

Expert Workshop: Methods for Signal Refinement in Active Medical Product Surveillance

Background

The U.S. Food and Drug Administration (FDA) reviews multiple data sources to evaluate medical product safety, including the premarket development program, reports submitted to the Adverse Events Reporting System (AERS), relevant medical literature, and postmarket safety studies. Development of the Sentinel System will augment FDA's postmarket safety assessment process by enhancing its active surveillance capabilities.

Conducting active surveillance may be thought of as a spectrum of phases that include three steps: signal generation, signal refinement, and signal evaluation.

Potential Steps in Active Surveillance



- **Signal generation** includes a collection of methods for identifying potential associations between medical products and health outcomes of interest (HOIs).
- **Signal refinement** is a process for evaluating the magnitude and clinical significance of a suspected association.
- **Signal evaluation** consists of the implementation of a formal epidemiological analysis to more definitively establish or refute causality between exposure to the medical product and the HOI.

Workshop Scope and Objectives

This workshop, convened by The Brookings Institution's Engelberg Center for Health Care Reform through a cooperative agreement with the FDA, focused on the signal refinement step of active surveillance. This stage begins with a potential association between a medical product and an adverse HOI that has emerged from available data. Two general signal refinement scenarios can be envisioned:

- Concern about a specific medical product-HOI pair emerges during the product's development program OR there is a desire at the time of marketing to monitor a product for an association with an HOI that tends to be medical product-related but is too rare to be observed reliably in a development program (e.g., acute liver failure, Guillain-Barre syndrome). In this case, FDA would want to monitor the potential association at a regular interval over time as the product is taken up by the market.
- Concern about a specific medical product-HOI pair emerges distant to the introduction of the medical product to the market (e.g., years later). In this case, a one-time evaluation may be conducted to assess the potential association using the entire extent of marketing history.

The types of analyses conducted during signal refinement may include but are not limited to approximate rates of exposures and outcomes, crude associations, adjusted associations, and evaluations of coherence (i.e., does the association make sense in light of all the other information that is known about the product and outcome, including possible alternative causes). To enable timely responses to potential safety concerns, the signal refinement process must proceed as rapidly as

possible. Further actions after signal refinement may include continued monitoring, regulatory action, or further evaluation, depending on the magnitude and clinical significance of the medical product-HOI association.

Objectives of the September 21 expert workshop included: (1) defining effective and efficient ways to refine a potential safety signal within the scope of the FDA's public health surveillance authority; (2) developing a generalized framework applicable to a wide range of medical products to help expedite the signal refinement process and increase confidence in the results; and (3) achieving greater clarity on the data needs, analytics, methods, and acceptable levels of uncertainty in signal refinement to support this generalized framework. This document highlights major points of discussion from the workshop.

Building a Generalized Framework for Signal Refinement

Certain guiding principles of signal refinement apply across the spectrum of medical products. As described in the sections that follow, panelists suggested that these principles could be used to systematize the approach to signal refinement. Doing so would help expedite the signal refinement process by providing investigators with a clear path forward once a signal is detected.

Despite the benefits of a generalized framework, panelists cautioned that the development of a standard protocol is neither feasible nor desirable to evaluate the range of potential product-HOI pairs. In particular, investigators need to consider attributes of the product, exposed patients, and HOIs for potential confounders. For example, diabetic patients are inherently more susceptible to acute myocardial infarction (AMI), so investigators must discern whether elevated rates of AMI are caused by an anti-diabetes intervention or due to the underlying condition. In order to make these types of determinations, evaluations must include carefully chosen comparator groups. Comparator groups should be comparable with regard to clinical conditions, disease severity, and other potential confounders.

Systematizing the Thought Process Guiding Signal Refinement

Dr. Alexander Walker of World Health Information Science Consultants presented a systematized approach to signal refinement that relies upon an iterative process of generating and testing hypotheses about the cause of a signal. This method uses available data, including the data that gave rise to the signal and other readily accessible information (e.g., the medical literature, observations from clinical trial data, other clinical and administrative databases) to test hypotheses, refine hypotheses based upon results, and test refined hypotheses. Refined hypotheses should then be evaluated for coherence, which involves considering whether there is consistent and supportive evidence elsewhere in the data and whether the signal has biological plausibility.

Potential Guiding Framework Based Upon Data Characteristics

Dr. Sebastian Schneeweiss of Harvard Medical School and Brigham and Women's Hospital presented a flowchart to guide protocol development based upon characteristics of the signal. In this approach, factors such as exposure characteristics, event characteristics, and background frequency inform basic design considerations, analytic methods, and sensitivity analysis. This approach is general enough to accommodate a majority of scenarios in signal refinement. As Dr. Schneeweiss explained, this approach is appealing because it prioritizes rapid protocol development, helps to reduce investigator error, and allows investigators to justify design choices.

