or safety information conveyed in the patient-directed REMS materials (e.g., how to recognize

[34] Dillman et al., p. 135 - 136.

[35] Dillman et al., p. 146-148.

and what to do if they experience symptoms of an adverse event). The following list includes some recommended considerations when designing a patient questionnaire:

- Derive the REMS risk-specific questions from information specified in the REMS goals and the REMS patient education materials, including the Medication Guide. As applicable, this includes all the risks or adverse events conveyed (real, potential, or theoretical), signs and symptoms of the adverse events, and what to do if symptoms of an adverse event occur.

- Use text from the patient-directed REMS materials verbatim for questions and answers.

- Ensure questions and answers are worded at the 6th- to 8th-grade reading level.

- When applicable, to help assess the distribution of the Medication Guide, include questions about receipt of the Medication Guide in the patient survey.

- The knowledge questions are the highest priority in the REMS assessment knowledge survey. When the survey includes questions other than those related to knowledge (e.g., questions about patient receipt of the Medication Guide), organize the questions so the risk-specific questions are listed first, followed by the other questions. Demographic information should be collected last or as part of any screening questions.

- Before questions about receipt of the Medication Guide, include text that describes a Medication Guide and, if possible and depending on how the survey is administered, a link to or a picture showing an illegible version of the Medication Guide.

  Example:

  Now we are going to ask you some questions about the Medication Guide you may have received with Drug X. The Medication Guide is a paper handout that contains important information about the risks associated with use of Drug X and how to use Drug X safely. Medication Guides always include the title *Medication Guide*, followed by the word *Drug X* and its pronunciation. The Medication Guide usually has sections titled *What is the most important information I should know about Drug X?*, *What is Drug X?*, and *Who should not take Drug X?*.

- When applicable, use the following (or similar) questions to assess receipt and use of the Medication Guide:

  - Who gave you the Medication Guide for Drug X? (Select all that apply.)
    a) My doctor or someone in my doctor's office.
    b) My pharmacist or someone at the pharmacy.
    c) Someone else (please explain): _____.
    d) I don't know.
    e) I did not get a Medication Guide for Drug X. (If you checked this, skip to question XXX)

- When did you receive the Medication Guide for Drug X? (Select all that apply.)
  a) With my first prescription only.
  b) Not with my first prescription, but with some refills.
  c) Not with my first prescription, but with every refill.
  d) With my first prescription and every refill.
  e) I don't know.

- Did someone explain the Medication Guide for Drug X to you?
  a) Yes, my doctor or someone in my doctor's office.
  b) Yes, my pharmacist or someone at the pharmacy.
  c) Yes, someone else (please explain): _____.
  d) No.
  e) I don't know.

2. Questionnaire Design Considerations for Healthcare Provider Surveys

The healthcare provider survey should include a section with questions about the specific risks and safety information conveyed in the REMS goals and REMS educational materials. The following list includes some recommended considerations when designing a healthcare provider questionnaire:

- Questions should cover all aspects of healthcare provider activities required under the REMS (e.g., knowledge of risks related to the REMS; proper patient selection criteria; proper patient counseling points; proper monitoring of patients; other REMS-compliance requirements; and receipt of REMS educational materials).

- Questions should solicit answers based on information contained in the Prescribing Information and REMS materials, not on the respondent's experience or opinion.

  Example:

  According to the Prescribing Information, Drug X can cause which of the following serious side effects? (Select all that apply.)

- Use the following (or similar) questions to assess receipt and use of the educational materials, as applicable. Include a question about each educational piece required as part of the REMS.

  Example:

  Before today, which of the following educational materials were you aware of, did you receive, and did you read/view with regard to Drug X? (Select all that apply.)

