Medical Product Safety: Ten Years of the U.S. Sentinel System

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Required Disclosures

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• No relationships to disclose

• The views expressed are the authors’ and not necessarily those of the Food and Drug Administration, or the Department of Health and Human Services
What is Sentinel?

- FDA’s medical product active safety surveillance system
  - To assess the use, safety, and effectiveness of regulated medical products
  - To develop data, informatics, and methodologic capabilities to support these activities
- Key components:
  - Distributed data network of 18 Data Partners
  - Electronic healthcare data
  - Common data model
  - Sophisticated quality assurance process
- Created in response to a U.S. Congressional mandate

https://www.sentinelinitiative.org/
History of the Sentinel Initiative

- **2007**: Congress passes Food and Drug Administration Amendments Act (FDAAAA)
- **2008**: FDA launches Sentinel Initiative
- **2009**: FDA launches Mini-Sentinel Pilot
- **2011**: Mini-Sentinel distributed dataset reaches 100 million lives mark mandated by FDAAA
- **2012**: Mini-Sentinel has suite of reusable programming tools for routine queries
- **2016**: FDA launches Sentinel System
Sec. 905. Active Postmarket Risk Identification and Analysis

(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 system to link and analyze safety data from multiple sources, with the goals of including, in aggregate—

(I) at least 25,000,000 patients by July 1, 2010; and

(II) at least 100,000,000 patients by July 1, 2012
SEC. 901. POSTMARKET STUDIES AND CLINICAL TRIALS REGARDING HUMAN DRUGS; RISK EVALUATION AND MITIGATION STRATEGIES.

“The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).”
Sentinel’s Active Risk Identification and Analysis (ARIA)

ARIA must be considered before a sponsor PMR can be issued
What is ARIA?

Electronic claims data, without manual medical record review

Pre-defined, parameterized, and re-usable to enable faster safety surveillance (vs. protocol based assessments with fully customized programming)
Determining ARIA Sufficiency

- What is the purpose of the analysis?
  - Signal detection, signal refinement, or signal evaluation?
- What is the desired study population?
- What are the treatment and comparator exposures?
- What are the outcome(s) of interest?
- What are relevant and important covariates for the analysis?
- What is the desired analytic approach?
Signal Identification

• FDAAA of 2007: “…create a robust system to identify adverse events and potential drug safety signals”
• Purpose: To detect new and unsuspected potential drug-related safety concerns
  – Hypothesis generation
  – Will be followed by clinical review and/or well-designed safety studies
• TreeScan is currently available in Sentinel
  – Multiple projects are ongoing to support and enhance signal identification methods

http://sentinelinitiative.org/sentinel/surveillance-tools/signal-identification-sentinel-system
Sentinel System:
Data, Tools, Methods
Sentinel Design Requirements

- Electronic health data for >100M persons
  - Include special populations (pregnant women, elderly)
  - Ability to link to external sources, e.g., National Death Index
  - Ability to access full text medical records

- Expertise in the way health care delivery and payment influence electronic healthcare data

- Rapid answers to many FDA safety questions

- Accuracy sufficient to support regulatory decision making

- Federal Information Security Management Act (FISMA)-compliant data security

- Ability to protect non-public information and to keep records on all data requests for public record-keeping
Sentinel Distributed Database

Data Partners (DPs) hold data in Common Data Model format:
- Enrollment
- Demographics
- Medical Utilization
- Pharmacy Prescriptions
- Diagnoses
- Procedures
- Laboratory Tests
- Vital Signs

Queries Distributed to Data Partners (DPs)

Sentinel Operations Center (SOC)

Query Results Reviewed and Returned to SOC (all direct identifiers removed)
Collaborating Organizations

Lead – HPHC Institute

Department of Population Medicine
Harvard Medical School
Harvard Pilgrim Health Care Institute

Data & Scientific Partners

OPTUM
HUMANA
Kaiser Permanente

Scientific Partners

Penn Medicine
IQVIA

https://www.sentinelinitiative.org/collaborators
Growth of the Sentinel Distributed Database

- 70 million members currently accruing new data

The area above depicts the cumulative number of unique patient identifiers in the Sentinel Distributed Database from 2010 to present. If patients move health plans, they may have more than one patient identifier.

http://www.sentinelinitiative.org/sentinel/data/snapshot-database-statistics
Sentinel Common Data Model Guiding Principles

- Includes claims, electronic health record (EHR), and registry data and flexible enough to accommodate new data domains (e.g., free text).
  - Typically, we do not include empty tables – we expand as needed when fit for purpose.

