

Active Pharmacovigilance and Healthcare Utilization

Jennifer S. Haas, MD, MSPH; Elissa Klinger, SM; Lucas Xavier Marinacci, BA;
Phyllis Brawarsky, MPH; E. John Orav, PhD; Gordon D. Schiff, MD;
and David W. Bates, MD, MSc

The safety of prescription drugs represents a major public health concern. Estimates suggest that approximately 0.5% of all emergency department (ED) visits and primary care visits result from an adverse drug event (ADE).^{1,2} While the US Food and Drug Administration (FDA) maintains a voluntary ADE reporting system for post-marketing surveillance, only 1% of ADEs are reported.³ Among the reasons for this underreporting are the difficulty that patients and providers may have linking a particular symptom or condition to a specific drug, particularly for individuals who have chronic illness and are taking several medications, a common clinical scenario in primary care. While the capacity for active surveillance using electronic medical records (EMRs) and claims data is expanding,⁴ these data will not fully capture the patient experience, as clinicians often fail to completely document a patient's symptoms.⁵

Interactive voice response system (IVRS) technology has the potential to systematically and efficiently contact large numbers of patients directly to assess adherence as well as symptoms. We previously described an IVRS system linked to our EMR, used to contact patients recently prescribed certain prescription medications to assess their symptoms in primary care practice.⁶ The goal of this study was to see whether participation in this type of systematic monitoring system was associated with subsequent changes in medication management or healthcare utilization. Our primary hypothesis was that patients who participated and completed our e-pharmacovigilance call would be more likely to have their medications stopped than those who did not complete the call, as these patients would be more likely to have symptoms identified attributable to their medications. The realization that their symptom may be related to a medication would result in more planned outpatient visits to primary care physicians or specialists but fewer unplanned acute care visits (eg, ED or hospitalization) or death because of earlier detection of problems. Our secondary hypothesis was that these effects would be mediated by the reporting of medication symptoms but, since symptom reporting was only available for participants, we addressed this hypothesis by comparing the same outcomes

as above between participants who did and did not report medication symptoms. This analysis provides some of the first data on the implications

Objectives: While active surveillance for adverse drug events using electronic medical records (EMRs) and claims data is expanding, these data do not fully capture patient experiences with medication-related symptoms. Our objective was to describe adherence and outcomes associated with an automated pharmacovigilance call.

Study Design/Methods: Prospective cohort of patients receiving a prescription for a target medication at a participating primary care clinic were eligible for an automated phone pharmacovigilance call. Outcomes, compared for participants who completed (n = 1184) versus did not complete the call (n = 407), included EMR documentation during the 6 months following the call that the patient had: stopped the medication, used acute care services or died, or received a specialty or primary care visit.

Results: Compared with those who agreed to participate but did not complete the pharmacovigilance call, subjects who completed the call had greater rates of EMR-documented medication cessation (3.9% vs 1.0%, adjusted *P* value = .007), and use of primary or specialty care (32.8% vs 18.7%, *P* value <.0001), but similar use of acute care services or death (12.2% vs 9.8%, *P* = .38). Of participants, 50.2% reported ≥1 symptom; of these, 22.0% thought the symptom was medication-related. In contrast to the low rates of EMR-documented medication cessation, 21.2% of participants said that they were no longer taking the medication; 69% said that their doctor did not know that they had stopped.

Conclusions: Automated phone pharmacovigilance provides important information about adherence, and was associated with greater EMR-documented medication cessation and planned service use.

(*Am J Manag Care.* 2012;18(11):e423-e428)

In this article

Take-Away Points / e424

Published as a Web exclusive

www.ajmc.com

For author information and disclosures,
see end of text.

Take-Away Points

Routine automated phone pharmacovigilance can provide important information about medication adherence and was associated with documentation of medication cessation, and use of outpatient care. One-half of patients experienced >1 symptom and almost one-fourth attributed the symptom to the target medication.

of active pharmacovigilance on healthcare utilization and outcomes.

