ENGELBERG CENTER for Health Care Reform at BROOKINGS

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DISCUSSION GUIDE

EXPERT WORKSHOP

Workshop 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 capacity to conduct active surveillance at the population level.

In 2009, FDA awarded a contract to Harvard Pilgrim Healthcare to establish a pilot system known as Mini-Sentinel that will inform the structure and operation of the full Sentinel System. Mini-Sentinel now has the capacity to rapidly query electronic health information in administrative claims systems containing data on over 70 million people; clinical data, including laboratory values, will be added in subsequent years.

One of Mini-Sentinel's key achievements in its first year was the establishment of a distributed data system. The system consists of a coordinating center and various data partners – health plans and integrated health systems – that maintain physical and operational control over their patient-level data. While source data remain behind data partners' institutional firewalls, a key requirement of the data partners is that they format their data according to a common data model. This enables the Mini-Sentinel coordinating center to distribute queries to each of the data partners that can be run consistently from site to site. Data partners execute the queries and return aggregated results to the coordinating center.

Active surveillance may be thought of in three sequential steps: signal generation, signal refinement, and signal evaluation.

Figure 1. 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.

This workshop will focus on several statistical and epidemiological issues encountered in the course of signal refinement, a stage in the active surveillance process that begins with a potential association between a medical product and an adverse HOI that has emerged from other information available to FDA. 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 may 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 (i.e., years later). In this case, a one-time evaluation may be conducted to assess the potential association using the entire extent of marketing history.

Distributed database systems require investigators to contend with data that are horizontally and/or vertically partitioned across data partners. Mini-Sentinel currently faces the problem of horizontally partitioned claims data, wherein multiple data partners collect the same types of claims data for different patient cohorts (see Figure 2). For example, individual health plans may have data on both exposure to a drug (e.g., through prescription drug claims) and potentially related HOIs (e.g., through diagnosis codes from inpatient and outpatient claims). Resolving the challenge of horizontal partitioning requires a way to appropriately combine active surveillance evaluation results across data partners.

Figure 2. Horizontal Partitioning

Health Plan A's Members

Patient Identifier	ICD-9 Code	NDC Code
5402	401.0	54868-1005-1
5673	401.0	00028-0071-10
6007	401.1	54868-1005-1

Health Plan B's Members

Patient Identifier	ICD-9 Code	NDC Code
6056	401.0	0028-0071-10
7051	401.1	0028-0071-10
8057	401.1	54868-1005-1

Within the next year, Mini-Sentinel will also encounter the problem of vertical partitioning (i.e., data on the same patients are held by multiple data partners) when it incorporates vaccine surveillance into its capabilities. As shown in Figure 3, in vaccine surveillance, exposure and outcomes data for each patient may come from different sites. For example, exposure data could be housed in state vaccine registries while adverse outcomes might be captured in inpatient or outpatient medical claims. Resolving the challenge of vertical partitioning requires a way to reliably link patient records across the different sites through identifiers that maintain patient privacy. This may be a particular challenge as patients change their health insurance coverage. In this context, data on exposures and outcomes could be vertically partitioned across different health plans, such that long-term follow-up of a particular patient requires accurate linking.

Figure 3. Vertical Partitioning

State Vaccine Registry

Patient Identifier	Vaccination Status
113	Yes
157	Yes
168	Yes
204	Yes
243	Yes

Inpatient Claims Database

Patient Identifier	DRG Code
113	179
157	179
168	178
204	N/A
243	203

Workshop Objectives

Accomplishing the goals of active medical product surveillance through the Sentinel System will require further development of new and existing methods and tools. The Engelberg Center for Health Care Reform at Brookings is convening this expert workshop, in cooperation with FDA, to facilitate discussion of specific methodological issues, identified in discussions with FDA, and through input from Mini-Sentinel and the Observational Medical Outcomes Partnership (OMOP):

- *Signal refinement in the context of large sample sizes*. FDA's active surveillance system was mandated by Congress to include 100 million people by July 2012. Such a large starting population could result in large cohorts for signal refinement. While large samples offer certain advantages such as statistical power (especially for rare adverse events) and the ability to analyze subgroups of patients, they also increase the risk of false positive signals. Specifically, large sample sizes can make relatively small and/or biased effect estimates appear highly statistically significant. This underscores the importance of design and analytic approaches to control for bias, including consideration of whether the relevant covariates are measured to enable appropriate adjustment, and prudent interpretation.

- *Analyzing horizontally or vertically partitioned data.* Using a distributed database model reduces risks to privacy and data security, but introduces the challenge of data partitioning. Depending on the analysis and required data sources, Sentinel will encounter data that are either horizontally and/or vertically partitioned across multiple data partners. Horizontal partitioning occurs when data partners collect the same data elements for different cohorts of patients. Vertical partitioning describes different data elements for the same cohort collected from different sites.

- *Evaluating the performance of active surveillance methods*. There are multiple methods for conducting signal refinement and a range of potential operating characteristics on which to evaluate and compare these methods. In order to ensure a high level of confidence in the results of signal refinement, it will be important to establish which of these operating characteristics is most relevant and determine reliable ways to evaluate and select from potential approaches using these operating characteristics.

The goal of this workshop is to identify and discuss alternatives in each of these areas, with a particular focus on how solutions may be applied within the context of Mini-Sentinel. Suggestions based on experiences in areas outside of drug safety are welcomed, as consideration of how to adopt these suggestions may lead to innovative solutions for active surveillance. To facilitate conversation on these topics, this workshop is organized into four sessions. Experts have been selected to provide prepared remarks in each session, with the goal of stimulating a broader discussion among workshop participants.

Discussion Questions

<u>Session I: Signal Refinement in the Context of Large Sample Sizes</u>

In this session we will discuss threats to valid inference that are posed by large samples, and strategies for managing these threats through the design, analytic methods, and interpretation of results.

Discussion questions will include:

- How can true signals be distinguished from false signals that appear statistically significant due to a large sample size?
- What types of statistical analyses are most appropriate for very large sample sizes?
- How can study designs and protocols incorporate such considerations?
- How well are potential confounders represented in the data available to Mini-Sentinel? What's the best course when potential confounders cannot be measured in the patient population?
- What principles should guide interpretation of results from analyses of large samples?

Session II: Meta-Analytic Approaches for Combining Multiple Results to the Same Query

This session will focus on meta-analysis, one approach to combining results from separate analyses of horizontally partitioned data. After applying the common data model, each of the data partners participating in Mini-Sentinel's distributed data network will return site-specific results to the coordinating center. Application of meta-analysis to these site-specific results raises important questions about when and how these results should be combined and how to deal with conflicting results. Depending on the question at hand, it may be preferable to combine results from individual sites to obtain a single answer or to conduct analyses on intermediate data (e.g., counts of patients experiencing adverse events) collected from individual sites. In order for the results of meta-analysis to be valid, special attention must also be paid to understanding and managing sources of bias and heterogeneity across data sources.

Key discussion questions may include:

- Within the context of a distributed system that uses a common data model for consistent analysis across sites, when is it appropriate to combine results from different databases? What considerations (e.g., population characteristics) are relevant in making this determination?
- What are the potential approaches to meta-analysis in this setting?
- Is it preferable to combine intermediate data prior to statistical testing, or to combine site-specific estimates? Does it matter?
- How should conflicting results from a query of multiple databases be interpreted?

Session III: Distributed Regression and Related Methods for Signal Refinement

Another approach to resolving both horizontal and vertical partitioning is the collection of methods for "privacy-preserving analysis." Unlike meta-analysis in which data elements from each data partner are kept distinct and results are combined if appropriate, privacy-preserving approaches offer a way of utilizing patient-level data from partitioned databases to generate a single estimate of the association. These approaches must balance the utility of the results obtained with the risk of data disclosures.

Within Mini-Sentinel, one might envision at least two distinct privacy concerns: patient confidentiality and protections for data partners. Use of a distributed data model helps to address patient privacy concerns by ensuring that patient-level data remain behind the firewall of each data partner. In addition, patients may be less insistent on strict privacy protections when their information is used for the purpose of monitoring medical product safety. In this context, participating data partners may want to ensure that their data remain anonymized because of the potential legal risk that they might incur if a signal were traced back to their data. Specifically, if it could be demonstrated that data partners knew of a safety concern, they may be concerned about liability arising from not fulfilling their duty to warn patients and providers.

Distributed regression is a type of "privacy-preserving analysis" that allows for regression analysis when data are not stored in a central location and full disclosure of data among parties is not feasible. This approach could return a single result to a safety question while revealing as little information as possible about each data partner. A variety of approaches to distributed regression exist.

Propensity score-based pooling is an alternative approach to distributed regression. This method allows investigators to pool databases containing patient-level information on exposure, outcomes of interest, and a propensity score meant to control for confounders while preserving privacy.[1] One potential advantage of propensity score-based pooling is that it may be less labor intensive than traditional distributed regression methods. Whether the score-based pooling provides distinct statistical advantages needs to be further investigated.

[1] Rassen JA, Avorn J, Schneeweiss S. Multivariate-adjusted pharmacoepidemiologic analyses of confidential information pooled from multiple health care utilization databases. Pharmacoepidemiology and Drug Safety 2010;19:848-57.

Ultimately, approaches to resolving horizontal and vertical partitioning of data must fulfill FDA's information needs without placing undue burden on data partners (e.g., as part of requirements for special data formatting) or putting patient privacy at risk. Specifically, given that the Sentinel System may eventually conduct multiple queries on different products simultaneously, routine methods should not be prohibitively labor-intensive.

Key discussion questions may include:

- How can these methods address the horizontal partitioning problem?
- How can these methods address the vertical partitioning problem?
- What are the advantages and disadvantages of distributed regression as an approach to protecting patient privacy in the context of safety surveillance?
- What are the practical alternatives to distributed regression for deriving a single estimate, and do these methods offer advantages over meta-analysis?

Session IV: Establishing Operating Characteristics of Active Surveillance Approaches

Multiple approaches exist to refine a signal and each is associated with certain benefits and limitations. Questions remain about factors affecting method performance and characterization of the circumstances under which each method is most appropriate. Investigators would benefit from a framework for selecting methods grounded in empirical comparisons of methods.

The Observational Medical Outcomes Partnership (OMOP) has conducted quantitative evaluations of the performance of different methods based on the ability to detect known associations between exposures and outcomes ("true positives" and negative controls) in a range of databases, both in centrally held databases and within a distributed system of data partners. Moving forward, their work will focus on elucidating specific operating characteristics that affect method performance. This session will explore ways to compare methods for signal refinement, drawing on the experiences of OMOP investigators and others working in the field.

Key discussion questions may include:

- What are the relevant operating characteristics of signal refinement methods?
- What is the role for using simulated data to establish operating characteristics?
- How can studies that compare multiple active surveillance approaches be designed?
- How can operating characteristics be compared across methods?

Relevant Resources

- FDA's Sentinel Initiative Website: http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
- Mini-Sentinel Website: http://mini-sentinel.org/
- Observational Medical Outcomes Partnership (OMOP) Website: http://omop.fnih.org/
- Engelberg Center for Health Care Reform at Brookings Sentinel Initiative Website: http://www.brookings.edu/health/Projects/surveillance.aspx
- Sentinel Initiative July 2010 Update Report: http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf