ENGELBERG CENTER for Health Care Reform at BROOKINGS

June 2011

MEETING SUMMARY

Expert Workshop: Setting Priorities for Methods Research and Development for Active Medical Product Surveillance

The Sentinel System will augment U.S. Food and Drug Administration (FDA)'s postmarket safety assessment capabilities by enhancing its capacity to actively monitor the safety of medical products in large populations. Conducting safety surveillance may be thought of as a spectrum of phases that includes three steps: signal generation, signal refinement, and signal evaluation.

- **Signal generation** uses a variety of methods and data sources to identify 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** includes one or more formal epidemiological analyses to more definitively establish or refute causality between exposure to the medical product and the HOI.

Need to Increase Confidence in Active Surveillance Methods

Recent efforts by a number of public and private initiatives have been directed towards developing appropriate and effective methods for active surveillance. These initiatives include the Mini-Sentinel pilot, the Observational Medical Outcomes partnership (OMOP), and the Center for Disease Control and Prevention's Vaccine Safety Datalink (VSD), among others.

FDA envisions that within three years, the system will be able to refine safety signals in near real-time. This will require approaches for:

- rapidly defining exposed cohorts;
- establishing algorithms to capture HOIs;
- using sophisticated modular programs capable of running assessments with minimal input from epidemiologists and clinicians, and limited or no ad hoc programming; and
- developing a framework to guide methodological approaches that include confounding adjustments to be available for safety surveillance assessments.

They also expect that approaches for signal generation will be under development.

Achieving FDA's vision for the Sentinel System presents a number of challenges including the ability to refine signals in as close to "real time" as possible and minimize the number of false positive signals that need to be assessed. A consistent and systematic approach to signal refinement can address both of these challenges; however developing such an approach requires substantial investment in methods

research and development. Conducting this work collaboratively among the various groups working in this area will ensure efficient use of resources, minimize research overlap, and facilitate knowledge sharing and coordination in research efforts.

On June 3, 2011, the Engelberg Center for Health Care Reform at Brookings, in cooperation with FDA, convened a group of stakeholders from academia, relevant government agencies, medical product developers, and representatives from ongoing activities in active surveillance, including both Mini-Sentinel and OMOP. The goal of this workshop was to establish priorities for research and development of methods for medical product safety surveillance over the next 2 to 3 years. This document highlights key priorities discussed during the workshop.

Near Term Initiatives

Data:

Claims data are designed for administrative purposes, but pose challenges when they are utilized for other purposes (i.e., secondary uses), such as medical product safety surveillance. Several factors can affect the ability to use claims data for these other purposes, including misclassification of exposure or HOI and missing data. Additionally, contextual issues that arise as a result of variations in how medical products are used in different health care settings, such as population heterogeneity, differences in product exposure rates, and differences in clinical practice guidelines impact patterns of product exposure and outcomes. The following data issues can begin to be realistically addressed within a one to two-year timeframe.

- **Developing approaches to rapidly understand variations across data partners and patient populations:** Signal refinement can still be conducted as long as the analyses appropriately consider data inconsistencies. Not all data sets are suitable for a particular assessment, and including inappropriate data may make the results less credible. Developing metrics to understand variations in exposure and outcome data arising from the contextual issues mentioned above, and developing standards to evaluate the appropriateness of including certain datasets in assessments will help address issues related to data interpretation.
- **Developing guidance on design and analytic approaches that can handle these variations:** Factors that affect data quality can be addressed directly through activities such as identifying systematic and deliberate miscoding (e.g., upcoding) or failure to code procedures, and incorporating additional data sources, such as electronic health records (EHRs) and registry data, into medical product safety surveillance initiatives, such as Mini-Sentinel and OMOP.

Methods:

Dealing with confounding and bias is a continual challenge to conducting signal refinement, but proper design choice and use of analytical tools can mitigate this challenge. However, current methods require further research and development before they can adequately handle confounding and bias with the scale and confidence required for medical product safety surveillance. The following methodological challenges can begin to be addressed within a one-year timeframe.

- **Select appropriate methods:** Not all methods are equally suited for a particular assessment. Factors such as the type of medical intervention (e.g., inpatient vs. outpatient use), the nature of the exposure (e.g., exposure persistence), the nature of the HOI (e.g., HOI onset), and population characteristics (e.g., background rates, co-morbidities) will affect method performance. Understanding the operating characteristics of different methods in specific settings can help guide appropriate method selection.
- **Develop sequential methods:** The VSD has created a system that uses administrative and EHR data to conduct safety monitoring of vaccines in near real-time. VSD has overcome a number of challenges related to conducting sequential analyses in observational data, demonstrating the feasibility and potential utility of sequential methods for active surveillance of vaccines. However, use of sequential methods for drugs and devices may require more sophisticated control of confounding, and will require more work before these methods can suitably be applied for products other than vaccines.
- **Develop optimal analytic approaches to mitigate confounding and bias:** Even with careful design and analysis, some residual error (i.e., confounding and bias) will likely still exist. Improving and developing tools, such as sensitivity analyses, for quantifying residual bias and confounding will provide appropriate caveats that will help to establish confidence in active surveillance results.
- **Develop approaches to interpret signal refinement results:** Signal refinement results should be interpreted in light of residual uncertainty created by limits from available data and methods, and in the broader context of available evidence from other sources. Over the last five years or so, the VSD detected 10 safety signals among about 50 exposure-outcome pairs evaluated; following subsequent analyses (including checking background rates, using another comparison group, conducting chart review) scientists concluded that only 1 of those signals represented a true association. A process for validating signal refinement results that is based on lessons learned from the VSD experience could be a useful tool to gain confidence in signal refinement assessments.
- **Develop a causal framework:** A framework that incorporates signal refinement results into a broader set of criteria to evaluate causality may be a useful tool to increase confidence in signal refinement results. Hill's causal inference framework[1] is a potential starting point, but it will need to be optimized before it can be used for safety surveillance. Steps for optimization include:
    - establishing the most appropriate set of criteria (e.g., temporality, strength of association, etc) that will be a part of the causal framework;
    - determining the relative importance of each criterion; and
    - developing ways to consistently evaluate the safety signal based on each criterion.

  OMOP has been working to adapt OMOP data analysis tools to facilitate assessing how exposure-outcome pairs meet the various Hill's criteria.

[1] Bradford-Hill, Austin." The Environment and Disease: Association or Causation?" *Proceedings of the Royal Society of Medicine* (1965). 58:295-300.

- **Coordinate Mini-Sentinel's Taxonomy Project and the OMOP experiment:** The Mini-Sentinel taxonomy project and OMOP both share the goal of providing guidance for optimally selecting signal refinement methodologies, but take somewhat different approaches. The Taxonomy Project aims to characterize methods based on theoretical capabilities and build a decision table that directs method selection. They are currently working to identify monitoring scenario characteristics that affect design and analytic choices, and to map each of these scenarios to the preferred methods. OMOP has been working to empirically evaluate the performance of a set of methods based on the ability to detect known associations between drug exposures and HOIs ("true positives" and negatives controls) in a range of databases. Evidence from the performance of methods in these empiric evaluations would direct recommendations for which methods to apply to monitoring scenarios.
  Opportunities exist to take advantage of expertise from both initiatives and maximize limited resources. One possible scenario for collaboration could involve using the OMOP drug-HOI pairs to empirically evaluate scenario options from the Taxonomy Project's decision table.

Medium Term Initiatives

Participants recognized that other challenges may require more effort and time than those outlined above. One area that can be realistically addressed within two to three years is the development of signal refinement approaches. FDA's plans for the Sentinel Initiative over the next three years include the development of signal generation methods. Signal refinement methods can be used to help inform development of these approaches, and some may also be suitable for signal generation.

Sentinel and Safety Science as a National Priority

The scientific methods developed for and lessons learned about working with observational data for safety surveillance are portable to other areas, such as comparative effectiveness research, product quality, and disease surveillance. Safety science shares a symbiotic relationship with other uses of observational data: it can apply lessons from these other areas, and similarly these areas can benefit from the development of safety science. A number of public and private sector activities are already underway to support development of scientific methods for secondary uses of observational data. Developing a coordinated research agenda for methods research and development across these secondary uses will benefit each discipline, as well as the national research agenda by taking advantage of the best scientific minds and making the most of limited resources.

Continued methods research and development for safety science will require funding and intellectual capital. Safety science can leverage the momentum and interest in other areas to involve a broader set of stakeholders, including the National Institutes of Health, the Agency for Healthcare Research and Quality, and the Patient-Centered Outcomes Research Institute, to fund, support, and collaborate on methods research and development and funding and support for training to new investigators. Support of training in epidemiology, biostatistics, and medical informatics is particularly important to promote the development of investigators who can conduct this work. A medical product surveillance training fellowship program may be one potential avenue for training new investigators, providing training and

experience to investigators at various sites, such as OMOP, the Mini-Sentinel Coordinating Center at Harvard Pilgrim, pharmacovigilance divisions within industry, and FDA, that are involved in development and application of drug surveillance techniques.

Next Steps

This meeting outlined a number of research priorities over the next few years to support development of the Sentinel System. Realizing these priorities, though, will require coordination among various research initiatives both within the field of safety science and among the broader research community.