
Survey Methodologies to Assess REMS Goals That Relate to Knowledge Guidance for Industry

DRAFT GUIDANCE

For questions regarding this draft document, contact (CDER) Office of Surveillance and Epidemiology, Division of Risk Management, Brian Gordon at 301-796-3960 or Doris Auth at 301-796-0487, or (CBER) Office of Communications, Outreach and Development at 800-835-4709 or 240-402-8010.

**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)**

**January 2019
Procedural**

Survey Methodologies to Assess REMS Goals That Relate to Knowledge Guidance for Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Room 2201
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714; Email: druginfo@fda.hhs.gov
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

and/or

*Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

**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)**

**January 2019
Procedural**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	1
III.	REMS ASSESSMENT KNOWLEDGE SURVEYS: DESIGN, CONDUCT, AND DATA ANALYSIS	3
A.	Endpoints of Interest	4
B.	Sampling Considerations	6
1.	<i>Stratified Random Samples</i>	<i>6</i>
2.	<i>Stratified Random Samples With Oversampling</i>	<i>7</i>
3.	<i>Cluster Samples (With or Without Stratification)</i>	<i>7</i>
C.	Sample Size Considerations	8
D.	Participant Recruitment	10
E.	Survey Conduct	11
1.	<i>Eligibility Criteria</i>	<i>11</i>
2.	<i>Survey Administration</i>	<i>11</i>
F.	Survey Questionnaire Development	13
1.	<i>Questionnaire Design Considerations for Patient Surveys</i>	<i>14</i>
2.	<i>Questionnaire Design Considerations for Healthcare Provider Surveys</i>	<i>16</i>
IV.	STATISTICAL CONSIDERATIONS WHEN ANALYZING AND PRESENTING RESULTS	17
V.	SUMMARY OF IMPORTANT POINTS	19
A.	Assessment Survey Protocol	19
B.	Survey Results and Interpretation	21
	REFERENCES	24

1 **Survey Methodologies to Assess REMS Goals That Relate to**
2 **Knowledge**
3 **Guidance for Industry¹**
4

5
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
8 binding on FDA or the public. You can use an alternative approach if the approach satisfies the
9 requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the
10 FDA staff responsible for this guidance as listed on the title page.
11

12
13
14 **I. INTRODUCTION**
15

16 This guidance provides recommendations to industry on conducting risk evaluation and
17 mitigation strategies (REMS) assessment surveys, used to evaluate respondent knowledge of
18 REMS-related information. This guidance discusses general principles and recommendations
19 related to conducting REMS assessment knowledge surveys, including study design, survey
20 instrument development, survey data collection and processing, and data analysis.
21

22 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
23 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
24 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
25 the word *should* in Agency guidances means that something is suggested or recommended, but
26 not required.
27

28 **II. BACKGROUND**
29

30 Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1), as
31 added by the Food and Drug Administration Amendments Act of 2007 (FDAAA) and later
32 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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

33 FDA to require REMS for certain drugs² if FDA determines that a REMS is necessary to ensure
34 the drug's benefits outweigh its risks.^{3,4,5}

35
36 REMS may include a Medication Guide, a patient package insert, and/or a communication plan.⁶
37 FDA also may require certain elements to assure safe use (ETASU) as part of a REMS for a
38 drug.⁷

39
40 Every proposed REMS for a new drug application (NDA) or biologics license application (BLA)
41 must have a timetable for submission of REMS assessments,⁸ that:

- 42
- 43 • Includes assessments submitted to the FDA by the dates that are 1) 18 months, 2) 3 years
44 after the strategy is initially approved, and 3) in the 7th year after the strategy is so
45 approved; and
 - 46 • Is at a frequency specified in the strategy, and can be increased or reduced in frequency
47 under certain circumstances and eliminated under certain circumstances.
- 48

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

55
56 Section 505-1(g)(3) of the FD&C Act specifies that a REMS assessment shall include, with
57 respect to each goal in the strategy, an assessment of the extent to which the approved strategy,
58 including the elements, is meeting the goal or whether the goal or elements should be modified.
59 The FD&C Act does not specifically describe how an applicant should conduct this assessment.

