Sentinel Overview

Richard Platt
February 10, 2016
Post-Market Safety Surveillance

Signal identification: Potential safety concern identified

Signal Refinement: Initial evaluation of safety concerns

Signal Evaluation: Detailed assessment

Data Mining

Summary Tables Modular Programs

Protocol-based Evaluations
Impact / Dissemination

- 4 FDA drug safety communications
  - Tri-valent inactivated flu vaccine and febrile seizures (no increased risk)
  - RotaTeq, Rotarix and intussusception (label change for RotaTeq, no label change for Rotarix)
  - Dabigatran and bleeding (no increased risk)
  - Olmesartan and sprue-like enteropathy (label change)

- 26 Presentations by FDA
- 48 Methods reports / white papers
- 70 Peer-reviewed articles
- 137 Assessments of products, conditions, product-outcome pairs
“The Mini-Sentinel ' provides an essential public health service. The current configuration — the data model, the methods development, and the investigative team — represents an impressive achievement..
Welcome to Mini-Sentinel

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products. Mini-Sentinel uses pre-existing electronic healthcare data from multiple sources. Collaborating institutions provide access to data as well as scientific and organizational expertise. Mini-Sentinel is part of the FDA’s Sentinel Initiative, which is exploring a variety of approaches for improving the Agency's ability to quickly identify and assess safety issues.

Most Mini-Sentinel activities focus on assessments, methods, or data. Visit the following links to learn more about each type of activity:

- **Assessments** - Medical product exposures, health outcomes, and links between them
- **Methods** - Techniques for identifying, validating, and linking medical product exposures and health outcomes
- **Data** - Mini-Sentinel Distributed Dataset and tools used to access the data

**Spotlight**

- Brookings Seventh Annual Sentinel Initiative Public Workshop (February 5, 2015 from 9am-4pm - registration required)
- Employment Opportunities
- FDA Sentinel Contract Awarded to Harvard Pilgrim Health Care Institute

**Latest Postings**

**Ongoing Projects**

- Decision Analysis for Surveillance and Health - Pandemic Influenza (PRISM)
- Quantifying Uncertainty in Protocol Based Assessments (PRIMA)
Sentinel Partner Organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners

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Hospital Corporation of America

168 hospitals and 113 surgery centers located in 20 states and The United Kingdom.

~5% of all inpatient care delivered in USA

Trust and Governance

Principles & Policies

The Mini-Sentinel statement of Principles and Policies governs actions of collaborators, both institutions and individuals, as they develop this pilot. This document has been approved by the FDA and the Collaborating Institutions.

- Data
- Privacy
- Confidentiality
- Communications
- Intellectual Property
- Conflict of Interest
- Glossary

Related Materials

- White Paper on HIPAA and Common Rule Compliance in the Mini-Sentinel Pilot
- Webinar on Data Privacy in Mini-Sentinel
Three major domains

- Data
- Methods
- Active surveillance
Three major domains

- Data
- Methods
- Active surveillance
Sentinel distributed database*

- Populations with well-defined person-time for which most medically-attended events are known
  - 193 million members**
  - 351 million person-years of observation time
  - 39 million people currently accruing new data
  - 4.8 billion dispensings
  - 5.5 billion unique encounters
    - 51 million acute inpatient stays
  - 33 million people with ≥1 laboratory test result

* As of August 2015, excludes HCA and BCBS of Massachusetts
** Double counting exists for individuals who change health plans
Mini-Sentinel’s Data Sources

- Administrative data
  - Enrollment
  - Demographics
  - Outpatient pharmacy dispensing
  - Utilization (encounters, diagnoses, procedures)

- EHR and laboratory test result data for 10%
  - Height, weight, blood pressure, temperature
  - Laboratory test results (selected tests)

- Registries
  - Immunization and birth certificates

- Full text records (small number to confirm selected exposures and outcomes – names, etc. redacted)

- Inpatient electronic health records
Mini-Sentinel Distributed Analysis

1- User creates and submits query (a computer program)

2- Data partners retrieve query

3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return results via secure network

6- Results are aggregated
Three major domains

- Data
- Methods
- Active surveillance
Domains of methods development / examples

<table>
<thead>
<tr>
<th>Data Fitness and Capacity</th>
<th>Evaluating Methods</th>
<th>Target Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Integrity (validity, completeness)</td>
<td>• Validity, power/robustness, time-to-signal detection</td>
<td>• Preparedness Design</td>
</tr>
<tr>
<td>• Environments</td>
<td>• Empirical, simulation</td>
<td>– Systematic selection</td>
</tr>
<tr>
<td>– <em>Claims, EHR, registries</em></td>
<td>• Heterogeneity across databases</td>
<td>– Self-controlled</td>
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<tr>
<td>– <em>Outpatient, inpatient</em></td>
<td>• In collaboration with IMEDS</td>
<td>– Cohort methods</td>
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<tr>
<td>• Anonymous linkage</td>
<td>• Data sharing</td>
<td>• Analysis</td>
</tr>
<tr>
<td>• Enriching the CDM</td>
<td>• Data Fitness and Capacity</td>
<td>– Confounder adjustment</td>
</tr>
<tr>
<td>– <em>Lab results</em></td>
<td>• Evaluation Methods</td>
<td>– Distributed methods</td>
</tr>
<tr>
<td>• Data sharing</td>
<td>• Target Monitoring</td>
<td>– Quantifying uncertainty</td>
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**Signal Generation**

