



Comprehensive Pharmacovigilance and eHealth Surveillance **Carl F. Canavan, PhD; Steven A. Grossman, JD; Johnny Walker, MBA,** **CPA**

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ABSTRACT:

The monitoring of newly approved drugs for safety, primarily by the pharmacovigilance of voluntary adverse event reporting, is broadly recognized as being haphazard, slow, and inaccurate. This paper proposes an alternative of integrating comprehensive pharmacovigilance with eHealth patient records for automatic, real-time adverse drug event reporting from across very large patient populations. Integrating comprehensive pharmacovigilance with eHealth patient records would provide the most accurate, precise, and timely post-approval detection and analysis of the risks of adverse drug events that is possible. Also, the connectivity to eHealth patient records would provide a direct link to notify patients and physicians of findings of drug risks and related information.

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Current Post-Approval Drug Safety Monitoring

Studies have shown that pre-marketing clinical trials in the drug approval process are inadequate for detecting adverse drug events that occur rarely or are interactions with co-morbidities, concomitant medications, and risk factors that are routinely excluded from clinical trial

enrollments. Also, adverse drug events sometimes resemble symptoms that are not unexpected in clinical trial enrollments and may, therefore, not be recognized as drug-related.¹⁻³

Consequently, drug safety can only be assured by post-approval monitoring that plugs the gaps in the detection of drug risks in pre-marketing clinical trials.⁴⁻⁶

Monitoring drug safety is based on the pharmacovigilance of patients and physicians submitting case reports to industry and Food and Drug Administration (FDA) adverse event reporting systems. However, since the reporting is voluntary and there is no supervision or incentive for patients and physicians to take the time to carefully follow the reporting procedures, only a small proportion of drug-related adverse events are reported. Even then, the submitted case reports are frequently incomplete, inaccurate, and made long after the onset of adverse events. These deficits in pharmacovigilance severely diminish the opportunity for timely and thorough detection of drug-related adverse events.^{3, 5-10}

Another source of drug safety monitoring is the post-marketing commitment studies that are mandated by the FDA for drugs granted accelerated approval. Accelerated approval status is granted on the basis of abbreviated clinical trial evidence that shows promise for treating serious, often life-threatening conditions. The approval is conditioned on the drug sponsor agreeing to verify the drug's safety and efficacy with post-marketing commitment studies. Experience has shown, though, that post-marketing commitment studies often languish, on average taking ten years to complete. These delays put patients at risk of not receiving the expected benefit or worse, compounding harm.¹¹⁻¹³

Failures in drug safety monitoring have resulted in patients being unwittingly exposed to hazardous drug risks, causing serious harm and even death. Instances of patient exposures to drug toxicities that would likely have been detected by responsible safety monitoring have eroded the confidence of patients and health care practitioners in the validity of the FDA's approval as an assurance of drug safety and efficacy. Likewise, public opinion of the competence, and even the honesty, of drug manufacturers has suffered.^{5, 10, 12, 14-17}

Perspectives on Monitoring Drug Safety

The FDA's own institutional reform in 2005 has been to establish a Drug Safety Oversight Board. This Board oversees the post-approval risk management for safe and effective drug availability and is composed of experts from FDA centers, HHS agencies and the Veterans Administration. The FDA will also practice greater transparency by making drug safety information available to the public sooner and by releasing details of its own deliberations for drug approvals and post-approval monitoring.^{9, 18} The Board's first meeting was June 17, so it is hard to judge its effectiveness. Thus far, though, some lawmakers have publicly criticized the Oversight Board for not fulfilling its mandate of remaining independent from the Center for Drug Evaluation and Research in the Board membership and for not holding open meetings.¹⁹

A number of proposals have been offered for improving post-approval drug safety monitoring. The most extreme is that the FDA should require post-approval, phase 4 clinical trials to be

completed within two years for all newly approved drugs. However, if post-approval trials are mandated to fit within a two to three year period, it will be likely that the trials will not detect those drug-related adverse events with delayed appearance that were not found in the phase 3 pre-marketing trials.^{11, 12} A 2003 Tufts Center for Drug Development²⁰ study found that the average time required for phase 3 clinical trials was 30.5 months.

