Examination of Respondent Bias and Patient Characteristics in Multiple REMS Assessment Surveys

Alicia W Gilsenan, Kelly Hollis, Laurie Zografos, Brian Calingaert, Elizabeth B Andrews

RTI Health Solutions, Research Triangle Park, NC, United States

ABSTRACT

Background: Draft FDA guidance requires Risk Evaluation and Mitigation Strategies (REMS) that include a medication guide to be assessed through a survey of patients' understanding of the serious risks of the drug. Such surveys should be designed to minimize selection and response bias, and allow analysis of characteristics associated with response/nonresponse. We conducted three surveys using data from a large nationwide pharmacy database to identify eligible participants. Invitations were mailed from the pharmacy headquarters, thereby minimizing potential for an intervention effect. Participants could complete the brief survey by phone or Web.

Objective: Determine whether the survey approach for patient accrual, including recruitment through a national pharmacy chain and bimodal survey, for three REMS patient surveys, was successful at enrolling a diverse population of respondents who were similar to the targeted populations.

Methods: Characteristics of patients invited to participate in surveys for three different drugs treating three types of conditions (acute: n = 50; intermittent: n = 208; or chronic: n = 200) were examined for response bias. The age/sex distribution of respondents was qualitatively compared with the expected age/sex distribution of patients using each of the three drugs.

Results: Between 50% to 66% of respondents opted to complete each survey by phone with older respondents more likely to select this mode. Respondents were geographically distributed across the US and were educationally diverse (27%-38% had ≤ high school education). For each survey, characteristics of respondents and nonrespondents were generally similar—% female (≤ 8% difference), % new prescription (< 5% difference), and payer type distribution (≤ 5% difference)—although respondents were slightly younger than nonrespondents. Age and sex distributions were consistent with what would be expected for the target population for each type of drug.

Conclusions: Identifying and recruiting participants through pharmacies and offering both Web and phone survey options yielded samples for each survey that closely resembled the expected target populations with no evidence of respondent bias.

Conflict of Interest Statement: The authors are employees of RTI Health Solutions, which conducts work for multiple pharmaceutical companies. This pooled analysis was supported in full by RTI Health Solutions.

BACKGROUND

Risk Evaluation and Mitigation Strategies

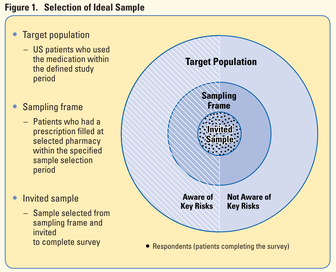
History

- Under the Food and Drug Administration (FDA) Amendments Act of 2007,[1] the FDA has enhanced responsibilities and authority with regard to pre- and postmarketing drug safety, including the authority to require Risk Evaluation and Mitigation Strategies (REMS) for certain drugs to ensure that a drug's benefits outweigh its risks. Nearly all products with REMS required a medication guide, and most products with a medication guide (medication-guide only REMS), were considered a REMS.
- In 2009, draft FDA Guidance for Industry relating to REMS[2] required any REMS that included a medication guide to be assessed through a survey of patients' understanding of the serious risks of the drug.
- In 2011, the FDA issued an additional draft Guidance for Industry relating to REMS,[3] allowing greater flexibility regarding when a medication guide would be considered part of a REMS. Since the new guidance was issued, more than 40 medications have been released from their REMS requirement.

Patient Surveys

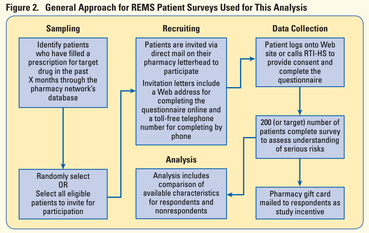
- Despite the new draft guidance, the FDA still has authority to require medication guides to be part of REMS and is likely to continue to require surveys to assess patients' understanding of the serious risk of certain drugs.
- Such surveys should be designed to minimize selection and response bias, and allow analysis of characteristics associated with response/nonresponse.