METHODS

Setting and Patient Eligibility

We conducted the study in 11 primary care clinics affiliated with the Brigham and Women's Primary Care Practice-Based Research Network. Adult, English-speaking patients were eligible if they had recently been started on 1 of the target medications listed in the Protocol section by a participating primary care physician (PCP). Patients with a visit during 2008 to 2010 were eligible. The study was reviewed and approved by the Partners Healthcare Institutional Review Board.

Protocol

Our protocol has been described previously.⁶ In brief, potentially eligible patients prescribed selected medications were identified from our EMR. Target medications were selected based on the date of FDA approval, as drugs are more likely to have unrecognized adverse events noted within 7 years of introduction to the market,⁷ and/or particular concerns about side effects. Our goal was to move beyond drugs that have been commonly associated with ADEs resulting in ED visits, like warfarin and hypoglycemic agents,⁸ to identify drugs that may cause more chronic disability and symptoms that interfere with daily life which may otherwise not be recognized. Drugs selected were: zolpidem, eszopiclone, sildenafil, vardenafil, tadalafil, losartan, valsartan, irbesartan, aliskerien, gabapentin, pregabalin, montelukast, fluticasone propionate-salmeterol, varenicline, rosuvastatin, ezetimibe-simvastatin, rosiglitazone, pioglitazone, exenatide, sitagliptin, risperidone, olanzapine, quetiapine, modafinil, aripiprazole, duloxetine, raloxifene, trospium, infliximab, ibandronate, and etanercept.⁶ Patients who did not opt-out after receiving an informational letter (91.1%) were called approximately 4 weeks following their primary care visit using IVRS (CallAssure, Vocantas, Inc). Overall, 22.5% of patients with a working phone number (30.6% of individuals in a household where a live individual answered the phone) completed the IVRS tool.

A standard script with branching logic first asked each

patient whether they were taking the target drug. If the patient stated that they were not taking the drug, they were asked whether their doctor knew that they had stopped taking the medication, and specific reasons for stopping

(including whether they experienced a side effect or symptom). If they were no longer taking the target medication and it was not stopped because of a side effect or symptom the survey was concluded. If they reported that they had stopped the medication for a side effect or symptom, they were then asked a standard checklist of symptoms that are potentially associated with ADEs among ambulatory patients.⁹ Patients who stated that they were still taking the medication were asked whether they experienced any of the symptoms on the checklist since their most recent PCP visit. If an individual reported a symptom, they were asked if they thought that the symptom was related to the target medication (coded as yes, no, don't know, or missing response). Information reported during the call was automatically documented for all patients in the EMR using a templated note. In addition, the system sent a single e-mail to the PCP if the patient: (1) reported that they had stopped taking a medication intended for chronic use and said they had not discussed this with their provider, (2) reported a pre-defined list of symptoms, specific to each drug, that were of clinical concern, or (3) requested that we send an e-mail to their provider.

Variables

The goal of this study was to evaluate the association between completion of the e-pharmacovigilance call and subsequent healthcare utilization and mortality.

Outcomes. The primary outcomes assessed included whether an individual: (1) stopped the target medication, as documented in the EMR by a healthcare provider; (2) visited a PCP or specialist physician; or (3) experienced a combined outcome of ED visit, hospitalization, or death. These 3 outcomes were assessed within 6 months of the date that the patient's phone number was uploaded to the IVRS server, the "eligibility date." As secondary outcomes, we compared self-reported with EMR-documented medication cessation, and the primary study outcomes listed above for those who participated and reported versus did not report a symptom.

Potential Confounders. While completion of the e-pharmacovigilance call was our primary predictor, we were concerned about potential confounding effects due to clinical and demographic differences between non-participants, and participants who completed versus did not complete the call. Therefore, we collected and analytically adjusted for patient characteristics that were potentially associated with the out-