Adding a layer of post-approval clinical trials would add significant costs to developing drugs and maintaining market viability. The Tufts Center study²¹ found that post-approval R&D increased the average, fully capitalized cost of developing a drug from \$802 million to \$897. The \$95 million increase for post-approval studies of long-term safety and effectiveness is for broader label use to patient subgroups, for new indications, and for new formulations. Thus, the cost figures for current phase 4 clinical trials, for selected patient subgroups, will be considerably less than clinical trials that aim to confirm the post-approval safety for the full diversity of the patient population. Also, there would be an onerous effect on the drug development in general, since mandating post-approval trials for all drugs extends to all new drugs while the current phase 4 are usually economic decisions with expected returns that warrant the further studies.

Successful post-approval drug safety monitoring must be based on timely pharmacovigilance that supports statistically valid incidence ratios and pharmacoepidemiologic studies.⁷ One proposal for improving the process of drug safety monitoring suggests implementing electronic access to pharmacovigilance case reports from industry and FDA adverse event reporting systems, as well as electronic access to payer data bases, to pre- and post-approval clinical trial databases, and to FDA epidemiologic databases.^{9, 14} Decision makers at the FDA have acknowledged that the most efficient and the most effective source for pharmacovigilance is electronic access to eHealth patient records.⁹

An interesting approach to post-approval drug safety surveillance is a program being developed by the Centers for Medicare and Medicaid that will compare Medicare prescription data with claims submitted for doctor and hospital care for detecting adverse drug event risks. While claims data is prone to errors, the resulting surveillance will still be useful and would occur in near real-time, would be automatic, and could potentially extend to the full diversity of millions of patients.²² It is also important that the prescription and claims data would be collected both for patients who experience adverse events and patients who do not, thus allowing more complete analysis of adverse event incidence ratios.

Using eHealth Information For Comprehensive Pharmacovigilance Surveillance

An optimal post-approval adverse drug event surveillance solution would follow the theme of *practical clinical trials*,²³ where clinical data is drawn from across the diversity of a patient population with large enough numbers and over long enough periods for statistically significant prospective detection of adverse drug risks. Integrating comprehensive surveillance into eHealth patient records enables real-time, automated, accurate and complete “good case reporting.”⁷ The protocol for the case reporting would be tailored for each drug to ensure the best possible detection and assessment of adverse drug events across the stages of disease progression, comorbidities, medications, and risk factors of the patient population. Such an eSurveillance program could differentiate drug safety and efficacy across patient subgroups. This would even

allow so-called, “personalized medicine,”²⁴ where serious toxicity that is experienced by a differentiable subgroup is not found to extend to the broader patient population.

Implementing eSurveillance involves pharmacovigilance with the health care decision process. As such, the connectivity to eHealth patient records could also be utilized as a real-time communication link for notifying patients and health care practitioners of adverse drug risk findings, including (i) medical alerts and withdrawals that require immediate action for all patients under treatment, (ii) specific warnings for at-risk patient profiles, (iii) changes in dosage guidelines, and (iv) statistical measures of outcome performance per patient profiles. The opportunity to have this drug safety and efficacy information delivered directly to the patient record in near real-time would certainly be an important component of improving health care.

Integrating comprehensive pharmacovigilance into eHealth patient records is feasible. There are a growing number of regional health information organizations (RHIOs) that extend eHealth patient records over large populations.²⁵ These eHealth networks form the infrastructure that would make integrating comprehensive pharmacovigilance with eHealth patient records possible on a very large scale. Issues of the security and privacy of access to eHealth patient record information are strictly controlled to at least conform to regulatory standards, if not higher.²⁵ Plus the federal government is weighing in heavily on the adoption of interoperable RHIOs with the Administration creating the Office of the National Coordinator for Health Information Technology (ONCHIT), the Congress drafting healthcare interoperability legislation²⁶ and HHS leadership expressing their strong support.