The approaches put forth by Drs. Walker and Schneeweiss are complementary. Dr. Schneeweiss' proposal provided a taxonomy-based approach to developing signal refinement protocols based upon characteristics of a given medical product-outcome pair that can serve as a starting point for signal refinement, while Dr. Walker presented a general schematic for thinking about the signal refinement process through hypothesis generation, testing and refinement that can inform the protocol development process laid out by Dr. Schneeweiss.

Strengths and Limitations of Data Sources

Data quality is critical to conducting accurate signal refinement. Some commonly cited inadequacies of claims data include limited claims specificity, inaccurate coding, and an overall absence of needed information. Inadequacies in data are important because they can introduce bias, potentially distorting the results of signal refinement even when optimal methods are applied.

These limitations need not prevent efforts to refine safety signals in administrative claims databases, but they must be acknowledged and considered when selecting data sources and analytic methods. They should also be considered when interpreting results.

Investigators have taken a number of approaches to improving data quality or mitigating the influence of data limitations. To directly address the issue of data quality, investigators may consider performing chart review to validate the coding algorithms used to identify outcomes. However, experts suggested that this approach may not always be logistically feasible because of time and resource constraints. Furthermore, techniques such as chart review do not address other important data limitations, such as insufficient detail and absence of needed information.

To address the issue of bias, which may arise due to differences in data elements, populations, or utilization patterns between data sources, investigators may perform the same analysis in multiple data sources. For example, comparing results from two different sources that represent different populations, such as payer claims data and Veteran Affairs (VA) data, is one potential mechanism to begin exploring such bias.

Investigators might also consider application of other types of data in addition to claims data (e.g., electronic health record databases, inpatient data, registries) to fill existing gaps. For example, Mini-Sentinel currently uses claims data for its analyses, but these data lack full clinical detail, so Mini-Sentinel plans to add electronic clinical data elements within the next year. Additional clinical information might also be provided by linking data sources (e.g., registries with claims data); however, linking data sources requires consensus in the research community regarding data standards, as well as approaches that maintain patient confidentiality.

Test-Beds for Methods Research and Development

Panelists discussed two specific projects that are evaluating signal refinement methods. One is the Observational Medical Outcomes Partnership (OMOP), which has been testing different signal refinement methods by applying each method to databases to look for known associations. Methods receive a score based on the ability to detect true positive and true negative signals in various data sets. OMOP's testing has revealed that method scores differ based upon the product-outcome pair, the data source, and the selected method and its combination of parameter settings, suggesting the need for further research.

Experience from the Vaccine Safety Datalink (VSD) project may also inform methods for signal refinement. The VSD utilizes a distributed data network to monitor vaccine safety in near real-time. Over the last five years or so, VSD identified ten potential signals, but upon further investigation, only one of these was found to represent a true association. False positive signals were attributed to errors in estimated background rates of events, confounding, and chance. This experience highlights the importance of having a process to validate the results of signal detection and signal refinement efforts.

Role of Signal Refinement in Active Surveillance

Panelists noted a lack of consensus on the definitions and boundaries of signal generation/detection, signal refinement, and signal evaluation. Although signal generation could potentially detect a large number of possible signals, there are no clear criteria for what should trigger signal refinement. Similarly, the threshold for moving from signal refinement into further stages (e.g., signal evaluation, regulatory action) of active surveillance requires further discussion.

Experts acknowledged that some residual uncertainty will always exist after the signal refinement step. The acceptable level of such uncertainty will likely differ according to the specifics of each medical product-HOI pair. Therefore, identifying a universal risk threshold across all medical products that triggers additional action and an acceptable level of uncertainty moving into signal evaluation does not seem feasible. Instead, panelists suggested that, for now, case-by-case determinations will be required. Conducting active surveillance on a number of signals in the Mini-Sentinel pilot may result in more clarity around the active surveillance process.

Summary and Next Steps

This meeting explored approaches for rapid and systematic signal refinement. Participants agreed that more systematic and standardized approaches to signal refinement have the potential to increase confidence in results and expedite this step of active surveillance, enhancing FDA's ability to respond sooner to potential safety concerns. Although currently available data are imperfect, experts indicated that data limitations should not preclude signal refinement; rather, investigators should take care to fully understand the limitations of particular data sources and take appropriate steps to mitigate bias.

The Engelberg Center for Health Care Reform at Brookings convened a related expert workshop on February 16, 2011 that explored selected statistical issues in active medical product surveillance, including appropriate analysis and interpretation in the context of large sample size, interpreting multiple results to the same query, distributed regression approaches, and defining operating characteristics for relevant statistical procedures.