60

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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

61 FDA reviews REMS Assessment Reports¹¹ to evaluate whether the REMS is meeting its goals.
62 The Assessment Report is the document applicants submit that contains information generated
63 from the analysis of the metrics outlined in the REMS Assessment Plan, which specifies how the
64 applicant intends to assess the performance of the REMS program in meeting its risk mitigation
65 goals and objectives¹².

66
67 Many REMS include a goal related to knowledge,¹³ such as to inform or educate patients and
68 healthcare providers (i.e., those who prescribe, dispense, or administer drugs) about the serious
69 risks associated with and safe use of a drug. When such knowledge goals are part of a REMS,
70 the REMS assessment plan generally includes, as appropriate, a survey to evaluate patients' and
71 healthcare providers' understanding^{14, 15} of the serious risks associated with, and safe use of, the
72 drug.

73
74 The majority of applicants use surveys to evaluate patients' and healthcare providers'
75 understanding of the serious risks associated with, and safe use of, their drugs to assess REMS
76 knowledge goals. Though surveys are not the only means to assess these types of goals, this
77 guidance describes best practices for the design, conduct, and data analysis of the results of
78 REMS assessment knowledge surveys. It incorporates input obtained from the June 7, 2012,
79 public workshop entitled "REMS Assessments: Social Science Methodologies to Assess Goals
80 Related to Knowledge,"¹⁶ and the comments regarding the public workshop and accompanying
81 FDA issue paper, submitted to the docket opened in association with the workshop.

82
83 **III. REMS ASSESSMENT KNOWLEDGE SURVEYS: DESIGN, CONDUCT, AND**
84 **DATA ANALYSIS**

85
86 When designing and conducting a REMS assessment knowledge survey, it is important to:

- 87
88
 - state the objective of the survey and how it relates to assessing the REMS goal(s)

89

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>

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 90 • identify the target population for the survey (e.g., patients, parents/caregivers, prescribers,
91 pharmacists, other healthcare providers)
92
- 93 • identify the REMS key messages based on the REMS goals and objectives and other
94 relevant REMS materials. These messages should be grouped into appropriate REMS
95 key message domains for assessment, each of which might cover several related REMS
96 key messages and can be assessed with multiple questions or items in the survey. For
97 example, the REMS key messages for Drug X are (a) risk A, (b) risk B, and (c) the need
98 for patient counseling. The proposed protocol might group these three REMS key
99 messages into two domains, Risk A and Risk B, with the relevant patient counseling
100 messages for risk A and risk B grouped into the domains of Risk A and Risk B,
101 respectively.
102
- 103 • specify and provide a rationale for the survey design used to meet the survey objectives
104 (e.g., participant selection and recruitment methods, survey administration modalities),
105 and for the statistical analysis plan (including any stratification by important factors,
106 sample size calculations, and response rate goals [i.e., the proportion of invited subjects
107 who actually completed the survey]).
108
- 109 • construct a survey instrument and test for reliability and validity with regard to survey
110 purposes
111
- 112 • prespecify which questions and items will be used to assess each REMS key message
113 domain
114
- 115 • minimize factors that might contribute to a biased survey (e.g., unrepresentative
116 sampling, faulty recruitment strategies, leading questions that bias the responses in a
117 particular direction, missing data)
118
- 119 • develop strategies to minimize burden on respondents and maximize participation
120

121 **A. Endpoints of Interest**
122

123 The endpoints of interest are measurements of knowledge of the REMS key messages in a target
124 population of interest (e.g., patients, prescribers, dispensers, or others, as appropriate). At the
125 subject level, the knowledge endpoint is a binary outcome indicating whether the subject knows
126 or does not know the key message. In a target population, the endpoint is the knowledge rate of
127 a REMS key message. The knowledge rate is the proportion of subjects who know the key
128 message out of all subjects; it is also the chance that a given subject in the target population
129 knows the key message.
130