Educational Material	Aware	Received	Read/Viewed
Full Prescribing Information	□ Yes □ No	□ Yes □ No □ Don't know	□ Yes □ No □ Don't know
Medication Guide	□ Yes □ No	□ Yes □ No □ Don't know	□ Yes □ No □ Don't know
Dear Healthcare Provider Letter	□ Yes □ No	□ Yes □ No □ Don't know	□ Yes □ No □ Don't know
Drug X Educational Brochure	□ Yes □ No	□ Yes □ No □ Don't know	□ Yes □ No □ Don't know
Drug X Educational Video	□ Yes □ No	□ Yes □ No □ Don't know	□ Yes □ No □ Don't know
Something else (please specify): _____	□ Yes □ No	□ Yes □ No □ Don't know	□ Yes □ No □ Don't know

- Use the following (or similar) question to assess which sources healthcare providers use to learn about the risks associated with the drug.

  Example:

  - From what sources have you learned about the risks associated with the use of Drug X? (Select all that apply.)
    a) Sales representative
    b) Drug X REMS.com
    c) Drug X.com
    d) Full Prescribing Information
    e) Drug X REMS Letter to Healthcare Providers Letter
    f) Drug X REMS Letter to Professional Societies
    g) Drug X REMS Factsheet for Healthcare Providers
    h) Drug and prescribing information databases
    i) Other (please specify): _____

IV. STATISTICAL CONSIDERATIONS WHEN ANALYZING AND PRESENTING RESULTS

When the survey is completed, analyses and presentations of results should follow the prespecified statistical analysis plan described in the survey protocol. The REMS assessment report should provide data management information, characteristics of study subjects, and assessment knowledge survey results.

The REMS assessment report should include study subjects' characteristics using a range of descriptive statistics, including means, standard deviations, medians, minimum and maximum values (for continuous variables), interquartile range, and frequency distributions (for nominal or ordinal variables). To demonstrate that the sample is representative of the target population, applicants should compare the characteristics of the sample to the known characteristics of the

sampling frame and target population and discuss the reasons for any discrepancy and its potential influence on the validity of the inference from the sample. Applicants should also compare known information about nonresponders to that of responders and discuss the potential impact of nonresponder bias on the study results.

In addition, the REMS assessment report should include knowledge rate estimates and their 95 percent confidence interval for each question and each REMS key message domain. For REMS key message domains measured by multiple questions and answers, prespecified and appropriately and meaningfully constructed composite scores can be used to present the findings regarding each domain.

For complex survey designs, such as stratified random sample or cluster sample surveys, the knowledge rate of a key message in the overall population should be estimated from a weighted average of knowledge rates in different clusters or strata, where the weights depend on the sampling design and any nonresponse adjustments that may be important. Both the knowledge rate estimates and the associated precision estimates should reflect the probability sampling design used for the study. Because the appropriate analysis methods for the point estimates and their precision depend on the design, they should be prespecified. Post hoc stratification and weighting cannot salvage a poorly designed survey or poorly collected data.

The REMS assessment report should also include analyses of data from all survey respondents during the reporting period. When the number of completed survey questionnaires received is higher than expected, all data from completed surveys should be included in the analysis and report; the report should not sample or select from the survey respondents.

When a returned or completed questionnaire contains unanswered items, unanswered questions should be considered as missing, not wrong. Results reporting should follow methods to handle missing values prespecified in the statistical analysis plan.

For each survey question, the results presented should include at least the total number of respondents that selected each answer choice, the number that did not select any answer, and the corresponding percentages of total respondents.

Example:

True or False: According to the Prescribing Information, [Serious Risk] is associated with the use of Drug X?

- Out of the 500 respondents who were asked this question, 450 responded
  - 200 (40% of 500) selected “True”
  - 125 (25% of 500) selected “False”
  - 125 (25% of 500) selected “I don’t know”
  - 50 (10%) did not select any answer

Finally, the REMS assessment report should include subgroup analyses when important subgroups are prespecified in the statistical analysis plan. Examples of possible subgroups of

interest are those patients who read or did not read the Medication Guide, those patients who have most recently been prescribed a drug, or those who have been taking it for some time. Additional examples are subgroups based on socioeconomic or ethnic background or high-risk medical conditions. FDA supports judicious reporting of subgroup analyses. However, conclusions based on the whole survey sample are the primary interest in a REMS knowledge assessment survey. Basing conclusions for the target population on a subset of the data is considered an inappropriate practice.[36] Presentation of a partial analysis as the main finding can distort the conclusion from the survey.

