ENGELBERG CENTER for Health Care Reform at BROOKINGS

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# DISCUSSION GUIDE

## Setting Priorities for Methods Research and Development in Active Medical Product Surveillance

### Background

The Sentinel System will augment FDA's postmarket safety assessment capabilities by enhancing its capacity to conduct active surveillance at the population level. Conducting active surveillance may be thought 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.

Recent efforts have been directed towards developing the signal refinement stage of active surveillance, which 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.

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 health outcomes of interest;
- using sophisticated modular programs capable of running evaluations 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 evaluations.

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

In order to inform the structure and operation of the eventual Sentinel System, FDA contracted with Harvard Pilgrim Health Care Institute to develop a pilot system known as Mini-Sentinel. Numerous other public and private initiatives have helped to inform Sentinel, including the Centers for Disease Control and Prevention's Vaccine Safety Data link, HMO Research Network, the Observational Medical Outcomes Partnership (OMOP), forums convened by the Brookings Institution on the topic of postmarket evidence, Agency for Healthcare Research and Quality's Effective Health Care Program and DecIDE Networks, CERTS, eHealth Initiatives's Connecting Communities for Drugs Safety collaboration, and operational and pilot efforts conducted by health plan-based organizations (e.g., i3 Drug Safety, Health Core) and numerous integrated healthcare delivery systems. Sentinel also builds upon decades of pharmacoepidemiology research.

Efforts from these initiatives have informed some key aspects of Sentinel, including using a distributed data system as Sentinel's framework. The importance of collaboration between FDA, data and analytic partners (e.g., health plans, integrated health plans), coordinating centers, and other stakeholders has become apparent. However, more work is needed to increase confidence in the methods for active surveillance.

**Workshop Objectives**

The primary objective of this workshop is to establish priorities for research and development of methods for medical product safety surveillance.

This meeting is intended to be highly interactive. In each session, a panel of representatives from OMOP and Mini-Sentinel will provide perspectives from their organizations. Following these presentations, a panel of external lead discussants will provide brief responses, with the goal of stimulating broader discussion.

**Discussion Guide**

<u>Session 1: Methods Research and Development: Lessons Learned, Current Activities, and Existing Gaps</u>

OMOP has demonstrated the feasibility of establishing both a centralized data environment and a distributed network to facilitate the development of a risk identification and analysis system. OMOP has developed a common data model and standardized terminology to enable systematic analysis across disparate data sources, both administrative claims and electronic health records, which was successfully applied across >10 sources and >200m patient lives. The OMOP methods community has implemented 14 methods as standardized tools, including typical epidemiology designs such as propensity-matched

inception cohort design, case-control surveillance, and self-controlled case series. The research team evaluated the performance of these tools by executing the methods across the data network for 10 drugs and 10 health outcomes of interest (9 positive controls and 44 negative controls) to measure operating characteristics, such as sensitivity, specificity, positive predictive value, and area under ROC curve. Results from these experiments were presented at the January 2011 OMOP Symposium (full details available at http://omop.fnih.org/OMOP2011Symposium).

Initial findings suggest a risk identification system can complement existing safety assessment practice by efficiently generating standardized evidence from across an observational network, but the degree of inconsistency between the estimated strength of association and the ground truth suggests caution in interpretation due to substantial risk of both false negatives and false positives. Future work is ongoing to expand the evaluation of method performance across a larger set of positive and negative controls, to refine existing methods and develop new analytical strategies to overcome limitations observed in prior experiments, and to extend the analysis of observational data beyond measuring strength of association to more broadly encompass additional aspects of a causal assessment. The aim is to develop and evaluate a risk identification and analysis system that can efficiently generate evidence to support safety assessments through the exploration of emerging safety concerns and by enabling proactive monitoring of all medical products within a standardized and reproducible process.

In its first two years, Mini-Sentinel investigators have advanced or are actively working in many methodological and applied areas to address FDA's active surveillance objectives by building on and expanding basic epidemiologic principles, including:

- Methods to improve **data** integrity, accessibility, and diversification
    - Common Data Model
        - Claims and demographic data (complete)
        - Clinical data (in progress)
    - Validation and Adjudication of health outcomes of interest: a) acute myocardial infarction (completed), b) severe liver injury, c) anaphylaxis, d) venous thromboembolism, e) intussusception
    - Characterize data sources for vaccine safety evaluations (pending)
    - Health Outcomes of Interest (HOI) evidence reviews/reports: ~20 complete, ~20 pending
    - Develop modular programs and query tools: 4 complete
    - Anonymous data linkage (protocol pending to evaluate a candidate method)
- Methods for active surveillance (**Signal Refinement**)
    - Evaluation design
        - Categorization/mapping of safety questions to appropriate evaluation designs (Taxonomy) (Phase 1, evaluation design, is complete; Phase 2, analytic approach, is under way)
        - Review and detailed guidance on use of case-based designs for safety monitoring (completed)
    - Analysis
        - Comparison of performance of sequential methods incorporating confounder adjustment (complete)
        - Implementation and testing of multivariate self-controlled case series method (complete)

        - Extension/evaluation of high-dimensional propensity score variable selection methods (complete)
    - Evaluate strategies for data sharing and analyses in distributed data settings
        - Enumerate/evaluate strengths/limits of a variety of analytic and data-handling strategies that will allow multivariable adjusted analysis in distributed systems (workgroup opportunity to be issued soon)
        - Compare performance of sequential monitoring approaches that use propensity score methods (e.g. inverse probability weighting) in a distributed data environment to monitor vaccines safety
- Methods for detecting unanticipated, non-specific adverse events (**Signal Generation**)
    - Pilot implementation of two data mining methods to detect outcomes after receipt of selected vaccines (in progress)
- Methods for rapid follow-up of signals (**Signal Evaluation**)
    - Develop a framework to examine the validity of the results of a signal refinement activity (response to workgroup opportunity under review)
- Methods to evaluate impact of **FDA regulatory actions**
- Applied evaluations
    - Prospective surveillance protocols, for new molecular entities
        - AMI/saxagliptin (implementation pending)
        - Rotavirus vaccine and intussusceptions (under development)
        - Human papilloma virus vaccine and venous thromboembolism (under development)
    - Retrospective surveillance protocols for older molecular entities (2 under development)
    - Evaluate the impacts of selected FDA regulatory actions (under development)
        - Impact on the changes in utilization of medical products
- Impact on the changes in the adverse outcomes related to the medical products