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

140
141 It is important to identify the endpoints pertaining to the REMS key messages for the target
142 population when developing the survey methodology and instruments. Consider, for example, a
143 drug that has a REMS which includes mandatory prescriber training and a goal of informing
144 prescribers about certain serious risks and safe use associated with the drug. The three REMS
145 key messages conveyed in the prescriber educational materials are (1) the serious risk, (2) the
146 dosing and administration considerations related to mitigating that risk, and (3) patient
147 monitoring requirements. Thus, the endpoints of interest would be the following knowledge
148 rates:

- 149
150 1. the proportion of prescribers who know about the serious risk
151
152 2. the proportion of prescribers who know the dosing and administration considerations
153
154 3. the proportion of prescribers who know the patient monitoring requirements
155
156 4. the proportions of prescribers who know only one, two, or all of the REMS key messages
157

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

160
161 A prescriber survey instrument could include questions to assess other endpoints of interest (e.g.,
162 the prescriber's knowledge of appropriate patient selection criteria, appropriate counseling
163 recommendations, and instructions to provide to patients). A patient survey instrument could
164 include questions to assess a patient's knowledge (e.g., of the serious risks, safe use, counseling
165 instructions, monitoring requirements, and which symptoms would necessitate contacting the
166 prescriber).

167
168 Before conducting a REMS assessment knowledge survey, it is important to propose and provide
169 justification for a performance threshold in the study protocol. This threshold is the minimum
170 knowledge rate that, if achieved, indicates the REMS met the goal of communicating the REMS
171 key messages (i.e., if the surveyed sample's knowledge rates of the REMS key messages meet or
172 exceed the threshold, then communicating this REMS key message would be considered
173 successful). In addition, if the knowledge rates are below the prespecified threshold, it is
174 important to propose steps to achieve the desired knowledge rates (e.g., by enhancing REMS
175 educational materials or outreach activities).

176
177 The performance threshold for each survey should be determined on a case-by-case basis. The
178 choice of the prespecified threshold should be informed by the public health implications of a
179 lack of knowledge of a REMS key message, which in turn depends on the indication, the severity
180 and prevalence of the safety concerns, and the target population. Although there is no standard

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

183
184 **B. Sampling Considerations**

185
186 Since it is rarely possible to survey the entire target population of those who take a drug, or those
187 who prescribe or dispense a drug, sampling of the target population is more feasible. REMS
188 assessment knowledge surveys should be based on the principle of statistical inference, which
189 generalizes findings from a sample to a target population.¹⁷ The generalizability of the survey
190 results to the target population is based on how representative the sample is of the target
191 population.

192
193 An initial step in designing the survey is identifying a sampling frame of the target population.
194 That is, a list of those in the target population from which the sample can be selected. Examples
195 of sampling frames for a REMS target population include individuals in a REMS-mandated
196 patient registry, patient enrollment database, or prescriber or pharmacy enrollment database.
197 When a REMS does not include mandatory databases, possible sampling frames of patients and
198 healthcare providers could be chain pharmacies, voluntary patient registries, or other sources. It
199 is important to provide the rationale for choosing the selected sampling frame that takes into
200 consideration the representativeness of the sampling frame relative to the target population.
201 Evaluating representativeness of a survey sample of the target population includes identifying the
202 demographic and clinical characteristics of the sample and comparing them to known
203 characteristics in the population.

204
205 To sample from the selected frame, we recommend using a probability random sample.
206 Probability random sampling assumes every member of the sampling frame has a known and
207 non-zero chance of selection into the sample and ensures the sample is representative of the
208 frame with respect to all characteristics, known or unknown, measured or unmeasured. This
209 ensures the sample is not subject to selection bias. Probability random sampling design does not
210 protect against nonresponse bias; however, when a bias exists because of nonresponse,
211 probability random sampling gives the ability to quantify the magnitude of this bias to assess its
212 impact on the main findings.¹⁸

213
214 A simple random sample (SRS) is a probability random sample in which each member in the
215 sampling frame has the same probability of selection into the sample. Stratified random samples,
216 stratified random samples with oversampling, and cluster samples (with or without stratification)
217 are more elaborate probability random samples, discussed in the remainder of this section.