■ **Table 1.** Description of the Study Sample

	Participated in IVRS?			<i>P</i>
	Yes N (%)		No N (%)	
	Completed Call	Did Not Complete Call		
Total	1184	407	5798	
Median age in years	59	60	56	<.0001
Female	714 (60.3%)	236 (58.0%)	3035 (52.4%)	<.0001
Race/ethnicity				<.0001
White	913 (77.1%)	315 (77.4%)	3574 (61.6%)	
Black	145 (12.3%)	47 (11.6%)	840 (14.5%)	
Hispanic	54 (4.6%)	16 (3.9%)	975 (16.8%)	
Other	72 (6.1%)	29 (7.1%)	409 (7.1%)	
Median household income of zip code of residence				<.0001
≤\$46,592	334 (28.6%)	94 (23.6%)	2190 (38.4%)	
\$46,593-\$62,817	395 (33.8%)	124 (31.2%)	1755 (30.7%)	
>\$62,817	440 (37.6%)	180 (45.2%)	1765 (30.9%)	
Count of comorbid conditions				<.0001
0	444 (37.5%)	189 (46.4%)	2653 (45.8%)	
1	280 (23.7%)	89 (21.9%)	1321 (22.8%)	
2	211 (17.8%)	47 (11.6%)	873 (15.1%)	
3	126 (10.6%)	39 (9.6%)	541 (9.3%)	
4 or more	123 (10.4%)	43 (10.6%)	410 (7.1%)	
Current smoker	75 (6.3%)	27 (6.6%)	413 (7.1%)	.60

IVRS indicates interactive voice response system.

comes, including age (continuous), gender, race/ethnicity (white, black, Hispanic, other), count of comorbid conditions including cancer, dementia, diabetes, heart problems, hypertension, elevated lipids, osteoporosis, vascular disease, and kidney, liver, lung, and psychiatric problems (0, 1, 2, 3, 4 or more), drug class (insomnia, erectile dysfunction, angiotensin receptor blockers, seizure, asthma, smoking cessation, lipid lowering, diabetes, psychiatric, other) and median household income of the patient's zip code and number of ED visits and hospitalizations (0, 1-5, 6 or more) and number of primary care and specialist visits (continuous) in the year prior to enrollment.

Data Analysis

We used bivariate analysis to examine the associations of completing the pharmacovigilance call with patient characteristics; χ^2 tests were used to determine statistical significance. We also compared those individuals who agreed to participate with those who were potentially eligible but did not participate. To compare healthcare utilization by completion status, we used multilevel logistic regression models, clus-

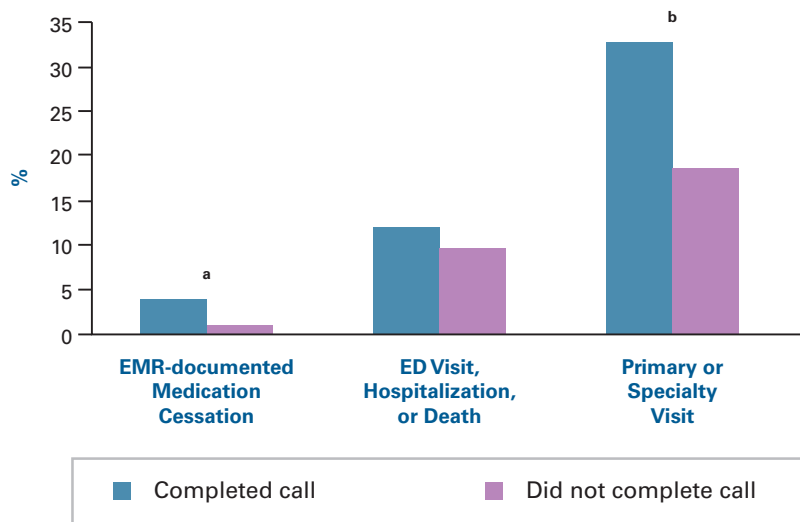
tered on primary care physician using SAS version 9.2 (SAS Institute, Cary, North Carolina). Multilevel models were then adjusted for patient characteristics including age, gender, race/ethnicity, count of comorbid conditions, drug class, median household income, prior ED visits and hospitalizations, and primary care and specialist visits, and also adjusted for primary care clinic.

RESULTS

Study Sample

The median age of individuals who completed the call as 59 years, compared with 60 years for those who agreed to participate but did not complete the call and 56 years for those who did not participate (Table). Women were more likely to complete the call. Compared with those who did not participate, individuals who participated in the e-pharmacovigilance system were more likely to be white, live in a zip code with a higher household income, and have more comorbid conditions than those who did not participate. Of the individuals who participated in the e-pharmacovigilance call, 799

■ **Figure 1.** Six-Month Outcomes Associated With Pharmacovigilance Call Completion Among Participants



ED indicates emergency department; EMR, electronic medical record.