<table>
<thead>
<tr>
<th>Signal Generation</th>
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<tbody>
<tr>
<td>• Data mining (untargeted)</td>
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<tr>
<td>• Sample size tools</td>
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</table>

**Signal Follow-up**

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<thead>
<tr>
<th>Signal Follow-up</th>
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<tbody>
<tr>
<td>• Data/code quality</td>
</tr>
<tr>
<td>• Sensitivity analyses</td>
</tr>
<tr>
<td>• Timing of signals</td>
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<tr>
<td>• 2-phase designs</td>
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**Decision Making**

<table>
<thead>
<tr>
<th>Decision Making</th>
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<tr>
<td>• Decision analysis framework</td>
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Health Outcome and Confounder Libraries

- Need standardized operational definitions for health outcomes and confounding conditions
- Summarize literature sources
- Document definitions used in protocol-based assessments
### Taxonomy

#### Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios

<table>
<thead>
<tr>
<th>Exposure persistence (transient, sustained)</th>
<th>Monitoring scenario characteristics with implication for design choice(^a)</th>
<th>Monitoring scenario characteristics with implication for analytic choice(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of exposure risk window</strong> (Immediate, delayed)</td>
<td><strong>Duration of exposure risk window</strong> (short, long)</td>
<td><strong>Strength of confounding</strong></td>
</tr>
<tr>
<td><strong>Within-person</strong> (negligible, needs to be addressed)</td>
<td><strong>Between-person</strong> (negligible, needs to be addressed)</td>
<td><strong>HOI onset</strong> (abrupt, insidious)</td>
</tr>
<tr>
<td>Immediate</td>
<td>Short</td>
<td>Negligible</td>
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<tr>
<td>3</td>
<td>4</td>
<td>5</td>
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</tbody>
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**Exposure-outcome scenarios linked to design strategies**

1. **Immediate**
2. **Short**
3. **Negligible**
4. **Abrupt**
5. **Infrequent**
6. **Rare**
7. **Insidious**
8. **Self-controlled or cohort**
9. **Rare**
10. **Infrequent**
11. **Rare**
12. **Infrequent**
13. **Rare**
14. **Infrequent**
15. **Rare**
16. **Infrequent**
17. **Rare**

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### Additional workgroups (selected)

<table>
<thead>
<tr>
<th>Data activities</th>
<th>Statistical and analysis tools</th>
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<tbody>
<tr>
<td>Feasibility of blood product safety surveillance</td>
<td>Prospective monitoring tools (PROMPT) enhancements</td>
</tr>
<tr>
<td>Clinical data elements, including lab test results</td>
<td>Robustness of surveillance</td>
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<tr>
<td>National Death Index linkage</td>
<td>Quantifying uncertainty in protocol-based assessments</td>
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<tr>
<td>Birth certificate linkage</td>
<td>Expansion of data mining (TreeScan Pilot and TreeScan power)</td>
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<tr>
<td>Diabetes registry linkage (SUPREME-DM)</td>
<td>Scan statistics and pregnancy</td>
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<tr>
<td>Medical Counter Measures</td>
<td>Practical guidance for signal follow-up</td>
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<tr>
<td>Sequential analysis of influenza vaccine safety</td>
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<tr>
<td>Linkage with PCORnet</td>
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</tbody>
</table>
Three major domains

- Data
- Methods
- Active surveillance
Rapid queries in 2015

- Summary tables
  - Reports: 34
  - Scenarios: 534

- Modular programs
  - Reports: 83
  - Scenarios: 1469
Protocol based assessments active in 2015

- 17 active protocols
  - Center for Biologics Evaluation and Research (CBER): 9
  - Center for Drug Evaluation and Research (CDER): 8
Selected Protocol Based Assessments Planned or Under Way

- **CDER**
  - Mirabegron and several outcomes (prospective monitoring)
  - Rivaroxaban and several outcomes (prospective monitoring)
  - Dabigatran and several outcomes
  - Metabolic effects of 2nd generation antipsychotics in youth
  - Diabetes drugs and acute myocardial infarction
  - IV Iron and anaphylaxis

- **CBER**
  - IV Immune Globulin and thromboembolic events
  - Gardasil and venous thromboembolism
  - Influenza vaccines and pregnancy outcomes
  - Gardasil 9 and Pregnancy Outcomes
  - Prevnar 13 and Kawasaki disease
  - Blood components and Transfusion-Related Lung Injury (TRALI)