Figure 1. Selection of Ideal Sample



- Figure 1 displays the ideal respondent population (a representative sample of the target population); however, throughout the process of identifying the sample that is ultimately invited, there are several opportunities for selection and respondent bias to be introduced.
- Given the challenge of identifying a representative sample in REMS surveys, we examined data across three completed surveys that used a pharmacy network to identify patients and a bimodal survey administration system to assess the effectiveness of this survey approach in minimizing measurable selection and respondent bias.
- Figure 2 provides a high-level overview of the general design approach for these patient surveys.

Figure 2. General Approach for REMS Patient Surveys Used for This Analysis



OBJECTIVE

- To determine whether the survey approach for patient accrual, including recruitment through a national pharmacy chain and bimodal survey, for three REMS patient surveys, was successful at enrolling diverse populations of respondents who were similar to the targeted populations.

METHODS

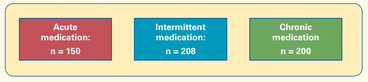
Source Data

Data from three cross-sectional REMS assessment patient surveys were included in the analysis. The purpose of the surveys was to assess knowledge of specific risks associated with three different drugs:

- One used to treat an acute condition
- One used to treat an intermittent condition
- One used to treat a chronic condition.

Figure 3 provides a visual representation of the survey samples included in this assessment.

Figure 3. Sample Descriptions



Source Population

- The source population for the sampling frame for each of the three surveys comprised patients who had filled prescriptions at a large national retail pharmacy chain that fills approximately 20% to 25% of all prescriptions in the United States (US). One survey also included a smaller national retail chain.
- The chain provides de-identified prescription information to a central pharmacy network that has the analytic and computing ability to identify the patients who meet study selection criteria.
- From this sampling frame, either a sample of or all patients who met the eligibility criteria for each survey (e.g., date of prescription fill within prior 30 days, aged 18 years or older) were invited with the aim of obtaining the target sample size for each survey (150-200 patients).

Analysis

Data from the three surveys were reviewed to compare available characteristics that may indicate possible selection and/or response bias including the following:

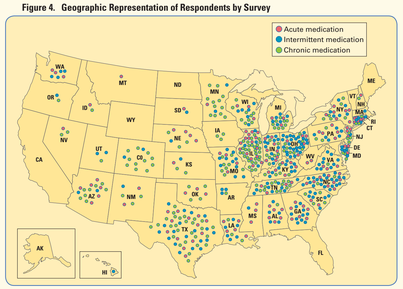
- Geographical dispersion, education, and race/ethnicity distribution of respondents
- Age, sex, new vs. refill, and type of insurance for respondents and nonrespondents
- Qualitative comparison of the age/sex distribution of respondents to the expected age/sex distribution of patient populations using each of the three drugs
- Percentage completing survey by mode (Web or telephone).

RESULTS

Diversity of Respondent Population

- Respondent populations reflected the broad distribution of the selected pharmacy chain locations across the US.
- Certain states (i.e., Massachusetts, California, and Florida) have legislation explicitly requiring patients to opt in to research studies; therefore, patients in these states were not eligible for invitation to complete the survey and are not represented in any of the response populations.

Figure 4. Geographic Representation of Respondents by Survey



- For characteristics available only for respondents (education and race), we examined the overall distribution and found there to be some representation across the various education levels and race, although it was limited (Table 1).

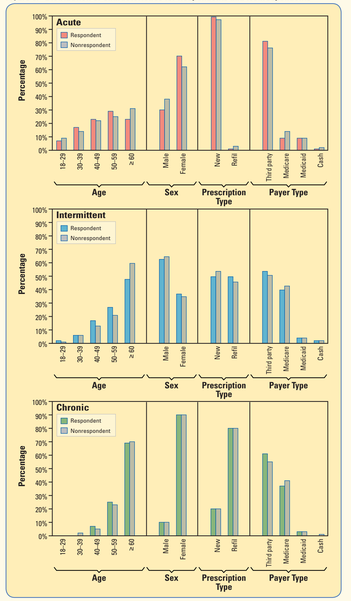
Table 1. Education and Race For Each Survey

Characteristic	Acute n = 150	Intermittent n = 208	Chronic n = 205
Education			
Less than high school graduate	1%	14%	6%
High school graduate/GED	23%	24%	23%
Associate/technical degree/some college	29%	31%	33%
College graduate or more	48%	30%	38%
Race			
White	85%	64%	93%
Nonwhite	15%	36%	7%

Characteristics of Respondents and Nonrespondents

- For each survey, characteristics available for comparison between respondents and nonrespondents were generally similar—percentage of females (≤ 8% difference), percentage of new prescriptions (< 5% difference), and payer type distribution (< 5% difference)—although respondents were slightly younger than nonrespondents (Figure 5).

