Implementation of Signal Detection Capabilities in the Sentinel System

Bethesda Hyatt Regency

December 3, 2018

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Welcome and Introductions

Join the conversation with **#sentinelinitiative**

Presentation: Signal Identification in the Sentinel System: Past, Present, and Future

Signal Identification in the Sentinel System: Past, Present, and Future

Michael D. Nguyen, MD
FDA Sentinel Program Lead
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

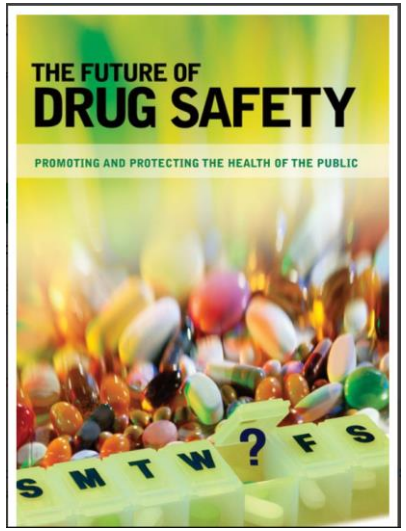
December 3, 2018

Plan for Talk

- Motivation for initiating signal identification in Sentinel
- Approach to building a signal identification program in Sentinel
- Signal identification operational pilot
- Establishing a scientific community

Workshop goal: Obtain scientific input

Institute of Medicine

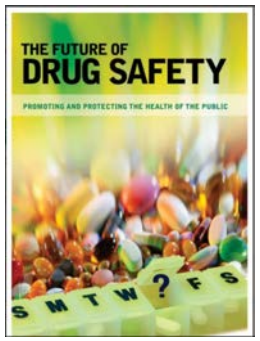


4.2: The committee recommends that in order to facilitate the formulation and testing of drug safety hypotheses, CDER

(a) Increase their intramural and extramural programs that access and study data from large automated healthcare databases and
(b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events of interest, and
(c) develop and implement active surveillance of specific drugs and diseases as needed in a variety of settings.

https://www.nap.edu/catalog/11750/the-future-of-drug-safety-promoting-and-protecting-the-health

FDA Amendment Act 2007



FDAAA 2007

SEC. 905. ACTIVE POSTMARKET RISK IDENTIFICATION AND ANALYSIS.

(a) IN GENERAL.—Subsection (k) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) is amended by adding at the end the following:

"(3) ACTIVE POSTMARKET RISK IDENTIFICATION.—

"(A) DEFINITION.—In this paragraph, the term 'data' refers to information with respect to a drug approved under this section or under section 351 of the Public Health Service Act, including claims data, patient survey data, standardized analytic files that allow for the pooling and analysis of data from disparate data environments, and any other data deemed appropriate by the Secretary.

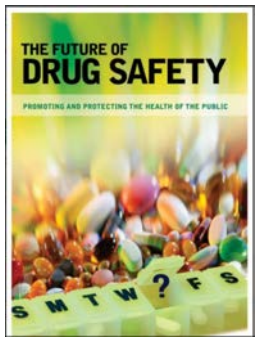
"(B) DEVELOPMENT OF POSTMARKET RISK IDENTIFICATION AND ANALYSIS METHODS.—The Secretary shall, not later than 2 years after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, in collaboration with public, academic, and private entities—

"(i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C);

"(ii) develop validated methods for the establishment of a postmarket risk identification and analysis

https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf

FDA Amendment Act 2007



FDAAA 2007

events submitted by patients, providers, and drug sponsors, when appropriate;

"(III) to provide for active adverse event surveillance using the following data sources, as available:

"(aa) Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs);

"(bb) private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data); and

"(cc) other data as the Secretary deems necessary to create a robust system to identify adverse events and potential drug safety signals;

"(IV) to identify certain trends and patterns with respect to data accessed by the system;

https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf

Early Goals Defined in the Mini-Sentinel Pilot

pharmacoepidemiology and drug safety 2012; 21(S1): 9–11
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.2311

ORIGINAL REPORT

The US Food and Drug Administration 's Sentinel Initiative: Expanding the horizons of medical product safety

Melissa A. Robb[1]*, Judith A. Racoosin[1], Rachel E. Sherman[1], Thomas P. Gross[2], Robert Ball[3], Marsha E. Reichman[4], Karen Midthun[5] and Janet Woodcock[6]

[1]Office of Medical Policy, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, USA
[2]Office of Surveillance and Biometrics, Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD 20993, USA
[3]Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD 20852, USA
[4]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993 USA
[5]Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD 20852, USA
[6]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, USA

key words—FDA; Sentinel System; active surveillance; medical product safety; common data model; patient privacy

"The system being created under the auspices of the Sentinel Initiative (the Sentinel System) will help **FDA identify and investigate postmarket safety signals**, a concern about an excess of adverse events compared with what is expected to be associated with a product's use, through the processes of **signal generation**, signal refinement, and signal evaluation."

https://onlinelibrary.wiley.com/doi/epdf/10.1002/pds.2311

Testing & Evaluation of Signal Identification

01 **Foundational Methods**

Evaluation with simulated data, creation of different methods, infrastructure for alert follow-up

02 **Shorter Term Exposures**

Tested on vaccines, antibiotics

03 **Longer Term Exposures**

Tested on statins, long acting reversible contraceptives, diabetes drugs


eGEMs

Generating Evidence & Methods to improve patient outcomes

Statistical Power for Postlicensure Medical Product Safety Data Mining

Judith C. Maro, PhD,[a] Michael D. Nguyen, MD,[a] Inna Dashevsky, MS,[a] Meghan A. Baker, MD, PhD,[a] Martin Kulldorff, PhD[b]

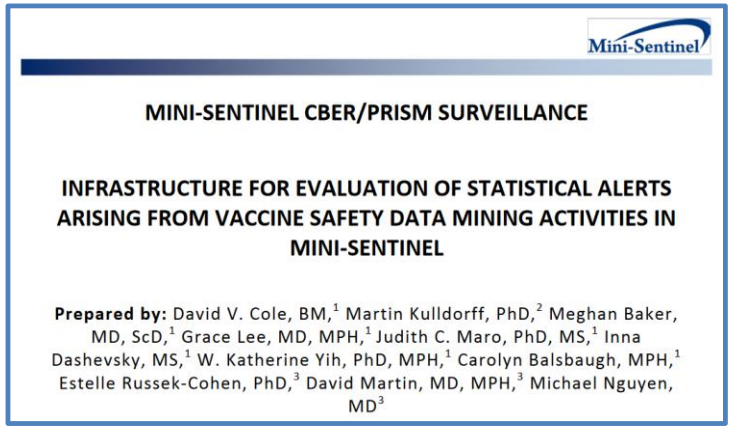
ABSTRACT

Objective: To perform sample size calculations when using tree-based scan statistics in longitudinal observational databases.


ORIGINAL ARTICLE

Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic

Shirley V. Wang,[a] Judith C. Maro,[b] Elande Baro,[c] Rima Izem,[c] Inna Dashevsky,[b] James R. Rogers,[a] Michael Nguyen,[d] Joshua J. Gagne,[a] Elisabetta Patorno,[a] Krista F. Huybrechts,[a] Jacqueline M. Major,[d] Esther Zhou,[d] Megan Reidy,[b] Austin Cosgrove,[b] Sebastian Schneeweiss,[a] and Martin Kulldorff[a]


Mini-Sentinel

MINI-SENTINEL CBER/PRISM SURVEILLANCE

INFRASTRUCTURE FOR EVALUATION OF STATISTICAL ALERTS ARISING FROM VACCINE SAFETY DATA MINING ACTIVITIES IN MINI-SENTINEL

Prepared by: David V. Cole, BM,[1] Martin Kulldorff, PhD,[2] Meghan Baker, MD, ScD,[1] Grace Lee, MD, MPH,[1] Judith C. Maro, PhD, MS,[1] Inna Dashevsky, MS,[1] W. Katherine Yih, PhD, MPH,[1] Carolyn Balsbaugh, MPH,[1] Estelle Russek-Cohen, PhD,[3] David Martin, MD, MPH,[3] Michael Nguyen, MD[3]

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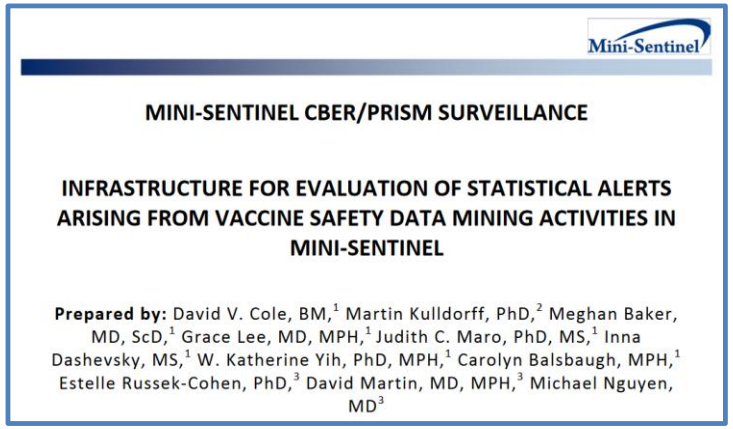

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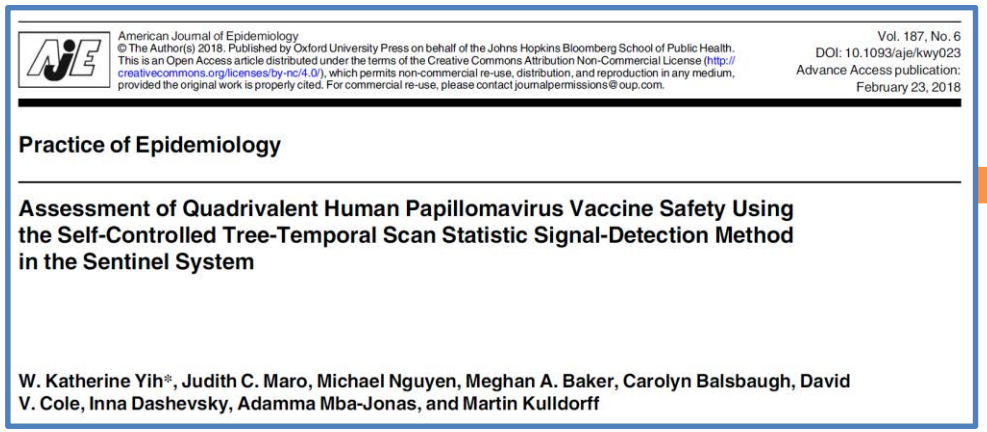

American Journal of Epidemiology
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Vol. 187, No. 6
DOI: 10.1093/aje/kwy023
Advance Access publication: February 23, 2018

Practice of Epidemiology

Assessment of Quadrivalent Human Papillomavirus Vaccine Safety Using the Self-Controlled Tree-Temporal Scan Statistic Signal-Detection Method in the Sentinel System

W. Katherine Yih*, Judith C. Maro, Michael Nguyen, Meghan A. Baker, Carolyn Balsbaugh, David V. Cole, Inna Dashevsky, Adamma Mba-Jonas, and Martin Kulldorff

pharmacoepidemiology and drug safety 2013; 22: 517–523
Published online 20 March 2013 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3423

ORIGINAL REPORT

Drug safety data mining with a tree-based scan statistic

Martin Kulldorff[1,2]*, Inna Dashevsky[1], Taliser R. Avery[1], Arnold K. Chan[3,4], Robert L. Davis[5], David Graham[6], Richard Platt[1,2], Susan E Andrade[2,7], Denise Boudreau[2,8], Margaret J. Gunter[2,9], Lisa J. Herrinton[2,10], Pamala A. Pawloski[2,11], Marsha A. Raebel[2,12], Douglas Roblin[2,5] and Jeffrey S. Brown[1,2]

Public Training on Signal Identification

Submit Comment

Public Sentinel Training at FDA - Day 2 of the Tenth Annual Sentinel Initiative Public Workshop

Project Title	**Public Sentinel Training at FDA - Day 2 of the Tenth Annual Sentinel Initiative Public Workshop**
Date	*Thursday, February 8, 2018*
Description	This workshop addressed advanced topics including Sentinel's inferential analytic capabilities and methods of identifying unexpected safety concerns. Presenters used example assessments to demonstrate propensity score matching analyses, self-controlled risk interval analyses, and analyses using the TreeScan software. This training was held on February 8, 2018 on the FDA's White Oak Campus in Silver Spring, MD.
Location	Recordings of the presentations are available via the following links: • Welcome, Introduction, Agenda, Learning Objectives • Review of Sentinel Capabilities *(skip ahead to 14:50)* • Propensity Score Analysis Tool *(skip ahead to 28:08)* • Self-Controlled Risk Interval Tool • TreeScan Analyses • Closing Remarks *(skip ahead to 57:18)* Sentinel Initiative Public Workshop Training Slides
Related Links	Day 1 of the Tenth Annual Sentinel Initiative Public Workshop

TreeScan™ User Guide

for version 1.4

https://www.treescan.org

https://www.sentinelinitiative.org/communications/sentinel-initiative-events/sentinel-initiative-public-workshop-tenth-annual-day-2

Discuss Challenges of Implementation

Received: 14 February 2018 | Revised: 21 March 2018 | Accepted: 22 March 2018
DOI: 10.1002/pds.4442

COMMENTARY

WILEY

Reuse of data sources to evaluate drug safety signals: When is it appropriate?

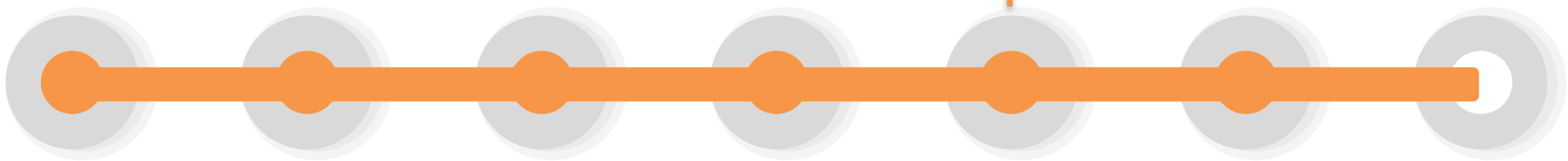
Shirley V. Wang [1] | Martin Kulldorff [1] | Robert J. Glynn [1] | Joshua J. Gagne [1] | Anton Pottegård [2] | Kenneth J. Rothman [3] | Sebastian Schneeweiss [1] | Alexander M. Walker [4]

Presentation: Key Statistical Considerations for Implementing Signal Identification in the Sentinel System
Mark Levenson, U.S. Food and Drug Administration

Panelist: *Darren Toh, Harvard Medical School*
Panelist: *Juhaeri Juhaeri, Sanofi*
Panelist: *Mary Beth Ritchey, RTI International*
Panelist: *Simone Pinheiro, U.S. Food and Drug Administration*

Presentation: Potential Processes for Communicating Result Uncertainty
Theresa Toigo, U.S. Food and Drug Administration

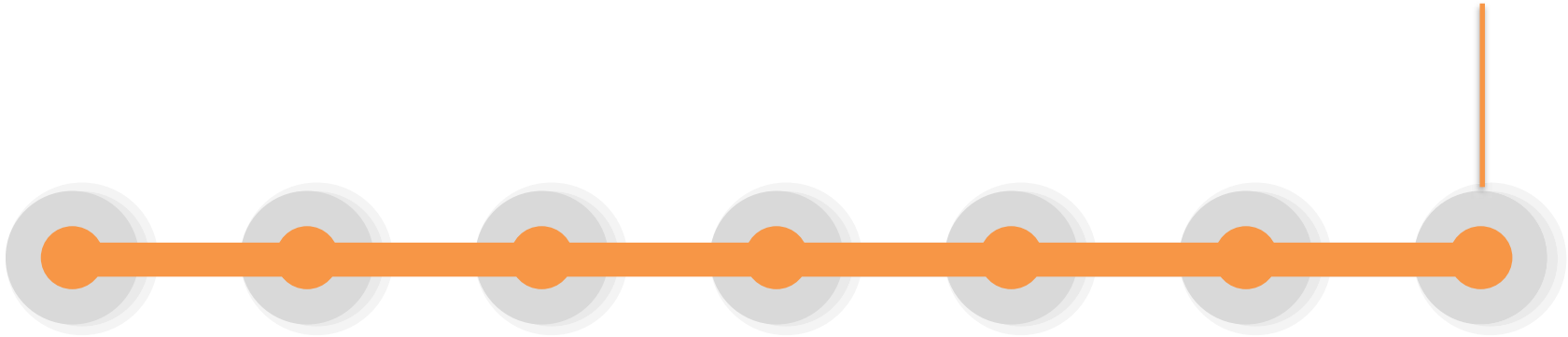
Panelist: *Stephen Evans, The London School of Hygiene & Tropical Medicine*
Panelist: *Joanne Waldstreicher, Johnson & Johnson*
Panelist: *Mary Frances Schubert, Merck & Company, Inc*
Panelist: *Diana Zuckerman, National Center for Health Research*



https://onlinelibrary.wiley.com/doi/full/10.1002/pds.4442

Next Steps

Next steps: conduct pilot of signal identification, learn in action, grow and enhance toolkit, and establish a best practices framework



https://www.sentinelinitiative.org/communications/sentinel-initiative-events/sentinel-initiative-public-workshop-tenth-annual-day-2

Plan for Talk

- Motivation for initiating signal identification in Sentinel
- **Approach to building a signal identification program in Sentinel**
- Signal identification operational pilot
- Establishing a scientific community

Signal Detection Approaches Available in Sentinel

Pre-Specified Panel of Select Outcomes

Prospective sequential surveillance tool (Level 3)

