

Leveraging Electronic Health Records

Regulators are increasingly using EHRs in their post-market surveillance activities. *Richard Gliklich* and *Michelle Leavy* report.

The emphasis on improving the safety of drugs and devices has increased in recent years, leading to efforts by regulators around the world to develop new methods and initiatives. While pre-market safety data remain vital, much of the attention has shifted towards improving the collection and reporting of post-market data. Post-market safety data may allow decision-makers to more effectively identify and characterise rare events not seen in clinical trials or events that occur in patients who are different (eg older or with more co-morbidities) than those included in clinical trials.

Currently, most post-market safety data come from adverse event reports, but there is also a focus on identifying and using new sources of data for surveillance activities, such as databases designed for electronic health records (EHR), insurance claims and registries. Particularly notable in this regard are the European Union's Adverse Drug Reactions (EU-ADR) project¹ and the Adverse Drug Event Spontaneous Triggered Event Reporting (ASTER) pilot in the US². The rapid change in EHR use in the US is supported by Congress, as can be seen by the \$19 billion in incentives provided for EHR adoption included in the American Recovery and Reinvestment Act of 2009.

Another major driving force behind new efforts in post-market safety surveillance is the US Food and Drug Administration Amendments Act of 2007 (FDAAA) – namely, the provisions that mandate the agency to develop the Sentinel Initiative, that give it the authority to require Risk Evaluation and Mitigation Strategies, and that allow it to demand post-market studies and call for safety labelling changes.

The heightened interest in safety monitoring has led to new efforts that leverage the increasing availability of EHR data. EHR data are a promising data source for safety monitoring, as they include detailed clinical information for large populations.

One example of an EHR-based initiative is the EU-ADR project. This project, funded by the European Commission, aims to design, develop and validate a surveillance system that analyses data from EHRs and biomedical databases to detect adverse events. In its first stage, the project is developing and validating new techniques for data mining in EHRs. These techniques include the creation of a ranked list of high-priority events that can be used to reduce the likelihood of generating false signals in data mining projects³.

EHRs are also being leveraged to streamline reporting of adverse events through the existing reporting system. The existing spontaneous adverse event reporting system, which relies on manually submitted reports, is often criticised as being burdensome to providers and inefficient. The availability of healthcare data in electronic format presents the opportunity to automate the process of generating and submitting an adverse event report.

The goals of an automated process are to reduce the burden of reporting, improve the frequency, timeliness and quality of reporting. One example of an automated reporting pilot project is the ASTER study. This study uses a new model for adverse event reporting, where data is gathered from electronic health records to generate automated safety reports. The study began in 2008, with 26 physicians participating. Of the 26 participants, 91% had not reported an adverse event to the FDA in the previous year. Over a three-month study period, more than 200 events were reported. The initial success of the ASTER pilot raises questions about whether an automated approach could be implemented more widely.

The Sentinel Initiative, launched by the FDA in 2008 in response to FDAAA, represents a major change in the FDA's approach to post-market surveillance. It is a long-term effort that will require collaboration with a large group of both public and private stakeholders.

The existing system for post-market surveillance is primarily passive, meaning that the FDA waits for adverse event reports to be submitted by healthcare providers, manufacturers and consumers. The Sentinel Initiative aims to develop a new database system that complements the current system by actively gathering information on post-market safety of regulated products.

As currently planned, the Sentinel System will consist of participating data sources, such as EHR systems, claims databases and patient registries. When questions about a product arise, the Sentinel System will send queries to the participating data sources. These sources will evaluate their data, while complying with any relevant privacy and security regulations, and submit summary results to the FDA. The databases will remain with the data owners, and the agency will only receive the summary results. By leaving identifiable data with the data owner (rather than creating a larger Sentinel database), the FDA may be able to avoid the privacy concerns related to holding

Efforts to enhance product safety has shifted towards improving post-market data reporting

The EU-ADR project is validating new techniques for data mining in EHRs

The Sentinel Initiative aims to develop a system that will actively gather post-market safety data

Richard Gliklich, MD, is president of Outcome Sciences, a provider of patient registries, studies and technologies for evaluating real-world outcomes, based in Cambridge, Massachusetts and Morges/Lonay, Switzerland. **Michelle Leavy**, MPH, is a senior research associate at Outcome Sciences. Website: www.outcome.com. Email: info@outcome.com.