218 Although selecting an SRS from a frame may be easier than more elaborate sampling designs, a
219 more elaborate design may have advantages over an SRS in ease of conduct.

220
221 *1. Stratified Random Samples*

222

¹⁷ Altman 1997, p. 490.

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

230

231 *2. Stratified Random Samples with Oversampling*

232

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

240

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

245

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

250

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

256

257 *3. Cluster Samples (With or Without Stratification)*

258

259 A cluster sample consists of all or a random sample of subjects from a random sample of
260 clusters. Example of a cluster is a clinic or a hospital. A cluster survey typically requires a
261 larger sample of subjects from a few clusters of entities, and requires a more complex sampling
262 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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

272
273 If an applicant demonstrates that using a probability random sample is not feasible, then the
274 applicant should discuss using other types of surveys to assess knowledge with the Agency.
275

C. Sample Size Considerations

276
277
278 In this section, *sample size* refers to the number of survey participants in a population of interest.
279 The number of subjects invited to participate in a survey should be larger than the target sample
280 size to account for nonresponse.

281
282 For a given target population, we recommend that the sample be large enough to precisely
283 estimate the knowledge rate in that population. Sample size calculation considers two important
284 elements: sampling design (see section III.B, above) and precision of the estimated knowledge
285 rate. This guidance discusses three sampling designs: SRS, cluster sample, and stratified
286 random sample.

287
288 *Precision* is a measure of sampling uncertainty. In this guidance, precision is the absolute
289 difference of the sample estimate and the lower bound of the two-sided 95 percent confidence
290 interval of this estimate. We recommend it be controlled at 5 percentage points or less in the
291 sample size calculation. This 5 percentage points represents an absolute value and is not relative
292 to the knowledge rate.

293
294 Other elements that may enter in the sample size calculation are the target population's size and
295 assumed knowledge rate:
296

- 297 • *Target population size* refers to the number of individuals in the target population. The
298 target population depends on the REMS goals and is usually one of three groups: all
299 subjects who take the drug, all subjects who prescribe the drug, or all subjects who
300 dispense the drug.
301
- 302 • *Assumed knowledge rate* used for the sample size calculation is the best guess or
303 expected knowledge rate in the target population based on relevant published literature,
304 similar surveys, or pilot studies. For a more conservative estimate of the sample size
305 while keeping everything else the same, one might choose to use a 50 percent knowledge
306 rate, which would yield the largest sample size estimate.

²² Levy and Lemeshow, p. 223-230.

307
 308 Determining the appropriate sample size is easier for an SRS survey than for a cluster sample or
 309 stratified random sample. Table 1 presents the estimated sample sizes with a target precision of
 310 4 percent for different assumed knowledge rates and target population sizes. It also shows how
 311 the appropriate sample size for an SRS survey with 4 percent target precision increases as the
 312 assumed knowledge rate approaches 50 percent, and the appropriate sample size for an SRS
 313 survey decreases from large target population sizes to small target population sizes. For example,
 314 given a target precision of 4 percent, an assumed knowledge rate of 50 percent, and a large target
 315 population size, the appropriate sample size is 601.

316
 317 **Table 1: Estimated Sample Size for a Simple Random Sample with a Target Precision of**
 318 **4% (Half-Width of 95% Confidence Interval) for Different Assumed Knowledge Rates and**
 319 **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

320
 321 For a clustered design, a stratified random sample, or other complex designs, the sample size to
 322 achieve a certain precision differs from the sample size in a SRS by the *design effect* factor.²³
 323 The design effect of a survey design is the ratio of the variance of estimates from that design,
 324 divided by the variance of estimates from an SRS of the same size. For example, when the
 325 design effect is 2, the sample size should be twice as large as an SRS survey to achieve the same
 326 target precision. Conversely, when the design effect is 0.5, the sample size can be half the size of
 327 an SRS survey to achieve the same target precision.

