Tenth Annual Sentinel Initiative Public Workshop

Bethesda Hyatt Regency
February 7, 2018

Join the conversation with #sentinelinitiative
Welcome & Overview
Keynote Address

Join the conversation with #sentinelinitiative
The Sentinel Initiative: What does the next 10 years hold?
Updates from Sentinel’s Network of Collaborators

Join the conversation with #sentinelinitiative
Why Sentinel developed as it did, how it is evolving

Richard Platt
Vinit Nair
Kenneth Sands
Marcus Wilson
February 7, 2018
Sentinel and Real World Evidence

- Plain Sentinel
- Sentinel with full text medical record adjudication
- Sentinel linked to registries
- Sentinel linked to EHRs
- Sentinel and patient generated data
- Sentinel as a home for clinical trials
- Why Sentinel evolved as it did
- Sentinel today
- The future
Sentinel Prototype

• Develop a coordinating center for a distributed system
  – Access three or more health data environments with varied attributes to conduct analyses
  – Convene a Planning Board to develop governing documents and establish a Safety Science Committee charged with the day-to-day operations
  – Develop a means for secure communication with contracted data holders

• Evaluate emerging methods in safety science
  – Develop epidemiological and statistical methodologies for signal detection, signal strengthening, and signal validation
  – Test such methodologies in the evaluation of FDA-identified medical product-adverse event pairs of concern
Sentinel Prototype

- Develop a **coordinating center for a distributed system**
  - Access three or more health data environments
  - Convene a Planning Board to **develop governing documents** and establish a Safety Science Committee charged with the day-to-day operations
  - Develop a means for **secure communication**

- **Evaluate emerging methods in safety science**
  - Develop **epidemiological and statistical methods** for signal detection, signal strengthening, and signal validation
  - Test such methodologies in the **evaluation of FDA-identified medical product-adverse event pairs** of concern
Why did Sentinel focus on claims (not EHRs)?

- Sufficiently large covered population
- Claims records are complete while individuals have coverage
- Use of claims well established for medication safety assessment
Risk of Guillain–Barré syndrome following pneumococcal conjugate vaccination

Priscilla Velentgas1,2*, Donnie P. Funch1,7, Thomas Cochrane3, K. Arnold Chan6,7, Patricia Gladowski8, Steven A. Greenberg3, Judith M. Kravitz5, Cynthia Nakasato11, Claire M. Spettel10, Beth L. Syat1, Y. Zhang1, Jeffrey S. Brown1 and Richard Platt1

5 health plans
Identical programs at each site
Why a distributed database?
Distributed vs single database

- Originally, no single database was large enough
- Major barriers to combining separate databases
- Distributed system guards against data dredging because analytic program is finalized before results are available
- Distributed network allows assessment of consistency/heterogeneity across systems
Results

Hazard Ratios and 95% Confidence Intervals for Comparison 1: Continuous or Extended vs. Cyclic Combined Oral Contraceptives and VTE (Matched Analysis)

*HRs were not calculated for DP02, DP07, DP08, or DP13 due to no events in one or both treatment groups. Results for DP10, DP11, DP12, and DP14 were excluded due to PS model convergence issues.
Results by Data Partner

Hazard Ratios and 95% Confidence Intervals for Comparison 1: Continuous or Extended vs. Cyclic Combined Oral Contraceptives and VTE (Matched Analysis)

*HRs were not calculated for DP02, DP07, DP08, or DP13 due to no events in one or both treatment groups. Results for DP10, DP11, DP12, and DP14 were excluded due to PS model convergence issues.
An Ideal Distributed Network Should...

- Accommodate many data holders’ data
- Minimize data exchange
- Maximize local control of data and uses
- Incorporate new kinds of data as they become available
- Include local experts in study design and interpretation
- Allow a study protocol to be implemented identically and efficiently across the network
- Support standardized, reusable components
Contributors to Sentinel’s success

- Sentinel is a public health program
  - Operates under FDA’s public health authority
  - The Common Rule governing research involving human subjects doesn’t apply
  - Follows HIPAA public health requirements
- All activities are opt-in
- Distributed data network greatly reduces need for sharing confidential and proprietary data
• Why Sentinel evolved as it did
• Sentinel today
• The future
Sentinel is a National Medical Product Monitoring System

- Background
- Coordinating Center
- Privacy and Security
- The Sentinel System Story
- Reagan-Udall Foundation and IMEDS

- MEDICAL PRODUCT ASSESSMENTS
  - Active Risk Identification and Analysis System
  - Ongoing ARIA Assessments
  - Assessments of Drugs
  - Assessments of Vaccines, Blood, & Biologics
  - FDA-Catalyst

- DATA AND SURVEILLANCE TOOLS
  - Distributed Database and Common Data Model
  - Complementary Data Sources
  - Routine Querying Tools

- COMMUNICATIONS
  - FDA Safety Communications
  - Publications and Presentations
  - Sentinel Initiative Events

- Latest Postings
  - SPOTLIGHT
    - Registration is Open for the Sentinel Initiative Public Workshop and Training - February 7-8, 2018
      Mon, 12/04/2017
  - PUBLICATIONS AND PRESENTATIONS
    - Outcomes of Dabigatran and Warfarin for Atrial Fibrillation in Contemporary Practice: A Retrospective Cohort Study
      Fri, 01/12/2018
  - MODULAR PROGRAMS AND SUMMARY TABLES
    - Use of Bortezomib
      Tue, 01/30/2018
    - Characterization of Pediatric Medical Conditions: Respiratory Syncytial Virus (RSV) Associated Illness
      Thu, 01/25/2018
“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..
Sentinel partner organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners
# Sentinel Common Data Model and Distributed Database

<table>
<thead>
<tr>
<th><strong>Enrollment</strong></th>
<th><strong>Demographic</strong></th>
<th><strong>Dispensing</strong></th>
<th>** Encounter**</th>
<th><strong>Diagnosis</strong></th>
<th><strong>Procedure</strong></th>
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<td></td>
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<td>Principal discharge diagnosis</td>
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<table>
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<tr>
<th><strong>Lab Result</strong></th>
<th><strong>Vital Signs</strong></th>
<th><strong>Inpatient Pharmacy</strong></th>
<th><strong>Inpatient Transfusion</strong></th>
<th><strong>Death</strong></th>
<th><strong>Cause of Death</strong></th>
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<td>Person ID</td>
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<tr>
<td>Result and specimen collection dates</td>
<td>Measurement date and time</td>
<td>Administration date and time</td>
<td>Blood product code and type</td>
<td>Death date</td>
<td>Cause of death</td>
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<td>Test type, immediacy &amp; location</td>
<td>Height and weight</td>
<td>Encounter ID</td>
<td>Encounter ID</td>
<td>Source</td>
<td>Context</td>
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<td>Logical Observation Identifiers Names and Codes (LOINC ®)</td>
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<td>National Drug Code (NDC)</td>
<td>Blood type</td>
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<td>Test result &amp; unit</td>
<td>Tobacco use &amp; type</td>
<td>Route</td>
<td>Administration start and end dates and times</td>
<td>Etc.</td>
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</table>
Data Quality Assurance Review Process

1. Perform Data Update
2. Execute data quality program package
3. Review output; identify and resolve issues
4. Deliver summary output to MSOC
5. Review #1 of data quality output
6. Prepare initial report of findings
7. Review #2 of data quality output
8. Annotate initial report of findings
9. Review and finalize report
10. Review report; resolve issues, respond to MSOC
11. Review Data Partner’s response to report; send additional questions if needed
12. Approve Data Update
## Sentinel Distributed Database

<table>
<thead>
<tr>
<th></th>
<th>Traditional Sentinel</th>
<th>Medicare Fee-For-Service</th>
<th>Total</th>
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<tr>
<td>Unique person IDs</td>
<td>239 million</td>
<td>53.5 million</td>
<td>292.5 million</td>
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<tr>
<td>People Accruing New Data</td>
<td>44.6 million</td>
<td>22.3 million</td>
<td>66.9 million</td>
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<tr>
<td>Pharmacy Dispensings</td>
<td>6.6 billion</td>
<td>7.7 billion</td>
<td>14.3 billion</td>
</tr>
<tr>
<td>Unique Medical encounters</td>
<td>7.8 billion</td>
<td>5.5 billion</td>
<td>13.3 billion</td>
</tr>
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<td>Members with &gt;1 Laboratory Test Result</td>
<td>45.6 million</td>
<td>Laboratory data unavailable</td>
<td>45.6 million</td>
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Sentinel’s tools

Cohort ID and Descriptive Analysis (CIDA) Tool

Options:
- Propensity Score Matching or Stratification
- Self-controlled Risk Interval Design
- Drug Use in Pregnancy | Mom-baby linkage
- Drug Utilization
- Concomitant Drug Utilization
- Pre/Post Index Tool
Modular Program Querying Sequence

1. Simple counts
2. Complex counts
3. Compare event rates
4. Follow-up

- Determine use and frequency
- Identify/describe population
- Comparative assessment
- New queries; Line Lists; Chart Review
ARIA Analyses 2016-7

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<th>Quarter</th>
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<th>2017</th>
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<td>Q1</td>
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<td></td>
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<tr>
<td>Q4</td>
<td>3</td>
<td>19</td>
</tr>
</tbody>
</table>

Summary Table: 145
Level 1: 93
Level 2: 16
Total: 254
Advantages of live systems – part 1

- Expert knowledge about whether, how, how well care is recorded and stored in automated data
- Local experts can address data quality concerns
- Able to obtain full text provider records
  - Allows validation of algorithms for identifying health outcomes of interest
  - Allows confirmation of diagnoses for specific individuals
- Why Sentinel evolved as it did
- Sentinel today
- The future
New directions

- Sentinel will expand its use of EHR data
- Machine learning to improve algorithms for identifying health outcomes of interest
- Natural language processing to use free text in EHRs
Making EHRs useful for Sentinel

- Need many separate, diverse EHR systems
- No standard for implementing machine learning and NLP in diverse systems
- Need to link them to claims
  - Distributed methods likely to be essential
Selected Activities

- Evaluation of New Technologies Associated with Chart Review (Workgroup)
  - Best practices to review medical records for case validation and algorithm development
  - Assess automation techniques that can be used in a distributed environment

- Improving the Efficiency of Outcome Validation in the Sentinel System (Workshop)
  - Experts in natural language processing, machine learning, and artificial intelligence to assess how technologies can support FDA Sentinel needs
  - Best practices for extracting standardized data from medical records
  - Technologies for identifying cohorts and outcomes from medical records
  - Strategic planning and prioritization for implementation within Sentinel
Advantages of live systems – part 2

- The ability to engage patients, members, and providers
Sentinel and Real World Evidence

- Plain Sentinel
- Sentinel with full text medical record adjudication
- Sentinel linked to registries
- Sentinel linked to EHRs
- Sentinel and patient generated data
- Sentinel as a home for clinical trials
FDA-Catalyst

- Combines direct contact with health plan members and/or providers with data included in the Sentinel distributed dataset
- Leverages the Sentinel infrastructure to answer a wider range of questions
A Mobile App for Studies of Medication Safety and Effectiveness
Origin

- Concept: Develop and test a reusable, flexible, and secure mobile app and patient data storage environment to complement Sentinel and PCORnet
- Patient Centered Outcomes Research Trust Fund grant awarded by the office of the Assistant Secretary for Planning and Evaluation to David Martin at FDA
- Workgroup:
Collecting Patient-Reported Data

- **Mobile App**
  - iOS and Android versions
  - Configuration portal for questions

- **Secure storage environment**
  - FISMA compliant
  - Partitioned for scalable distributed research

- **Linkage to distributed electronic health data**
Pilot Study: Medication Use in Pregnancy

- Kaiser Permanente Washington Health Research Institute served as a scientific and data partner
- Patient input informed the design of questionnaires and app engagement features
- 1,070 pregnant women invited to participate
- 62 enrolled in the study
Learnings from Pilot Study

- Women completed a median of 22 questionnaires
- Women were willing to report sensitive information on drug and alcohol use
- Some reported medication use patterns differed from inferences based on electronic health data
- Women reported the app was generally easy to use
- Future directions
  - Expand to additional data partners & new populations
  - Explore using financial incentives to increase participation rates (common in clinical research)
Sentinel and Real World Evidence

- Plain Sentinel
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- Sentinel and patient generated data
- **Sentinel as a home for clinical trials**
IMPACT-AFib, an 80,000 person randomized trial

Implementation of a randomized controlled trial to improve treatment with oral Anticoagulants in patients with Atrial Fibrillation

- Direct mailer to:
  - health plan members with AFib, high risk for stroke and no oral anticoagulant treatment, and to
  - their providers, to encourage consideration of treatment
Rationale for IMPACT-AFib trial

• Anti-coagulant underuse is a public health priority
• Also a priority of health plans
• Interventions (mailings) are consistent with routine health plan interventions
• Eligible population are identifiable and major outcomes measurable using Sentinel Distributed Database
Patients with AFib, CHADS-VASc $\geq 2$

**RANDOMIZE**

Usual Care and Delayed Provider intervention

Early Patient-level and Provider-level intervention

Access Pharmacy Records

- OAC in prior 12 months
  - Excluded
- No OAC in prior 12 months
  - Intervention Mailed

12-months
Primary outcome: Proportion of AFib patients started on anticoagulant over the course of the 12-month trial

Secondary outcomes:
- Proportion of days covered with OAC prescription
- Number of patients on OAC at end of one year
- Admissions for stroke or TIA
- Admissions for stroke
- Admissions for bleeding
- Deaths (subset)
Intervention Materials

PATIENTS
- Letter from health plan
- Patient brochure – information on AF and OACs
- Patient pocket card – designed to facilitate conversation between patient and provider

PROVIDERS
- Letter from health plan
- Provider enclosure – myths and facts on OACs
- Response mailer – providers to share feedback
Early Intervention Mailings

Patients Contacted via Mailing

38,000

25-Sep-17  9-Oct-17  23-Oct-17  6-Nov-17  20-Nov-17  4-Dec-17  18-Dec-17  1-Jan-18  15-Jan-18  29-Jan-18
Developing the Sentinel System — A National Resource for Evidence Development

Rachel E. Behrman, M.D., M.P.H., Joshua S. Benner, Pharm.D., Sc.D., Jeffrey S. Brown, Ph.D., Mark McClellan, M.D., Ph.D., Janet Woodcock, M.D., and Richard Platt, M.D.