- Data are stored at most **granular/raw level possible** with minimal mapping.
  - Distinct data types should be kept separate (e.g., prescriptions, dispensings)
  - Construction of medical concepts (e.g., outcome algorithms) from these elemental data is a **project-specific** design choice.
  - Sentinel stores these algorithms in a library for future use.

- Appropriate use and interpretation of local data requires the Data Partners’ local knowledge and data expertise.
  - Not all tables are populated by all Data Partners ➔ site-specificity is allowed.

- Designed to meet FDA needs for analytic flexibility, transparency, and control.
# Available Data Elements

## Administrative Data

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Demographic</th>
<th>Dispensing</th>
<th>Encounter</th>
<th>Diagnosis</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Enrollment Start &amp; End Dates</td>
<td>Birth date</td>
<td>Dispensing Date</td>
<td>Service Date(s)</td>
<td>Service Date(s)</td>
<td>Service Date(s)</td>
</tr>
<tr>
<td>Drug Coverage</td>
<td>Sex</td>
<td>National Drug Code (NDC)</td>
<td>Encounter ID</td>
<td>Encounter ID</td>
<td>Encounter ID</td>
</tr>
<tr>
<td>Medical Coverage</td>
<td>Zip code</td>
<td>Days Supply</td>
<td>Encounter Type and Provider</td>
<td>Encounter Type and Provider</td>
<td>Encounter Type and Provider</td>
</tr>
<tr>
<td>Medical Record Availability</td>
<td>Etc.</td>
<td>Amount Dispensed</td>
<td>Facility</td>
<td>Diagnosis Code &amp; Type</td>
<td>Procedure Code &amp; Type</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Etc.</td>
<td>Principle Discharge Diagnosis</td>
<td>Etc.</td>
</tr>
</tbody>
</table>

## Registry Data

<table>
<thead>
<tr>
<th>Death</th>
<th>Cause of Death</th>
<th>State Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Death Date</td>
<td>Cause of Death</td>
<td>Vaccination Date</td>
</tr>
<tr>
<td>Source</td>
<td>Source</td>
<td>Admission Date</td>
</tr>
<tr>
<td>Confidence</td>
<td>Confidence</td>
<td>Vaccine Code &amp; Type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provider</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etc.</td>
</tr>
</tbody>
</table>

## Inpatient Data

### Inpatient Pharmacy

- Patient ID
- Administration Date & Time
- Encounter ID
- National Drug Code (NDC)
- Route
- Dose
- Etc.

### Inpatient Transfusion

- Patient ID
- Administration Start & End Date & Time
- Encounter ID
- Transfusion Administration ID
- Transfusion Product Code
- Blood Type
- Etc.

## Clinical Data

<table>
<thead>
<tr>
<th>Lab Result</th>
<th>Vital Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID</td>
<td>Patient ID</td>
</tr>
<tr>
<td>Result &amp; Specimen Collection Dates</td>
<td>Measurement Date &amp; Time</td>
</tr>
<tr>
<td>Test Type, Immediacy &amp; Location</td>
<td>Height &amp; Weight</td>
</tr>
<tr>
<td>Logical Observation Identifiers Names and Codes (LOINC®)</td>
<td>Diastolic &amp; Systolic BP</td>
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<td></td>
<td>Tobacco Use &amp; Type</td>
</tr>
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<td>Etc.</td>
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</table>

## Mother-Infant Linkage Data

<table>
<thead>
<tr>
<th>Mother-Infant Linkage</th>
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</thead>
<tbody>
<tr>
<td>Mother ID</td>
</tr>
<tr>
<td>Mother Birth Date</td>
</tr>
<tr>
<td>Encounter ID &amp; Type</td>
</tr>
<tr>
<td>Admission &amp; Discharge Date</td>
</tr>
<tr>
<td>Child ID</td>
</tr>
<tr>
<td>Child Birth Date</td>
</tr>
<tr>
<td>Mother-Infant Match Method</td>
</tr>
</tbody>
</table>
## Single Patient Example Data in Model