328
 329 The appropriate sample size to achieve a certain precision is higher in a cluster design than in an
 330 SRS by the design effect factor because the variance of estimates in the cluster design is higher
 331 than in an SRS (i.e., design effect factor > 1).²⁴ The design effect in a cluster design increases
 332 with the number of subjects in each cluster and with intra-cluster correlation coefficients (ICC)²⁵.

333
 334 The appropriate sample size to achieve a certain precision is generally lower in a stratified design
 335 than in an SRS by the design effect factor because the variance of estimates in a stratified design
 336 is lower than for an SRS (i.e., design effect factor ≤ 1).²⁶ The variance in a stratified design
 337 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.

338
339 When there are multiple REMS key messages, presenting a 95 percent confidence interval for
340 each REMS key risk message independently can give a false sense of precision, as the overall
341 confidence level for all REMS key messages is much less than 95 percent due to multiplicity.
342 Therefore, we recommend having as few REMS key message domains as possible. Any REMS
343 key message domains should be constructed in a meaningful way.

344
345 **D. Participant Recruitment**

346
347 Recruiting participants for REMS assessment knowledge surveys can be challenging. There is
348 no single best way to recruit participants for these surveys because of the variation in how drugs
349 are prescribed and dispensed and in patient populations. In general, we recommend a
350 multimodal approach be used to recruit participants (e.g., sending survey invitations via U.S.
351 mail, email, and phone).²⁷

352
353 A description of the recruitment sources and justification for selecting the recruitment sources
354 should be provided in the survey protocol. Combining several sources of potential survey
355 participants may ensure a broader cross section of the patient or healthcare provider population
356 of interest in the sampling frame, provide a robust approach to lower nonresponse, meet the
357 target sample size, and lower potential nonresponse bias. Survey participants should be made
358 aware that taking part in the survey is voluntary.

359
360 *1. Methods to Minimize Non-Response*

361
362 Using multiple recruitment sources might still result in a low response rate unless additional
363 recruitment methods are employed. Follow-up contact to nonrespondents using a different mode
364 than what was used to make initial contact can increase response rates during recruiting.²⁸ Using
365 social validation is especially useful in nonrespondent follow-up. For example, informing
366 nonrespondents that others have completed the survey can encourage them to respond to the
367 survey.²⁹

368
369 Finally, cluster samples and multi-stage survey sampling can make reaching participants easier
370 and increase response rates.

371
372 Using multimodal approaches and other study designs can not only reduce nonresponse rates, it
373 can also reduce nonresponse bias, which is possible even in probability surveys because
374 knowledge of key messages of subjects who chose to respond to a survey may be different from
375 knowledge of those subjects who chose not to respond to a survey. Thus, high nonresponse
376 threatens the validity of a survey. By increasing response rate, the survey and estimated
377 knowledge rate are more generalizable to the target population.

378

²⁷ Dillman et al., p. 400 - 403.

²⁸ Dillman et al., p. 417 - 418.

²⁹ Dillman et al., p. 30.

379 **E. Survey Conduct**

380

381 1. *Eligibility Criteria*

382

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

387

388 In general, eligible *patient* participants should:

389

390 • be age 18 or older (or have a parent/caregiver respond for a patient who takes the drug
391 and is under 18 years of age)

392

393 • be currently taking the drug with the approved REMS, or have taken the drug within a
394 reasonable timeframe³⁰

395

396 • not be currently participating in a clinical trial involving the drug

397

398 • not have participated in a previous REMS assessment survey for the same drug

399

400 • Not be currently employed by the applicant, FDA, or the third party conducting the
401 REMS knowledge assessment survey, or have other conflicts of interest that might affect
402 their answers

403

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

405

406 • be certified and/or enrolled to prescribe or dispense the drug³¹ *or* have prescribed or
407 dispensed the drug within a reasonable timeframe

408

409 • not have participated in a previous REMS assessment survey for the same drug

410

411 • not be currently employed by the applicant, FDA, or the third party conducting the
412 REMS knowledge assessment survey, or have other conflicts of interest that might affect
413 their answers.