The Food and Drug Administration (FDA) now has the capacity to “query” the electronic health information of more than 60 million people, posing specific questions in order to monitor the safety of approved medical products. This information to answer additional
The Innovation in Medical Evidence Development and Surveillance (IMEDS) program provides an entry point for private and public sector stakeholders that would like to use Sentinel data, tools, and methods.

IMEDS is currently operational and has been used by external stakeholders to address pending regulatory issues.
NIH Collaboratory Distributed Research Network

Millions of people. Strong collaborations. Privacy first.

The NIH Collaboratory Distributed Research Network enables investigators to collaborate with each other in the use of electronic health dat multisite research programs.

The Network’s querying capabilities reduce the need to share confidential or proprietary data by enabling authorized researchers to send queries to data partners. In some cases, queries can take the form of computer programs that a data partner can execute on a preexisting dataset. The data is aggregated (count) data, rather than the data itself. This form of remote querying reduces legal, regulatory, privacy, proprietary, and technical issues.

The network seeks to build strong and trusted collaborations to support the research that will lead to improved health for millions of people.

What does the NIH Collaboratory Distributed Research Network do?

- Provides infrastructure and mechanisms to facilitate multicenter studies using electronic clinical, administrative, and research data
- Allows searchable discovery of available data resources, health systems, researchers, and re-usable analytic tools
- Enables authorized investigators to identify clinical, administrative, and research datasets of interest
- Facilitates multisite distributed querying of data resources, while allowing the data to remain in the control of the data owners
- Serves as a repository of tools to leverage EHRs to support clinical research across multiple health systems

www.nihcollaboratory.org/Pages/distributed-research-network.aspx
PCORnet: The National Patient-Centered Clinical Research Network

The Patient-Centered Outcomes Research Institute (PCORI) is supporting the development of PCORnet, the National Patient-Centered Clinical Research Network, to create a large, highly representative, national network for conducting clinical outcomes research.

PCORnet will transform clinical research by engaging patients, care providers, and health systems in collaborative partnerships to improve healthcare and advance medical knowledge. By bringing research and patient care together, this innovative health data network will be able to explore the questions that matter most to patients and their families. Read more ....
Thank you!
Updates from Sentinel’s Network of Collaborators

Join the conversation with #sentinelinitiative
Break

Join the conversation with #sentinelinitiative
Key Sentinel Achievements
FDA’s Sentinel System: Progress to Date

Sentinel Annual Public Workshop
February 7, 2018

Michael D. Nguyen, MD
FDA Sentinel Program Lead
Deputy Director, Regulatory Science Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Overview

• Measuring progress through the lens of independent assessments

• Review the system we’ve created and how we’re using it in CDER

• Why having a system matters
Fulfilling PDUFA Commitments for Independent Assessments

September 2015

Sentinel Program Interim Assessment (FY 15)
To evaluate the strengths, limitations, and the appropriate use of Sentinel for informing regulatory actions to manage safety issues.

September 2017

https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm464042.htm
A Longitudinal Perspective

• Longitudinal view

• Interviews with FDA staff, Sentinel Operations Center, data partners

• Electronic survey

• Review of key operational metrics

• Review of publications, reports

• Measure program against predefined qualitative criteria in the Sentinel Maturity Model
Interim Sentinel Assessment

September 2015

Exhibit 15: Summary of Interim Assessment of Sentinel Initiative: CBER/CDER maturity

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<th>Dimension</th>
<th>Maturity rating (0 – 4)</th>
<th>Description</th>
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<td>Talent &amp; organization</td>
<td>1</td>
<td>• Both Centers have skilled users, but broader user base needs additional training</td>
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<td>• CBER has integrated users well, but need a continuously updated training program and some additional resources to handle higher demand</td>
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<tr>
<td>Governance</td>
<td>2</td>
<td>• CDER users have role clarity but need more process transparency</td>
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<tr>
<td></td>
<td></td>
<td>• CBER has strong oversight and transparency but lacks some user autonomy</td>
</tr>
<tr>
<td>Process</td>
<td>1</td>
<td>• CDER processes are operational but not codified or formalized, creating ambiguity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CBER has created formal procedures and SOPs, but queries remain bespoke and effort-intensive and have not been proven to handle a higher volume</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>• Both Centers need to develop metrics to measure performance, satisfaction, and usage trends</td>
</tr>
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N.B.: Maturity ratings not designed for a relative comparison between CBER and CDER. Given the size and scope differences between the Centers, and the corresponding separate approaches to Mini-Sentinel implementation, these maturity ratings were independently determined, making relative comparisons not meaningful.
By 2017, aspirations for Sentinel System capabilities include the following:

- **Increased user participation** in Sentinel Initiative workshops and development of Sentinel Initiative methodologies across both CBER and CDER
- **Access to a full set of modular programs and tools**, particularly for CDER users
- **More systematic and consistent processes** for triggering the Sentinel System and processing safety questions across both CBER and CDER
- **Assurance that CDER users have greater transparency** of Sentinel studies under way to increase familiarity and comfort with Sentinel use, in addition to improving user knowledge

By 2020, a fully mature Sentinel System should be accessible to all FDA scientists, who can use it to do the following:

- **Take advantage of high-level customization capabilities** to identify, refine, and evaluate safety questions with few or no backlogs
- **Regularly use the Sentinel System** in the course of safety and risk assessment to deliver on FDA’s vision for the Sentinel Initiative as a valuable resource to support regulatory decision making
Progress in 2 Years

"... Sentinel has been widely accepted within the FDA as a useful regulatory decision-making tool for safety issues; awareness of its capabilities among FDA staff has materially increased; it has been incorporated into the regulatory process; and its outputs have been instrumental in deciding a number of critical public health and safety questions. Its data infrastructure and associated suite of tools and methods are increasingly robust, and the question now is no longer if Sentinel will be used in regulatory decision-making, but rather how best to cost-effectively scale and embed it even further."
Sentinel Maturity Model Gains

- Process
- Governance
- Talent and Organization
- Methods
- Analytical Tools and Technology
- Strategy and Value

2015 - 2017

High Maturity
Overview

• Measuring progress through the lens of independent assessments
  – The growth we needed in 2015
  – The progress we achieved by 2017

• Review the system we’ve created and how we’re using it in CDER

• Why Having a System Matters
  – Makes large scale endeavors cost effective and faster
  – Makes small(er) scale endeavors more likely and more frequent
Requirement to Consider Sufficiency of ARIA before PMR

“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).”

Section 905
Mandates creation of ARIA

Section 901
New FDAAA PMR authority

FDAAA = FDA Amendments Act 2007
Defining ARIA Sufficiency

• Adequate data
• Appropriate methods
• To answer the question of interest
• To lead to a satisfactory level of precision
ARIA is FDA’s active post-market risk identification and analysis system, which is comprised of pre-defined, parameterized, reusable routine querying tools, combined with the electronic data in the Sentinel Common Data Model. Because ARIA uses parameterized tools and a trusted multi-site distributed database that undergoes continuous quality checks and refreshes, safety analyses can be done more efficiently to conduct medical product safety surveillance to fulfill the mandate in the FDA Amendments Act of 2007.

INTENT TO STUDY SAFETY ISSUE IN SENTINEL ARIA SYSTEM

The Food and Drug Administration Amendments Act of 2007 (FDAAA)[1] required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate Sinuva (mometasone furoate) Sinus Implant, in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel’s Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to assess the following serious risks: potential adverse events of concern with repeat use of the Sinuva Sinus Implant which include nasal septal perforation, cataracts and glaucoma.

The ARIA safety assessment will be posted to the Sentinel website at this location: https://www.sentinelinitiative.org/drugs/ongoing-aria-assessments. Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website. FDA will notify you prior to posting the analysis plan and prior to posting the results.
ARIA Analyses By Quarter (N = 254)

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Legend:
- **Summary Table**
- **Level 1**
- **Level 2**
# How ARIA Analyses Have Been Used By FDA

<table>
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<tr>
<th>Drug Name</th>
<th>Outcome Assessed</th>
<th>ARIA Analysis</th>
<th>Regulatory Determination / Use</th>
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</thead>
</table>
| Kepra (levetiracetam)            | Anaphylaxis and angioedema                    | Level 1       | Drug Safety Label Change, Warnings and Precautions  
- Results  
- FDA Drug Safety Labeling Changes Page                                                                                                                                                                                                 | 11/30/2017   |
| Ketoconazole oral tablets        | Drug use trends after safety label change and use in labeled indications | Level 1       | Citizen Petition Response  
- Results  
- Letter from FDA (Docket No. FDA-2015-P-0570)                                                                                                                                                                                                 | 12/4/2017    |
| Antipsychotic agents             | Ischemic and hemorrhagic stroke               | Level 1, Level 2 | FDA decided that no action is necessary at this time, based on available information.  
- Level 1 Results  
- Level 2 Results  
- Results among SSRI Users  
- 2017 ICPE Symposium                                                                                                                                                                                                                         | 12/8/2017    |
| Gadolinium-based contrast agents | Exposure in pregnancy                         | Level 1       | Advisory Committee Presentation & FDA Drug Safety Communication  
- Results  
- Medical Imaging Drugs Advisory Committee (MIDAC) Slides  
- FDA Drug Safety Communication                                                                                                                                                                                                             | 12/19/2017   |
| TNF-alpha inhibitors             | Exposure in pregnancy                         | Level 1       | Drug Safety Label Change, Pregnancy and Lactation  
- Results  
- FDA Drug Safety Labeling Changes Page Enbrel (etanercept)                                                                                                                                                                                 | 12/21/2017   |
| None                             | Respiratory syncytial virus associated illness (RSV-AI) | Level 1       | Epidemiological assessment of RSV-AI and patterns of health care utilization to help inform development of novel RSV therapeutics  
- Results                                                                                                                                                                                                                                         | 1/25/2018    |
| Sinuva (mometasone furoate)      |  
- Nasal septal perforation  
- Cataracts  
- Glaucoma                  | Level 1       | Feasibility assessment of ARIA sufficiency to replace a Sponsor postmarketing requirement (PMR) safety study                                                                                                                                 | 2/5/2018     |
Serious Safety Issues Evaluated in ARIA by Sufficiency and Year*

* Preliminary data

N = 89
Overall: 49% sufficient
Serious Safety Issues Evaluated in ARIA by Sufficiency and Regulatory Phase*

* Preliminary data
Reasons for ARIA Insufficiency*

* Preliminary data
## ARIA Insufficiency Informs Development

### Select Examples

<table>
<thead>
<tr>
<th>Insufficiency Reason</th>
<th>Methods and Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mother infant linkage or analysis tool</td>
<td>New mother infant linkage and analysis tool - <em>anticipated October 2018</em></td>
</tr>
<tr>
<td>Inadequate sample size due to limited access to populations &gt;65 years</td>
<td>Integrate Medicare data - <em>released January 2018</em></td>
</tr>
<tr>
<td>Incomplete cause of death data</td>
<td>Facilitate linkage to NDI - <em>pending completion of ASPE-sponsored project</em></td>
</tr>
<tr>
<td>Need to improve performance of claims for outcome identification</td>
<td>Explore NLP, machine learning, and improve efficiency of chart review - <em>ongoing</em></td>
</tr>
</tbody>
</table>
Transparency and Access

• CDER notifying sponsors and posting all Level 2 inferential analyses
  – Integrating Sentinel into FDA Approval Letter
  – Listing L2 analyses on “Ongoing Assessments” page
  – Posting includes analysis parameters and results

• Support IMEDS to enable access to Sentinel infrastructure for external entities

• Will create a publicly available synthetic Medicare dataset, with fully worked L1 and L2 examples

• Public training on tools and methods
Overview

• Measuring progress through the lens of independent assessments
  – The growth we needed in 2015
  – The progress we achieved by 2017