^aAdjusted $P = .007$.

^bAdjusted $P < .0001$.

Adjusted and clustered models adjusted for age, sex, race/ethnicity (categorized as white, black, Hispanic, or other), median income, primary care clinic, number of comorbid conditions, drug class and ED visits or hospitalization and primary care or specialist visits within 1 year prior to enrollment date.

(50.2%) reported at least 1 symptom. Of the 261 participants whose call generated an e-mail to their provider (16.4% of all participants), 10.0% indicated that the patient was no longer taking the study medication, 28.0% because the patient requested that their provider be notified, and 62% because they reported a pre-specified symptom.

Outcomes Associated With Participation in e-Pharmacovigilance

While only 3.9% of patients who completed the e-pharmacovigilance call and 1.0% of patients who did not complete the call had discontinuation of the target medication recorded in the EMR within 6 months of their eligibility date, this difference was statistically significant (Figure 1).

In contrast to the low rates of medication cessation documented in the EMR, 21.2% of participants said that they were no longer taking the medication at the time of the pharmacovigilance phone call. Self-reported medication cessation was higher than cessation documented in the EMR for all drugs, including those used for diabetes (12.8%) and lipids (8.0%), but the self-reported rate was highest for varenicline (39.5%). Of those who said that they were no longer taking the medication, 10.1% said it was because they had had at least 1 symptom, 7.1% because of cost, 11.8% because they thought the medication did not work, and 27.2% because they thought that the medication was no longer necessary. Sixty-nine percent said that their doctor did not know that they had stopped the medication, consistent with the lower rates of documentation in the EMR.

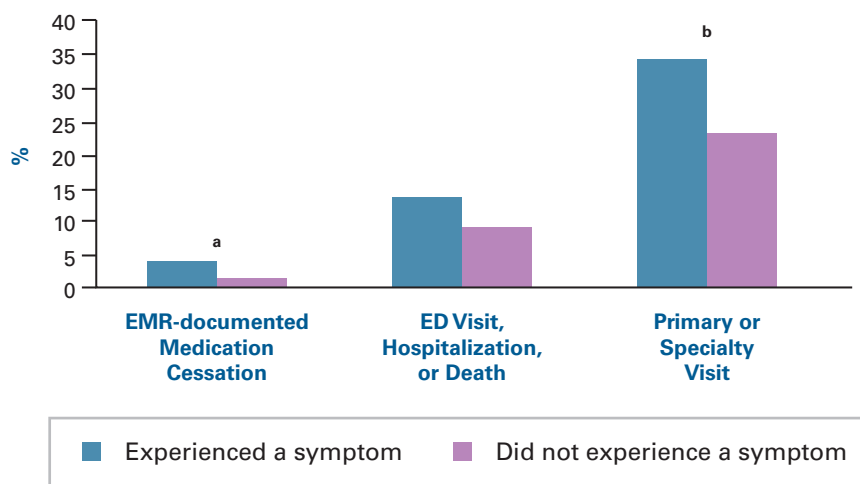
Rates of the combined outcome of ED visit, hospitalization, or death were not significantly different between participants who completed versus did not complete the call (12.2% vs 9.8%; $P = .38$). Rates of primary or specialty care visits were higher for participants who completed versus did not complete the call (32.8% vs 18.7%, $P < .0001$).

Among the patients who participated in the e-pharmacovigilance call, those who experienced a symptom were much more likely than those who did not report a symptom to have documentation in the EMR that their medication stopped (4.5% vs 1.8%, adjusted P value = .01) (Figure 2). Patients who reported a symptom were more likely to have a primary or specialty care visit (34.8% vs 23.5%, $P = .0005$), but there was no difference in the combined outcome of ED visit, hospitalization, or death (13.9% vs 9.2%, $P = .17$).

Patient’s Assessment of Whether a Symptom Was Associated With the Target Medication

Among the sub-group of 799 participants who noted at least 1 symptom, 176 (22.0%) attributed their symptom to the medication, 406 (50.8%) thought that the medication was not related to the symptom, and the remaining 217 (27.2%) did not know or did not report whether there was an association. Patients who thought that their symptom was related to the medication were more likely to report that they had stopped the medication (13.1%) compared with those who did not think that the symptom was related to the medication (1.5%) or who did not respond (3.0%, P value for $\chi^2 < .0001$).