### DEMOGRAPHIC

<table>
<thead>
<tr>
<th>PATID</th>
<th>BIRTH_DATE</th>
<th>SEX</th>
<th>HISPANIC</th>
<th>RACE</th>
<th>zip</th>
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</thead>
<tbody>
<tr>
<td>PatID1</td>
<td>2/2/1964</td>
<td>F</td>
<td>N</td>
<td>5</td>
<td>32818</td>
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### DISPENSING

<table>
<thead>
<tr>
<th>PATID</th>
<th>RXDATE</th>
<th>NDC</th>
<th>RXSUP</th>
<th>RXAMT</th>
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<tbody>
<tr>
<td>PatID1</td>
<td>10/14/2005 00006074031</td>
<td>30</td>
<td>30</td>
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<td>PatID1</td>
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<td>30</td>
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### ENROLLMENT

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<th>DRUGCOV</th>
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<td>PatID1</td>
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<td>1/1/2005</td>
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### ENCOUNTER

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<th>ENCOUNTERID</th>
<th>ADATE</th>
<th>DDATE</th>
<th>ENCTYPE</th>
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<tbody>
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<td>PatID1</td>
<td>EnclID1</td>
<td>10/18/2005</td>
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### DIAGNOSIS

<table>
<thead>
<tr>
<th>PATID</th>
<th>ENCOUNTERID</th>
<th>ADATE</th>
<th>PROVIDER</th>
<th>ENCTYPE</th>
<th>DX</th>
<th>DX_CODETYPE</th>
<th>PDX</th>
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<tbody>
<tr>
<td>PatID1</td>
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<td>Provider1 IP</td>
<td>296.2</td>
<td>9 P</td>
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<td>EnclID1</td>
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<td>PatID1</td>
<td>EnclID1</td>
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<td>Provider1 IP</td>
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<td>PatID1</td>
<td>EnclID1</td>
<td>10/18/2005</td>
<td>Provider1 IP</td>
<td>401.9</td>
<td>9 S</td>
<td></td>
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<td>PatID1</td>
<td>EnclID1</td>
<td>10/18/2005</td>
<td>Provider1 IP</td>
<td>493.9</td>
<td>9 S</td>
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<td></td>
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<td>EnclID1</td>
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<td>9 S</td>
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### PROCEDURE

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<th>ENCTYPE</th>
<th>PK</th>
<th>PX_CODETYPE</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td>PatID1</td>
<td>EnclID1</td>
<td>10/18/2005</td>
<td>Provider1 IP</td>
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<td>EnclID1</td>
<td>10/18/2005</td>
<td>Provider1 IP</td>
<td>99238 C4</td>
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<td></td>
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<td>PatID1</td>
<td>EnclID1</td>
<td>10/18/2005</td>
<td>Provider2 IP</td>
<td>27445 C4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### DEATH

<table>
<thead>
<tr>
<th>PATID</th>
<th>DEATHDT</th>
<th>DTIMPUTE</th>
<th>SOURCE</th>
<th>CONFIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PatID1</td>
<td>12/27/2005</td>
<td>N</td>
<td>S</td>
<td>E</td>
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</tbody>
</table>

### CAUSE OF DEATH

<table>
<thead>
<tr>
<th>PATID</th>
<th>COD</th>
<th>CODETYPE</th>
<th>CAUSETYPE</th>
<th>SOURCE</th>
<th>CONFIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PatID1</td>
<td>J18.0</td>
<td>10</td>
<td>U</td>
<td>S</td>
<td>E</td>
</tr>
</tbody>
</table>
Data Quality Review and Characterization Process

1. **Preparation**
   - **Sentinel Operations Center** prepares quality review and characterization package for new ETL

2. **Transformation**
   - **Data Partner** transforms source data into the Sentinel Common Data Model

3. **Distribution**
   - **Sentinel Operations Center** distributes quality assurance package to Data Partners