V. SUMMARY OF IMPORTANT POINTS

To assist in developing survey protocol and presenting REMS assessment knowledge survey methodology and results, the following detailed information should be included in the submissions of proposed survey protocol[37] and REMS assessment report, as applicable:

A. Assessment Survey Protocol

- background information on the regulatory history of the REMS, epidemiological data of the risks that the REMS is intended to address, and epidemiological data on the target populations for REMS assessment knowledge surveys (e.g., the number of patients and prescribers)

- inclusion and exclusion criteria for potential survey participants and reasons for the selected criteria

- main characteristics of each target population group, including a description of the population for each of the following target groups, as appropriate:

    - those who are prescribed the drug (as much as possible in terms of age, race, ethnicity, education, gender, geography, indication for use)
    - those who prescribe the drug (as much as possible in terms of geography, indication for which they prescribe the drug, medical specialty, gender)
    - those who dispense the drug

- rationale for choosing a particular sampling frame and a description of the sampling frame and its relationship to the target population

- for each REMS key message domain, specify which questions are used to evaluate it, how each question is scored, and how the endpoint for each key message is derived from these questions

[36] Altman, p. 486.

[37] See the draft guidance for industry *REMS Assessment: Planning and Reporting,* available at [insert website], in which procedures for REMS assessment submission are outlined

- prespecified thresholds for success and their justification for each REMS key message domain

- rationale for choosing a particular survey design, such as cluster or stratified random sample

- description of impact of design on overall population knowledge rate estimate and precision

- derivation of the appropriate sample size of responders based on the sampling frame, the survey design, the anticipated non-response rate, and the target precision of the knowledge rate

- derivation of the number of people to be contacted to achieve the targeted number of participants

- strategy used to select sources of potential survey participants

- recruitment plan, including the modes that will be used

- plan to provide any incentive to participants

- recruitment materials

- rationale for the planned survey administration modalities

- strategies to minimize nonresponse

- description of the steps used to develop the survey instrument

- methods used to pretest the survey questionnaire and its findings

- survey instruments, including any introductory text and screening questions

- techniques used to train surveyors (if applicable).

- statistical analysis plan

- methods used to control for potential limitations or bias

- methods to handle missing values in responses to the items of the questionnaire

- system for coding, entering, and verifying study data

- planned procedures for coding, categorizing, and analyzing verbatim responses to open-ended questions

- answer key for all close-ended questions

- process for offering education for incorrect responses

B. Survey Results and Interpretation

- methodology used, including a description of any deviations from the proposed protocol

- nature of the recruitment effort and the response rate, defined as the proportion of invited subjects who took the survey

- relevant demographic characteristics of respondents compared to nonrespondents based on available information

- relevant demographic characteristics of survey respondents and whether they completed the survey

- reasons why respondents failed to complete the survey, when known

- representativeness of the survey sample of the target population

- the knowledge rates, with 95 percent confidence intervals, for each domain of REMS key messages and each question related to each domain of REMS key messages

- potential biases, the suspected magnitude and direction of these biases, and their potential impact on the interpretation of the survey findings

- a conclusion about the extent to which the REMS goals related to knowledge are met, how that determination was made, and proposed changes to the REMS, when applicable.

REFERENCES

Aday, Lu Ann, and Llewellyn J. Cornelieus. *Designing and Conducting Health Surveys: A Comprehensive Guide* (Third Edition), San Francisco, CA: Wiley, 2006.

Altman, Douglas G. *Practical Statistics for Medical Research*, New York: Chapman & Hall, 1997.

Dillman, Don A., Jolene D. Smyth, and Leah Melani Christian. *Internet, Phone, Mail, and Mixed-mode Surveys: The Tailored Design Method* (Fourth Edition), Hoboken, New Jersey: John Wiley & Sons, Inc., 2014.

Levy, Paul S., and Stanley Lemeshow. *Sampling of Populations: Methods and Applications* (Fourth Edition), New York: John Wiley & Sons, Inc., 2008.