One Product, All Outcomes

TreeScan

One Outcome, All Products

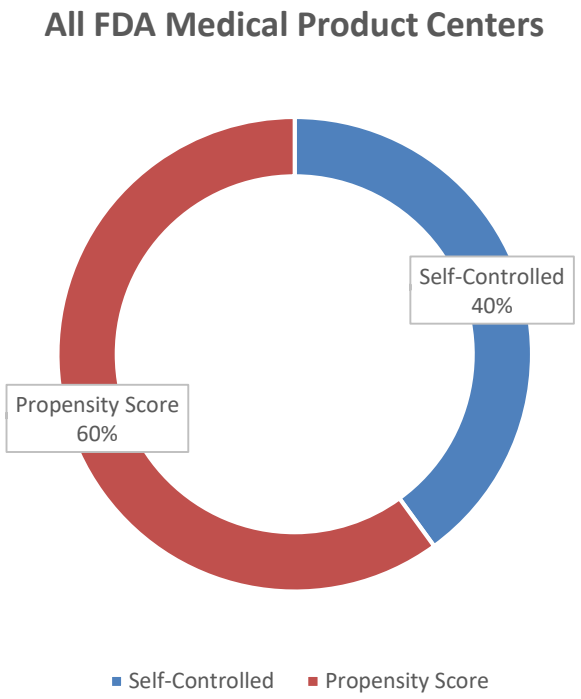
DrugScan

All Products, All Outcomes

No existing tool in Sentinel

No One Best Method: Need for Broad Toolkit

Inferential Analyses in Sentinel System, 2016-2018

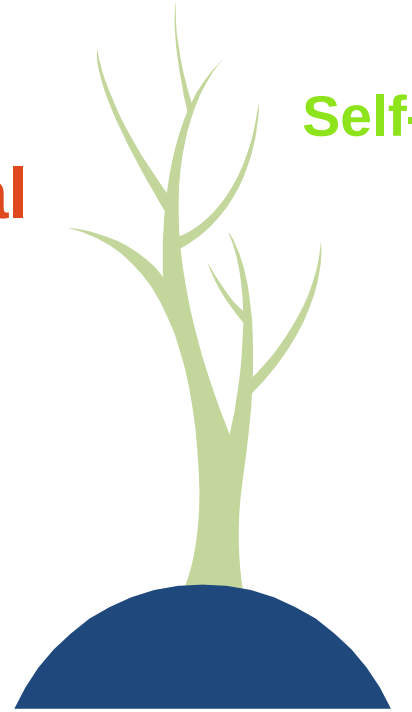


Varieties of TreeScan

Propensity Score Matched

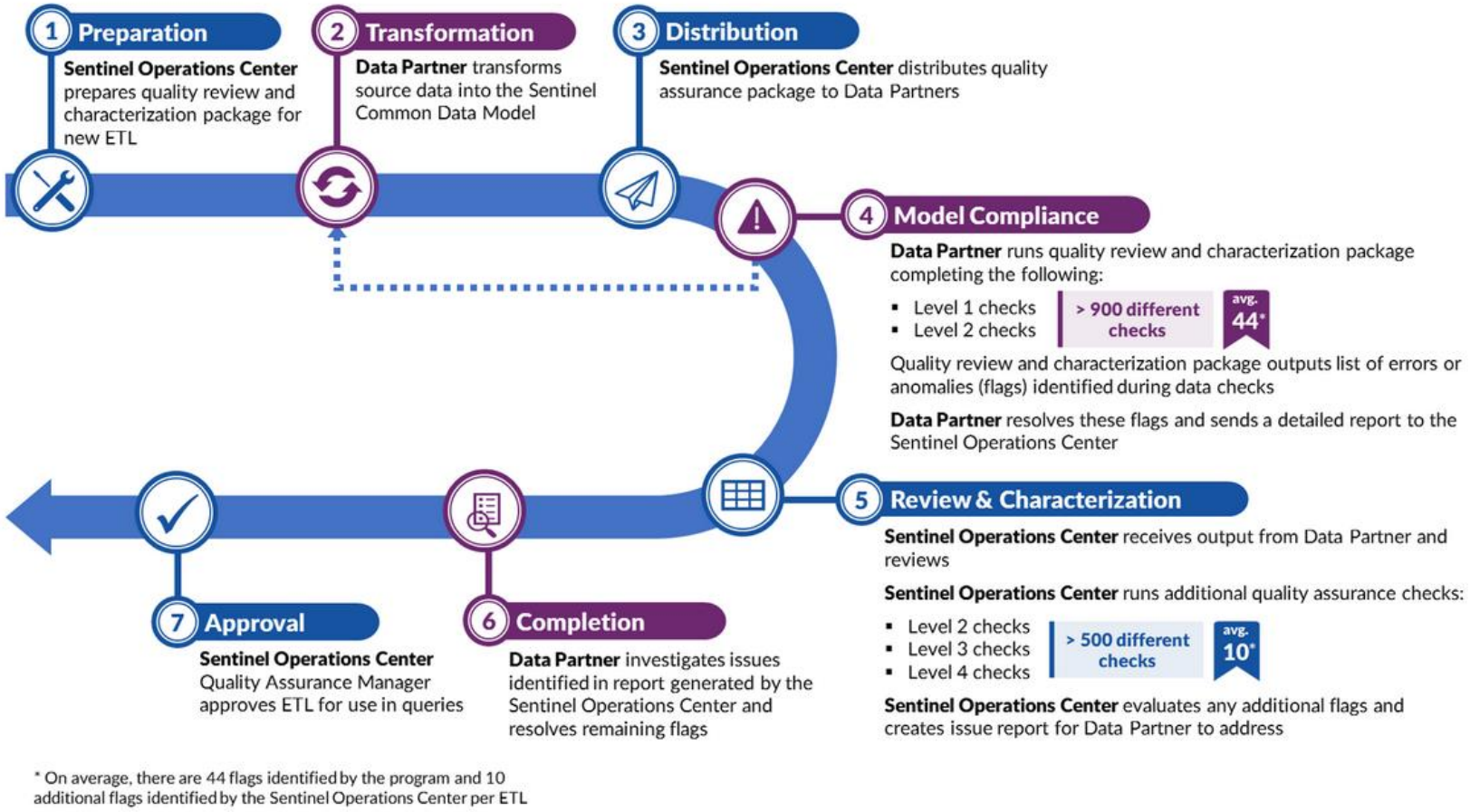
Tree-temporal

Self-controlled



Foundation for Signal Identification

Data Quality Review and Characterization



https://www.sentinelinitiative.org/sentinel/data-quality-review-and-characterization

Plan for Talk

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Proposed Sentinel Signal Identification Process

Integrated Safety Summary

Clinical Trial Data | **Prescribing Information**

Signal identification led by **Divisions of Pharmacovigilance** and Sentinel Program Team

Follow up investigations to be conducted by **Divisions of Epidemiology**

1. Select 1 product
2. Choose study design(s) or tool
3. Conduct analysis
4. Review and classify statistical alerts
5. Integrate results with other sources of information

Identify Outcome for Further Evaluation (if any)

Adapting Lessons Learned to a New Program

Active Risk Identification and Analysis System (ARIA)

Serious safety concern

Determined by statistical power and study design considerations

Established roles, templates, processes across FDA divisions

Established templates, webpages to share ongoing analyses, results, regulatory outcomes

Initiation

Timing

Process

Communication

Sentinel Signal Identification Program

Use risk-based approach, need to determine if system is “fit for purpose” for drug of interest

Balance desire for timeliness with statistical power

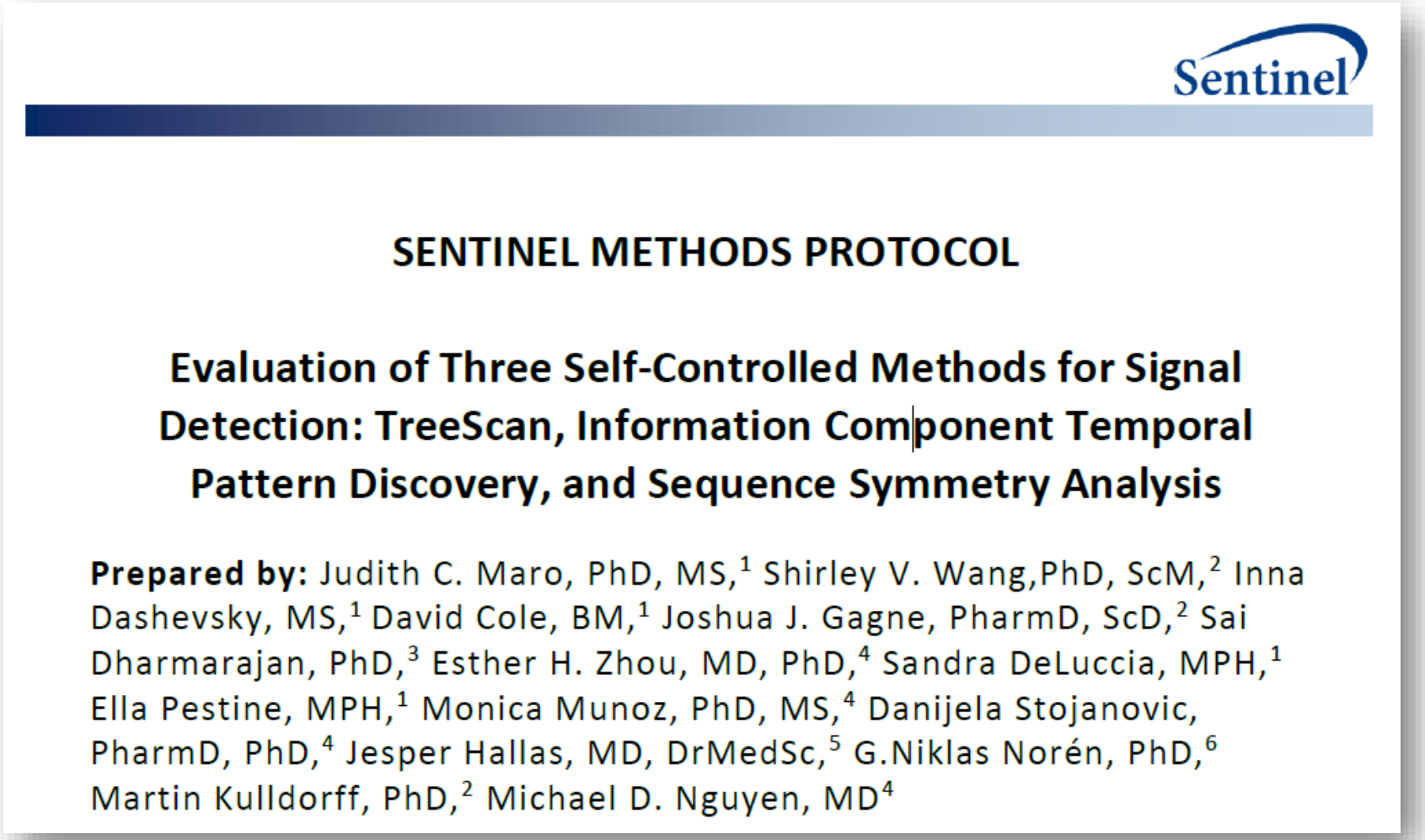
Develop and pilot roles, templates, processes across FDA divisions. Build upon existing ARIA process

Build upon existing ARIA framework

Plan for Talk

- Motivation for initiating signal identification in Sentinel
- Approach to building a signal identification program in Sentinel
- Signal identification operational pilot
- **Establishing a scientific community**

New Investigators in Sentinel Projects



Sentinel

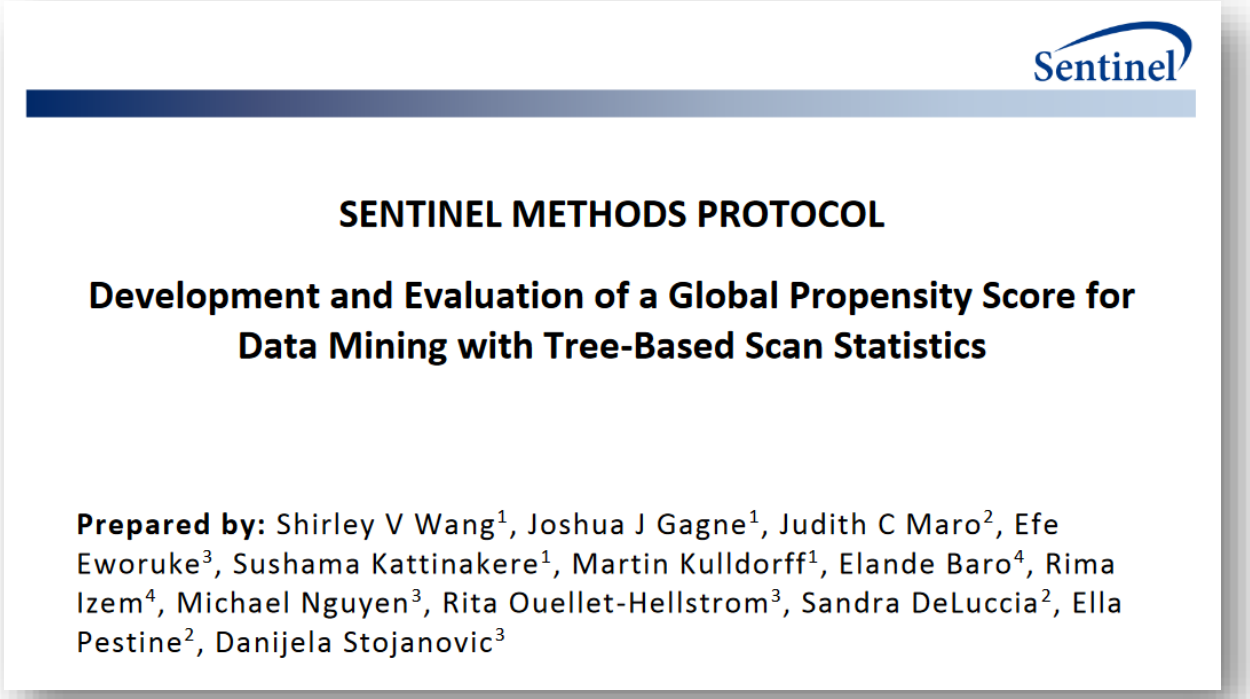
SENTINEL METHODS PROTOCOL

Evaluation of Three Self-Controlled Methods for Signal Detection: TreeScan, Information Component Temporal Pattern Discovery, and Sequence Symmetry Analysis

Prepared by: Judith C. Maro, PhD, MS,[1] Shirley V. Wang,PhD, ScM,[2] Inna Dashevsky, MS,[1] David Cole, BM,[1] Joshua J. Gagne, PharmD, ScD,[2] Sai Dharmarajan, PhD,[3] Esther H. Zhou, MD, PhD,[4] Sandra DeLuccia, MPH,[1] Ella Pestine, MPH,[1] Monica Munoz, PhD, MS,[4] Danijela Stojanovic, PharmD, PhD,[4] Jesper Hallas, MD, DrMedSc,[5] G.Niklas Norén, PhD,[6] Martin Kulldorff, PhD,[2] Michael D. Nguyen, MD[4]

https://www.sentinelinitiative.org/sentinel/methods/evaluation-three-self-controlled-methods-signal-detection-treescan-sequence

Public Engagement Through Posting of Study Protocols for Comment

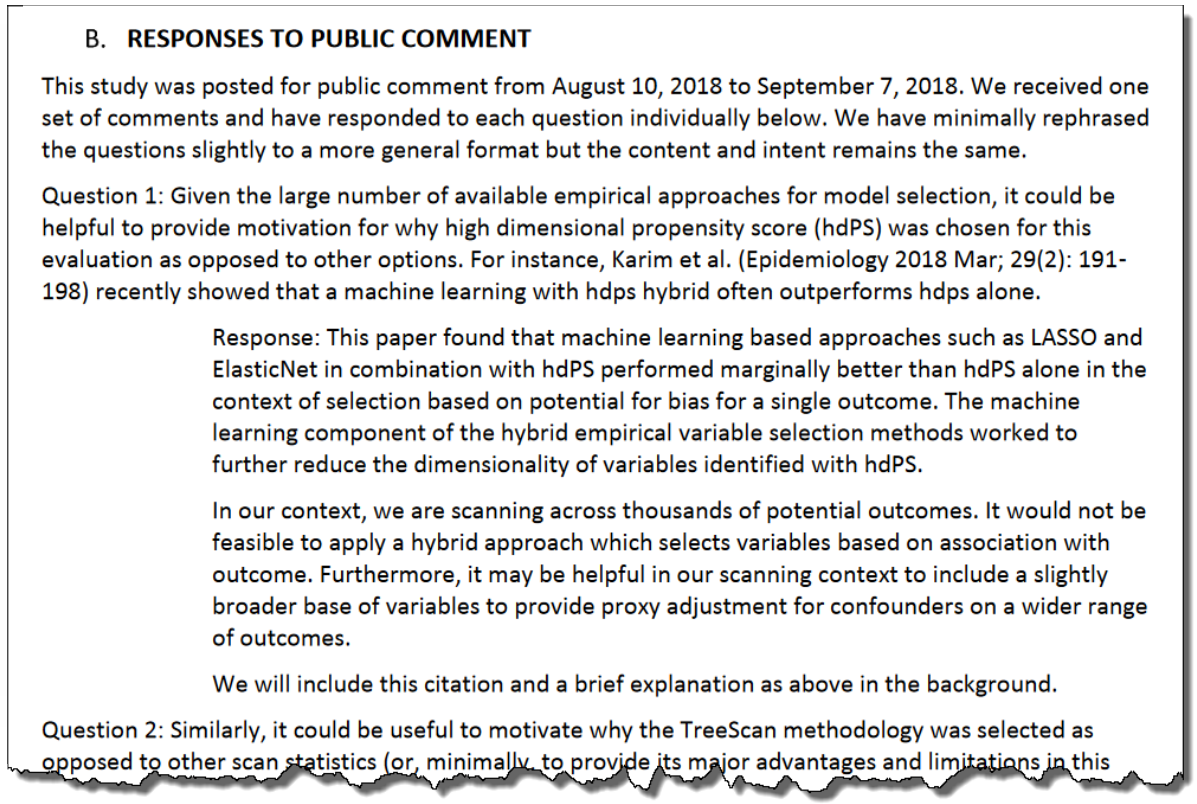


Sentinel

SENTINEL METHODS PROTOCOL

Development and Evaluation of a Global Propensity Score for Data Mining with Tree-Based Scan Statistics

Prepared by: Shirley V Wang[1], Joshua J Gagne[1], Judith C Maro[2], Efe Eworuke[3], Sushama Kattinakere[1], Martin Kulldorff[1], Elande Baro[4], Rima Izem[4], Michael Nguyen[3], Rita Ouellet-Hellstrom[3], Sandra DeLuccia[2], Ella Pestine[2], Danijela Stojanovic[3]



B. **RESPONSES TO PUBLIC COMMENT**

This study was posted for public comment from August 10, 2018 to September 7, 2018. We received one set of comments and have responded to each question individually below. We have minimally rephrased the questions slightly to a more general format but the content and intent remains the same.

Question 1: Given the large number of available empirical approaches for model selection, it could be helpful to provide motivation for why high dimensional propensity score (hdPS) was chosen for this evaluation as opposed to other options. For instance, Karim et al. (Epidemiology 2018 Mar; 29(2): 191-198) recently showed that a machine learning with hdps hybrid often outperforms hdps alone.

Response: This paper found that machine learning based approaches such as LASSO and ElasticNet in combination with hdPS performed marginally better than hdPS alone in the context of selection based on potential for bias for a single outcome. The machine learning component of the hybrid empirical variable selection methods worked to further reduce the dimensionality of variables identified with hdPS.

In our context, we are scanning across thousands of potential outcomes. It would not be feasible to apply a hybrid approach which selects variables based on association with outcome. Furthermore, it may be helpful in our scanning context to include a slightly broader base of variables to provide proxy adjustment for confounders on a wider range of outcomes.

We will include this citation and a brief explanation as above in the background.

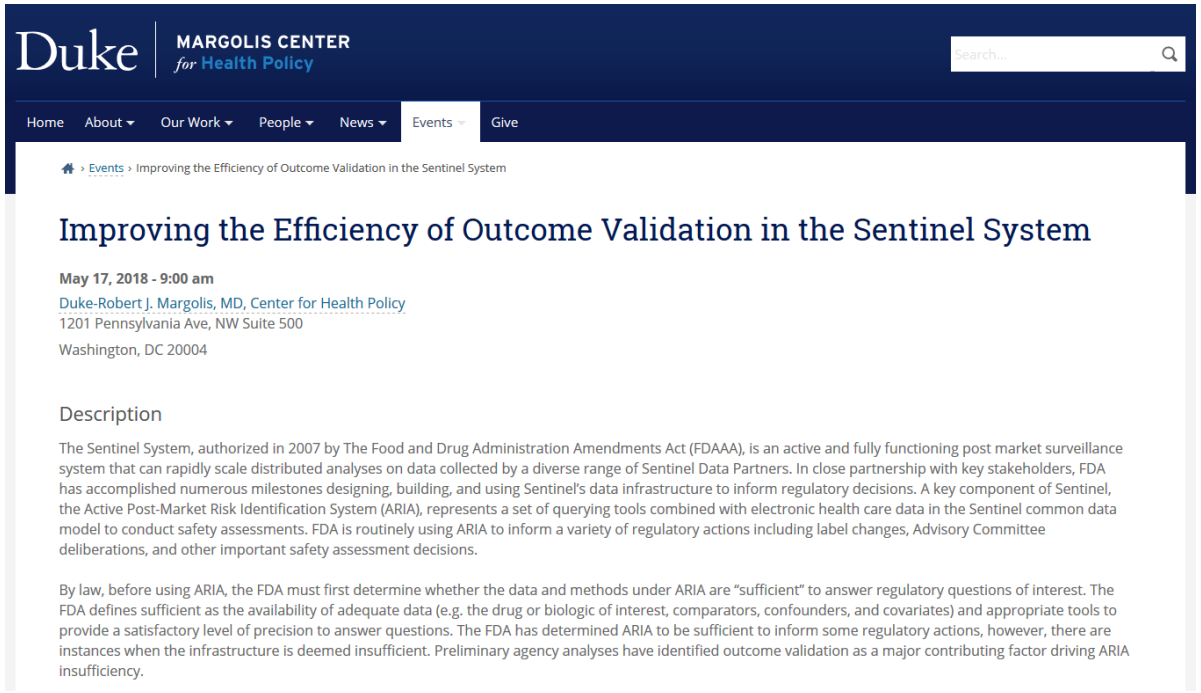
Question 2: Similarly, it could be useful to motivate why the TreeScan methodology was selected as opposed to other scan statistics (or, minimally, to provide its major advantages and limitations in this

https://www.sentinelinitiative.org/sentinel/methods/development-and-evaluation-global-propensity-score-data-mining-tree-based-scan

Planned Future Projects

- Development of sequential TreeScan to enable multiple looks over time
- Evaluation of TreeScan for pregnancy outcomes

Advancing the Sentinel System



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› Events › Improving the Efficiency of Outcome Validation in the Sentinel System

Improving the Efficiency of Outcome Validation in the Sentinel System

May 17, 2018 - 9:00 am

Duke-Robert J. Margolis, MD, Center for Health Policy
1201 Pennsylvania Ave, NW Suite 500
Washington, DC 20004

Description

The Sentinel System, authorized in 2007 by The Food and Drug Administration Amendments Act (FDAAA), is an active and fully functioning post market surveillance system that can rapidly scale distributed analyses on data collected by a diverse range of Sentinel Data Partners. In close partnership with key stakeholders, FDA has accomplished numerous milestones designing, building, and using Sentinel's data infrastructure to inform regulatory decisions. A key component of Sentinel, the Active Post-Market Risk Identification System (ARIA), represents a set of querying tools combined with electronic health care data in the Sentinel common data model to conduct safety assessments. FDA is routinely using ARIA to inform a variety of regulatory actions including label changes, Advisory Committee deliberations, and other important safety assessment decisions.

By law, before using ARIA, the FDA must first determine whether the data and methods under ARIA are "sufficient" to answer regulatory questions of interest. The FDA defines sufficient as the availability of adequate data (e.g. the drug or biologic of interest, comparators, confounders, and covariates) and appropriate tools to provide a satisfactory level of precision to answer questions. The FDA has determined ARIA to be sufficient to inform some regulatory actions, however, there are instances when the infrastructure is deemed insufficient. Preliminary agency analyses have identified outcome validation as a major contributing factor driving ARIA insufficiency.

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› Events › Public Webinar: Planned Next Steps to Advance the Sentinel System

Public Webinar: Planned Next Steps to Advance the Sentinel System

July 26, 2018 -
2:00 pm to 3:00 pm

Register now

Contact Info

Sarah Supsiri
5187968992
sarah.supsiri@duke.edu

Description

In cooperative agreement with the U.S. Food and Drug Administration (FDA), The Robert J. Margolis, MD, Center for Health Policy is convening a public webinar on planned next steps to advance FDA's Sentinel System.

Speakers

- *Gregory Daniel, Duke-Robert J. Margolis, MD, Center for Health Policy*
- *Robert Ball, U.S. Food and Drug Administration*
- *Jeffrey Brown, Harvard Medical School & Harvard Pilgrim Health Care Institute*

The Sentinel System, authorized in 2007 by The Food and Drug Administration Amendments Act (FDAAA), is an active and fully functioning post market surveillance system that can rapidly scale distributed analyses on data collected by a diverse range of Sentinel Data Partners. The Active Post-Market Risk Identification System (ARIA), a key component of the Sentinel System, represents a set of querying tools combined with electronic health care data in the Sentinel common data model to conduct safety assessments on pharmaceutical products. FDA is routinely using ARIA to inform a variety of regulatory actions including label changes, Advisory Committee deliberations, and other important safety assessment decisions.

- **Explore opportunities to leverage advances in machine learning, natural language processing, artificial intelligence**
- **Expand the Sentinel Common Data Model**
- **Enhance existing data sources, particularly with electronic health records**

https://healthpolicy.duke.edu/events/improving-efficiency-outcome-validation-sentinel-system
https://healthpolicy.duke.edu/events/public-webinar-planned-next-steps-advance-sentinel-system

Summary

- Establishing a Sentinel signal identification program fulfills a congressional mandate and expands the utility of the system
- Sentinel signal identification program can build upon prior experience using the Sentinel System
  - Will be integrated into existing regulatory processes
- Next steps include a pilot program, and establishing durable processes and best practices
- FDA will continue to engage the scientific community, expand its analytic toolkit, and disseminate lessons learned
- FDA is interested in obtaining input from this meeting

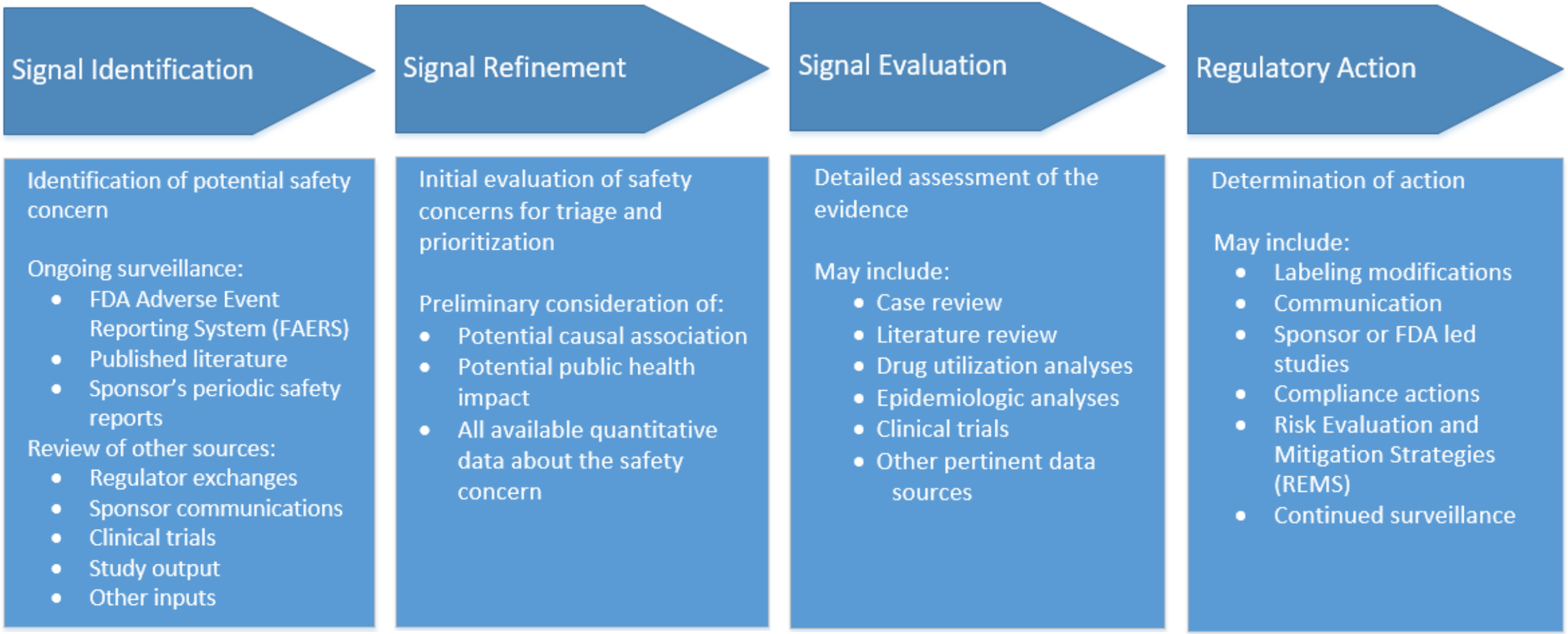

FDA
U.S. FOOD & DRUG
ADMINISTRATION

Presentation: Integrating Signal Identification into FDA's Pharmacovigilance Framework

Integrating Signal Identification with Sentinel into FDA's Pharmacovigilance Framework

CDR Monica Muñoz, PharmD, MS
Deputy Director
Division of Pharmacovigilance I
Office of Surveillance and Epidemiology
Center of Drug Evaluation and Research
December 3, 2018

Current Signal Management



Current Signal Identification Practices

- Screening FAERS, published literature
  - Review of individual reports/articles
  - Disproportionality analyses
- Cumulative analyses
  - Cumulative review of FAERS, literature, and Sponsor's periodic safety reports
  - Risk-based approach* to frequency and product selection

* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/UCM567959.pdf

Current Signal Sources

Post-market drug safety evidence sources: an analysis of FDA drug safety communications

Chieko Ishiguro Research Expert[1], Marni Hall[2], George A. Neyarapally[2,*] and Gerald Dal Pan[2]

Version of Record online: 3 OCT 2012

DOI: 10.1002/pds.3317

Issue

Pharmacoepidemiology and Drug Safety

Volume 21, Issue 10, pages 1134–1136, October 2012

- 57% of FDA Drug Safety Communications were informed by FAERS data

Evaluation of FDA safety-related drug label changes in 2010

Jean Lester[1,2,*], George A. Neyarapally[2], Earlene Lipowski[1], Cheryl Fossum Graham[2], Marni Hall[2] and Gerald Dal Pan[2]

Version of Record online: 2 JAN 2013

DOI: 10.1002/pds.3395

Issue

Pharmacoepidemiology and Drug Safety

Volume 22, Issue 3, pages 302–305, March 2013

- Most common evidence sources:
  - Spontaneous reports (52%)
  - Clinical trials (16%)
  - Pharmacokinetic studies (11%)

FAERS as a Signal Source

- FAERS is a valuable source of safety information
  - Good for detecting rare and acute events
  - Captures all products and settings of use
  - Can provide a patient perspective

FAERS as a Signal Source

- FAERS has important limitations
  - Unknown denominator, underreporting, stimulated reporting, variable information quality, etc.
- Difficult to identify and evaluate signals associated with long latency, worsening disease, or high background rates
- Limitations preclude quantifying risks

Sentinel as a Signal Source

- Leverages the following advantages:
  - Exposure denominator
  - Exposure/event capture not dependent on voluntary process
  - Longitudinal data
  - Ability to control for confounding variables

Signal Identification Opportunities

- Surveillance activities currently reliant on passive data sources
- Active hypothesis-free signal identification in Sentinel can complement current surveillance tools

Future Signal Identification Practices

- Sentinel signal identification output integrated into surveillance
  - FDA to pilot Sentinel signal identification
- Continue other pharmacovigilance practices to identify new postmarket safety issues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Session I: Statistical Considerations for Implementing Signal Identification in the Sentinel System

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Statistical Considerations for Implementing Signal Identification in the Sentinel System

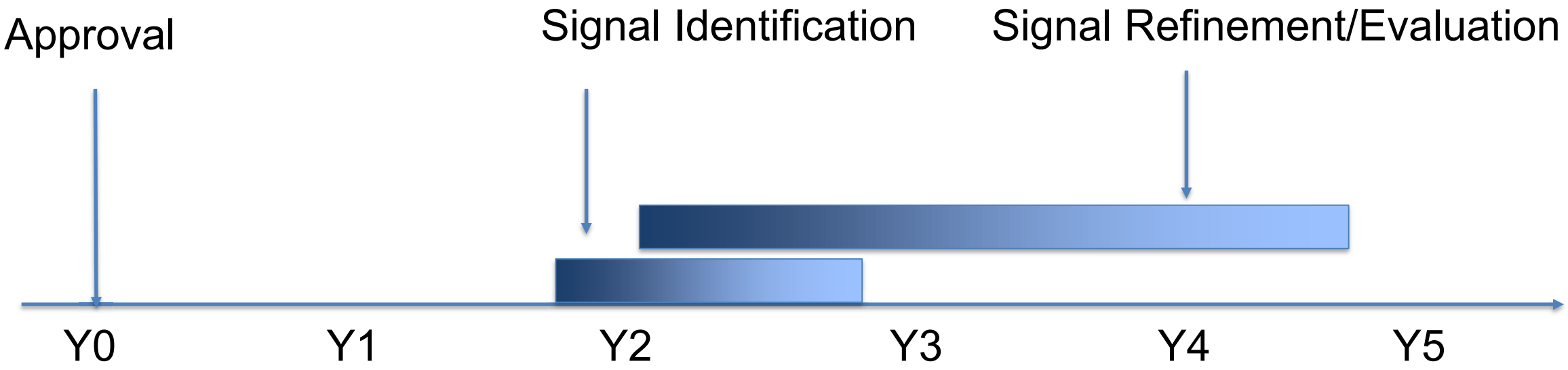
December 3, 2018

Mark Levenson, Ph.D.
Office of Biostatistics
Center for Drug Evaluation and Research

Goals

- Propose the use case for signal identification followed by signal refinement or evaluation (both in Sentinel)
- Clarify objectives of use case
- Set the stage for panel discussion with concepts and terminology

Signal Identification and Refinement/Evaluation (In Sentinel)