4. **Model Compliance**
   - **Data Partner** runs quality review and characterization package completing the following:
     - Level 1 checks
     - Level 2 checks
   - Quality review and characterization package outputs list of errors or anomalies (flags) identified during data checks
   - **Data Partner** resolves these flags and sends a detailed report to the Sentinel Operations Center

5. **Review & Characterization**
   - **Sentinel Operations Center** receives output from Data Partner and reviews
   - **Sentinel Operations Center** runs additional quality assurance checks:
     - Level 2 checks
     - Level 3 checks
     - Level 4 checks
   - **Sentinel Operations Center** evaluates any additional flags and creates issue report for Data Partner to address

6. **Completion**
   - **Data Partner** investigates issues identified in report generated by the Sentinel Operations Center and resolves remaining flags

7. **Approval**
   - **Sentinel Operations Center** Quality Assurance Manager approves ETL for use in queries

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*On average, there are 44 flags identified by the program and 10 additional flags identified by the Sentinel Operations Center per ETL*

https://www.sentinelinitiative.org/sentinel/data-quality-review-and-characterization
# Data Quality Checks and Examples

<table>
<thead>
<tr>
<th>Level 1 Checks</th>
<th>Completeness</th>
<th>✓ Admission date is not missing value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Validity</td>
<td>✓ Admission date is in date format</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2 Checks</th>
<th>Accuracy</th>
<th>✓ Admission date occurs before the patient's discharge date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Integrity</td>
<td>✓ Admission date occurs within the patient’s active enrollment period</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3 Checks</th>
<th>Consistency of Trends</th>
<th>✓ There is no sizable percent change in admission date record counts by month-year</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Level 4 Checks</th>
<th>Plausibility</th>
<th>✓ There is no sizable percent change in the number of prostate cancer encounters by sex*</th>
</tr>
</thead>
</table>

*Under development
Quality Review and Characterization Program Logic

- Compliance checks for all tables are mandatory.
- Quality Review and Characterization Program will abort after it runs through all compliance checks, producing an automatically created report on failures.
Active Risk Identification and Analysis (ARIA)

- Template computer programs with standardized questions
- Parameterized at program execution
- Pre-tested and quality-checked
- Standard output

Cohort Identification and Descriptive Analysis (CIDA)

OVERVIEW

The purpose of this repository is to document version 7.3.0 of the Sentinel Routine Querying System. Functional documentation sections describe the capabilities of the tools in the system. Technical documentation sections specify the tools' inputs and outputs and provide the information required to build analytic packages to address research questions of interest.

SENTINEL ROUTINE QUERYING SYSTEM TOOLS

Sentinel’s Routine Querying System includes three tools:

The COHORT IDENTIFICATION AND DESCRIPTIVE ANALYSIS (CIDA) TOOL identifies and extracts cohorts of interest from the Sentinel Distributed Database based on requester-defined options (e.g., exposures, outcomes, continuous enrollment requirements, incidence criteria, inclusion/exclusion criteria, relevant age groups, demographics).

The CIDA tool calculates descriptive statistics for the cohort(s) of interest and outputs datasets that may be useful for additional analyses. The CIDA tool may be used alone or in conjunction with the Propensity Score Analysis Tool or the Multiple Factor Matching Tool.

There are six cohort identification strategies available:

- Type 1: Extract information to calculate background rates
- Type 2: Extract information on exposures and follow-up time
- Type 3: Extract information for a self-controlled risk interval design
- Type 4: Extract information for medical product use during pregnancy
- Type 5: Extract information for medical product utilization
- Type 6: Extract information on manufacturer-level product utilization and switching patterns

https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse
Downloading Sentinel Analytic Packages

Sentinel Analytic Packages

Overview
A Sentinel analytic package is a standard folder structure containing detailed user-defined specifications, input files, SAS® macros, and SAS programs used to conduct Sentinel's routine querying analyses. A package allows the user to select the cohort(s) of interest in order to examine their health profile and outcomes.

Sentinel's analytic request packages are intended to run on data formatted in accordance with the Sentinel Common Data Model (SCDM). Note that data must be in SAS datasets to use these analytic programs.