The Sentinel System must develop approaches to assess the risk of misclassifying exposures or outcomes in databases

identifiable, patient-level data⁴. In addition, the creation of a single database holding data for 100 million patients by 2012, as required under FDAAA, would likely pose logistical, administrative and financial challenges.

A key step in creating the Sentinel System is the development of new methods for identifying and evaluating signals and conducting analyses in distributed data sets. To identify and evaluate signals, the Sentinel System will need to develop approaches for assessing the potential for misclassification of exposures or outcomes within the participating databases and for understanding and addressing data quality issues across all data sources.

In conducting analyses of distributed data sets, a major challenge is the inability to conduct extensive multivariate analyses. Novel approaches to address this challenge are being developed. These include propensity-score based pooling across multiple databases and exploration of new statistical methods for running multivariate regression models iteratively but sequentially through multiple databases without pooling⁵. These methods will need to be developed and become widely accepted as valid before they can be used within the Sentinel System.

The FDA has launched a "Mini-Sentinel" pilot programme to evaluate the potential approaches and barriers to implementing the full system.

The goal of data mining efforts, such as EU-ADR and the Sentinel Initiative, is to identify and report new safety issues. However, these efforts raise questions on how to effectively respond to and manage newly identified, potential risks. Under FDAAA, the FDA has additional tools to manage the potential safety risks of marketed products. For example, the FDA can now require REMS when the agency deems them "necessary to ensure that the benefits of the drug outweigh the risks of the drug". Prior to FDAAA, the FDA used risk minimisation action plans (RiskMAPs) to evaluate and manage post-market safety risks. A REMS may consist of a medication guide, and can also include a communication plan directed at prescribers and pharmacists to alert them of potential risks or to advise them on safe product use, or a restricted access programme. The FDA can require a REMS at the time of product approval, or after approval, if the agency becomes aware of new safety information (such as from adverse event reports or post-approval studies) and determines that a REMS is necessary.

As of July 2010, the FDA listed 129 REMS on its website

The FDA maintains a website listing all approved REMS; as of July 2010, the website listed 129 REMS. Of these, 86 consisted of a medication guide, while 28 required a medication guide and a communication plan. The remaining 15 all required elements to assure safe use, along with some combination of a medication guide, communication plan or implementation system⁶.

In addition to REMS, FDAAA gives the FDA new authority to require post-approval studies to examine a potential safety issue and safety labelling changes. Between March 2008 and September 2009, the agency issued 74 letters with post-marketing requirements. For the first time, the studies and clinical trials described in these letters are required, not voluntary, and the time frames for conducting the studies are enforceable. The agency has also required over 20 safety label changes since 2008, using its new authority under the legislation.

New developments are occurring rapidly in the area of post-market safety surveillance. Regulators are increasingly seeking to leverage electronic health care databases, such as EHR systems, for data mining, signal detection and facilitated adverse event reporting. These will require the continued development of new, scientifically sound methods to ensure that false signals are not being generated and that potential signals can be properly evaluated. As EHRs become more widely used, EHR-based safety monitoring initiatives are likely to increase.

The extensive requirements included in FDAAA are driving many of these changes. The initiatives raise many questions, such as how to design observational studies for safety monitoring, how to ensure sufficient data quality in distributed data sources, which statistical techniques will be appropriate for analysing these new data sources, what legal and privacy concerns will arise with using existing databases in new ways, and how to manage newly identified risks in marketed products. The FDAAA requirements are complex and far-reaching, and the legislation's impact on safety surveillance in the US is just beginning to be felt.

The impact of FDAAA on safety surveillance is just beginning to be felt

References

1. EU-ADR, www.alert-project.org/
2. The *ASTER Pilot Project: Improving the Reporting of Adverse Events, www.asterstudy.com
3. Trifiro G, Pariente A, Coloma PM, et al, Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor?, *Pharmacoepidemiology and Drug Safety*, 2009, **18**, 1176-1184
4. Rosati K, Using Electronic Health Information for Pharmacovigilance: The Promise and the Pitfalls, *Journal of Health & Life Sciences Law*, 2009, **2**(4):171
5. Velentgas P, Bohn RL, Brown JS, et al, A distributed research network model for post-marketing safety studies: the Meningococcal Vaccine Study, *Pharmacoepidemiology and Drug Safety*, 2008, **17**, 1226-1234
6. FDA, Approved Risk Evaluation and Mitigation Strategies, www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm