Duke | Robert J. Margolis, MD Center for Health Policy

Implementation of Signal Detection Capabilities in the Sentinel System

Bethesda Hyatt Regency • Bethesda, MD
December 3, 2018

Discussion Guide

Introduction and Background for the Workshop

During clinical development of medical products and prior to regulatory review and approval, it is nearly impossible to anticipate and study all possible very rare safety concerns. Challenges to measuring these include relatively small sample sizes and shorter durations of clinical trials as well as patient populations and prescription drug uses that may vary from what was studied. To address these challenges, the U.S. Food and Drug Administration (FDA) implements a variety of safety surveillance approaches that include continuous monitoring and assessment. These approaches require close collaboration between key stakeholders to effectively capture and analyze potential signals of adverse events, and to communicate messages about the safety of medicines.

Traditionally, the FDA has relied on passive approaches to identify safety signals based on reports of possible safety issues submitted by patients, providers, and drug manufacturers to the FDA. Given the limitations of passive surveillance (including reporting time lags, variable quality of reports that FDA receives, as well as substantial under-reporting) the FDA has developed an active safety surveillance system called the Sentinel System to complement and enhance passive surveillance.

The Sentinel System provides the Agency with unique capabilities to improve the speed and efficiency of safety assessments to analyze uptake or usage of new drugs or therapies on a more diverse range of patient populations. The Sentinel System was developed in response to a mandate in the Food and Drug Amendments Act of 2007 (P.L. 110-85) to implement an active postmarket risk identification and analysis (ARIA) system utilizing data collected as part of routine care delivery. There are three categories of active safety surveillance activities outlined in the legislation, which include assessment of:

- Unexpected serious risks when available data indicates potential for serious risk (i.e., signal detection and/or signal refinement),
- Signals of serious risk related to the use of the drug (i.e., signal refinement), and
- Known serious risks related to the use of the drug (i.e., signal evaluation).*

The FDA initially prioritized the development of signal refinement and evaluation capabilities.[1] Since its launch, Sentinel has matured into a fully functional and core part of FDA's safety surveillance portfolio of activities, and the Agency now intends to strengthen and enhance Sentinel's signal detection capabilities. Successfully implementing signal detection in the Sentinel System will require developing solutions for a variety of challenges related to determining when the Agency should conduct signal detection, weighing statistical and operational considerations when using the same database for both

* Appendix A provides an updated glossary of key terms used in the Sentinel System presented at the 10th Annual Sentinel Initiative Public Workshop convened on February 7, 2018, and includes complete definitions for signal detection, signal refinement, and signal evaluation.

signal identification and subsequent analysis, and developing transparent processes for communicating potentially uncertain study results to stakeholders.

The Robert J. Margolis, MD, Center for Health Policy at Duke University is convening a public workshop on December 3, 2018, under cooperative agreement with the FDA to solicit broad stakeholder input on potential frameworks for implementing signal detection. This discussion will consider the landscape of methodological approaches and opportunities, as well as challenges involved with operationalizing these approaches within Sentinel's distributed data network.

Current Approaches for Detecting Potential Signals of Adverse Drug Events

Monitoring product safety is traditionally implemented through passive surveillance systems. These systems seek to gather risk information about adverse events, medication error reports, product quality complaints, and other serious events that may be associated with use of an FDA regulated medical product. This information is documented by health care professionals, consumers, patients, and others as a voluntary or spontaneous report. These reports are then submitted voluntarily either to the product's manufacturer, who will subsequently report them to the FDA according to regulations, or to the FDA directly via the MedWatch program.[2]

The primary data source of passive surveillance monitoring is the FDA Adverse Event Reporting System (FAERS) database.[3,4] The FDA relies on FAERS for activities such as detecting new safety concerns that might be related to a marketed product or evaluating a manufacturer's compliance with reporting regulations. While FAERS data serve as one source of voluntary reporting to detect signals, there are also other data sources such as prelicensure safety data, local or regional data sources (e.g., Joint Commission, medical literature, as well as postmarket studies conducted as part of a postmarket commitment or requirement). These data sources provide the FDA with an important and effective tool to analyze health outcome data and to identify and mitigate risk, especially for signals of serious and rare adverse event outcomes.

While passive data sources are an important part of FDA's portfolio of safety surveillance tools, these data sources also have limitations. There is often a large time lag with reporting potential risk since providers and other key stakeholders are unaware of unknown adverse events when the product receives marketing approval. There is widely acknowledged variability in the quality of reports, and substantial under reporting of events despite the large number of reports that FDA receives annually (1.8 million reports in 2017[†]). The information provided in these reports alone does not usually allow for establishing of causality between a medical product and adverse event, which makes it challenging to determine the severity and magnitude of the safety event being reported.[5,6] While a number of innovative and promising approaches have been developed to quickly mine large volumes of data from passive reporting systems, such as text mining and natural language processing, they are not yet used routinely.[7,8]

[†] Statistic cited from the FAERS Public Dashboard: https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis.

Opportunities to Complement Passive Surveillance with the Sentinel System

Given the gaps and challenges with passive surveillance, there is a unique opportunity for the FDA and stakeholders to further explore opportunities for routinely utilizing Sentinel's distributed data network and constituent Data Partners to perform signal detection.

Sentinel Data Partners consist of national health insurance plans, large integrated delivery systems, and health care organizations that collaborate with the Sentinel Operations Center (SOC) to conduct active safety surveillance activities.[‡] Data Partners share summary information derived from longitudinal claims data and growing amounts of clinical data derived from electronic health records (EHRs) through a common data model (CDM). These data provide superior quality relative to spontaneous reports and can generate signals of potential risks based on elevated rates of adverse event outcomes. Such data also provides a clear denominator of exposed patient populations with important information on specific medications dispensed, including dosage and duration that can inform benefit risk profiles of drugs.[5] The CDM makes it possible to execute standardized modular programs developed by the SOC, as well as protocol-based assessments, to conduct rapid safety assessments.

When the FDA established the Sentinel System, the initial priority was developing the data infrastructure needed to monitor and rapidly assess known safety concerns. This includes potential issues identified in pre-approval clinical trials or through data sources of passive surveillance systems. With the growing maturity of the Sentinel System's data infrastructure and demonstrated successes impacting regulatory decision making, it may now be feasible to implement signal detection capabilities.

Given the importance of and need to quickly identify potential signals of unexpected risk, the FDA intends to incorporate signal detection tools into its existing suite of modular programs to enable rapid identification of patient populations exposed to the medical product and assessment of adverse event outcomes. While not a complete list, a range of approaches that will be discussed at the public meeting are briefly summarized in Table 1; and additional background information is provided on these techniques in Appendix B. These strategies apply different types of controls, pre- and post- exposure windows, and other key operating characteristics aimed at reducing biases and key confounders that would otherwise lead to false positive safety signals and systematic error.

Table 1. Potential Statistical Approaches for Implementing Signal Detection in the Sentinel System.

Method	Brief Description
TreeScan[9,10]	Statistical signal detection approach grounded in well-known epidemiologic designs and scan statistics. Unconditional approaches require external information to specify the null hypothesis whereas conditional approaches are conditioned on the incoming dataset.
Bayesian Shrinkage Techniques and Meta-Analyses[11,12,13,14]	These techniques reduce variation by combining multiple examples to allow borrowing strength after estimating a prior distribution of average effects.
Large-Scale Comparative Effectiveness Studies with Propensity Models[15,16,17]	Analytical approach used to systematically apply best practices for observational studies at large-scale using propensity score stratification, expert-crafted outcome definitions, and multiple sensitivity analyses to answer hundreds of thousands of research questions in a distributed network of databases. Negative and positive controls (i.e. research

[‡] A list of current Sentinel Data Partners is provided in Appendix C.

	questions with known answers) are used to evaluate residual bias, and empirical calibration of p-values and confidence intervals.
Temporal Pattern Discovery[18,19,20,21]	The self-controlled cohort analysis within the Temporal Pattern Discovery framework compares the observed-to-expected ratio of medical events during post-exposure risk window(s) with those in a set of distinct control windows in the same patients. It utilizes an external control group to account for systematic differences between the different windows, thus combining within- and between-patient confounder adjustment in a single measure.

While these techniques serve as promising approaches for implementing signal detection, the purpose of this workshop is not to select a single, best method, but rather to identify a range of options that account for the strengths and potential limitations of each technique given a set of parameters for signal detection analyses. It may also be possible to combine these techniques in a way that complements and further enhances the strengths of each approach while reducing their limitations to control against key biases and confounding variables.

Key Statistical Challenges and Operational Considerations for Implementing Signal Detection in the Sentinel System's Distributed Data Environment.

Beyond the considerations for implementing a specific signal detection technique, there are also important statistical challenges and operational needs that must be addressed to implement signal detection within Sentinel's distributed database approach. These include statistical issues regarding data reuse and considerations for communicating potential result uncertainty to key stakeholders as part of a comprehensive signal management strategy.

Systematic errors including selection bias, information bias, and confounding could persist when re-using data from the same database to both generate and subsequently refine signals identified with a medical product and adverse event outcome pair.[22] One proposed solution is a partitioned dataset, however some situations may not allow for this when sample size and statistical power is important to the analysis. Moreover, this would principally reduce random error, but systematic errors may persist in the follow-up investigation.

In 2011, the FDA charged an expert committee to deliberate and provide non-binding recommendations for using modular programs that would allow for comparison of adverse event rates between different exposure groups. The committee developed a framework to potentially address false positive and false negative signals when conducting rapid assessments with modular programs for signal generation, signal refinement, and signal evaluation.[23] A key element of this framework included categorizing safety surveillance activities according to the strength of knowledge for a suspected association (also known as a "prior"); however, the committee did not seek to define levels of strength.

In response to the committee's findings, some stakeholders noted that the dynamic nature of evidence development and shifting patterns of medical product use may make it difficult to establish standardized definitions for strength of prior evidence, and therefore challenging to decide when a signal detection analysis is appropriate to implement. Further, implementing an approach that relies on well-defined parameters may exclude other important regulatory factors such as the seriousness of the adverse event.[24]

In addition to these important statistical considerations, policies and processes are also needed to communicate potential signal risk with key stakeholders. These processes could build on the FDA's foundation of communication and transparency commitments, and become integrated into existing processes the FDA uses to communicate with sponsors and other key stakeholders. For Sentinel signal refinement and evaluation studies, the Agency already posts the analytic tool used, outcome findings, and regulatory actions taken for the associated medical product on the Sentinel Initiative's public website.[§] Posting this information allows for replication of analyses by stakeholders using other data systems, and aligns with the key founding principles of privacy, security, and transparency in which the Sentinel System was built. While FDA has robust regulatory systems in place for serious, known safety events, the Agency is committed to strengthening this framework to identify and mitigate unexpected safety events using signal detection.

Stakeholder feedback obtained during the workshop will inform FDA's strategic planning to develop and implement signal detection capabilities, and support the Agency's continuing commitment to advance and modernize the Sentinel System.

Funding for this conference was made possible in part by a cooperative agreement from the U.S. Food and Drug Administration Center for Drug Evaluation and Research. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.

[§] Sentinel analyses and findings can be viewed at: https://www.sentinelinitiative.org/drugs/how-aria-analyses-have-been-used-fda.

Appendix A: Glossary of Sentinel System Terms

Active Risk Identification and Analysis (ARIA): The U.S. Food and Drug Administration's (FDA) active post-market risk identification and analysis system, which is comprised of pre-defined, parameterized, reusable routine querying tools, combined with the electronic data in the Sentinel Common Data Model. Because ARIA uses parameterized tools and a trusted multi-site distributed database that undergoes continuous quality checks and refreshes, safety analyses can be done more efficiently to conduct medical product safety surveillance to fulfill the mandate in the FDA Amendments Act of 2007.

Biologics Effectiveness and Safety (BEST) Initiative: A system currently being developed to expand and enhance FDA's Center for Biologics Evaluation and Research (CBER) post-market surveillance capabilities. The primary goals of BEST are a) to develop a system using electronic health records (EHR) and claims data sources covering a large proportion of the U.S. population, automated query tools, and additional infrastructure; b) to develop improved automated adverse events data collection, analysis, and reporting techniques for biologics by using methods such as natural language processing and machine learning.

Blood Safety Surveillance Continuous Active Network (BloodSCAN): A subcomponent of the CBER Sentinel Program focusing on surveillance and recipient safety evaluation of blood components and blood-derived products.

Cohort Identification and Descriptive Analysis (CIDA) Tool: CIDA serves as the foundation of the routine querying system, and is responsible for identifying, extracting, and characterizing cohorts of interest from the SDD based on the specification of a number of requester-defined options (e.g., continuous enrollment requirements, incidence criteria, inclusion/exclusion criteria).

FDA-Catalyst: Activities leverage the Sentinel Infrastructure by utilizing the data available through its data partners and supplementing it with data from interventions or interactions with members and/or providers.

Post-licensure Rapid Immunization Safety Monitoring (PRISM): A subcomponent of CBER Sentinel Program focusing on vaccine safety surveillance for evaluation of potential safety signals identified during pre-market and post-market reviews.

Routine Querying Tools (Modular Programs): Sentinel's routine querying tools include modular programs, summary tables, and software toolkits. Modular programs are grouped into three levels:

- **Level 1** modular program queries identify cohorts of interest and, for some cohorts, can perform unadjusted and minimally adjusted (i.e., by Data Partner, age group, sex, and year) analyses.
- **Level 2** modular program queries identify cohorts of interest, perform more complex adjustment for confounding, and generate effect estimates and confidence intervals.
- **Level 3** modular program queries identify cohorts of interest and perform more complex adjustment for confounding repeatedly as part of prospective sequential analysis.

Sentinel Collaborating Institutions: A network of Data and Academic Partners that work with the FDA and Sentinel Coordinating Center to provide access to both healthcare data and scientific, technical, and organizational expertise.

Sentinel Coordinating Center: The Sentinel Coordinating Center includes the Sentinel Operations Center (SOC), comprised of the Applied Surveillance, Scientific Systems, and Administration Divisions housed at the Harvard Pilgrim Health Care Institute (HPHCI), and advisory groups. Both the Sentinel Coordinating Center and the SOC are led by the Sentinel Principal Investigator at HPHCI.

Sentinel Data Partners: Data Partners in the Sentinel System include a diverse group of organizations including academic medical centers, healthcare systems, and health insurance companies. Sentinel Data Partners maintain physical and operational control over electronic data in their existing environments.

Sentinel Infrastructure: The underlying data infrastructure created to enable analysis within the Sentinel System. The Sentinel Infrastructure involves: 1) a distributed data approach in which Data Partners maintain physical and operational control over electronic data in their existing environments; and 2) a Common Data Model consisting of standardized administrative and clinical information across Data Partners. The Sentinel Infrastructure has the potential to allow analysis of the data for other purposes besides safety for the FDA or those outside the FDA.

Sentinel Initiative: A multi-year effort beginning in 2008 to create a national electronic system for monitoring the performance of FDA-regulated medical products to improve the FDA's ability to identify and assess medical product safety issues.

Sentinel System: An active surveillance system that uses routine querying tools and pre-existing electronic healthcare data from multiple sources to monitor the safety of regulated medical products. Subcomponents of the Sentinel System include: ARIA, PRISM, BloodSCAN and STAT.

Signal Detection: An approach that uses statistical methods to identify medical product–adverse outcome associations that may be safety signals; no particular medical produce exposure or adverse outcome is pre-specified.

Signal Evaluation: Consists of the implementation of a full epidemiological analysis to more thoroughly evaluate the causal relationship between exposure to the medical product and the adverse outcome of interest.

Signal Refinement: A process by which an identified potential safety signal is further investigated to determine whether evidence exists to support a relationship between the medical product exposure and the outcome.

Surveillance of Tissues and Advanced Therapeutics (STAT): A subcomponent of the CBER Sentinel Program focusing on surveillance and recipient safety evaluation of human cell-, gene-, tissue-based products, other advanced therapies, and antivenins.

Appendix B: Overview of Signal Detection Techniques

Method	Description	Study Design Compatibility	Key Parameters and Assumptions	Data Resources and Capabilities Required	Strengths	Limitations
TreeScan: Tree-based Poisson Scan Statistic	Statistical signal detection approach grounded in well-known epidemiologic designs and scan statistics. Unconditional approaches require user-specified values for the null hypothesis whereas the null hypothesis is derived (conditioned) on the incoming data in conditional approaches.	Stratified Cohort Designs with Reference Cohort.	Outcomes are Poisson-distributed. Parameters include stratified background rates for all nodes in the tree.	Summary data from multiple sites/ databases using a distributed database approach can be used to perform a TreeScan analysis. Rapid iteration is not required.	Takes advantage of hierarchical nature of clinical concepts in the form of a tree structure. Investigator does not need to understand how outcome data is coded. Formal control for multiple hypothesis testing and overall Type I error.	Most of the limitations are inherent to the epidemiologic design that supports the tree-based scan statistic. Parameters are set for ALL outcomes in the tree (~8000+) and therefore are not customizable by outcome.
TreeScan: Tree-based Bernoulli Scan Statistic		Self-Controlled Designs. Fixed Match Ratio Designs.	Outcomes are distributed per the user-specified matching ratio or based on the dataset. Parameters include the probability of occurring in the treatment group/risk window.			
TreeScan: Tree-temporal Scan Statistic		Self-Controlled Designs.	Outcomes are distributed according to the time contributed or based on the incoming dataset. Parameters include various Scanning Window Parameters.			
Large-Scale Comparative Effectiveness	Analytical approach used to systematically apply best practices for observational studies at large-scale using	Any observational study design can be used. To date,	A key parameter is the scope of the analysis (e.g. limit to	Requires outcomes to be defined in the network of	Full study diagnostics, such as propensity score overlap, covariate	Requires adjustment for multiple testing when interpreting results in

Studies with Propensity Models and Empirical Calibration	propensity score stratification, expert-crafted outcome definitions, and multiple sensitivity analyses to answer hundreds of thousands of research questions in a distributed network of databases. Negative and positive controls (i.e. research questions with known answers) are used to evaluate residual bias, and empirical calibration of p-values and confidence intervals.	this approach has been applied to new-user cohort designs to mimic targeted randomized trials.	one exposure, all exposures in a class, or all treatments for a particular indication). When using a new-user cohort design it assumes some comparator exposure exists with sufficient overlap in population characteristics.	databases, as well as a set of negative control exposure-outcome pairs.	balance, sensitivity analyses results, and empirical performance on negative and positive controls are readily available to interpret potential findings.	the context of signal detection.
Self-Controlled Designs with Temporal Pattern Discovery	The self-controlled cohort analysis within the Temporal Pattern Discovery framework compares the observed-to-expected ratio of medical events during post-exposure risk window(s) with those in a set of distinct control windows in the same patients. It utilizes an external control group to account for systematic differences between the different windows, thus combining within- and between-patient confounder adjustment in a single measure.	Cohort, New User	Choice of risk window(s) (e.g. days 1-30, days 1-90). Choice of control window(s) (e.g. day of event, 1-30 days before start of treatment, and 180 to 540 days before start of treatment). Choice of external control group (default: prescriptions of any drug in the database as with disproportionality analysis for spontaneous reports).	Data on all patients exposed to the drug(s) of interest plus corresponding data for an external control group used for calibration.	Self-controlled analysis adjusts for time-constant confounders and provides a reasonably versatile and general approach to statistical signal detection in longitudinal observational data. Use of external control group offers calibration for systematic differences between the different windows (e.g. different lengths, censoring, overall differences in likelihood of certain events such as those that are sometimes fatal and at different points in time relative to the start of treatment).	Not suitable for fatal events, because of being self-controlled (not ideal for events with high fatality, although calibration by external control group may make it more robust to this than other self-controlled designs). Vulnerable to time-varying confounding and especially to protopathic biases. Use of generic analysis strategy makes manual review of findings a necessity – emphasis on reducing false positive findings for example through use of multiple control windows will increase risk of false negatives instead.

					Leveraging Gamma-Poisson shrinkage with a fixed G(½, ½) distribution, this technique offers a simple, but powerful approach to reduce the risk of spurious associations from both random variability and artificially low expected values (on which we condition).	
Bayesian Shrinkage Techniques and Meta-Analyses	These techniques reduce variation by combining multiple examples to allow borrowing strength after estimating a prior distribution of average effects.	Effective when study design seeks estimates for many parallel problems.	Assumes similarity of effects or sources of variation across multiple problems.	Needs large databases to draw on multiple estimations and measure variance components.	Often provides accurate adjustments for multiple comparisons conundrums that are especially problematic for safety surveillance analyses.	Results can mislead if individual problems are black swan outliers that don't follow the general pattern of most other examples.

Appendix C: List of Current Sentinel Data Partners**

- Aetna Informatics
- Blue Cross Blue Shield of Massachusetts
- Department of Population Health Sciences, Duke University School of Medicine
- HealthCore, Inc. Government & Academic Research
- Harvard Pilgrim Health Care Institute
- HealthPartners Institute
- Humana, Inc., Comprehensive Health Insights
- Marshfield Clinic Research Institute
- Meyers Primary Care Institute, a joint endeavor of Fallon Community Health Plan
- Hospital Corporation of America
- Kaiser Permanente Colorado Institute for Health Research
- Kaiser Permanente Center for Health Research Hawaii
- Kaiser Foundation Health Plan of the Mid-Atlantic States, Inc.
- Kaiser Permanente Northern California, Division of Research
- Kaiser Permanente Northwest Center for Health Research
- Kaiser Permanente Washington Health Research Institute
- Optum
- Vanderbilt University School of Medicine, Department of Health Policy

** List adapted from: https://www.sentinelinitiative.org/collaborators.

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