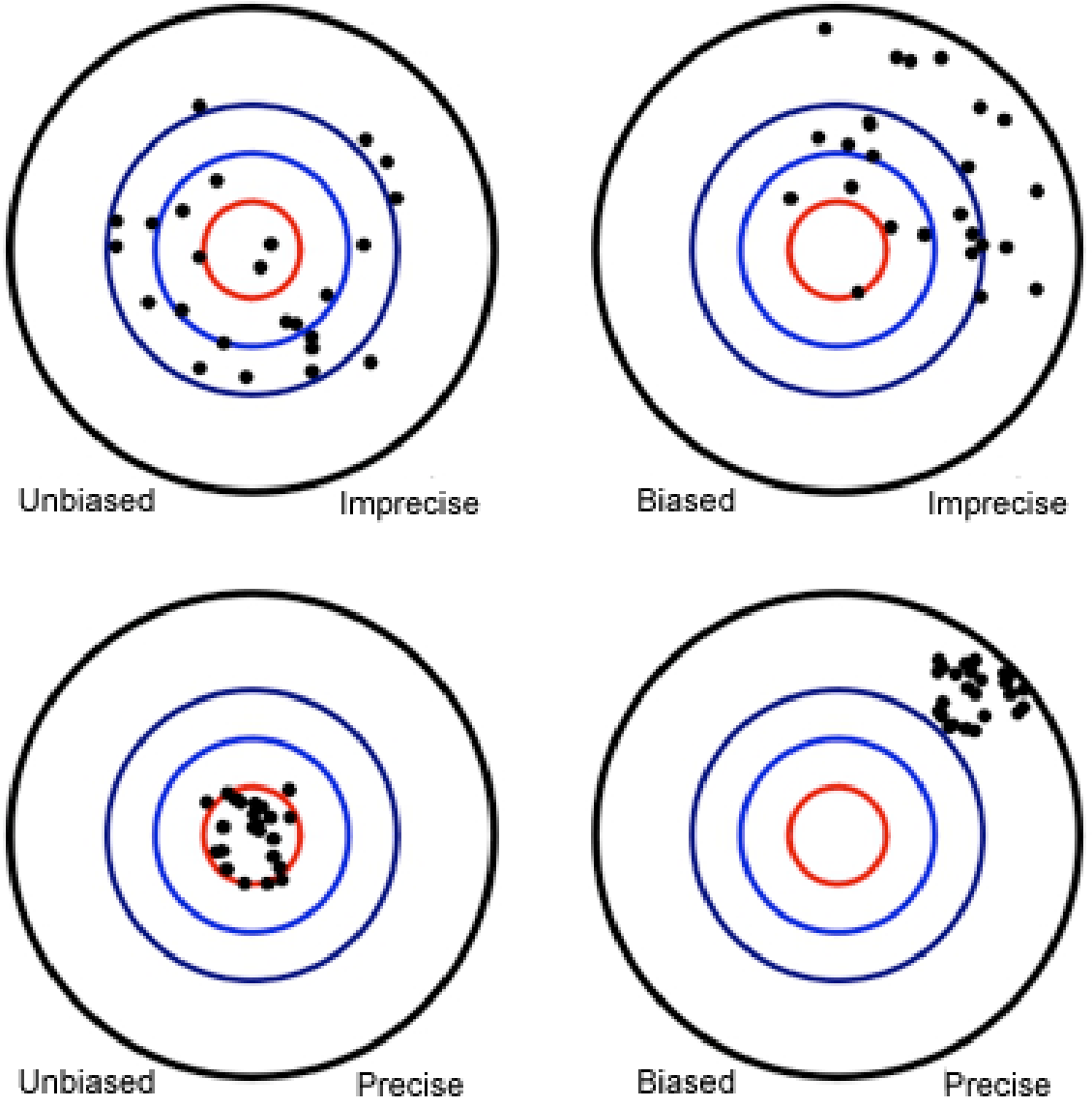
Integrate Sentinel into FDA's risk-based pharmacovigilance

Depending on drug uptake, conduct signal identification in Sentinel

Follow-up signals in Sentinel

Some Details

- Address case where Sentinel is used for both signal identification and signal refinement/evaluation
- Propose to use all or some of the same data for both signal identification and signal refinement/evaluation (Data Reuse)
  - Maximizes use of available data
- Objective of refinement/evaluation: Strengthen evidence for or against signal by reducing bias and confounding
  - Not seeking independent replication/reproduction



Refinement/Evaluation

Typical Biases

Sources

- Difference in prognostic factors between comparator groups (confounding)
- Errors in outcome ascertainment

Remedies

- Careful consideration of confounding and adjustment
- More specific outcome definition or chart review
- Narrower analysis population

What Is the Concern With Data Reuse?

Worrisome, but not in scope

- Fabricating or misreporting research data
- Inappropriate research and statistical methods
- Failure to properly document and preserve research results
- Etc.

Concerns about data reuse

- Analyzing data in enough different ways to observe an association
- Selectively focusing on analyses that are statistically significant
- Not properly accounting for multiple statistical testing
- Variations of above

What Is the Concern With Data Reuse?

Worrisome, but not in scope	Concerns about data reuse
• Fabricating or misreporting	• Analyzing data in enough different

Remedies:

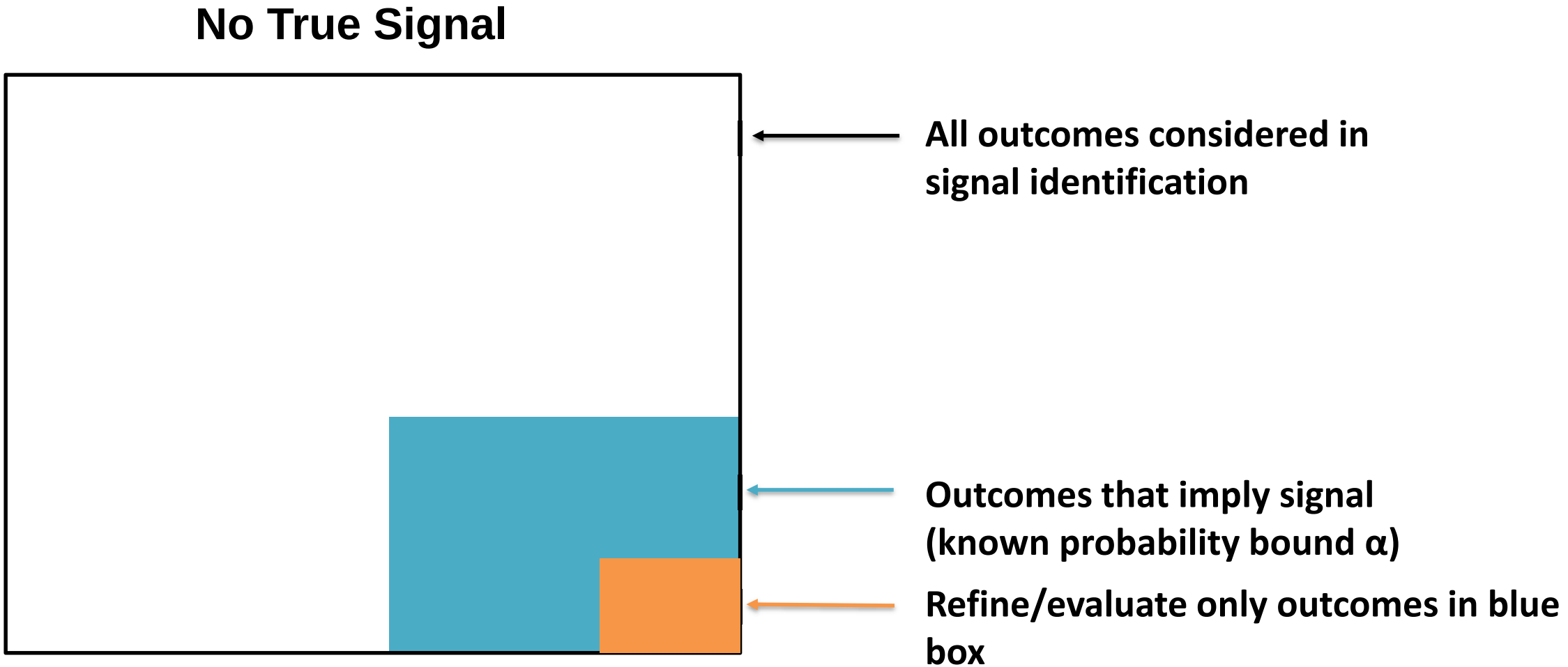
1. Prespefication and transparency of analysis plan and results
2. Proper attention to statistical testing and errors

Type 1 and 2 Errors

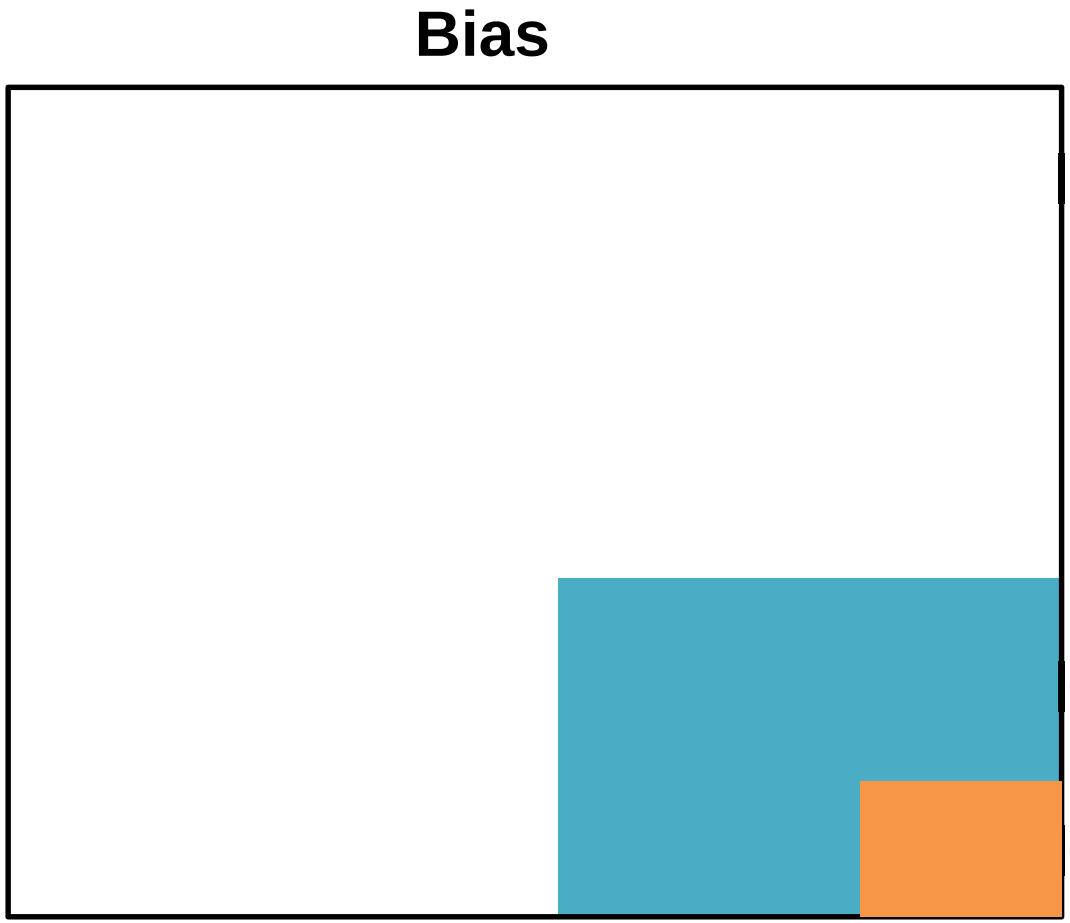
- Type 1 (false positive): Concluding there is a signal when there is not one
  - Usually attempt to probabilistically bound at eg, $\alpha = 0.01$ or 0.05

- Type 2 (false negative): Concluding there is no signal when there is one

Type 1 Error Consideration



Bias Consideration



Analysis with little or no control for biases (confounding and outcome ascertainment)

Bias remaining after signal identification

Bias remaining after focused signal refinement/evaluation

End Result After Signal Identification and Refinement/Evaluation

- Understanding of probability of false positives
- Reduction of biases and some understanding of residual biases

Other Considerations

- Type 1 and 2 errors can be tuned to achieve sensitivity (finding true signals) and specificity (not finding false signals)
  - May need to delay analyses until sufficient data are available
- Assessment signals after identification and refinement/evaluation will require clinical, epidemiological, and statistical review
  - Biological plausibility
  - Magnitude and uncertainty of findings
  - Residual confounding

Conclusion

- Signal identification and signal refinement/evaluation may use the same data source IF
  - Goal is to reduce bias and not to provide replication
  - There is control of Type 1 and 2 errors at both signal identification and signal refinement/evaluation stages
  - Prespecification and transparency of plans and results are prescribed

Session I: Statistical Considerations for Implementing Signal Identification in the Sentinel System

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BREAK

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Session II: Effectively Communicating Sentinel Signal Identification Information

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Effectively Communicating Sentinel Signal Identification Information

December 3, 2018

Theresa (Terry) Toigo, M.B.A., R.Ph.
Associate Director for Drug Safety Operations
Center for Drug Evaluation and Research

Overview

- Drug Safety Transparency Initiatives
- Transparency and Sentinel Signal Identification
- Signal Identification and Regulatory Processes
- Pilot Framework for Communicating Signal Identification Information

Select FDA Transparency Initiatives

- **1993: Launched MedWatch Program**
  - Facilitates reporting by providers; also informs providers about FDA regulatory actions.