<u>Session 2: Developing an Agenda to Advance Methods Research and Development</u>

The reality of limited resources underscores the value of conducting methods research efficiently and strategically. While there may be a long list of gaps in methods development, it will be important to prioritize these gaps and work collaboratively to develop a research agenda that builds upon the strengths of existing research while minimizing unnecessary overlap. OMOP and Mini-Sentinel have identified a number of objectives that they view as being central to the continued development of Sentinel over the next few years.

OMOP's objectives of future research aim to maximize the utility of observational data for safety assessment by developing and testing a suite of standardized tools for data exploration and analysis for use by the entire research community, and include:

- Creating a shared central resource to enable collaborative methodological research and development across all stakeholders and establish common practices for data analysis validation and evaluation;
- Developing and evaluate alternative strategies for synthesizing effect estimates across an observational data network, including quantifying and adjusting for heterogeneity across sources and parameter sensitivity within methods;

- Determining appropriate heuristics to guide study design decisions for specific drug-outcome scenarios, and establish practices for comprehensive sensitivity analyses;
- Establishing a quantitative framework for integrating disparate information, including formalizing causal framework within observational data and synthesizing observational evidence with other sources (pre-clinical toxicology, clinical trials, spontaneous reporting) as part of holistic safety assessment;
- Researching and develop new methods for patient segmentation, including predictive modeling for prognosis of which patients have higher risk of outcomes and how alternative treatment decisions may impact the risks; and
- Establishing a standardized procedure for creating and evaluating health outcome of interest definitions.

Mini-Sentinel has compiled a list of unanswered questions in the current understanding of methods for use in safety surveillance that they would like to see incorporated into the research agenda:

- What will be the preferred approach(es) to data handling and analyses in a distributed data structure?
- What will be the preferred approach(es) to confounding adjustment?
- What will be the preferred approach(es) to account for misclassification (e.g., of outcomes)?
- How do existing methods need to be adapted to handle the unpredictable rate and differential uptake (with respect to site and other confounders) of a new medical product?
- What is the performance of a variety of alerting algorithms that identify "sufficient" excess risk in direct comparison?
- Can we put the safety surveillance process into a decision science framework? What are the inputs and values for deciding when observed risk is acceptable (product is safe) vs. when it triggers an alert (product is unsafe)? What are the gains in evidence compared to the costs of delaying an alert? Again, what are the inputs and values? What statistics are most useful to inform decisions (e.g., relative risk or risk difference)?

The Mini-Sentinel team recommends attention to the following methods topics to support a robust active surveillance program:

- Methods to improve **data** integrity, accessibility, and diversification
    - *Develop additional fast query tools and more sophisticated modular programs*
    - *Anonymous data linkage (additional methods)*
    - *Health Outcomes of Interest (HOI) evidence reviews/reports*
    - Develop additional capacity for linking between multiple data types with and without direct patient identifier ("anonymous linkage"). Types of linkage include: claims to registries, claims to EHRs, claims to claims, etc.
    - EHR data – how to handle missing data in single and multiple variables of interest?
    - Distributed analysis of horizontally and vertically partitioned data that allow multivariable adjustment
    - Transition to ICD-10

- Methods for **active surveillance** for new molecular entities (**Signal Refinement**)
    - Develop a systematic framework to assess when (i.e., for which outcome:exposure pairs) database surveillance can be addressed validly (e.g., based on data accuracy, confounding, risk:benefit, outcome severity…)
    - Create an operational framework for an active surveillance system
        - Focus first on claims, then add additional data types.
        - Emphasize approaches that shorten the time for developing active surveillance protocols and simplify their execution.
    - Evaluation design
        - *Categorization/mapping of safety questions to appropriate evaluation designs (Taxonomy) (Phase 3, signaling methods)*
        - Methods for long latency outcomes
    - Further develop sequential testing methods for use in distributed safety surveillance system
        - Develop and assess flexible sequential methods for risk/rate difference, risk/rate ratio or hazard ratio effect measures.
    - Approaches that improve the validity of refinement methods
        - Account for misclassification (e.g., sampling strategies (case-cohort, case-control, 2-stage) to validate outcomes in near real-time)
        - Better confounding adjustment (e.g., further develop propensity score methods to accommodate >2 exposure categories (e.g. multiple comparison groups, dose groups)
        - Develop a set of standard sensitivity analyses and understand their interpretation
        - Methods that adjust for time-varying confounders
- Specific methodological aspects for **active surveillance** for blood and blood products, tissue allografts
- Specific methodological aspects for **active surveillance** for devices
- Specific methodological aspects for **active surveillance** for biosimilars
- Specific methodological aspects for **active surveillance** for drug-drug interactions
- Methods for rapid follow-up of signals identified in a Signal Refinement evaluation (**Signal Evaluation**)
    - Extend signal cluster detection methods to explore whether signals cluster in time or across subgroups
- Methods for detecting unanticipated, non-specific adverse events (**Signal Generation**)
    - Develop, test, and implement methods for non-specific (i.e., all-by-all) pairs
    - Develop, test and implement approaches to evaluate signal generation methods