• Review the system we’ve created and how we’re using it in CDER

• Why Having a System Matters
  – Makes large scale endeavors cost effective and faster
  – Makes small(er) scale endeavors more likely and more frequent
Launching a Multisite Study

1. Identify & Prioritize
2. Allocate Resources
3. Contracting (RFP, Award)
4. Study Design (Protocol)
5. Extract/QC Data (multiple sites)
6. Custom code (Write and QC)
7. Feasibility Analyses
8. Inferential Analysis
Multisite Study Within a System

- Identify & Prioritize
- Allocate Resources
- Contracting (RFP, Award)
- Study Design (Protocol)
- Extract/QC Data (multiple sites)
- Custom code (Write and QC)
- Feasibility Analyses
- Inferential Analysis

Scalable to many studies

Lower costs due to economies

Faster start up and greatly reduced time-to-completion
Makes Large Scale Endeavors Cost Effective and Faster

- Structural improvements capitalize upon existing postmarket safety infrastructure
  - Integration of Medicare data
  - Development of new signal detection tools

- **A unified common platform enables collaboration with other systems**
  - Adoption of Sentinel Common Data Model by CNODES (Canadian Network for Observational Drug Effect Studies)
  - Partnership with PCORnet

- **Enables expansion beyond postmarket safety**
FDA-Catalyst

• Under the 21st Century Cures Act the FDA is evaluating the use of real world evidence (RWE) to support the approval of a new indication for an approved drug
• The Office of Medical Policy is supporting demonstration projects to expand the potential utility of RWE
• Two key milestones supporting distributed pragmatic trials occurred in 2017
  – Using a mobile app, informed consent was obtained remotely and secondary electronic health data in Sentinel were supplemented with primary data from patients
  – The first of 80,000 intervention letters were mailed to members from multiple data partners as part of a large randomized trial
Makes Small(er) Scale Endeavors More Likely and More Frequent

• Address a wide variety of Agency needs without the need to marshal organizational support each time
  – Reduces activation energy of extending into novel areas
• Sentinel System supports many safety inquiries
  – Medication errors
  – Safe use recommendations and risk mitigation strategies
  – Biosimilars
  – Generic drugs
  – Pregnancy safety
  – Pediatrics
Summary

• Sentinel is a mature, semi-automated safety surveillance system that is distinctive in its use of parameterized, reusable analytic tools, combined with a continuously quality-checked multisite database

• Sentinel provides a single common platform to help meet FDA’s evidentiary needs in evaluating the safety of medical products after approval

• The challenge for FDA, Sentinel and its collaborators is to build upon the successes to date by continuing to advance postmarket safety through automation and innovation, while expanding to meet growing needs in other areas
Key Sentinel Achievements
Key Achievements in 2017
CBER Sentinel Program

Azadeh Shoaibi, Ph.D., M.H.S.
CBER Sentinel Lead
On behalf of the CBER Sentinel Central Team
February 7, 2018
CBER-Regulated Products: BIOLOGICS

- Vaccines (preventative and therapeutic)
- Blood (components and derived)
- Human Tissues and Cellular Products
- Gene Therapies
- Xenotransplantation Products
CBER Sentinel Program
Accomplishments

• Initiated development of a semi-automated national biovigilance program

• Supported regulatory decisions for biologics

• Improved transparency and governance
  – Established CBER Sentinel Advisory Committee

• Increased engagement with CBER product offices
  – Office of Vaccines Research and Review
  – Office of Blood Research and Review
  – Office of Tissue and Advanced Therapies
‘Better, Faster, Cheaper’

- Main priority of 2017:
  - Increase capacity
  - Decrease cost
  - Reduce data lag
  - Access Electronic Health Record (EHR) data sources
Summary of Accomplishments
January – December 2017

HARVARD PILGRIM HEALTHCARE INSTITUTE (HP)
## Summary of Accomplishments: (HP)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>41 Queries</strong></td>
<td>• Increased by 63% from 2016</td>
</tr>
<tr>
<td>(ARIA)</td>
<td></td>
</tr>
<tr>
<td><strong>10 Protocol-Based</strong></td>
<td>• Completed in 2017</td>
</tr>
<tr>
<td><strong>Activities</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Outreach</strong></td>
<td>• Conducted 2 CBER trainings</td>
</tr>
</tbody>
</table>
Query Types (HP)

<table>
<thead>
<tr>
<th>Query Type (ARIA)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive Analysis</td>
<td>37</td>
</tr>
<tr>
<td>Inferential Analysis</td>
<td>3</td>
</tr>
<tr>
<td>Sequential Inferential Analysis</td>
<td>1</td>
</tr>
</tbody>
</table>

Regulatory Decisions

– Geographic incidence of babesiosis
– Adverse events related to transfusion of leukoreduced blood
– Rate of transfusion in high risk populations (pregnant women, immunocompromised, elderly)
## Protocol-Based Activities (HP)

<table>
<thead>
<tr>
<th>Type</th>
<th>Regulatory Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infrastructure &amp; Methods Development (N = 6)</strong></td>
<td>Medical code management and code lookup for blood</td>
</tr>
<tr>
<td></td>
<td>Safety of vaccines in pregnancy (2)</td>
</tr>
<tr>
<td></td>
<td>Enhancement of signal detection method (TreeScan)</td>
</tr>
<tr>
<td></td>
<td>Quantitative bias analysis to determine chart review validation threshold</td>
</tr>
<tr>
<td></td>
<td>Vaccine effectiveness feasibility</td>
</tr>
<tr>
<td><strong>Product Assessments (N = 4)</strong></td>
<td>Safety of blood components and products (transfusion-related adverse events) (2)</td>
</tr>
<tr>
<td></td>
<td>Safety of HPV9 and influenza vaccines (2)</td>
</tr>
</tbody>
</table>
2 one-year contracts awarded in September 2017

IQVIA Institute (formerly QuintilesIMS)

OHDSI (Observational Health Data Sciences and Informatics) Collaborative
BEST Initiative: Objectives

1) Develop additional surveillance capabilities specifically required for biologics:
   - Access to EHR data sources

2) Utilize innovative methods such as natural language processing, machine learning, and artificial intelligence to mine unstructured data in EHR data sources
CBER Sentinel Program

- Harvard Pilgrim Healthcare Institute (HP)
- IQVIA/OHDSI (BEST)
Summary of Accomplishments

October – December 2017

BIOLOGICS EFFECTIVENESS AND SAFETY INITIATIVE (BEST)
IQVIA / OHDSI
# Data Partners: BEST

<table>
<thead>
<tr>
<th>Data Partner</th>
<th>Data* Type</th>
<th>Patient Records (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQVIA</td>
<td>Claims</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>400 Hospitals (Billing Data)</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Ambulatory Care (EHR)</td>
<td>44</td>
</tr>
<tr>
<td>Columbia University</td>
<td>EHR</td>
<td>5.5</td>
</tr>
<tr>
<td>Stanford University</td>
<td>EHR</td>
<td>2.3</td>
</tr>
<tr>
<td>Indiana University/Regenstrief Institute</td>
<td>EHR &amp; Claims</td>
<td>17</td>
</tr>
</tbody>
</table>

*Quarterly refresh into OMOP CDM
Tools: BEST

• Observational Health Data Sciences and Informatics (OHDSI) freely available tools

https://ohdsi.org/analytic-tools/

• Tools
  – Direct access for FDA staff and any other scientist
  – Automated generation of:
    • Protocols
    • Validated R packages
    • Figures, Tables
    • Draft manuscripts
Welcome to ATLAS.

ATLAS is an open source application developed for the analysis of patient level data and analytics.

Documentation

The ATLAS user guide can be found here.

Getting Started

Define a New Cohort

intend to study

Search the Vocabulary

data around the world
Research question

To compare the risk of [OHDSI estimation tutorial] Children with febrile seizure between [OHDSI estimation tutorial] Children with MMRV vaccine and [OHDSI estimation tutorial] Children with MMR vaccine and separate Varicella vaccine on same day, we will estimate the population-level effect of exposure on the rate of the outcome during the period from 7 days from cohort start date to 10 days from cohort start date.

Study Design:

This study will follow a retrospective, observational, comparative cohort design. We define ‘retrospective’ to mean the study will be conducted using data already collected prior to the start of the study. We define ‘observational’ to mean there is no intervention or treatment assignment imposed by the study. We define ‘cohort’ to mean a set of patients satisfying a one or more inclusion criteria for a duration of time. We define ‘comparative cohort design’ to mean the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of an outcome during a defined time period after cohort entry.

In this study, we compare [OHDSI estimation tutorial] Children with MMRV vaccine with [OHDSI estimation tutorial] Children with MMR vaccine and separate Varicella vaccine on same day for the rate of [OHDSI estimation tutorial] Children with febrile seizure from 7 days from cohort start date to 10 days from cohort start date.

The overall study population could be considered to be patients who entered either the target cohort or comparator cohort. Patients were excluded from consideration is they qualified for both the target cohort and comparator cohort at any time in their record.

The rate of outcomes among patients in the target and comparator cohorts is determined by counting the number of outcome occurrences of [OHDSI estimation tutorial] Children with febrile seizure during the time-at-risk of 7 days from cohort start date to 10 days from cohort start date.

Patients with [OHDSI estimation tutorial] Children with febrile seizure prior to target or comparator cohort entry were excluded from consideration.
Automated R Code Generation (BEST)

Population Level Effect Estimation

[OHDSI estimation tutorial]: MMRV vs MMR+V and risk of febrile seizure

Multi-Analysis Approach

Copy To Clipboard

```r
# Study: ----
# [OHDSI estimation tutorial]: MMRV vs MMR+V and
# risk of febrile seizure

# CohortMethod Installation & Load ----

# Uncomment to install CohortMethod
# install.packages("devtools")
# library(devtools)
# install_github("ohdsi/SqlRender")
# install_github("ohdsi/DatabaseConnector")
# install_github("ohdsi/OhdsiRTools")
```
Accomplishments: BEST

• Built a library consisting of multiple coding systems for blood exposure identification in claims and EHR databases
  – Queried ~4000 codes

• Incorporated ISBT-128 Coding System into the OMOP CDM
  • ~14,000 codes for blood and other products

• Conducted 3 training sessions for OBE staff
Accomplishments: BEST
Data and Infrastructure

1. Addition of EHR data sources
2. Use of a flexible and expandable CDM
3. Access to data refreshed quarterly
4. Direct access to advanced query tools
5. Use of innovative methods to identify and report blood transfusion-related AEs
6. Significant cost reduction
2 Requests for Information (RFI) FY2018

• 2 RFIs released in January 2018

• https://www.fbo.gov/spg/HHS/FDA/NCTR/FDA194037/listing.html

• https://www.fbo.gov/spg/HHS/FDA/NCTR/FDA194238/listing.html
FDA Public Meeting: Industry Day

- February 12, 2018
- FDA White Oak Campus
- [https://www.eventbrite.com/e/industry-day-2018-tickets-41093453626](https://www.eventbrite.com/e/industry-day-2018-tickets-41093453626)
Summary

• Major expansion and enhancement of biologics surveillance system
  – EHR data sources
  – Advanced automated tools
  – Shorter data lag
  – Flexible and expandable CDM
• Integration of Sentinel surveillance activities into the regulatory decision making process
• Make the program cost-effective and Sustainable
• Steps taken toward building the semi-automated national biovigilance system
Acknowledgements

• CBER Sentinel Central Team
  – Kinnera Chada, PhD
  – Joyce Obidi, PhD
  – Joann Gruber, PhD

• Office of Biostatistics and Epidemiology Staff

• Members of CBER product offices

• Harvard Pilgrim Health Care Institute
  – Data Partners
  – Collaborating scientists

• IQVIA Institute

• OHDSI collaborating scientists
  – Columbia University
  – Indiana University/Regenstrief Institute
  – Stanford University
  – Georgia Tech
  – UCLA
Key Sentinel Achievements

Join the conversation with #sentinelinitiative
Lunch Break
The Evolution of the Sentinel System: Evidence, Engagement, and Expansion
Device Evaluation of Use of Laparoscopic Power Morcellators Using Sentinel System

Allison O’Neill, PhD, MA
Epidemiologist
Center for Devices and Radiological Health (CDRH), FDA
Laparoscopic Procedures

Source: https://en.wikipedia.org/wiki/laparoscopy
Laparoscopic Power Morcellators (LPM)

- LPMs are a class II device used in laparoscopic procedures to cut tissue into smaller pieces, to facilitate removal of fibroid tissue.

Safety concern

• Uncontained intraperitoneal morcellation of uterine tissue which contains an unsuspected sarcoma (or other malignancy) may result in dissemination and implantation of malignant tissue and upstaging of malignancy.

• FDA estimate of prevalence of hidden uterine sarcoma:
  – 1 in 225 to 1 in 580 women undergoing surgery for uterine fibroids.
Immediately In Effect Guidance
(April 2014)

CONTRAINDICATION: Laparoscopic power morcellators are contraindicated in gynecologic surgery in which the tissue to be morcellated is known or suspected to contain malignancy.

CONTRAINDICATION: Laparoscopic power morcellators are contraindicated for removal of uterine tissue containing suspected fibroids in patients who are:

- peri- or post-menopausal, or
- candidates for en bloc tissue removal, for example, through the vagina or via a mini-laparotomy incision.

WARNING: Uterine tissue may contain unsuspected cancer. The use of laparoscopic power morcellators during fibroid surgery may spread cancer, and decrease the long-term survival of patients. This information should be shared with patients when considering surgery with the use of these devices.

Source:
FDA actions resulted in decrease in use of LPM. Did this result in fewer minimally invasive surgeries?

Table 3. Changes in Procedure Types (Pre- and Post-2014 FDA Actions)- Medical Literature

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Barron$^{50}$</th>
<th>Wright$^{51}$</th>
<th>Harris$^{52}$</th>
<th>Zaritsky$^{53}$</th>
<th>Ottarsdottir$^{54}$</th>
<th>Stentz$^{55}$</th>
<th>Pereira$^{56}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Procedures</td>
<td>14.3% → 20.1%</td>
<td>27.1% → 31.8%</td>
<td>22.9% → 24.6%</td>
<td>11.5% → 6.9%</td>
<td>19.0% → 29.0%</td>
<td>49.1% → 60.0%</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic Procedures</td>
<td></td>
<td>55.2% → 51.1%</td>
<td>66.3% → 69.7%</td>
<td>71.3% → 65.3%</td>
<td>50.9% → 40.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally Invasive Surgery Procedures</td>
<td>85.7% → 79.9%</td>
<td>59.7% → 56.2%</td>
<td></td>
<td>47.3% → 48.1%</td>
<td>5.6% → 2.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supracervical Hysterectomy – Lap</td>
<td>13.9% → 5.6%</td>
<td>11.0% → 4.5%</td>
<td></td>
<td>47.3% → 48.1%</td>
<td>5.6% → 2.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Hysterectomy</td>
<td>9.7% → 7.1%</td>
<td>21.9% → 24.3%</td>
<td>22.2% → 23.4%</td>
<td>5.6% → 2.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPM use</td>
<td>13.7% → 2.8%</td>
<td>11.4% → 0.02%</td>
<td></td>
<td>47.3% → 48.1%</td>
<td>5.6% → 2.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: FDA Updated Assessment of the Use of Laparoscopic Power Morcellators to Treat Uterine Fibroids (December 2017)

Study Questions

• Did use of morcellators decrease after FDA’s safety communication in 2014?
• Did proportion of laparoscopic hysterectomy and myomectomy procedures decrease after FDA’s safety communication in 2014?
Methods

• Level 1 query
• Exposure: HCPCS Level II code C1782, “Morcellator”
• Dates: January 1, 2008 – June 30, 2016
• Procedures: Laparoscopic, abdominal, vaginal hysterectomies or myomectomies (except radical procedures to remove cancer)
• Inclusion Criteria: Female, 6 months continuous enrollment, no previous hysterectomy
• Sample size:
  – 85,538,591 eligible members
  – 247,833,156 member-years
Percentage of Laparoscopic Procedures (with or without morcellation)
Discussion

• The use of LPMs in hysterectomy and myomectomy procedures drastically declined after FDA’s safety communication.

• The percentage of procedures performed laparoscopically experienced small decline and plateau, but a large decrease was not seen.

• 2017: FDA updated assessment confirms conclusions from 2014
  – Lit review
  – MDR
  – Sentinel data
Obstacles and Limitations

- Coding for medical devices vs. drugs
  - No NDC code; must rely on CPT/ICD
  - Consistency and detail of coding
Future Directions for CDRH & Sentinel

- More analyses and more advanced analyses
- UDI (Unique Device Identifier)
- NEST (National Evaluation System for health Technology): possible linkages
Conclusions

• Sentinel data represent a valuable opportunity to study real world use of certain devices.
• Despite limitations, analyses provided a look at real world data and the potential impact of FDA’s actions regarding one device.
• Future opportunities for CDRH and NEST
Acknowledgements

• Sentinel team (CDER & SOC)
• Signal management team
• CDRH/OSB/Division of Epidemiology

Thank you!
The Evolution of the Sentinel System: Evidence, Engagement, and Expansion

Join the conversation with #sentinelinitiative
IMPACT-Afib and Beyond: Using Sentinel as a Platform for Randomized Controlled Trials

Christopher Granger, MD
Duke Clinical Research Institute

(NIH Collaboratory Grand Rounds, January 5, 2018. IMPACT-AFib: An 80,000 Person Randomized Trial Using the Sentinel Initiative Platform)
MINI-SENTINEL and CLINICAL TRIALS TRANSFORMATION INITIATIVE
DEVELOPING APPROACHES TO CONDUCTING RANDOMIZED TRIALS USING THE
MINI-SENTINEL DISTRIBUTED DATABASE
February 28, 2014
FDA-Catalyst: IMPACT-AFib randomized trial

Implementation of a randomized controlled trial to improve treatment with oral Anticoagulants in patients with Atrial Fibrillation

• Direct mailer to health plan members with AFib, high risk for stroke and no oral anticoagulant (OAC) treatment, and to their providers, to encourage use of OACs
IMPACT-Afib Workgroup

Duke Clinical Research Institute
Department of Population Medicine
Harvard Medical School
Harvard Pilgrim Health Care Institute

Patient representative

FDA
U.S. Food & Drug Administration

Clinical Trials Transformation Initiative

IMPACT-AFib
What is Atrial Fibrillation and How Does it Cause Stroke?
# Rates of Anticoagulation for Atrial Fibrillation – Preliminary Sentinel Data

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially eligible members (Aetna, Humana, Harvard Pilgrim)</td>
<td>16.2 million</td>
</tr>
<tr>
<td>Patients with &gt;1 AF diagnosis</td>
<td>231,696 (1.4% of all members)</td>
</tr>
<tr>
<td>AF pts with CHA$_2$DS$_2$-VASc ≥ 2</td>
<td>201,882 (87% of AF patients)</td>
</tr>
<tr>
<td>Patients with at least one oral anticoagulation fill</td>
<td>105,256 (52% of AF patients with CHA$_2$DS$_2$-VASc ≥ 2)</td>
</tr>
<tr>
<td>Proportion of days covered by anticoagulation in AF patients</td>
<td>32%</td>
</tr>
</tbody>
</table>

*Pokorney S et al. Am College of Cardiol 2016*
Interventions (including patient education) can be effective at increasing the proportion of patients with Afib and risk for stroke who are treated with oral anticoagulation.

A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial

Dragos Vinereanu, Renato D Lopes, M Cecilia Bahit, Denis Xavier, Jie Jiang, Hussein R Al-Khalidi, Wensheng He, Ying Xian, Andrea O Ciobanu, Deepak Y Kamath, Kathleen A Fox, Meena P Rao, Sean D Pokorney, Otavio Berwanger, Carlos Tajer, Pedro G M de Barros e Silva, Mayme L Roettig, Yong Huo, Christopher B Granger, on behalf of the IMPACT-AF investigators*

The Lancet (published online August 28 2017)
**FDA-Catalyst: IMPACT-AFib Randomized Trial**

**Patients**
- Atrial fibrillation (AF) (≥ 2 claims)
- CHADS-VASc ≥ 2
- No admission for bleeding in prior 6 months
- No anticoagulant for past year

**Randomize**
- ~ 80,000 patients from 5 large US health plans
- Aim to increase the use of oral anticoagulation (OAC) among patients with AF and risk of stroke

**Control**

**Patient (and provider) level intervention**

**Primary comparison**: difference in proportion of patients initiated on OAC over one year

**Secondary outcomes**: admissions for stroke; number of patients on OAC at end of one year; days on OAC; admissions for bleeding; deaths

ClinicalTrials.gov Identifier: NCT03259373
Intervention Materials

PATIENTS

• Letter from health plan
• Patient brochure – information on AF and OACs
• Patient pocket card – designed to facilitate conversation between patient and provider

PROVIDERS

• Letter from health plan
• Provider enclosure – myths and facts on OACs
• Response mailer – providers to share feedback
Early Intervention Launch

Patients Contacted via Mailing

25-Sep-17 25-Oct-17 25-Nov-17 25-Dec-17
Early intervention, not on treatment

36% of patients were not on treatment at time of randomization.
Acknowledgements

- **Aetna**: Cheryl Walraven, Annemarie Kline, Daniel Knecht
- **Clinical Trials Transformation Initiative**: Jennifer Goldsack
- **Duke Clinical Research Institute**: Hussein Al-Khalidi, Wensheng He, Emily O’Brien, Jennifer Rymer, Sana Al-Khatib
- **DPM/HPHCI**: Crystal Garcia, Robert Jin, Hana Lipowicz
- **HealthCore**: Kevin Haynes, Lauren Parlett
- **Humana**: Vinit Nair, Thomas Harkins, Yunping Zhou
- **Optum**: Nancy Lin
- **Patient Representative**: Debbe McCall
- **U.S Food & Drug Administration**: Jacqueline Corrigan-Curay, Dianne Paraoan, David Martin, Melissa Robb, Patrick Archdeacon
Conclusions

• The IMPACT-Afib team has shown that it is possible to conduct an efficient, large pragmatic RCT using the Sentinel platform, addressing a critical health issue

• Now that we know it can be done, it is important to explore other opportunities to do further randomized trials using Sentinel.
Leveraging IMPACT-Afib Experience for Further Clinical Trial Opportunities

• Low risk, simple interventions (like patient or provider education)
• Large gaps in care, large potential to improve important outcomes
• Avoiding need for patient consent has been an essential element to IMPACT-Afib
• Some possible clinical gaps to address
  – Statin intolerance
  – Under treatment of diabetes with proven treatments to prevent cardiovascular events
The Evolution of the Sentinel System: Evidence, Engagement, and Expansion
CANADIAN NETWORK FOR OBSERVATIONAL DRUG EFFECT STUDIES (CNODES)

CNODES Sentinel Common Data Model: Pilot Project

Robert Platt
FDA Sentinel Initiative Public Workshop
February 7, 2018
# CNODES funding and investigators

Canadian Network for Observational Drug Effect Studies (CNODES), a collaborating center of the Drug Safety and Effectiveness Network (DSEN), is funded by the Canadian Institutes of Health Research (CIHR, Grant #DSE – 146021).

## CNODES INVESTIGATORS

<table>
<thead>
<tr>
<th>Region</th>
<th>Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Executive</strong></td>
<td>Samy Suissa (NPI*), Robert Platt</td>
</tr>
<tr>
<td><strong>British Columbia</strong></td>
<td>Colin Dormuth</td>
</tr>
<tr>
<td><strong>Alberta</strong></td>
<td>Brenda Hemmelgarn</td>
</tr>
<tr>
<td><strong>Saskatchewan</strong></td>
<td>Gary Teare</td>
</tr>
<tr>
<td><strong>Manitoba</strong></td>
<td>Patricia Caetano, Dan Chateau</td>
</tr>
<tr>
<td><strong>Ontario</strong></td>
<td>David Henry, Michael Paterson</td>
</tr>
<tr>
<td><strong>Québec</strong></td>
<td>Jacques LeLorier</td>
</tr>
<tr>
<td><strong>Atlantic (NB, NL, NS, PEI)</strong></td>
<td>Adrian Levy, Ingrid Sketris</td>
</tr>
<tr>
<td><strong>UK CPRD</strong></td>
<td>Pierre Ernst, Kristian Filion</td>
</tr>
</tbody>
</table>

*Nominated Principal Investigator*
**CNODES Processes**

- Safety queries from stakeholders (e.g., Health Canada)
- Protocol development/query refinement
- Statistical plan development and testing
- SAP implemented on local data
- Results lodged at coordinating centre and meta-analyzed
## Product