Figure 5. Distribution of Characteristics for Respondents and Nonrespondents



Respondent Versus Expected Medication User Population

- Although market research data for the medication user population were not available for all drugs surveyed, a qualitative comparison of the expected age, sex, and race distribution for the indicated condition of each drug was made to the distribution of those variables within respondents.
- Overall the respondent population was consistent with what was expected for these medication user populations. Tables 2 through 4 display the respondent characteristics and notes regarding the characteristics of the expected user population.

Acute Condition

Table 2. Age, Sex, and Race Distribution Compared With Expected Medication Users

Characteristic	Respondent Distribution n = 214	Characteristics of Approved Indications
Age, years		
18-29	8%	Indicated for multiple acute infectious conditions in adults aged 18 years and older
30-39	15%	
40-49	22%	
50-59	27%	
≥ 60	28%	
Sex		
Male	30%	Indicated for multiple conditions, several with a higher prevalence in men, but difficult to ascertain accurate sex comparison due to use in treatment of multiple conditions
Female	70%	
Race		
White	86%	Approved for multiple acute infectious conditions, no striking racial differences for most indications
Black	8%	
Other	6%	

Intermittent Condition

Table 3. Age, Sex, and Race Distribution Compared With Expected Medication Users

Characteristic	Respondent Distribution n = 208	Characteristics of Approved Indication
Age, years		
18-29	3%	Most common in ages 40-60 in men and 60-80 in women
30-39	13%	
40-49	21%	
50-59	27%	
≥ 60	36%	
Sex		
Male	63%	Incidence rate in men is more than double incidence rate in women
Female	38%	
Race		
White	64%	Incidence rate in blacks more than double incidence rate in whites
Black	28%	
Other	8%	

Chronic Condition

Table 4. Age, Sex, and Race Distribution Compared With Expected Medication Users

Characteristic	Respondent Distribution n = 214	Characteristics of Approved Indication
Age, years		
18-29	6%	Most common in patients over 50 and increases with age
30-39	25%	
40-49	32%	
50-59	36%	
≥ 60	28%	
Sex		
Male	10%	Incidence in women is more than twice that of men; this distribution matches market research data of actual medication users
Female	90%	
Race		
White	93%	Condition much more common in whites than other races (four times more common compared with blacks)
Black	2%	
Other	5%	

Mode of Survey

- Overall, 50% to 66% of respondents opted to complete the survey by phone, while the remainder completed survey by Web.

CONCLUSIONS

- Identifying and recruiting participants through pharmacies and offering both Web and phone survey options yielded samples for each survey that closely resembled the expected target populations with no evidence of strong respondent bias.
- Direct recruitment through pharmacies is an efficient way to identify patients within the target population.
- As with all surveys, it is possible that respondents and nonrespondents may differ in important ways, including medication compliance and awareness of risks.
- Comparing respondents and nonrespondents as well as respondents to the characteristics of medication users is one approach for detecting major imbalances that could indicate potential for bias in results.

REFERENCES

1. Food and Drug Administration (FDA). Food and Drug Administration Amendments Act of 2007 (P.L. 110-85). Available at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110 Accessed July 21, 2011.
2. Food and Drug Administration (FDA). Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications, Draft Guidance, September 2009. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf. Accessed July 21, 2011.
3. Food And Drug Administration (FDA). Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS). Draft Guidance. February 2011. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf . Accessed July 21, 2011.

CONTACT INFORMATION

Alicia Gilsenan, PhD
Senior Director, Epidemiology

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: +1.919.541.8745
Fax: +1.919.541.6830
E-mail: agilsenan@rti.org

Presented at:

27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management

August 14-17, 2010

Chicago, IL, United States