414

415 2. *Survey Administration*

416

417 It is important to inform potential survey participants that their participation is voluntary, they
418 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.

Contains Nonbinding Recommendations
Draft — Not for Implementation

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

422
423 The purpose of the REMS knowledge assessment survey is to evaluate the target populations’
424 knowledge retention about the serious risks and safe use of the drug, not to evaluate their ability
425 to read and comprehend the educational materials at the time of the survey. Therefore,
426 respondents should not be offered an opportunity to read or see the Medication Guide,
427 prescribing information, or any other REMS-related educational materials as part of the survey
428 process. To remind the survey respondents what these REMS-related educational materials are,
429 respondents may be provided a text description of the Medication Guide and illegible rendition
430 of these materials for relevant survey questions.

431
432 Two general methods should be considered to administer the survey and collect survey data,
433 each with its own advantages and disadvantages: self-administration (mail or Internet survey)
434 and use of a trained interviewer (e.g., individual or group interviews, in-person or telephone
435 interviews) to ask the questions. Survey administration modality should be decided based on the
436 study question and target population, as well as the following additional factors:

- 437
438
- potential response rate
 - 439
 - noncoverage and nonresponse bias³²
 - 441
 - complexity of concepts and survey questions
 - 443
 - length of questionnaire and time needed to complete the survey
 - 445
 - special characteristics of the population of interest
- 447

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

- 451
- reduce coverage error when a single mode cannot adequately cover the population of
452 interest
 - 453
 - improve response rate, with the recognition that some people prefer certain modes and
454 may not respond to others
 - 455
 - reduce nonresponse bias by obtaining responses from people who may be difficult to
456 reach via certain modes
 - 457
 -
 - 458
 -
 - 459
 -
 - 460

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 461 • reduce measurement error by offering modes to ask/answer questions in non-
462 embarrassing ways or allowing adequate time for survey participants to read and answer
463 questions at their own pace
464
465 • improve timeliness of survey completion by reaching the target sample size quickly³³
466

467 **F. Survey Questionnaire Development**
468

469 The survey questionnaire should be designed to accurately capture respondents' understanding of
470 the REMS key messages and optimize the validity of the information collected. Wording,
471 question structure, and question sequences can significantly affect the validity and
472 interpretability of the data collected. Experts in questionnaire design should be involved when
473 designing the questionnaire. Applicants should ensure that the proposed survey instrument's
474 reliability and validity are tested and the results are acceptable.
475

476 The following recommendations merit particular consideration when designing the survey
477 questionnaire:
478

- 479 • Use audience-appropriate vocabulary and pretested questions.
480
481 • Use direct, specific, and unambiguous questions.
482
483 • Use a variety of question types, such as open-ended, close-ended, multiple-choice, and
484 true/false.
485
486 • Design questions to ask about knowledge, not about opinions. Appropriate responses to
487 true/false questions are not "agree" or "disagree."
488
489 • Frame questions in a positive way.
490

491 Examples of positively worded questions (recommended format):
492

- 493 ○ You should tell your healthcare provider about [Symptom] before taking Drug X.
494 (True/False/I don't know)
495 ○ [Serious Risk] is associated with the use of Drug X. (True/False/I don't know)
496

497 Examples of negatively worded questions:
498

- 499 ○ You should not tell your healthcare provider about [Symptom] before taking Drug X.
500 (True/False/I don't know)
501 ○ Treatment with Drug X does not cause [Serious Risk]. (True/False/I don't know)
502

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

³³ Dillman et al., p. 400 - 403.