- **2005: Launched Drug Watch webpage**
  - Posted significant emerging safety information FDA received about certain drugs (or classes of drugs) while the agency continues to actively evaluate the information.

- **2007: Replaced Drug Watch with Index to Drug-Specific Information webpage**
  - Includes drugs that have been the subject of a drug safety communication.

- **2008: Launched Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) webpage**
  - Section 921 of FDAAA requires quarterly posting on the FAERS website of potential signals of serious risks and new safety information.

Sentinel Transparency Initiatives

Analysis Tools and Use Counts

- SAS tools available online
- Synthetic public use dataset
- FDA use metrics

Study Design and Parameters

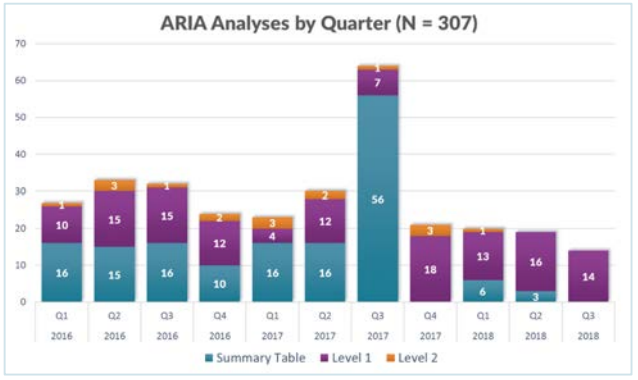
- Executable SAS programs that can run on other datasets formatted in Sentinel CDM
- Contains study design, parameters, algorithms

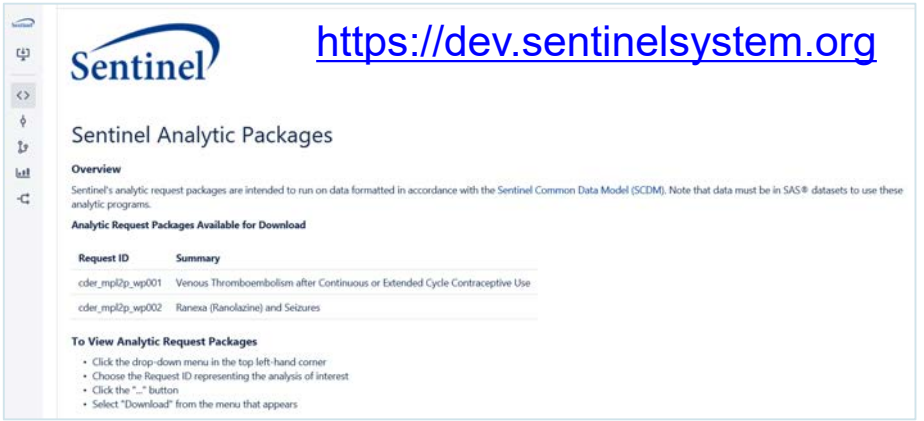
Study Results

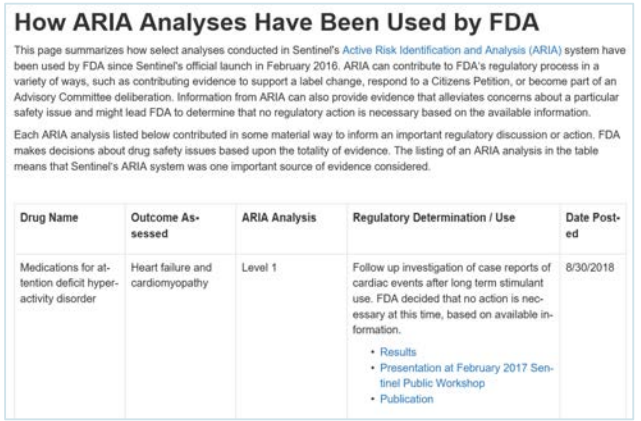
- Full analytic results organized in tabular format
- Publication

Regulatory Outcomes

- Brief description of how Sentinel data contributed to a decision, regulatory outcome, or action







Sentinel Signal Identification Transparency Goals

- Communicate FDA efforts to proactively monitor the safety of newly approved medications in Sentinel
- Balance desire for transparency with preliminary nature of results from signal identification studies
  - Represents possibility of new concern (not an actual new risk)
  - Results alone don't constitute actionable evidence for a patient or FDA
  - Statistical alerts require further study and clinical correlation
  - May later be refuted, refined, or strengthened upon further investigation

Challenges to Transparency

DESIRABLE ENDPOINTS

- Demonstrating proactive efforts of FDA signal identification studies
- Sharing valuable knowledge gained from Sentinel to patients, consumers, and industry
- Enabling a robust FDA signal identification program by addressing the need to carefully adjudicate data before dissemination

PITFALLS TO AVOID

- Sharing premature information that might lead to drug discontinuation or drug avoidance with consequent loss of drug's beneficial effects
- Inadvertently contributing to patient anxiety with uncertain information
- Not distinguishing between actionable information and preliminary data in communications
- Alert fatigue

Sentinel Signal Identification General Principles

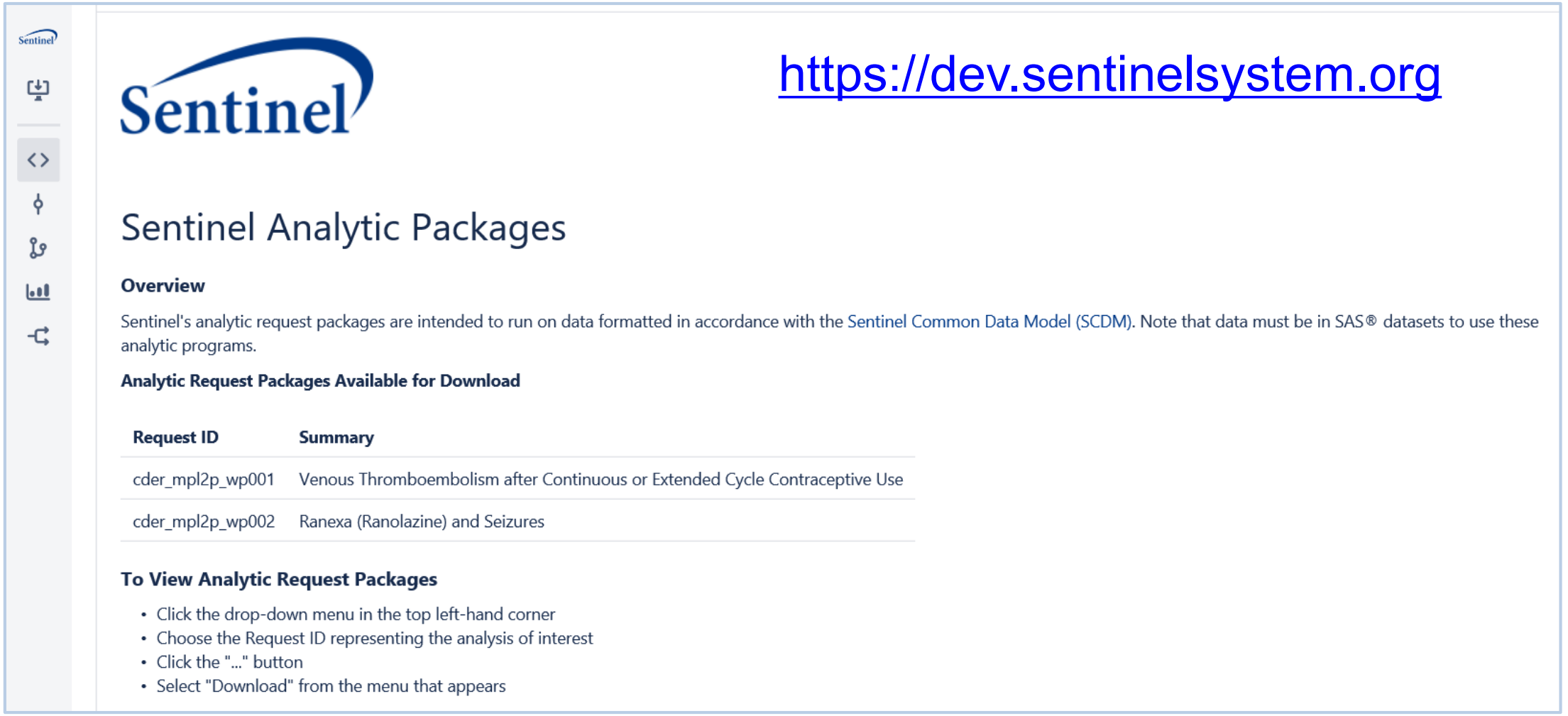
- FDA goal to strengthen an already robust pharmacovigilance framework
  - Sentinel is a new analytic tool that will augment, not replace, existing systems
- Signal identification activities will be integrated into existing regulatory processes, e.g.
  - Sponsor communication will continue through existing processes, such as 21st Century review, safety labeling changes, tracked safety issue notification
  - Public risk communication will leverage existing Drug Safety Communication approaches
- Build on the existing transparency initiatives in Sentinel

Signal Identification Builds on Existing Sentinel Transparency Initiatives

	Sentinel ARIA Targeted Outcome Study (L2)	Signal Identification Hypothesis Generation in Sentinel
Information about the analysis tool itself	✓	✓
- SAS code, worked examples online	✓	✓
Information about when FDA uses signal identification	✓	✓
- Utilization summary online	✓	✓
Information about signal identification results	✓	✓
- Results posted online	✓	✓
Information about regulatory outcome	✓	✓
- Outcome posted online	✓	✓