A demonstration community integrating comprehensive pharmacovigilance using existing data and data standards for prescriptions, diagnosis and lab results would be the natural next step. What has been heretofore missing is the trusted third party to the various stakeholders to make those current e-silos of computerized data accessible to each other, while protecting patients’ privacy and the proprietary use of data. Now there are regional non-profit organizations as well as a national non-profit firm filling the needed trusted third party role.

A common objection raised to this approach is the small percentage of electronic records in the ambulatory setting. This is true but not the obstacle it is often made out to be. The ubiquitous paper record in the physician’s office holds needed lab, drug and diagnosis/problem list information. However, this information is generally available electronically elsewhere (the lab companies or hospitals, Pharmacy Benefit Managers (PBMs) and RxHub, pharmacies and SureScripts, payers, and even patient portals). Additionally, dictated patient records are a rich source of electronic information that is now largely untapped, but a currently available resource. By linking a limited number of national data sources, a large portion of the necessary data can be accessed right now. Over time as connectivity drives electronic adoption in the physician office, the quality and quantity of the data can only increase.

Patient interest in eSurveillance may be inferred from the willingness of patients to participate in clinical trials. A Harris Interactive survey²⁷ found that 71% of patient respondents were positively influenced to participate if they believed there was a personal or societal benefit. It would therefore be reasonable to expect that patients would be at least as willing to participate in eSurveillance. Participation would not be inconvenient and would not put patients at any risk.

Likewise, a CenterWatch survey²⁷ of physician attitudes towards referring patients for clinical trials found that almost three-quarters of interviewed physicians had an interest in learning more about investigational treatments to supplement their knowledge. As with the patient survey, it is reasonable to expect that physicians would be at least as willing to participate in eSurveillance, since participation would provide important information for health care choices and no inconvenience.

Implementing eSurveillance Would Be Straightforward:

- 1 Drug manufacturers would agree, either voluntarily or by FDA mandate, to use eSurveillance and automated notification. The eSurveillance should be extended to all newly approved drugs, especially in place of post-marketing commitment studies.
- 2 Patients choose to participate and provide consent to eSurveillance at the time of, and in conjunction with, a provider's decision to prescribe a recently approved drug therapy. The choice to participate at that time, before actually beginning treatment, allows collection of pre-treatment baseline data, such as disease severity, co-morbidities, risk factors, concomitant treatments, and demographic information. The eSurveillance would provide tracking information for both patients that experience drug-related adverse events and patients that do not. The data transmissions would be automatic and in real-time to the FDA and to the drug sponsor. The sponsor of the eSurveillance would follow good case reporting⁷ as well as a protocol for the most accurate and precise incidence ratios and pharmacoepidemiologic studies.

Comments on eSurveillance

The data collection of the voluntary adverse event case reporting is a very poor data sampling from extraordinarily complex processes. The rudimentary quality of the data limits the statistical techniques that are available to crude surveys of numbers of reported adverse events and simple correlations of possible interactions. The FDA warns that this information is not reliable and should not be used for statistical analysis. Testing for whether the incidence of adverse events may be drug related or not, or even whether adverse events even exist, is often confounded by the noise of unexplained data relationships⁷. This is especially the case since the adverse drug events that are not detected in pre-marketing clinical trials are often asymptomatic, appear long after initial drug use, and/or are similar to adverse events of unrelated, and not uncommon, diseases. Finally, even when there is an indication of possible adverse events from case reports, statistical verification by pharmacoepidemiologic studies must resort to completely new data collection⁷, thus delaying the findings, perhaps for years.

On the other hand, by virtue of the access of eSurveillance-based pharmacovigilance to the health and medical information of eHealth patient records, it would be entirely possible to collect cross-sectional and temporal data panels for reliable statistical tests of the incidence of adverse drug events. Incidence ratios could be estimated for alternative predictors of adverse events, drug related and not, over the diversity of the patient population. Moreover, eSurveillance pharmacovigilance would support sophisticated pharmacoepidemiologic modeling of disease progressions to adverse outcomes and benign outcomes. Both could be carried out nearly

simultaneously, thus allowing near real-time availability of reliable adverse drug event incidence and verified modeling of the effect of the drug use on outcomes.

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