Contains Nonbinding Recommendations

Draft — Not for Implementation

505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544

- 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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

- 547
- 548 • Derive the REMS risk-specific questions from information specified in the REMS goals
549 and the REMS patient education materials, including the Medication Guide. As
550 applicable, this includes all the risks or adverse events conveyed (real, potential, or
551 theoretical), signs and symptoms of the adverse events, and what to do if symptoms of an
552 adverse event occur.
 - 553
 - 554 • Use text from the patient-directed REMS materials verbatim for questions and answers.
555
 - 556 • Ensure questions and answers are worded at the 6th- to 8th-grade reading level.
557
 - 558 • When applicable, to help assess the distribution of the Medication Guide, include
559 questions about receipt of the Medication Guide in the patient survey.
560
 - 561 • The knowledge questions are the highest priority in the REMS assessment knowledge
562 survey. When the survey includes questions other than those related to knowledge (e.g.,
563 questions about patient receipt of the Medication Guide), organize the questions so the
564 risk-specific questions are listed first, followed by the other questions. Demographic
565 information should be collected last or as part of any screening questions.
566
 - 567 • Before questions about receipt of the Medication Guide, include text that describes a
568 Medication Guide and, if possible and depending on how the survey is administered, a
569 link to or a picture showing an illegible version of the Medication Guide.

570
571 Example:

572
573 Now we are going to ask you some questions about the Medication Guide you
574 may have received with Drug X. The Medication Guide is a paper handout that
575 contains important information about the risks associated with use of Drug X and
576 how to use Drug X safely. Medication Guides always include the title *Medication*
577 *Guide*, followed by the word *Drug X* and its pronunciation. The Medication
578 Guide usually has sections titled *What is the most important information I should*
579 *know about Drug X?*, *What is Drug X?*, and *Who should not take Drug X?*.

- 580
- 581 • When applicable, use the following (or similar) questions to assess receipt and use of the
582 Medication Guide:
583
 - 584 ○ Who gave you the Medication Guide for Drug X? (Select all that apply.)
585 a) My doctor or someone in my doctor's office.
586 b) My pharmacist or someone at the pharmacy.
587 c) Someone else (please explain): _____.
 - 588 d) I don't know.
 - 589 e) I did not get a Medication Guide for Drug X. (If you checked this, skip to
590 question XXX)

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
- 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.

606
607
2. *Questionnaire Design Considerations for Healthcare Provider Surveys*

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

- 612
613
614
615
616
617
618
619
620
- 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.

621 Example:

622
623 According to the Prescribing Information, Drug X can cause which of the following
624 serious side effects? (Select all that apply.)

- 625
626
627
628
629
- 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.

630 Example:

631
632 Before today, which of the following educational materials were you aware of, did you
633 receive, and did you read/view with regard to Drug X? (Select all that apply.)
634

Contains Nonbinding Recommendations
Draft — Not for Implementation

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

635

636

637

638

639

640

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

Example:

641

642

643

644

645

646

647

648

649

650

651

652

- 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): _____

653

654

655

IV. STATISTICAL CONSIDERATIONS WHEN ANALYZING AND PRESENTING RESULTS

656

657

658

659

660

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.

661

662

663

664

665

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

670
671 In addition, the REMS assessment report should include knowledge rate estimates and their 95
672 percent confidence interval for each question and each REMS key message domain. For REMS
673 key message domains measured by multiple questions and answers, prespecified and
674 appropriately and meaningfully constructed composite scores can be used to present the findings
675 regarding each domain.

676
677 For complex survey designs, such as stratified random sample or cluster sample surveys, the
678 knowledge rate of a key message in the overall population should be estimated from a weighted
679 average of knowledge rates in different clusters or strata, where the weights depend on the
680 sampling design and any nonresponse adjustments that may be important. Both the knowledge
681 rate estimates and the associated precision estimates should reflect the probability sampling
682 design used for the study. Because the appropriate analysis methods for the point estimates and
683 their precision depend on the design, they should be prespecified. Post hoc stratification and
684 weighting cannot salvage a poorly designed survey or poorly collected data.