Analytic Request Packages Available for Download

<table>
<thead>
<tr>
<th>Request ID</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>cdr_mpl2p_wp009</td>
<td>Stroke, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Apixaban or Warfarin Use in Patients with Non-Valvular Atrial Fibrillation: a Propensity Score Matched Analysis</td>
</tr>
<tr>
<td>cdr_mpl2p_wp006</td>
<td>Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis (an update to cdr_mpl2p_wp002)</td>
</tr>
<tr>
<td>cdr_mpl2p_wp005</td>
<td>Stroke following Atypical Antipsychotic or Z-Hypnotic Use in Patients with Prior Use of Selective Serotonin Reuptake Inhibitors (SSRIs): a Propensity Score Matched Analysis</td>
</tr>
<tr>
<td>cdr_mpl2p_wp001</td>
<td>Venous Thromboembolism following Continuous or Extended Cycle Contraceptive Use: a Propensity Score Matched Analysis</td>
</tr>
<tr>
<td>cdr_mpl2p_wp004</td>
<td>Stroke following Typical or Atypical Antipsychotic Use in non-Elderly Patients: a Propensity Score Matched Analysis</td>
</tr>
<tr>
<td>cdr_mpl2p_wp002</td>
<td>Seizure following Ranolazine Use: a Self-Controlled Risk Interval Analysis</td>
</tr>
</tbody>
</table>

https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse
Extension of Disease Risk Score–Based Confounding Adjustments for Multiple Outcomes of Interest: An Empirical Evaluation

Rishi J Desai, Austin Cosgrove, Rita Ouellet

American Journal of Epidemiology /aje/kwy1300
Published: 24 April 2019 | https://doi.org/10.1002/pds.4784

Evaluating the use of bootstrapping in cohort studies conducted with 1:1 propensity score matching—a plasmode simulation study

Rishi J. Desai, Richard Wyss, Younathan Abdia, Sengwee Toh, Margaret Johnson, Hana Lee, Sara Karami, Jacqueline M. Major, Michael Nguyen, Shirley V. Wang, Jessica M. Franklin, Joshua J. Gagne
Comparison of privacy-protecting analytic and data-sharing methods: A simulation study

Kazuki Yoshida, Susan Gruber, Bruce H. Fireman, Sengwee Toh

First published: 18 July 2018 | https://doi.org/10.1002/pds.4615
Methods Development: Signal Detection

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

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

+ Author Information
Methods Development in Sentinel: Machine Learning

Evaluating automated approaches to anaphylaxis case classification using unstructured data from the FDA Sentinel System

Robert Ball, Sengwee Toh, Jamie Nolan, Kevin Haynes, Richard Forshee, Taxiarchis Botsis

First published: 28 August 2018 | https://doi.org/10.1002/pds.4645
FDA'S USE OF THE SENTINEL SYSTEM TO ADDRESS REGULATORY QUESTIONS
How is Sentinel Used?

• To evaluate safety signals identified during the pre-market review of new drug applications
• To evaluate safety signals identified during the post-market period
• To identify new potential safety signals during the post-market period
## How is Sentinel Used?

<table>
<thead>
<tr>
<th>Update the benefit risk for a product</th>
<th>Support population-level data questions</th>
<th>Assist with public-facing decision making</th>
<th>Establish system capabilities</th>
<th>Information dissemination</th>
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<tbody>
<tr>
<td>Drug Safety Communication</td>
<td>Address questions on real-world population exposure</td>
<td>Support an Advisory Committee (AC)</td>
<td>Assess feasibility of potential inferential analysis</td>
<td>International scientific conference</td>
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<td>Label change</td>
<td>Provide context for other safety data</td>
<td>Response to a Citizen Petition</td>
<td>Conducted by sponsor (e.g., PMR, PASS)</td>
<td>Publication</td>
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<tr>
<td>Modification of patient medication guide</td>
<td>Enrollment in pregnancy registries</td>
<td>Response to a Congressional inquiry</td>
<td>Conducted by regulatory agency</td>
<td>Sentinel website</td>
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<td>Downgrade of TE rating for a generic drug</td>
<td>Comparison with clinical trial data</td>
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<td>Product or packaging redesign</td>
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<tr>
<td>Determine that no action is needed</td>
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</table>
Real-World Example: Ranolazine

• Exposure: Ranolazine (Ranexa)
  – Indicated for the treatment of chronic angina
• Outcome: Seizure
• Analysis: Self-controlled risk interval design
• Regulatory determination: FDA decided that no action is necessary at this time, based on available information
  – Combined with evidence from a study done in the U.S. Medicare population, risk of seizure was determined to be driven primarily by underlying comorbidities

http://sentinelinitiative.org/drugs/assessments/ranexa-ranolazine-and-seizures
Real-World Example: Ranolazine

ICPE Symposium, August 2017
Real-World Example: Febuxostat

- Exposure: febuxostat (Uloric)
  - Indicated for the chronic management of hyperuricemia in adult patients with gout
- Outcomes: User characteristics, duration of use, switching between urate-lowering therapies
- Analysis: Level 1, Level 1
- Regulatory Use: Presented at an Advisory Committee meeting

http://sentinelinitiative.org/drugs/assessments/characteristics-gout-patients-and-useurate-lowering-therapies
AC Presentation on Febuxostat

- In light of a post-market clinical trial that identified an elevated risk of CV events, Sentinel analyses described real-world use of urate-lowering therapies.
- Results informed the Advisory Committee’s determination that a population exists for whom the benefit-risk is favorable.
Additional Real-World Examples

Incidence of Heart Failure and Cardiomyopathy Following Initiation of Medications for Attention-Deficit/Hyperactivity Disorder: A Descriptive Study

Andrew D. Mosholder; Lockwood Taylor; Glenn Mannheim; Lisa Ortendahl; Tiffany S. Woodworth; Sengwee Toh

Use of tumor necrosis factor-alpha inhibitors during pregnancy among women who delivered live born infants

Efe Ewouke, Genna Panucci, Margie Goulding, Rosemarie Neuner, Sengwee Toh

First published: 14 November 2018 | https://doi.org/10.1002/pds.4695

This project was presented at the 33rd Annual International Conference on Pharmacoepidemiology and Therapeutic Risk Management.

Original Investigation
October 1, 2018
Association of Risk for Venous Thromboembolism With Use of Low-Dose Extended- and Continuous-Cycle Combined Oral Contraceptives
A Safety Study Using the Sentinel Distributed Database

Jie Li, PhD1; Genna Panucci, SM2; David Moeny, RPh1; et al

Author Affiliations
JAMA Intern Med. Published online October 1, 2018. doi:10.1001/jamainternmed.2018.4251
### Regulatory Uses of Sentinel Analyses

#### How ARIA Analyses Have Been Used by FDA

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Outcome Assessed</th>
<th>ARIA Analysis</th>
<th>Regulatory Determination / Use</th>
<th>Date Posted</th>
</tr>
</thead>
</table>
| Non-insulin antidiabetics | • Duration of follow-up  
• Duration of use | Level 1 | Feasibility assessment that supported an ARIA sufficiency determination to replace a sponsor postmarketing requirement (PMR) safety study for canagliflozin and renal cell carcinoma.  
• Results  
• Efficacy Supplement Approval Letter | 04/02/2019 |
| Sodium glucose cotransporter-2 (SGLT-2) Inhibitors | • Use in type 1 diabetes mellitus (T1DM)  
• Diabetic ketoacidosis (DKA) | Level 1 | In response to clinical trials showing an increased risk of DKA with sotagliflozin in T1DM, FDA assessed off-label use of SGLT2 inhibitors (approved for use in T2DM) and real-world rates of DKA when used in patients with T1DM. Elevated rates of DKA with off-label SGLT2 inhibitor use among patients with T1DM were seen compared to clinical trials. These findings were presented at the Advisory Committee meeting for sotagliflozin, and this helped inform the committee member discussion on the benefit-risk assessment.  
• Results  
• Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Materials | 04/01/2019 |
| Dolutegravir (Tivicay and combination products Juluva, Truvada) | • Exposure in pregnancy | Level 1 | FDA assessed the feasibility of conducting a postmarket study in Sentinel to further investigate preliminary results from an observational study suggesting a higher risk of neural tube defects among offspring of pregnant women using | 03/28/2019 |

[https://www.sentinelinitiative.org/drugs/how-aria-analyses-have-been-used-fda](https://www.sentinelinitiative.org/drugs/how-aria-analyses-have-been-used-fda)
Sentinel Analyses are Publicly Available

Assessments
This webpage provides access to Sentinel assessments that have been conducted by the FDA Center for Drug Evaluation and Research (CDER). The search options below can be used to find material based on medical product, safety outcome, and the following study types:
- **Exploratory Analyses** characterize the rates of health outcomes, examine medical product use, and explore the feasibility of more detailed evaluations.
- **Safety Analyses** build on exploratory work and formally evaluate medical product-outcome associations using more advanced study designs and statistical methods to control for confounding.

Disclaimer
The information contained on this website is provided as part of FDA's commitment to place knowledge acquired from Sentinel into the public domain as soon as possible. Please read the disclaimer.

Product Name

Safety Outcome

Assessment Type

Submit
Show All

Most Recent Drug Assessments

<table>
<thead>
<tr>
<th>Title</th>
<th>Date Posted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentinel Modular Program Report: Use of Multiple Sclerosis Drugs Among Pregnant Women</td>
<td>12/06/2018</td>
</tr>
<tr>
<td>Sentinel Modular Program Report: Pulmonary Arterial Hypertension and Interstitial Lung Disease Events Among AOSD and SJIA Cohorts, Report 1</td>
<td>12/03/2018</td>
</tr>
<tr>
<td>Sentinel Modular Program Report: Pulmonary Arterial Hypertension and Interstitial Lung Disease Events Among Interleukin Inhibitor Users, Report 2</td>
<td>12/09/2018</td>
</tr>
</tbody>
</table>

Overview for Request cdr_mpl1p_wsp09_dsdp_v01

Request ID: cdr_mpl1p_wsp09_dsdp_v01
Request Description: This report contains estimates of multiple sclerosis (MS) drug use before, during, and after pregnancies resulting in a live-born delivery, among women in the Sentinel Distributed Database (SDD).
Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDa) tool, version 5.0.5, with additional ad hoc programming.
Data Source: Data from January 1, 2003 to August 31, 2017 from 16 Data Partners contributing to the SDD were included in this report. See Appendix A for a list of the dates of available data for each Data Partner. This request was distributed to Data Partners on November 20, 2017.
Study Design: The total number of pregnancies and the number and percentage of pregnancies with multiple sclerosis drug exposure were assessed among women of reproductive age. Results were stratified by exposure during the 183 to 91 and 91 to 1 days prior to pregnancy start, pregnancy trimester, and during the 90 and 183 days after delivery. Additionally, the results were stratified by maternal age at delivery, and by calendar year of delivery. An age-matched cohort of non-pregnant women was used as a comparator during the same time period in which pregnancy episodes were assessed.
Cohort Eligibility Criteria: Women members in the following age groups were included in the cohort: 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49. Eligible women were enrolled in the cohort if they had at least one drug claim and drug exposure during the time period of interest.

Table 1: Prevalence of Multiple Sclerosis (MS) Drug Use among Women with Live-Birth Deliveries in the Sentinel Distributed Database, by Trimester

<table>
<thead>
<tr>
<th>Pregnant Cohort</th>
<th>Use in the 183 Days Post-Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the 91-183 Days Post-Pregnancy</td>
<td>2,205,383</td>
</tr>
<tr>
<td>In the 90-91 Days Post-Pregnancy</td>
<td>2,205,383</td>
</tr>
<tr>
<td>In the 30-90 Days Post-Pregnancy</td>
<td>2,205,383</td>
</tr>
<tr>
<td>In the 10-30 Days Post-Pregnancy</td>
<td>2,205,383</td>
</tr>
<tr>
<td>In the 1 - 10 Days Post-Pregnancy</td>
<td>2,205,383</td>
</tr>
</tbody>
</table>

https://www.sentinelinitiative.org/drugs/assessments
FDA-CATALYST
The 21st Century Cures Act

- FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:
  - Approval of new indication for a drug approved under section 505(c)
  - Satisfy post-approval study requirements
- Program will be based on a framework that:
  - Categorizes sources of RWE and gaps in data collection activities
  - Identifies standards and methodologies for collection and analysis
  - Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address
- Draft Guidance to be issued by 2021
- PDUFA commitments aligned with 21st Century Cures Act
Sentinel Initiative