### High-Potency Statins and Diabetes

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Lower Potency Cases</th>
<th>Lower Potency Controls</th>
<th>Higher Potency Cases</th>
<th>Higher Potency Controls</th>
<th>Weight</th>
<th>Rate Ratio IV, Fixed, 95% CI</th>
<th>Rate Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>68</td>
<td>531</td>
<td>90</td>
<td>944</td>
<td>5.2%</td>
<td>0.66 [0.44, 0.98]</td>
<td></td>
</tr>
<tr>
<td>CPRD</td>
<td>103</td>
<td>1,064</td>
<td>247</td>
<td>2,266</td>
<td>9.2%</td>
<td>1.17 [0.87, 1.57]</td>
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</tr>
<tr>
<td>Manitoba</td>
<td>47</td>
<td>447</td>
<td>170</td>
<td>1,514</td>
<td>5.2%</td>
<td>1.27 [0.85, 1.88]</td>
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<tr>
<td>Marketscan</td>
<td>180</td>
<td>1,853</td>
<td>502</td>
<td>4,652</td>
<td>25.3%</td>
<td>1.12 [0.94, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>18</td>
<td>125</td>
<td>23</td>
<td>216</td>
<td>1.3%</td>
<td>0.54 [0.24, 1.21]</td>
<td></td>
</tr>
<tr>
<td>Ontario</td>
<td>236</td>
<td>2,658</td>
<td>675</td>
<td>6,196</td>
<td>26.5%</td>
<td>1.29 [1.08, 1.53]</td>
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</tr>
<tr>
<td>Quebec</td>
<td>260</td>
<td>2,775</td>
<td>507</td>
<td>4,681</td>
<td>23.1%</td>
<td>1.21 [1.00, 1.46]</td>
<td></td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>42</td>
<td>378</td>
<td>188</td>
<td>1,585</td>
<td>4.3%</td>
<td>1.04 [0.67, 1.61]</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>954</td>
<td>9,831</td>
<td>2,402</td>
<td>22,054</td>
<td>100.0%</td>
<td>1.15 [1.05, 1.26]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 13.32, df = 7 (P = 0.06); I² = 47%
Test for overall effect: Z = 3.00 (P = 0.003)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Lower Potency Cases</th>
<th>Lower Potency Controls</th>
<th>Higher Potency Cases</th>
<th>Higher Potency Controls</th>
<th>Weight</th>
<th>Rate Ratio IV, Fixed, 95% CI</th>
<th>Rate Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>26</td>
<td>159</td>
<td>31</td>
<td>306</td>
<td>6.3%</td>
<td>0.57 [0.30, 1.07]</td>
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<tr>
<td>CPRD</td>
<td>30</td>
<td>282</td>
<td>50</td>
<td>495</td>
<td>7.9%</td>
<td>0.96 [0.55, 1.69]</td>
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<tr>
<td>Manitoba</td>
<td>9</td>
<td>113</td>
<td>52</td>
<td>425</td>
<td>3.9%</td>
<td>1.89 [0.85, 4.20]</td>
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<tr>
<td>Marketscan</td>
<td>86</td>
<td>773</td>
<td>195</td>
<td>1,452</td>
<td>33.0%</td>
<td>1.29 [0.98, 1.70]</td>
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<tr>
<td>Nova Scotia</td>
<td>9</td>
<td>46</td>
<td>1</td>
<td>56</td>
<td>1.1%</td>
<td>0.20 [0.04, 0.91]</td>
<td></td>
</tr>
<tr>
<td>Ontario</td>
<td>62</td>
<td>758</td>
<td>197</td>
<td>1,696</td>
<td>23.8%</td>
<td>1.52 [1.10, 2.11]</td>
<td></td>
</tr>
<tr>
<td>Quebec</td>
<td>57</td>
<td>550</td>
<td>123</td>
<td>959</td>
<td>18.7%</td>
<td>1.40 [0.97, 2.02]</td>
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</tr>
<tr>
<td>Saskatchewan</td>
<td>17</td>
<td>137</td>
<td>69</td>
<td>442</td>
<td>5.3%</td>
<td>1.31 [0.66, 2.60]</td>
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</tr>
<tr>
<td>Subtotal</td>
<td>296</td>
<td>2,818</td>
<td>720</td>
<td>5,831</td>
<td>100.0%</td>
<td>1.26 [1.07, 1.47]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 15.22, df = 7 (P = 0.03); I² = 54%
Test for overall effect: Z = 2.84 (P = 0.004)

Dormuth et al, BMJ 2014;348:g3244
Typical Timeline

High-Potency Statins and Diabetes

- **CNODES receives approval by DSEN CO**
  - June 2012

- **Project team formed**
  - Sep. 2012

- **First draft of scientific protocol**

- **Scientific protocol finalized, submitted**
  - Jan. 2013

- **Project team meeting to discuss SAP**
  - May 2014

- **First draft of statistical analysis plan (SAP)**

- **SAP pilot tested, refined, finalized**

- **8 studies + meta-analysis**

- **Presentation of results to Query Author (followed by full report, manuscript, published March 2014)**

- **June 2012**
- **Sep. 2012**
- **Oct. 2012**
- **Jan. 2013**
- **May 2014**
Advantages of CNODES’ Current Approach to Distributed Analytics

• Analytical flexibility
  • Study design, data sources, statistical methods

• Capacity building
  • Local data repository development
  • Analytical and methods expertise

• Policy relevance
  • Query author actively involved in question refinement and protocol development
Main Challenge of CNODES Approach

- **Timeliness**
  - Data access
    - Improved at some sites, but continues to be a challenge at others (BC, QC)
  - Efficiency in protocol development
    - Reference documents and tools
    - Standardization
      - Study cohort and covariate definitions, exposures (predefined ATC and DIN extract protocols), outcomes (ICD code library)
      - Maximum use of standardized, tested SAS code, macros
CNODES Common Data Model Pilot Project

- Launch April 2017
- Initially, 3 sites with prompt data access: SK, MB, ON
  - Anticipated query response times: 2-3 weeks
  - NS coming on line
  - Other provinces in planning stage
- CNODES CDM tables
  - Enrollment, Demographic, Dispensing, Encounter, Diagnosis, Procedure, Death (+ Location)
- Using Sentinel CDM structure
- Demonstration queries and operational structure, process
  - Determined with input from Advisory Committee chaired by DSEN Coordinating Office and members, including Health Canada and Canadian Institute for Health Information (CIHI)
Progress to Date

• Table conversions complete
  • Generally straightforward process
  • Minor tweaks/decisions to be made
    • Fields we don’t use but are necessary for query tools
    • Field digit lengths (e.g., ICD codes) need standardizing
• Advisory committee met to prioritize first queries
  • One each of: simple drug utilization, utilization within defined cohort, compute outcome rates among users
Validation

• Work in progress

• Formal:
  • Implement Sentinel standard QC tools
  • Initial CDM queries will be run 3 ways
    • CDM
    • CNODES “standard” tools
    • CIHI for utilization

• Informal:
  • Collaboration with Sentinel
  • Replicate early CNODES study using same (MarketScan) data and CDM
Why Sentinel CDM?

- Pragmatic
  - Close relationship with Sentinel team
  - Demonstrated process working with regulator
  - Close mapping of their core data tables/elements to our core admin data sources
  - Well-established data QA processes and procedures
  - Potential for cross-jurisdiction collaborations (Canada/US/EMA)
**Why Sentinel CDM?**

- **Technical**
  - Alignment and ready availability of well tested query tools (SAS programs) of proven value to a regulator
  - Data granularity: no recoding/collapsing of data (“minimal mapping”)
    - Allows different definitions of key exposures and events across projects
    - Data relatively homogeneous, so no need for common vocabulary a la OMOP
  - Scalability with other data sources, e.g. in Manitoba where other data may be easily brought on board
Future Directions

- CNODES CDM should facilitate rapid responses to simple queries from HC
- Should enable cross-jurisdiction collaborations
  - FDA, HC can specify common studies and get rapid results
- Complementary studies:
  - US larger population
  - Canada longer average follow-up
Concluding Thoughts

• Sentinel data structures and analytic tools are easy to implement
  • Possibility for Sentinel/CNODES (FDA/HC) collaborations seen as a strength
• CDM will advance response times for some queries
  • Utilization/combinations/event rates
  • Will not eliminate need for CNODES standard tools (signal evaluation)
Thank you
Visit us at www.cnodes.ca
The Evolution of the Sentinel System: Evidence, Engagement, and Expansion

Join the conversation with #sentinelinitiative
Use of Mini-Sentinel Tools to Assess Cardiovascular Outcomes with Treatment of Overactive Bladder

Beth L. Nordstrom, PhD

Tenth Annual Sentinel Initiative Public Workshop
February 7, 2018
Acknowledgements

- This work was conducted in collaboration with:
  - Jason Simeone, Evidera
  - Samuel Huse, Evidera
  - Kwame Appenteng, Astellas
  - Milbhor D’Silva, Astellas
Introduction

- Sentinel (and earlier Mini-Sentinel) tools have been made available for public use:
  - Study protocols
  - Programming modules

- Properly formatted claims or electronic medical record (EMR) data can easily be run through a Sentinel analysis

- A 2014 Mini-Sentinel project examined the risk of acute myocardial infarction (AMI) and stroke with overactive bladder (OAB) treatment (mirabegron vs. oxybutynin)

- Our study replicated the Mini-Sentinel analysis in other databases
  - Truven MarketScan claims
  - IMS PharMetrics claims
Approach

01 Transform data extracts into common data model

02 Create lists of NDC drug codes

03 Build input configuration files

04 Run through programming modules for cohort selection and analysis

05 Produce additional descriptive tables and reformat output

06 Interpret results and write report
Cohort Selection

All mirabegron and oxybutynin users from July 2012 to June 2015 (MarketScan)
July 2012 to September 2015 (PharMetrics)

Exclude persons:
- Under 20 years old
- Initiating more than 1 OAB drug on the same day
- History of the outcome within 30 days prior to cohort entry

Primary Analysis
New Users (naïve to all OAB treatment)
- PharMetrics AMI (N= Mira: 12,429; Oxy: 61,548)
- PharMetrics Stroke (N= Mira: 12,379; Oxy: 61,411)
- MarketScan AMI (N= Mira: 17,182; Oxy: 63,962)
- MarketScan Stroke (N= Mira: 17,138; Oxy: 63,835)

Secondary Analysis
Non-new Users (prior use of OAB drug):
- PharMetrics AMI (N= Mira: 9,025; Oxy: 7,899)
- PharMetrics Stroke (N= Mira: 8,959; Oxy: 7,872)
- MarketScan AMI (N= Mira: 15,252; Oxy: 11,374)
- MarketScan Stroke (N= Mira: 15,173; Oxy: 11,314)
Statistical Analysis

- Analyses conducted by PROMPT 2 module:
  - Propensity score models of mirabegron and oxybutynin-exposed patients in each analysis
  - Matching by propensity score at 1:1 ratio
  - Counts of patients in denominator and patients with events
  - Person-time in denominators
  - Risk, risk difference, and rate difference
  - Cox regression models with output of hazard ratios and 95% confidence intervals

- Separate analyses needed to produce descriptive tables:
  - Pre- and post-matching
    - Demographics
    - Comorbidities
    - Baseline resource utilization
## Selected Baseline Characteristics for New User Analyses of AMI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-matching Mirabegron</th>
<th>Pre-matching Oxybutynin</th>
<th>Post-matching Mirabegron</th>
<th>Post-matching Oxybutynin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMS PharMetrics (N)</strong></td>
<td>12,429</td>
<td>61,548</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>55.6 (12.3)</td>
<td>52.9 (13.3)</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>Female gender</td>
<td>73.8%</td>
<td>64.0%</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>Mean (SD) Charlson-Elixhauser Score</td>
<td>0.4 (1.3)</td>
<td>0.5 (1.6)</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>Mean (SD) inpatient hospitalizations</td>
<td>0.6 (3.6)</td>
<td>1.3 (5.8)</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td><strong>Truven MarketScan (N)</strong></td>
<td>17,182</td>
<td>63,962</td>
<td>16,452</td>
<td>16,452</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>64.7 (15.2)</td>
<td>59.7 (16.2)</td>
<td>64.5 (15.2)</td>
<td>62.0 (16.1)</td>
</tr>
<tr>
<td>Female gender</td>
<td>68.0%</td>
<td>63.2%</td>
<td>67.9%</td>
<td>68.3%</td>
</tr>
<tr>
<td>Mean (SD) Charlson-Elixhauser Score</td>
<td>0.6 (1.5)</td>
<td>0.7 (1.8)</td>
<td>0.6 (1.5)</td>
<td>0.6 (1.6)</td>
</tr>
<tr>
<td>Mean (SD) inpatient hospitalizations</td>
<td>0.4 (2.1)</td>
<td>0.6 (2.5)</td>
<td>0.4 (2.1)</td>
<td>0.4 (1.7)</td>
</tr>
</tbody>
</table>

*Note: The propensity score matching model for the AMI analysis in IMS PharMetrics did not converge, no post-matching results are presented.