685
686 The REMS assessment report should also include analyses of data from all survey respondents
687 during the reporting period. When the number of completed survey questionnaires received is
688 higher than expected, all data from completed surveys should be included in the analysis and
689 report; the report should not sample or select from the survey respondents.

690
691 When a returned or completed questionnaire contains unanswered items, unanswered questions
692 should be considered as missing, not wrong. Results reporting should follow methods to handle
693 missing values prespecified in the statistical analysis plan.

694
695 For each survey question, the results presented should include at least the total number of
696 respondents that selected each answer choice, the number that did not select any answer, and the
697 corresponding percentages of total respondents.

698
699 Example:

700
701 True or False: According to the Prescribing Information, [Serious Risk] is associated
702 with the use of Drug X?

- 703
- 704 • Out of the 500 respondents who were asked this question, 450 responded
 - 705 ○ 200 (40% of 500) selected “True”
 - 706 ○ 125 (25% of 500) selected “False”
 - 707 ○ 125 (25% of 500) selected “I don’t know”
 - 708 ○ 50 (10%) did not select any answer
- 709

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

720

721 **V. SUMMARY OF IMPORTANT POINTS**

722

723 To assist in developing survey protocol and presenting REMS assessment knowledge survey
724 methodology and results, the following detailed information should be included in the
725 submissions of proposed survey protocol³⁷ and REMS assessment report, as applicable:

726

727 **A. Assessment Survey Protocol**

728

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

733

734 • inclusion and exclusion criteria for potential survey participants and reasons for the
735 selected criteria

736

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

739

740 ○ those who are prescribed the drug (as much as possible in terms of age, race,
741 ethnicity, education, gender, geography, indication for use)

742 ○ those who prescribe the drug (as much as possible in terms of geography,
743 indication for which they prescribe the drug, medical specialty, gender)

744 ○ those who dispense the drug

745

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

748

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

752

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 753 • prespecified thresholds for success and their justification for each REMS key message
754 domain
755
- 756 • rationale for choosing a particular survey design, such as cluster or stratified random
757 sample
758
- 759 • description of impact of design on overall population knowledge rate estimate and
760 precision
761
- 762 • derivation of the appropriate sample size of responders based on the sampling frame, the
763 survey design, the anticipated non-response rate, and the target precision of the
764 knowledge rate
765
- 766 • derivation of the number of people to be contacted to achieve the targeted number of
767 participants
768
- 769 • strategy used to select sources of potential survey participants
770
- 771 • recruitment plan, including the modes that will be used
772
- 773 • plan to provide any incentive to participants
774
- 775 • recruitment materials
776
- 777 • rationale for the planned survey administration modalities
778
- 779 • strategies to minimize nonresponse
780
- 781 • description of the steps used to develop the survey instrument
782
- 783 • methods used to pretest the survey questionnaire and its findings
784
- 785 • survey instruments, including any introductory text and screening questions
786
- 787 • techniques used to train surveyors (if applicable).
788
- 789 • statistical analysis plan
790
- 791 • methods used to control for potential limitations or bias
792
- 793 • methods to handle missing values in responses to the items of the questionnaire
794
- 795 • system for coding, entering, and verifying study data
796

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

799

800 • answer key for all close-ended questions

801

802 • process for offering education for incorrect responses

803

804 **B. Survey Results and Interpretation**

805

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

807

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

810

811 • relevant demographic characteristics of respondents compared to nonrespondents based
812 on available information

813

814 • relevant demographic characteristics of survey respondents and whether they completed
815 the survey

816

817 • reasons why respondents failed to complete the survey, when known

818

819 • representativeness of the survey sample of the target population

820

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

823

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

826

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

829

Contains Nonbinding Recommendations

Draft — Not for Implementation

830
831
832
833
834
835
836
837
838
839
840
841
842
843

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.