■ **Figure 2.** Six-Month Outcomes Among Participants Who Reported a Symptom Compared With Those Who Did Not



ED indicates emergency department; EMR, electronic medical record.

^aAdjusted $P = .01$.

^bAdjusted $P = .0005$.

Adjusted and clustered models adjusted for age, sex, race/ethnicity (categorized as white, black, Hispanic, or other), median income, primary care clinic, number of comorbid conditions, drug class and ED visits or hospitalization and primary care or specialist visits within 1 year prior to enrollment date.

DISCUSSION

This study provides important data on the potential implications of a new approach to active pharmacovigilance on healthcare utilization and outcomes. Supporting our hypothesis, completion of this e-pharmacovigilance call was associated with a difference in EMR-documented medication cessation and greater use of planned visits, but we did not see a decline in unanticipated healthcare. Importantly we also found that rates of documentation in the EMR were substantially lower than the rates of discontinuation noted by the patients, suggesting that this may be an important tool for improving physician-patient communication about medication adherence. Of patients who reported a symptom on the e-pharmacovigilance call, one-fourth thought that the symptom was related to the medication and one-third did not know whether there was an association. This finding highlights both how difficult it can be for patients to decide to attribute a symptom to a drug, a necessary step for ADE reporting, but also suggests that many patients think that they are experiencing a medication-related symptom. Ascertaining information directly from patients is crucial to prevent potential medication-related morbidity and is also necessary to improve adherence when a symptom is unlikely to be related to a particular medication. The large discrepancy between self-reported medication cessation and documentation in the EMR also underscores the importance of adding the patient perspective to safety studies that are based solely on claims or chart review.

Few studies have integrated the patient perspective in the surveillance of ADEs.⁹⁻¹⁴ A phone survey of outpatients from 4 primary care clinics in the United States who received at least 1 prescription drug during a 1-month period found that 25% reported an ADE, but did not look at subsequent utilization.⁹ The United Kingdom's "yellow card scheme" allows a patient to spontaneously report potential ADEs by mail, phone, or Internet. An evaluation of this reporting call found that ADE reports from patients included more detail about reactions than those from healthcare providers and were as likely to be categorized as serious after evaluation.¹⁰ Dutch pharmacists invited first time users of pregabalin to participate in a web-based survey at pre-specified intervals.¹¹ This study did not report whether participation was associated with differences in utilization. IVRS has been used as part of chronic disease management programs to detect adverse events among patients with diabetes,¹² and the management of oral anticoagulants.¹³ This work supports the finding that IVRS may document events that were otherwise unknown to providers.^{12,14}

These data highlight the complexity of identifying ADEs in primary care practice. Given the high frequency of symptoms, the substantial burden of chronic illness, and the frequent use of multiple medications, it is challenging for both patients and primary care providers to identify ADEs.^{15,16} Patients may be more likely to attribute a symptom to a disease than a medication.¹⁶ Providers may under-recognize ADEs that are not severe.¹⁵ Future work should apply statistical approaches currently being used with claims and medical records to enhance surveillance using patient-reported symptoms.¹⁷⁻¹⁹

This study had several limitations. Because individuals who completed our non-randomized pharmacovigilance call may differ from those who did not complete the call or those who did not participate, we cannot attribute our findings to participation. Future studies should evaluate this type of system in a randomized design. Ideally one would have compared the outcomes of patients with symptoms based on participation status. As symptoms were only documented through participation, we are not able to make this comparison. We present the most conservative analysis as our primary analysis, but our secondary outcomes suggest that those who reported symptoms to the IVRS were more likely to have their medications stopped and had greater healthcare utilization. Finally, we included a limited set of medications. Our findings should be considered exploratory and should be confirmed in other settings and with other drugs.