N/A = not applicable; SD = standard deviation

In general, patterns were also similar for stroke and non-new user analyses
Forest Plot of AMI Cox Models

**PharMetrics, new user analysis**
- Less likely to have AMI following mirabegron use: HR 0.67 [0.33, 1.37]
- More likely to have AMI following mirabegron use: HR 0.57 [0.17, 1.95]

**MarketScan, new user analysis**
- Less likely to have AMI following mirabegron use: HR 0.80 [0.32, 2.03]
- More likely to have AMI following mirabegron use: HR 2.00 [0.37, 10.92]

**PharMetrics, non-new user analysis**
- Less likely to have AMI following mirabegron use: HR 0.67 [0.33, 1.37]
- More likely to have AMI following mirabegron use: HR 0.57 [0.17, 1.95]

**MarketScan, non-new user analysis**
- Less likely to have AMI following mirabegron use: HR 0.80 [0.32, 2.03]
- More likely to have AMI following mirabegron use: HR 2.00 [0.37, 10.92]
Forest Plot of Stroke Cox Models

PharMetrics, new user analysis
- Less likely to have stroke following mirabegron use: HR 0.62 [0.34, 1.13]
- More likely to have stroke following mirabegron use: HR 0.69 [0.30, 1.62]

MarketScan, new user analysis
- Less likely to have stroke following mirabegron use: HR 0.25 [0.03, 2.24]
- More likely to have stroke following mirabegron use: HR 0.92 [0.40, 2.08]

PharMetrics, non-new user analysis

MarketScan, non-new user analysis

Hazard ratios and 95% confidence intervals
Benefits and Limitations of Mini-Sentinel Tools

**Benefits**

- Much faster than custom analysis
- Study design and methods have undergone careful planning/review
- Programs have been fully validated
- Some study options customizable

**Limitations**

- Unable to adapt programming to fit data
- Some elements not fully specified (e.g., NDC lists)
- Black box programming with long run time
- May need custom programming for desired output
Potential Applications of Sentinel Tools

**Share Findings**
- Establish a repository for findings

**Change Drugs**
- Different drug cohorts, same analyses

**Change Outcomes**
- Same cohort, different outcomes

**Direct Replication**
- Same analysis, different data

**Sensitivity Analysis**
- Similar analysis, different definitions

**Subgroup Analysis**
- Divide cohort and rerun analyses
Thank you!

Beth L. Nordstrom, PhD, MPH
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The Evolution of the Sentinel System: Evidence, Engagement, and Expansion
Venous Thromboembolism in Rheumatoid Arthritis

Contextualization of Safety using IMEDS Distributed Data

Sentinel Public Workshop
February 7, 2018

Claudia A. Salinas, PhD
Kenneth Hornbuckle, PhD
Lynn Reynolds, BPharm

Global Patient Safety
Eli Lilly and Company
Contextualizing the Safety Profile of Patients with RA

♦ **Motivation:** Safety profile of the underlying population of patients with rheumatoid arthritis

♦ **Query Objective:** To estimate the incidence of venous thromboembolism (VTE) among patients treated for rheumatoid arthritis (RA) in the IMEDS Distributed Database

  • Additional queries for pulmonary embolism (PE) and deep vein thrombosis (DVT)
Data Source for Non-FDA Researchers

Innovation in medical evidence development and surveillance
IMEDS Distributed Data

**Pharmaceutical companies**
(Non-FDA researchers)

The Sentinel System includes the surveillance data available to FDA for national pharmacovigilance of postmarketed products.

Innovation in Medical Evidence Development and Surveillance (IMEDS) is the research data subset of the Sentinel data.

IMEDS Distributed Database

Harvard Pilgrim Healthcare Institute

Sentinel data partners
Query Members

♦ Reagan-Udall Foundation (RUF)
♦ FDA Liaison to IMEDS
♦ Eli Lilly and Company
♦ Data Partners (n=5 partners)
♦ IMEDS Analytic Center: Harvard Pilgrim Health Care Institute
Contextualizing the Safety Profile of Patients with RA

**STUDY POPULATION**: Patients diagnosed with RA who were new users of a DMARD (Oct2010 – Sept2015)

- 75 million in IMEDS data (5 data partners joined) → ~69,000 RA *treatment episodes* in the largest group
Developing the Query

1. Contracting from an industry perspective (chicken or the egg?)
2. Understanding the Level 1 Module and the Specifications
3. Testing the Specifications
4. Final Specifications sent to Data Partners
5. Query Results
   - Data partners review
   - Results delivered to us by RUF
## Specifications

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Care Setting</th>
<th>Incident w/ Respect to</th>
<th>Incidence Care Setting</th>
<th>Washout (Days)</th>
<th>Cohort Definition</th>
<th>Episode Gap</th>
<th>Episode Extension Period</th>
<th>Censor due to Death</th>
<th>Censor due to User Defined</th>
<th>Censor due to Query End</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Pre-Existing Condition</th>
<th>Care Setting</th>
<th>Include/Exclude</th>
<th>Lookback Period</th>
<th>Outcome</th>
<th>Care Setting</th>
<th>Incidence w/ respect to</th>
<th>Incidence Care Setting</th>
<th>Washout (Days)</th>
<th>Black Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>cDMARDS$^{12}$</td>
<td>Any</td>
<td>cDMARDS</td>
<td>Any</td>
<td>365</td>
<td><em>Include the first valid exposure per patient</em></td>
<td>37</td>
<td>37</td>
<td>Yes</td>
<td>Yes</td>
<td><strong>BDMARDS, JAK inhibitor</strong></td>
<td><strong>RA diagnosis</strong></td>
<td>AV, IP, ED</td>
<td>Include 2 within (7,965) of each other</td>
<td><strong>-365, 0</strong></td>
<td>VTE (PE OR DVT) AND anticoagulants (within 0.31 of VTE)</td>
<td>AV</td>
<td>PE or DVT</td>
<td>Any</td>
<td>365</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>bDMARDS, JAK inhibitors</td>
<td>Any</td>
<td>Exclude</td>
<td>-365, 0</td>
<td>VTE (PE OR DVT)</td>
<td>IP or ED</td>
<td>PE or DVT</td>
<td>Any</td>
<td>365</td>
<td>1</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All RA medications (NDC+PX)$^{2}$</td>
<td>Any</td>
<td>All RA medications (NDC+PX)</td>
<td>Any</td>
<td>0</td>
<td><em>Include the first valid exposure per patient</em></td>
<td>46</td>
<td>46</td>
<td>Yes</td>
<td>Yes</td>
<td><strong>RA diagnosis</strong></td>
<td><strong>AV, IP, ED</strong></td>
<td>Include 2 within (7,965) of each other</td>
<td><strong>-365, 0</strong></td>
<td>VTE (PE OR DVT) AND anticoagulants (within 0.31 of VTE)</td>
<td>AV</td>
<td>PE or DVT</td>
<td>Any</td>
<td>365</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE (PE OR DVT)</td>
<td>IP or ED</td>
<td>PE or DVT</td>
<td>Any</td>
<td>365</td>
<td>1</td>
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<td></td>
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</table>
Case Definition

1. Venous thromboembolism (VTE)
   **Compound definition:**
   a. Inpatient diagnoses based on ICD-9-CM diagnostic codes
   b. Outpatient diagnoses based on ICD-9-CM diagnostic codes + anticoagulant dispensing within 31 days of diagnosis

2. Pulmonary embolism (PE) or Deep Vein Thrombosis (DVT)
   • Based on diagnostic codes
# Results: Incidence of VTE Among RA Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>New User (n)</th>
<th>Events (n)</th>
<th>Years at Risk</th>
<th>Incidence rate per 100 PY (95% CI)</th>
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<tbody>
<tr>
<td>cDMARDs</td>
<td>19,001</td>
<td>197</td>
<td>13,184.0</td>
<td>1.49 (1.30, 1.71)</td>
</tr>
<tr>
<td>bDMARDs</td>
<td>19,146</td>
<td>147</td>
<td>15,053.0</td>
<td>0.98 (0.83, 1.14)</td>
</tr>
</tbody>
</table>

Note: DMARD = Disease-Modifying Anti-Rheumatic Drug; b = biologic; c = conventional
### Results: Incidence of VTE Among RA Patients, by Age

<table>
<thead>
<tr>
<th>Treatment, by age (years)</th>
<th>New Users</th>
<th>Events (n)</th>
<th>Years at Risk</th>
<th>Incidence rate per 100 PY (95% CI)</th>
</tr>
</thead>
<tbody>
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<td><strong>cDMARDs</strong></td>
<td>19,001</td>
<td>197</td>
<td>13,184.0</td>
<td>1.49 (1.30, 1.71)</td>
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<tr>
<td>18-49</td>
<td>22.0%</td>
<td>11</td>
<td></td>
<td>0.46 (0.23, 0.83)</td>
</tr>
<tr>
<td>50-59</td>
<td>26.5%</td>
<td>21</td>
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<td>0.65 (0.40, 0.99)</td>
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<tr>
<td>60-64</td>
<td>13.4%</td>
<td>18</td>
<td></td>
<td>1.10 (0.65, 1.74)</td>
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<tr>
<td>65+</td>
<td>38.1%</td>
<td>147</td>
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<td>2.48 (2.10, 2.90)</td>
</tr>
<tr>
<td><strong>bDMARDs</strong></td>
<td>19,146</td>
<td>147</td>
<td>15,053.0</td>
<td>0.98 (0.83, 1.14)</td>
</tr>
<tr>
<td>18-49</td>
<td>30.5%</td>
<td>33</td>
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<td>0.69 (0.48, 0.95)</td>
</tr>
<tr>
<td>50-59</td>
<td>32.4%</td>
<td>35</td>
<td></td>
<td>0.65 (0.46, 0.90)</td>
</tr>
<tr>
<td>60-64</td>
<td>13.9%</td>
<td>19</td>
<td></td>
<td>0.94 (0.56, 1.46)</td>
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<tr>
<td>65+</td>
<td>23.3%</td>
<td>60</td>
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<td>2.11 (1.63, 2.70)</td>
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Future directions

♦ For this query:
  • External presentation and publication
  • Work to validate the case definition is ongoing
  • Replication of query by Lilly, using custom programming to allow further investigation including sensitivity analyses

♦ For IMEDS:
  • Expand access and public awareness of IMEDS Access Program
  • Expand to other Sentinel data partners and other data sources, including primary data collection
  • Expand to other non-FDA stakeholders, e.g., academia, non-profit research
Acknowledgments

♦ Contributing data partners
♦ Reagan-Udall Foundation
♦ FDA Sentinel Director
♦ Harvard Pilgrim Health Care Institute

All the FDA, academic, and industry partners who made Sentinel & IMEDS possible
The Evolution of the Sentinel System: Evidence, Engagement, and Expansion

Join the conversation with #sentinelinitiative
Break
A Look Into the Future of the Sentinel System

Join the conversation with #sentinelinitiative
The CBER Biologics Effectiveness and Safety (BEST) Sentinel Initiative: Development of New and Innovative Methods for Automated Reporting for CBER-Regulated Biological Products

Alan E Williams, Ph.D.
Associate Director for Regulatory Affairs
Office of Biostatistics and Epidemiology, CBER, FDA

10th Annual Sentinel Initiative Public Workshop
“A Look into the Future of the Sentinel System”
February 7, 2018
Using innovative new approaches and electronic health records (EHR) to accomplish more effective and efficient post-market surveillance and public health impact

– Blood Component Hemovigilance Example
  • Improved Exposure Data
  • Improved Outcome Data

– Improved benchmarking
– Improved intervention design and evaluation
Major Blood Components for Transfusion

Red Blood Cells   (12.5 million units/2015) (CDC NBCUS)
Platelets        (2.4 million units/2015)
Plasma           (3.7 million units/2015)

Manufacturing steps may include, automated component collection, leukoreduction, irradiation, pathogen reduction, specialty testing such as anti-CMV, HLA markers, etc

(Transfusable blood components are distinct from plasma-derived blood products (e.g. IGIV, Factor VIII, albumin, etc), which are pharmaceuticals manufactured from human plasma and by recombinant processes)
Hemovigilance in the United States

- Fourteen blood component recipient adverse events (AE) (aka reactions) are recognized

- Hemolytic, non-hemolytic, infectious, unclassified

- Severe adverse outcomes are uncommon, but (rarely) may be fatal

- International Society for Blood Transfusion (ISBT) Working Party (WP) on Haemovigilance has promulgated transfusion reaction case definitions
  
  (ISBT Science Series (2014)9,91–97)
US Hemovigilance Characteristics

Although there have been devoted efforts at many levels, hemovigilance in the US has been relatively difficult:

- Absence of a national health system to facilitate data collection
- Small industry, limited resources
- Transfusion recipients often have serious underlying medical conditions which complicate post-transfusion (PT) AE diagnosis
- Each transfused component is a “lot” – biological characteristics can and do vary
- Availability and validity of transfusion exposure and PT AE outcome data for individual patients has been challenging
The Sentinel BEST program: Improved Quality and Availability of Blood Transfusion Exposure Data

• Sentinel BEST currently working to electronically capture ISBT-128 blood component labeling codes for transfused products instead of transfusion billing codes

• Machine readable (21 CFR 606.121(c)(13)(ii-iii))

• Accurate and detailed descriptions of transfused components

• ISBT-128 labeling codes may need to be accessed and linked from the blood bank database

• Incorporated into OMOP Common Data Model (CDM)
Sentinel BEST Critical Role of the OMOP Common Data Model

- In the absence of EHR interoperability, a CDM provides a critical common data platform.

- OMOP CDM interoperability (mapping) across different code languages (e.g. SNOMED, MedDRA).

- For advanced EHR analytics, the OMOP CDM can efficiently incorporate a range of new coded variables, as well as provide very rapid output for iterative processing.