Sentinel Infrastructure

**Sentinel System**
Routine queries and other activities that use pre-existing data
- PRISM
- BloodSCAN
- ARIA

**FDA-Catalyst**
Routine queries + interventions and interactions with members and/or providers
**IMPACT Afib Trial**

**Implementation** of a randomized controlled trial to imProve treatment with oral AntiCoagulanTs in patients with Atrial Fibrillation

Test the ability of an education intervention to increase the appropriate use of oral anticoagulants in a patient population with atrial fibrillation (afib) at high risk of stroke

Enrollment of approximately 80,000 individuals in the early and late intervention arms
FDA MyStudies

• **Mobile App**
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)

• **Web-based Configuration Portal (WCP)**
  - Enables support of multiple types of medical product effectiveness and safety studies with minimal software development

• **Secure Storage Environment**
  - Generates secure tokens
  - Separates registration information and responses
  - Partitioned for multisite, decentralized, or distributed models

www.fda.gov
Smartphone use among U.S. adults is increasing\(^1\)

- 77% now own Smartphones (35% in 2011)
- Fewer (73%) own a laptop or desktop

Growth of “smartphone only” internet use\(^2\)

- 20% of US adults do not rely on traditional home internet service for access

Variation in “smartphone only” internet use\(^3\)

Reliance on smartphones for online access is especially common among younger adults (<50), non-whites and lower-income Americans.

www.fda.gov
Key System Attributes

• **Scalable:** Capability to simultaneously support multiple studies for a research organization

• **Modular:** Various modular components of the platform can be integrated with external/3rd party system of choice to create a tailored solution for your organization.

• **Secure:** Partitions all data and provides robust access controls

• **Compliant:** Can be deployed to comply with HIPAA, FISMA, and 21 CFR Part 11

• **Customizable:** All study content as seen in the app can be authored and updated via the WCP web application rather than through new software development per study or app

• **Tested:** FDA and PCORI sponsored clinical research demonstration projects

• **Open-source and ready for research organizations to re-brand, publish, and use!**
RELIENCE Trial

- RofLumilast or Azithromycin to prevent COPD Exacerbations
  - Randomized “real world” trial; 1,600 adults in each arm
  - Azithromycin - macrolide with anti-inflammatory properties
  - Roflumilast - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor

- Primary outcomes
  - All cause hospitalization
  - All cause mortality

- Follow-up
  - 6-36 months, no visits, call center, Patient Portal, Site EMR
  - CMS linkage through FDA-Catalyst for outcomes and exposures
    - Enrollment files: all cause mortality
    - Inpatient claims files: all cause hospitalization for fee for service
    - Part C (Medicare Managed Care): new data source – will request if feasible
    - Part D: medication dispensing
Limit JIA trial

- Randomized real world trial in patients with Limited Juvenile Idiopathic Arthritis (<=4 joints affected and no uveitis)
  - Six month course of subcutaneous Abatacept (T cell co-stimulation inhibitor) plus usual care with NSAIDs and intra-articular glucocorticoids vs. usual care alone
  - Outcome: extension to more than 4 joints, new uveitis, and/or need for treatment with systemic medication at 18 months

- FDA-Catalyst is aligning with the trial by providing support from the MyStudies App
  - First use of FDA-Catalyst to support a pediatric trial
  - Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry
  - Collection of primary outcome (uveitis) from ophthalmology appointments - Configured
  - Collection of adherence information/adverse events for study drug with “drug diary” – Configuration stage
SPARC registry

• **SPARC Inflammatory Bowel Disease cohort within the IBD Plexus research exchange platform**
  – Provider based recruitment of individuals >18 years of age with a confirmed IBD diagnosis from academic and community sites

• **FDA-Catalyst is aligning registry by providing support from the My Studies App**
  – Configuration stage

• Registry responses will be included in the [PCORI Comparative Effectiveness of Biologic or Small Molecule Therapies in Inflammatory Bowel Disease study](#) (prospective cohort for patient reported outcomes)
Discussion