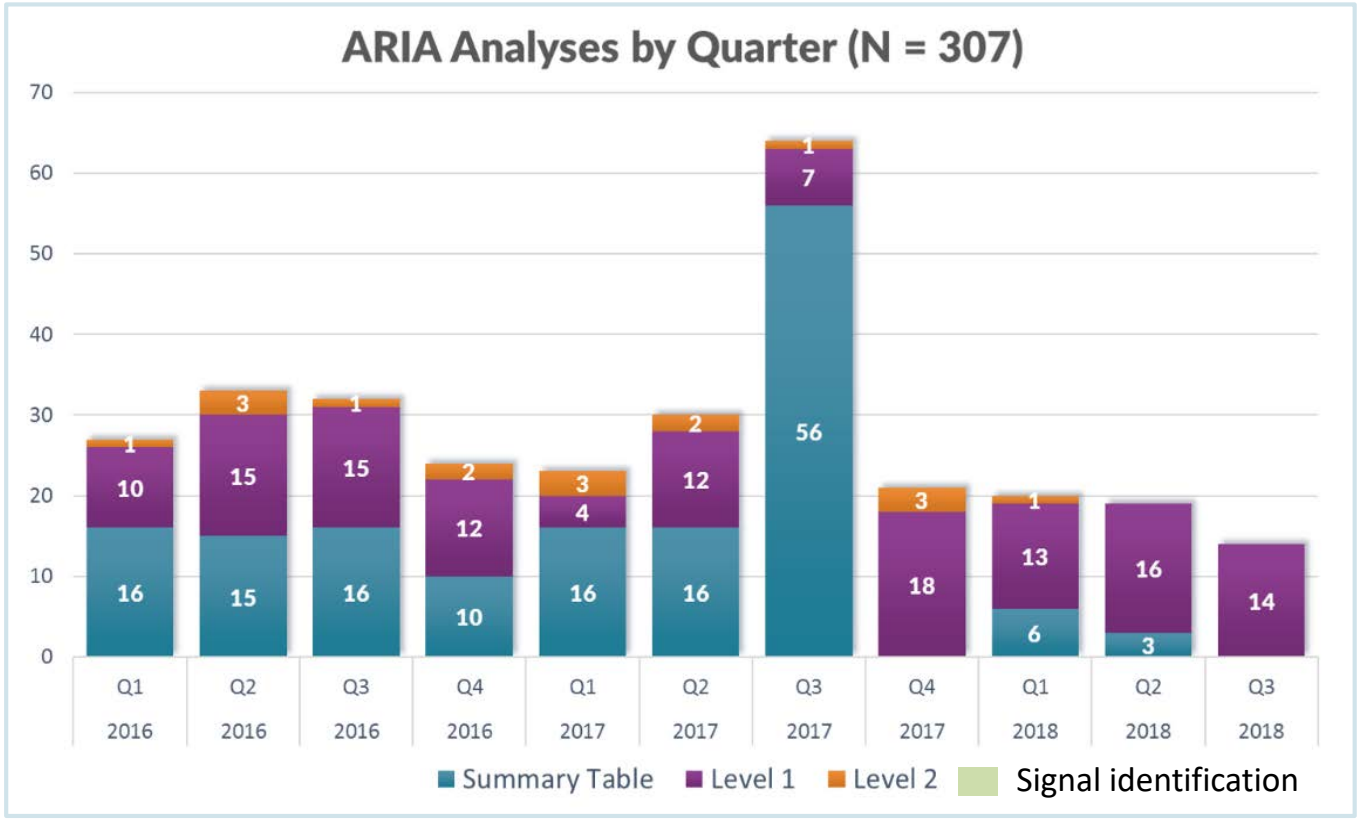
Information About the Tool

SAS Code Hosted on GitHub Site



Information About When FDA Uses Signal Identification

Signal Identification Will Be Added to Existing Sentinel Use Summaries Available Online

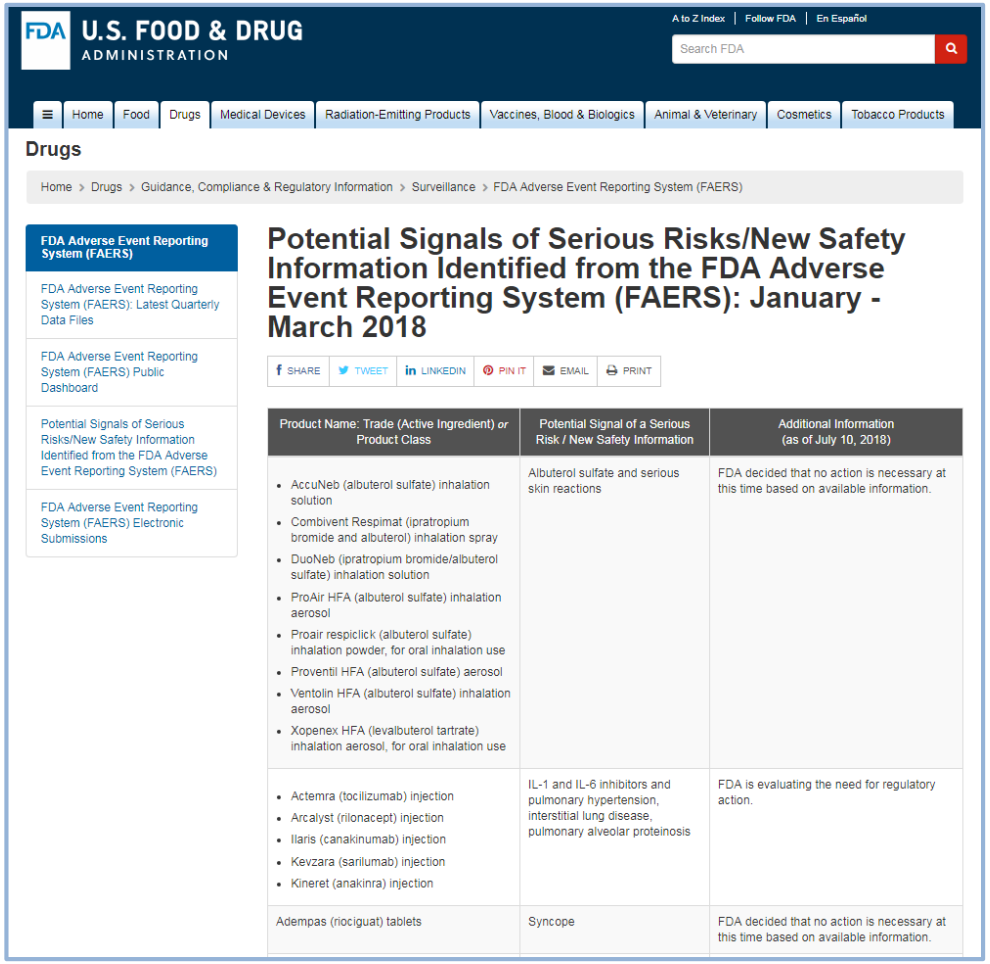


Information About Results and Outcomes

FAERS

Signal Identification Using Spontaneous Reports

- All Reports Downloadable
- Online Query Tool / Public Dashboard
- Post Potential Safety Concerns
- Update When FDA Action is Taken



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FDA Adverse Event Reporting System (FAERS)

- FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files
- FDA Adverse Event Reporting System (FAERS) Public Dashboard
- Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)
- FDA Adverse Event Reporting System (FAERS) Electronic Submissions

Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS): January - March 2018

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Product Name: Trade (Active Ingredient) *or* Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of July 10, 2018)
• AccuNeb (albuterol sulfate) inhalation solution • Combivent Respimat (ipratropium bromide and albuterol) inhalation spray • DuoNeb (ipratropium bromide/albuterol sulfate) inhalation solution • ProAir HFA (albuterol sulfate) inhalation aerosol • Proair respiclick (albuterol sulfate) inhalation powder, for oral inhalation use • Proventil HFA (albuterol sulfate) aerosol • Ventolin HFA (albuterol sulfate) inhalation aerosol • Xopenex HFA (levalbuterol tartrate) inhalation aerosol, for oral inhalation use	Albuterol sulfate and serious skin reactions	FDA decided that no action is necessary at this time based on available information.
• Actemra (tocilizumab) injection • Arcalyst (rilonacept) injection • Ilaris (canakinumab) injection • Kevzara (sarilumab) injection • Kineret (anakinra) injection	IL-1 and IL-6 inhibitors and pulmonary hypertension, interstitial lung disease, pulmonary alveolar proteinosis	FDA is evaluating the need for regulatory action.
Adempas (riociguat) tablets	Syncope	FDA decided that no action is necessary at this time based on available information.

Information About Results and Outcomes (*cont.*)

How ARIA Analyses Have Been Used by FDA

This page summarizes how select analyses conducted in Sentinel's Active Risk Identification and Analysis (ARIA) system have been used by FDA since Sentinel's official launch in February 2016. ARIA can contribute to FDA's regulatory process in a variety of ways, such as contributing evidence to support a label change, respond to a Citizens Petition, or become part of an Advisory Committee deliberation. Information from ARIA can also provide evidence that alleviates concerns about a particular safety issue and might lead FDA to determine that no regulatory action is necessary based on the available information.

Each ARIA analysis listed below contributed in some material way to inform an important regulatory discussion or action. FDA makes decisions about drug safety issues based upon the totality of evidence. The listing of an ARIA analysis in the table means that Sentinel's ARIA system was one important source of evidence considered.

Drug Name	Outcome Assessed	ARIA Analysis	Regulatory Determination / Use	Date Posted
Medications for attention deficit hyperactivity disorder	Heart failure and cardiomyopathy	Level 1	Follow up investigation of case reports of cardiac events after long term stimulant use. FDA decided that no action is necessary at this time, based on available information. • Results • Presentation at February 2017 Sentinel Public Workshop • Publication	8/30/2018

Pilot Framework for Communicating Signal Identification Information

Drug Name	Outcome Assessed	ARIA Analysis	Regulatory Determination / Use	Date Posted
Drug A	Signal identification of multiple outcomes	TreeScan	FDA will further investigate outcomes A and B in a Level 2 analysis. • Results	Date
Drug A	• Outcome A • Outcome B	Level 2	Outcome A was added to Warnings and Precautions. Following further investigation of outcome B, FDA decided that no action is needed at this time based on available information. • Level 2 Results • Revised Label	Date + 10 months

Summary

- Sentinel is a new signal identification tool that will augment, not replace, existing systems
- FDA goal
  - strengthen an already robust pharmacovigilance framework
  - integrate signal identification activities into existing regulatory processes
    - Sentinel-specific processes
    - General regulatory processes for all marketed drugs
  - post results in a meaningful but not misleading manner
- FDA plans to pilot a framework for communicating signal identification information and evaluate the pilot

Session II: Effectively Communicating Sentinel Signal Identification Information

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