Routine pharmacovigilance integrated with an EMR allows for the opportunity to reconcile differences in patient-reported adherence to what is documented in the EMR and allows providers to learn of symptoms experienced by patients. Patients who completed the pharmacovigilance call had more planned outpatient visits and greater cessation of the target medication, perhaps because ADEs were recognized, compared with those who participated but did not complete the pharmacovigilance call. The effect of this type of pharmacovigilance system on healthcare utilization deserves further study.

Author Affiliations: From Division of General Medicine and Primary Care, Brigham and Women's Hospital (JSH, EK, LXM, PB, EJO, GDS, DWB), Boston, MA; Department of Society Human Development, and Health (JSH, DWB), Department of Health Policy and Management (DWB), Harvard School of Public Health, Boston, MA.

Funding Source: Agency for Healthcare Research and Quality (U18HS016970).

Author Disclosures: Dr Orav reports the receipt of grants from the National Institutes of Health. The other authors (JSH, EK, LXM, PB, GSD, DWB) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (JSH, GDS, DWB); acquisition of data (JSH, EK, DWB); analysis and interpretation of data (JSH, LXM, PB, EJO, GDS, DWB); drafting of the manuscript (JSH, DWB); critical revision of the manuscript for important intellectual content (EK, PB, EJO, GDS, DWB); statistical analysis (LXM, EJO); obtaining funding (JSH, DWB); administrative, technical, or logistic support (JSH, EK, LXM); and supervision (JSH).

Address correspondence to: Jennifer S. Haas, MD, MSPH, Division of General Medicine and Primary Care, 1620 Tremont St, Boston, MA 02120. E-mail: jhaas@partners.org.

REFERENCES

- Budnitz DS, Pollock DA, Weide nbach KN, Mendelsohn AB, Schroeder TJ, Anest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 2006;296(15):1858-1866.
- Sarkar U, Lopez A, Maselli JH, Gonzales R. Adverse drug events in U.S. adult ambulatory medical care. *Health Serv Res*. 2011;46(5):1517-1533.
- Weingart SN, Gandhi TK, Seger AC, et al. Patient-reported medication symptoms in primary care. *Arch Intern Med*. 2005;165(2):234-240.
- Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the sentinel system - a national resource for evidence development. *N Engl J Med*. 2011;364(6):498-499.
- Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med*. 2009;362(10):865-869.
- Haas JS, Iyer A, Orav EJ, Schiff GD, Bates DW. Participation in an ambulatory e-pharmacovigilance system. *Pharmacoepidemiol Drug Saf*. 2010;19(9):961-969.
- Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA*. 2002;287(17):2215-2220.
- Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365(21):2002-2012.
- Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348(16):1556-1564.
- Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assess*. 011;15(20):1-234, iii-iv.
- Harmark L, Puijenbroek E, Grootheest K. Longitudinal monitoring of the safety of drugs by using a web-based system: the case of pregabalin. *Pharmacoepidemiol Drug Saf*. 2011;20(6):591-597.
- Sarkar U, Handley MA, Gupta R, et al. Use of an interactive, telephone-based self-management support program to identify adverse events among ambulatory diabetes patients. *J Gen Intern Med*. 2008;23(4):459-465.
- Oake N, van Walraven C, Rodger MA, Forster AJ. Effect of an interactive voice response system on oral anticoagulant management. *Cmaj*. 2009;180(9):927-933.
- Forster AJ, Boyle L, Shojania KG, Feasby TE, van Walraven C. Identifying patients with post-discharge care problems using an interactive voice response system. *J Gen Intern Med*. 2009;24(4):520-525.
- Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. *Drug Saf*. 2009;32(1):19-31.
- Shiyanbola OO, Farris KB. Variation in patients' and pharmacists' attribution of symptoms and the relationship to patients' concern beliefs in medications. *Res Social Adm Pharm*. 2010;6(4):334-344.
- Yih WK, Kulldorff M, Fireman BH, et al. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink project. *Pediatr*. 2011;127(suppl 1):S54-S64.
- Resnic FS, Gross TP, Marinac-Dabic D, et al. Automated surveillance to detect postprocedure safety signals of approved cardiovascular devices. *JAMA*. 2010;304(18):2019-2027.
- Brown JS, Kulldorff M, Petronis KR, et al. Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations. *Pharmacoepidemiol Drug Saf*. 2009;18(3):226-234. ■