- Supports report generation and semi-automated electronic ICSR transmission to FDA.
Sentinel BEST: Improved quality and Availability of Blood Transfusion Adverse Event Data

Working to optimize the identification of blood transfusion-related adverse events (outcomes) among blood component recipients using electronic health records and a combination of diagnostic codes, condition codes, and data mining from chart text

Why needed?
Sentinel BEST: Improved quality and Availability of Blood Transfusion Adverse Event Data

• The quality of blood transfusion outcome data can be improved and should benefit from new and innovative approaches

• A recent data validity study by the AABB (formerly American Association of Blood Banks) demonstrates this
CDC/AABB National Health Safety Network (NHSN) Hemovigilance Program

- Established ~2010 as a voluntary collaborative effort between the Centers for Disease Control and Prevention, AABB, and participating hospitals
- Post-transfusion surveillance design based on ISBT Hemovigilance WP definitions
- Transfusion recipient denominator data reported
- ~220 US hospitals currently enrolled
AABB Validation Study of the CDC National Healthcare Safety Network’s Hemovigilance Module Adverse Events Definitions Protocol

March 2014
Barbee l Whitaker PhD
James P. AuBuchon MD, Mark Fung MD, Jacquelyn Malasky MPH

www.aabb.org

AABB Validation Study
CDC NHSN-HV AE Definitions

Methods
• Standardized Hemovigilance Case Definitions (ISBT WP)
• Survey of 36 fictional PT AE cases - 12 different diagnostic groups
• Twenty two academic medical centers (50% NHSN-trained)
• Reported on case diagnosis, severity, imputability
• Concordance determined vs. expert assessment
• One response submitted from each institution
Results: Case Diagnosis

- Only 72.1% of individual responses for transfusion reaction diagnoses matched the intended expert assessments

- Two important outcomes Transfusion-associated dyspnea (TAD); and Transfusion-associated circulatory overload (TACO) had 36% correlation

- No differences observed between reports from NHSN participants (trained) and other institutions
Sentinel BEST: Development of New and Innovative Methods to Improve Outcome Assessment

• Data Mining may include Natural Language Processing (NLP) Artificial Intelligence (AI), Machine Learning, and others

• Data mining can be used to retrieve outcome information from EHR text as well as structure and encode it
**Sentinel BEST: Current Focus on Natural Language Processing (NLP)**

- Focus on automated information retrieval from EHR clinical text (Bacterial Sepsis, TACO, TRALI)*
  
  *Transfusion-Related Acute Lung Injury

- Ongoing work includes development of computational phenotypes based on ISBT WP case definitions and incorporation into the OMOP CDM for iterative analysis

- Mined data, diagnostic codes (e.g. ICH-10), and condition codes (e.g. SNOMED) are all relevant to defining patient outcomes of importance

- Comparison of outcome predictive value vs. gold standard
WHAT DATA CAN BE RETRIEVED?

- Clinical Features (Diagnoses, Symptoms, etc)
- Temporal Information and Relationships
- Medication Information
- Laboratory Information
- Other
Beyond Observation....

- Post-transfusion sepsis
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated circulatory overload (TACO)

...with strong hemovigilance capabilities, all are amenable to intervention (with evaluation).
Sentinel BEST: Summary

Current BEST activities are focused on improving blood transfusion exposure and AE outcome ascertainment from electronic health records with the goals of:

- Improving the quality of hemovigilance in the US
- Establishing an electronic platform for semi-automated reporting of post-transfusion AEs to FDA.
- Ultimately improving data availability, quality, and processing for CBER products so as to support end uses that go beyond observation.

CBER intends to solicit new proposals to expand and extend these efforts across all CBER Biologics.
Acknowledgements

• Steven Anderson, PhD, MPP  Director OBE
• Hussein, Ezzeldin, PhD  OBE
• Ann Eder, MD  Office of Blood Research and Review, CBER
• Emily Storch, MD  Office of Blood Research and Review, CBER
• Richard Forshee, PhD  OBE
• Taxiarchis Botsis, PhD  OBE
• Manette Niu, MD  OBE
• Azadeh Shoaibi, PhD. MHS and the CBER Sentinel Central Team!
A Look Into the Future of the Sentinel System

Join the conversation with #sentinelinitiative
Analyzing patient experience from multiple data sources without physical pooling or linkages

Darren Toh, ScD
Department of Population Medicine
Harvard Medical School & Harvard Pilgrim Health Care Institute
February 7, 2018
Our data are being collected in multiple data sources

- Delivery systems (clinical data)
- Health plans (administrative claims data)
- Treatment & condition registries (e.g., risk factors, dietary intake)
- Wearables (e.g., physical activity)
- Mobile devices (e.g., patient-reported info)
- Social media (e.g., social behavioral data)
Combining data from various data sources

- Many of these data sources complement each other
- Combining patient experience from multiple data sources allow us to generate more valid evidence
Data sharing in conventional multi-database studies
Data sharing in conventional multi-database studies
Data sharing in conventional multi-database studies

Pooling the entire databases
Data sharing in typical distributed data networks
Data sharing in typical distributed data networks

Pooling study-specific individual-level datasets
Datasets shared in typical distributed data networks

| PatID | Treatment | Outcome | Age | Sex | Diabetes | CVD | NSAID | ...
|-------|-----------|---------|-----|-----|----------|-----|-------|-----
| 001   | 1         | 0       | 0   | 1   | 0        | 1   | 1     | ...
| 002   | 0         | 0       | 1   | 1   | 0        | 1   | 0     | ...
| 003   | 0         | 0       | 1   | 0   | 0        | 0   | 0     | ...
| 004   | 0         | 0       | 2   | 0   | 1        | 0   | 0     | ...
| 005   | 0         | 1       | 3   | 0   | 0        | 1   | 0     | ...
| 006   | 1         | 1       | 3   | 1   | 0        | 0   | 1     | ...
| 007   | 1         | 0       | 1   | 1   | 1        | 0   | 1     | ...
| 008   | 1         | 0       | 0   | 0   | 1        | 0   | 0     | ...
| 009   | 0         | 1       | 2   | 1   | 0        | 0   | 0     | ...
| 010   | 0         | 0       | 1   | 1   | 0        | 0   | 0     | ...
| 011   | 0         | 0       | 1   | 0   | 0        | 0   | 0     | ...
| ...   | ...       | ...     | ... | ... | ...      | ... | ...   | ...

Datasets shared in typical distributed data networks

| PatID | Treatment | Outcome | Age | Sex | Diabetes | CVD | NSAID | ...
|-------|-----------|---------|-----|-----|----------|-----|-------|-----
| 001   | 1         | 0       | 0   | 1   | 0        | 1   | 1     | ... |
| 002   | 0         | 0       | 1   | 1   | 0        | 1   | 0     | ... |
| 003   | 0         |         |     |     |          |     |       |     |
| 004   | 0         |         |     |     |          |     |       |     |
| 005   | 0         | 1       | 3   | 0   | 0        | 1   | 0     | ... |
| 006   | 1         | 1       | 3   | 1   | 0        | 0   | 1     | ... |
| 007   | 1         | 0       | 1   | 1   | 1        | 0   | 1     | ... |
| 008   | 1         | 0       | 0   | 0   | 1        | 0   | 0     | ... |
| 009   | 0         | 1       | 2   | 1   | 0        | 0   | 0     | ... |
| 010   | 0         | 0       | 1   | 1   | 0        | 0   | 0     | ... |
| 011   | 0         | 0       | 1   | 0   | 0        | 0   | 0     | ... |
| ...   | ...       | ...     | ... | ... | ...      | ... | ...   | ... |

Each row represents an individual
Datasets shared in typical distributed data networks

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</tr>
</tbody>
</table>

Each column represents a variable
Data sharing – A balancing act

Data we need to conduct the desired analysis

What data partners are willing or able to share
Concerns about sharing (de-identified) patient-level data

- Patient privacy and confidentiality
- Data security
- Unauthorized uses of data
- Inaccurate analysis or interpretation of data
- Disclosures of sensitive institutional or corporate information
- Contractual restrictions
Data sharing in Operations Center
Data sharing in Sentinel

Pooling study-specific summary-level datasets
Combining claims data from DP1 with EHR data from DP2

<table>
<thead>
<tr>
<th>ID</th>
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Data partner 1 (Claims)

Data partner 2 (EHR)

Analysis center
Challenges

- What if data partners can’t share patient-level data?

- Is there a way to analyze the data without physically combining them in a centralized location?
Distributed regression

- Regular regression analysis, but with data stored at different sites
- Transfer of summary or intermediate statistics only
- Results identical to those from corresponding pooled patient-level analysis

## Distributed regression vs. patient-level data analysis

Analyst inputs patient-level dataset into statistical software

<table>
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Hypothetical numbers, for illustrative purposes only
### Distributed regression vs. patient-level data analysis

**Analyst inputs patient-level dataset into statistical software**

**Statistical software produces intermediate statistics as part of computing process**

Hypothetical numbers, for illustrative purposes only

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Distributed regression vs. patient-level data analysis

Analyst inputs patient-level dataset into statistical software

Statistical software produces intermediate statistics as part of computing process

Statistical software produces final results

Hypothetical numbers, for illustrative purposes only

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**Distributed regression vs. patient-level data analysis**

**Analyst inputs patient-level dataset into statistical software**

**Statistical software produces intermediate statistics as part of computing process**

**Statistical software produces final results**

**Distributed regression shares this**

Hypothetical numbers, for illustrative purposes only
Data sharing with distributed regression

<table>
<thead>
<tr>
<th>ID</th>
<th>Treatment</th>
<th>Age</th>
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Data sharing with distributed regression

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Hypothetical numbers, for illustrative purposes only
### Statistical performance

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From test data
## Statistical performance

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From test data
### Statistical performance

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It is possible to get results that are even more statistically equivalent (ongoing work)

From test data
Typical analysis in distributed data networks

1- User creates and submits query
2- Data partners retrieve query
3- Data partners review and run query against their local data
4- Data partners review output
5- Data partners return outputs via secure network
6- Outputs are aggregated and analyzed

https://www.sentinelinitiative.org/privacy-and-security
Distributed regression requires multiple iterations

1- User creates and submits query
2- Data partners retrieve query
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4- Data partners review output
5- Data partners return outputs via secure network
6- Outputs are aggregated and analyzed

https://www.sentinelinitiative.org/privacy-and-security
Developing automatable distributed regression analysis

Ongoing work funded by FDA/ASPE (HHSF22301006T) and NIH/NIBIB (U01EB023683)
Current progress

- **Statistical code** for distributed linear and logistic regression
  - In R (prototype available; being refined)
  - In SAS (being developed)
  - Continuing efforts to accommodate more robust secure protocols

- **Communication code** for automating file/information transfer
  - Developed and tested
  - Being refined to accommodate more settings

Note: More progress has been made for horizontally partitioned data environments
Need a “global key”

- A common key to “virtually” link the same individuals across databases (e.g., unique de-identified hashed ID)

- The only patient-level data element shared

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Conclusion

- It is possible to analyze data collected in multiple sources without physically pooling the them

- More privacy-protecting methods like distributed regression enable us to analyze data that are otherwise not accessible
Darren_Toh@harvardpilgrim.org
Novel signal detection approaches in longitudinal databases

Joshua J Gagne

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School

Department of Medicine, Harvard T.H. Chan School of Public Health
Signal detection methods

Methods for safety signal detection in healthcare databases: a literature review

Mickael Arnaud\textsuperscript{a,b}, Bernard Bégaud\textsuperscript{a,b,c}, Nicolas Thurin\textsuperscript{a,b,d}, Nicholas Moore\textsuperscript{a,b,c,d}, Antoine Pariente\textsuperscript{a,b,c,d} and Francesco Salvo\textsuperscript{a,b,c}

\textsuperscript{a}University of Bordeaux, Bordeaux, France; \textsuperscript{b}Bordeaux Population Health Research Centre, Pharmacoepidemiology team, INSERM UMR1219, Bordeaux, France; \textsuperscript{c}CHU Bordeaux, Service de Pharmacologie Médicale, Bordeaux, France; \textsuperscript{d}CIC Bordeaux

# Signal detection methods

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<th>Method</th>
<th>Strengths</th>
<th>Limitations</th>
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<tr>
<td>Disproportionality analysis</td>
<td><strong>SIR-like methods</strong> [30] Easy to implement. Can incorporate shrinkage for preventing detecting some spurious signals related to very rare events.</td>
<td>Does not provide risk estimates. Loss of information due to aggregated data.</td>
</tr>
<tr>
<td></td>
<td><strong>LGPS-LEOPARD</strong> [31] Provides risk estimates. Uses shrinkage for preventing detecting spurious some signals related to very rare events.</td>
<td>Unable to handle numerous confounders. Sensitive to proaesthetic and indication biases.</td>
</tr>
<tr>
<td>Traditional pharmacoepidemiological designs</td>
<td><strong>New user cohort design</strong> [32] Provides risk estimates. Allows controlling for high-dimensional confounding.</td>
<td>Needs very large dataset to have enough power to detect signals related to rare events.</td>
</tr>
<tr>
<td></td>
<td><strong>Matched case-control design</strong> [33] Provides risk estimates. Allows controlling for some confounders thanks to matching and nesting.</td>
<td>Difficulties to determine the settings as these are not supposed to be standardized for all the drug-event associations screened.</td>
</tr>
<tr>
<td>SCCS design [34]</td>
<td>Provides risk estimates. Robust to confounders that are stable over time. Allows controlling for high-dimensional time-varying confounding.</td>
<td>Theoretically inappropriate for chronic drug use and for nonrecurrent events.</td>
</tr>
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<td>Does not address time-varying confounding.</td>
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<td>SCC design [36]</td>
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<td>Theoretically inappropriate for chronic drug use and for nonrecurrent events.</td>
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<td>Does not address time-varying confounding.</td>
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<tr>
<td>Sequence symmetry analysis</td>
<td>Provides risk estimates. Robust toward confounders that are stable over time and easy to understand and to implement.</td>
<td>Inapplicable for death. Sensitive to proaesthetic and indication biases.</td>
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Signal detection methods

