

Implementation of Signal Identification Capabilities in the Sentinel System

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The opinions expressed in this lecture are those of the presenter, and do not necessarily represent the views of the US Food and Drug Administration or the US Government

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Learning Objectives



- Define signal identification in the context of the Sentinel System
- Describe the motivation and approach towards building signal identification capabilities in Sentinel
- Identify where further information on signal identification in the Sentinel System can be found

Defining Key Terms

Signal Identification in the Sentinel System

The Food and Drug Administration Amendments Act (FDAAA) of 2007 mandated that FDA “create a robust system to identify adverse events and potential drug safety signals.” Federal Food, Drug, and Cosmetic Act Section 505(k)(3)(C)(i)(3)(cc) (21 U.S.C. 355(k)(3)(C)(i)(III)(cc)). FDA defines **signal identification as a process of systematically evaluating potential adverse events related to the use of medical products without prespecifying an outcome of interest.** Several statistical approaches exist in Sentinel that can be applied to the electronic healthcare data to detect new and unsuspected potential safety concerns. These analytic tools are not intended to establish causal associations between medical products and potential adverse events. These approaches provide information about unexpected elevated frequencies of a health outcome after product exposure and should always be followed by clinical review and/or safety studies specifically designed to quantify the magnitude of effect with confounding control targeted at the specific outcome of interest.



Detection of New and
Unsuspected Potential
Safety Concerns

Current Signal Sources

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

Chieko Ishiguro Research Expert¹, Marni Hall², George A. Neyarapally^{2,*} and Gerald Dal Pan²

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

Evaluation of FDA safety-related drug label changes in 2010

Jean Lester^{1,2,*}, George A. Neyarapally², Earlene Lipowski¹, Cheryl Fossum Graham², Marni Hall² and Gerald Dal Pan²

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

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



Signal Identification

Identification of potential safety concern

Ongoing surveillance:

- FDA Adverse Event Reporting System (FAERS)
- Published literature
- Sponsor's periodic safety reports

Review of other sources:

- Regulator exchanges
- Sponsor communications
- Clinical trials
- Study output
- Other inputs

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

Signal Identification 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

TreeScan



- A **signal detection/data-mining** method
- Automatically adjusts for **multiple hypothesis testing**
- Scans electronic health data that are grouped into **hierarchical tree** structures

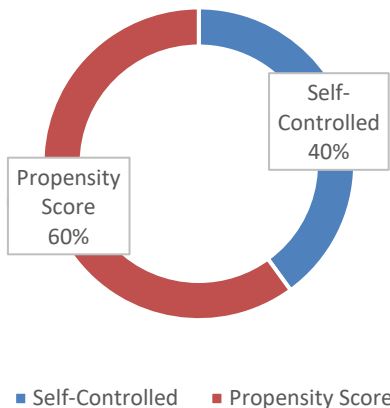


No One Best Method: Need for Broad Toolkit



Inferential Analyses in Sentinel System, 2016-2018

All FDA Medical Product Centers



Varieties of TreeScan

Propensity Score Matched

Tree-temporal

Self-controlled



What is a TreeScan “Alert”?

- A statistically significant difference in the observed frequency of a coded outcome relative to the expected counts depending on the specific tree-based scan statistic being utilized.
- An “Alert” is not a “Signal”
 - Alerts may not represent “new safety information”
- Unanticipated alerts require further triage
 - Consideration of a product’s known safety, outcome characteristics, clinical context, etc.
 - Alerts may be refuted, refined, or strengthened upon further investigation

Future Signal Identification Practices



- Sentinel signal identification output integrated into surveillance
 - FDA to pilot Sentinel signal identification
 - Develop processes for integration into surveillance activities
- Continue other pharmacovigilance practices to identify new postmarket safety issues
- Communicate FDA efforts to proactively monitor the safety of newly approved medications in Sentinel

More Information



- Sentinel Signal Identification Information Online
 - Overview and FAQs
 - Trainings, public meetings
 - Projects and publications

<https://www.sentinelinitiative.org/sentinel/surveillance-tools/signal-identification-sentinel-system>

The screenshot shows a web interface for the Sentinel System. At the top, there's a header "Overview of Signal Identification Techniques Utilized by the Sentinel System". Below this is a "Resources" section with a link for "Trainings and Public Meetings". The main content area is titled "Signal Identification Projects". It features a search bar with the label "Keywords", a "Search" button, and a "Show All" button. Below the search bar is a table listing projects. The first project is "TreeScan in Pregnancy", which is marked as "In progress" and dated "01/16/2020". A "Submit Comment" button is visible next to the project title. Below the table, there is a detailed view of the "TreeScan in Pregnancy" project, showing its title, date posted, status, and description.

| Title | Status | Date Posted |
|-----------------------|-------------|-------------|
| TreeScan in Pregnancy | In progress | 01/16/2020 |

| TreeScan in Pregnancy | |
|-----------------------|---|
| Project Title | TreeScan in Pregnancy |
| Date Posted | Thursday, January 16, 2020 |
| Status | In progress |
| Description | The goals of this methods project are to evaluate the performance of TreeScan to assess maternal and infant outcomes, test signal identification methods in a pregnancy setting, and evaluate methods performance using older drugs with relatively well-characterized safety profiles. |

Summary

- FDA goal to strengthen an already robust pharmacovigilance framework
- Signal identification activities will be integrated into existing regulatory processes
- Build on the existing transparency initiatives in Sentinel
- Continue to enhance signal identification capabilities in the Sentinel System

Challenge Question #1



Compared to spontaneous reporting data, the Sentinel System has which of the following advantages:

- A. Ability to adjust for confounding
- B. Longitudinal followup
- C. Known exposure denominator
- D. All of the above

Challenge Question #2



True or False:

Alerts identified by TreeScan represent new safety signals that need additional analyses.

False

Acknowledgements

- CDR Michael Nguyen, CDER, FDA
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Questions?

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