**Table 1: Strengths and limitations of the methods tested for safety signal detection on health-care databases.**

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<tr>
<td>SR-like methods [30]</td>
<td>Easy to implement</td>
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</tr>
<tr>
<td>Matched case-control design [33]</td>
<td>Provides risk estimates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allows controlling for some confounders thanks to matching and nesting</td>
<td></td>
</tr>
<tr>
<td>SCCS design [34]</td>
<td>Provides risk estimates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Robust to confounders that are stable over time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allows controlling for high-dimensional time-varying confounding</td>
<td></td>
</tr>
<tr>
<td>CC design [35]</td>
<td>Provides risk estimates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Robust to confounders that are stable over time</td>
<td></td>
</tr>
<tr>
<td>SCC design [36]</td>
<td>Provides risk estimates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Robust to confounders that are stable over time</td>
<td></td>
</tr>
<tr>
<td>Sequence symmetry analysis [37]</td>
<td>Provides risk estimates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Robust toward confounders that are stable over time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Easy to understand and to implement</td>
<td></td>
</tr>
<tr>
<td>Sequential statistical testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MaxSPRT [38,39]</td>
<td>Maintains type I error at 0.05 across multiple testing</td>
<td>Does not provide risk estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of information due to aggregated data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inappropriate for chronic exposure and for very rare events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losses information when using matching, otherwise requires large historical data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity to prescriptive and indication biases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Computational load</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not provide risk estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unable to handle confounders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity to prescriptive and indication biases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not maintain type I error at 0.05 across multiple testing when there are many strata computational heaviness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inapplicable for death</td>
</tr>
<tr>
<td>Temporal association rule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUTARA/HUNT [41,42]</td>
<td>Incorporates a filter that prevents detecting expected signals</td>
<td>Does not provide risk estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inapplicable for death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not have a natural trend for discriminating positive to negative signals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inappropriate for death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not provide risk estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficulties to address time-varying confounding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inapplicable for death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on imputability criteria for signal detection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not provide risk estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficulties to define the imputability criteria for an automated use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitive to prescriptive and indication biases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not have a natural trend for discriminating positive to negative signals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not provide risk estimates</td>
</tr>
<tr>
<td>Supervised machine learning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(45,46)</td>
<td>Based on Bradford-Hill’s causality criteria that make the method more robust to the detection of false positive signals</td>
<td>Needs both large data and a large reference set for training efficiently the random forest model</td>
</tr>
<tr>
<td></td>
<td>Performance for signal detection should improve with increased data</td>
<td>Needs to set up one random forest model per drug screened</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitive to prescriptive and indication biases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Computational load</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not provide risk estimates</td>
</tr>
<tr>
<td>Tree-based scan statistic [47]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintains type I error at 0.05 across multiple testing</td>
<td>Does not provide risk estimates</td>
</tr>
<tr>
<td></td>
<td>Tests simultaneously different event definitions</td>
<td>Inapplicable for the death event</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inapplicable for the death event</td>
</tr>
</tbody>
</table>

**Table 1: (Continued).**

<table>
<thead>
<tr>
<th>Method</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>S: spontaneous report; LGPS: longitudinal gamma Poisson shrinker; LEOPARD: longitudinal evaluation of observational profiles of adverse events related to drugs; SCCS: self-controlled case series; CC: case crossover; SCC: self-controlled cohort; maxSPRT: maximized sequential probability ratio test; CSSP: conditional sequential sampling procedure; TAR: temporal association rule; MUTARA: mining the unexpected TARs given the antecedent; HUNT: highlighting TARs negating TARs; TPD: temporal pattern discovery.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sources of ’signals’

• ’Big data’ creates huge opportunity for false positives (and false negatives)

• Sources of ‘signals’ can be put into epidemiologic and statistical terms
  • Cause and effect
  • Chance
  • Bias (e.g., confounding, selection bias, information bias [e.g., misclassification])

• The solutions are also epidemiologic and statistical, as well as clinical
Common components of detection algorithms

- Some mechanism to estimate and compare observed and expected counts or rates (i.e., the design, to address signals due to bias)
  - Cohort-based approaches (e.g., cohort, case-control)
  - Self-controlled approaches (e.g., case-crossover, self-controlled case series, sequence symmetry)

- Some way to rank or prioritize observed and expected counts or rates (i.e., the analysis, to address signals due to chance)
  - Alpha-based approaches (with or without adjusting for multiple testing)
  - Bayesian approaches (e.g., ranking estimates after Bayesian shrinkage)
Signal detection paradigms

• From target to broad:
  • Targeted: is a specific drug associated with pre-specified outcomes?
    • Could be done retrospectively (a ‘one-time look’) or prospectively (sequentially)
  • Single drug, many outcomes | single outcome, many drugs
    • Single drug: scan for whether a specific drug is associated with any number of possible outcomes
    • Single outcome: scan for whether a specific outcome is associated with any number of possible drugs
  • All-by-all
Signal detection paradigms

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  • Targeted: is a specific drug associated with pre-specified outcomes?
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Targeted, retrospective example

Safety assessment of niacin in the US Food and Drug Administration's mini-sentinel system

Joshua J. Gagne¹  |  Monika Houstoun²  |  Marsha E. Reichman²  |  Christian Hampp²  |  James H. Marshall³  |  Sengwee Toh³
Targeted, retrospective example

### TABLE 2  Event frequencies, follow-up time, and hazard ratios for each outcome in unmatched, 1:1 matched, and variable ratio matched analyses in primary cohort

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Analysis</th>
<th>Extended-Release Niacin</th>
<th></th>
<th></th>
<th>Fenofibrate</th>
<th></th>
<th></th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>No. Events</td>
<td>Person-Years of Follow-Up</td>
<td>N</td>
<td>No. Events</td>
<td>Person-Years of Follow-Up</td>
<td></td>
</tr>
<tr>
<td>Major gastrointestinal bleeding</td>
<td>Unadjusted</td>
<td>234 242</td>
<td>482</td>
<td>86 168</td>
<td>387 837</td>
<td>1016</td>
<td>177 552</td>
<td>1.01 (0.91, 1.13)</td>
</tr>
<tr>
<td></td>
<td>1:1 matched</td>
<td>210 389</td>
<td>400</td>
<td>73 730</td>
<td>210 389</td>
<td>595</td>
<td>102 194</td>
<td>0.98 (0.82, 1.18)</td>
</tr>
<tr>
<td></td>
<td>Variable matched</td>
<td>210 400</td>
<td>397</td>
<td>73 842</td>
<td>387 819</td>
<td>1018</td>
<td>177 556</td>
<td>0.98 (0.83, 1.16)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Unadjusted</td>
<td>234 355</td>
<td>59</td>
<td>86 355</td>
<td>387 978</td>
<td>90</td>
<td>177 945</td>
<td>1.45 (1.04, 2.03)</td>
</tr>
<tr>
<td></td>
<td>1:1 matched</td>
<td>210 473</td>
<td>45</td>
<td>74 086</td>
<td>210 473</td>
<td>57</td>
<td>102 590</td>
<td>1.21 (0.66, 2.22)</td>
</tr>
<tr>
<td></td>
<td>Variable matched</td>
<td>210 483</td>
<td>46</td>
<td>74 095</td>
<td>387 960</td>
<td>90</td>
<td>177 951</td>
<td>1.21 (0.71, 2.06)</td>
</tr>
</tbody>
</table>

Targeted, prospective example

Prospsective Postmarketing Surveillance of Acute Myocardial Infarction in New Users of Saxagliptin: A Population-Based Study

Diabetes Care 2018;41:39–48 | https://doi.org/10.2337/dc17-0476

Targeted, prospective example

Signal detection paradigms

- From target to broad:
  - Targeted: is a specific drug associated with pre-specified outcomes?
    - Could be done retrospectively (a ‘one-time look’) or prospectively (sequentially)
  - Single drug, many outcomes | single outcome, many drugs
    - Single drug: scan for whether a specific drug is associated with any number of possible outcomes
    - Single outcome: scan for whether a specific outcome is associated with any number of possible drugs
  - All-by-all
TreeScan

- Uses tree-based structure to organize outcomes (or drugs) and specify level of granularity (e.g., MLCCS, but any hierarchy can be used)

- Agnostic to the design that yields observed and expected counts
  - Cohort-based approaches (e.g., cohort, case-control)
  - Self-controlled approaches (e.g., case-crossover, self-controlled case series, sequence symmetry)

- Automatically adjusts for multiple testing

www.treeScan.org
TreeScan with self-controlled design

Among:
- Cellulitis and abscess of the arm (known)
- Other complications of surgical and medical procedures (known)
- Pilot evaluation finishing that examined 3 drug examples using TreeScan with a self-controlled risk interval design

TreeScan with cohort and propensity score matching

- Cohort designs are often preferred for evaluating drugs
- Project finishing that examined the TreeScan with PS-matched cohorts in simulated data
- Empirical evaluations being planned

https://www.sentinelinitiative.org/sentinel/methods/treescan-propensity-scores
Challenges still to be addressed

• As confounding is outcome-specific, how can/should propensity scores account for risk factors for every possible outcome?

• Prospective signal detection

• Issues related to data reuse
  • Evaluate orthogonal hypotheses in the same data
  • Randomly split the data
  • Use an external data source for either signal generation or evaluation
Discussion

Marianthi Markatou
Department of Biostatistics
University at Buffalo
Methodological Research

• **Direction 1**: transfer of “technology” from different fields, where the word technology is used in a broad semantic sense. For example, in the context of signal identification, the use of 2X2 contingency tables.

Methodological Research

- 2) Gruber, S. & Tchetgen, Tchetgen, E. (2016). Limitations of empirical calibration of p-values using observational data. *Stat. in Medicine*, 35(22), 3869-82 (and associated response by the authors of the first listed paper);


- The aforementioned works suggest a foundational assessment at the issues involved that inform the proposed solutions.
Schuemie et al. (2014): P-value calibration

- Biases inherent in observational studies affect measures of statistical significance (such as confidence intervals and p-values).
- A novel way to adjust type I error, under the null hypothesis of no association between the medical product and an outcome, is proposed by adjusting for the systematic error component.
Gruber & Tchetgen Tchetgen (2016)

- Investigated the method’s control over the type I and II error rates using simulation and real world data.
- These authors found that the performance of the method depends on the true unknown distribution of the systematic error.
- Yet, this is the only method available for adjusting for systematic bias effects.
Huang, Zalkikar and Tiwari (2011)

• Propose a *likelihood ratio test procedure* for testing the association between medical products and adverse outcomes.
• Although the original paper discusses the performance characteristics of the procedure in a setting applicable to clinical trials (AE-based, single drug) new work shows that it can be equally applied to post-marketing data.
Evidence Generation
Amiodarone and Sofosbuvir
Dangerous Drug-Drug Interaction (DDI)
Hepatitis C virus Infection

• Hepatitis C virus (HCV) infects up to 5 million individuals in the United States and is leading indication for liver transplant.
  – Causes end-stage liver disease, cirrhosis and liver cancer
• HCV treatments have progressed very quickly over the past five years with development of direct acting antivirals.
• Sofosbuvir (Sovaldi) was approved by the US FDA in 12/13 for HCV treatment.
• Sofosbuvir in combination with ledipasvir (Harvoni) was approved by the US FDA in October 2014.
FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug

[3-24-2015]

Safety Announcement
Identification of Dangerous DDI

• Case reports identified severe bradycardia in patients treated with amiodarone and sofosbuvir-containing compounds when combined with another HCV medication.
  – One death
  – Three patients needed pacemaker insertion

• Additions were made to Warnings and Precautions, Drug Interactions, and Postmarketing Experience sections of the drug labels for Harvoni and Sovaldi.
What is the Value of Case Reports?
Back to Evidence Generation

• Abundance and heterogeneity of data can provide evidence for the presence of small-scale structures called patterns.
• Discovering a pattern is but the first step. A vital question, once a potential local structure has been identified as of interest, is that of whether the pattern represents some real underlying aspect of the data generation mechanism or is merely a feature of chance fluctuation in the data which happen to have been observed. This is the question of addressing uncertainty in pattern discovery.
• In the context of the aforementioned case report this was done via infusion of outside knowledge. How can expert knowledge be incorporated into algorithms for signal identification?
• Pattern identification—case based reasoning (information retrieval)
Evidence Generation

- The fundamental statistical question that needs to be addressed here is that of selecting controls. Can we tease out the implicit knowledge brought into the process of deciding the significance/non-significance of a case report? What are the comparators that inform this process?
- Future questions
  - Can we quantify systematic error as an alternative to seeking to eliminate bias?
  - What are the important components contributing to systematic error that should be assessed?
Closing Remarks
Adjournment

Join the conversation with #sentinelinitiative