Public Webinar

Planned Next Steps to Advance the Sentinel System

Convened by the Duke-Robert J. Margolis, MD, Center for Health Policy

July 26, 2018
Welcome, Overview, and Webinar Objectives
Improving the Efficiency of Outcome Validation in the Sentinel System

Defining the Problem

Robert Ball, MD, MPH, ScM
Deputy Director
Office of Surveillance and Epidemiology
Center of Drug Evaluation and Research
Case Classification the Old-fashioned Way

Sounds like Guillain-Barré Syndrome

- Bilateral weakness in lower extremities
- Bilateral areflexia in lower extremities

CSF Mononuclear WBC count
3 cells/mm³; Protein 50 mg/dL

Electrodiagnostics Abnormal, consistent with polyneuropathy

Data abstraction

Medical Records

Study database

Case Definition

Expert Case Review
• Post Marketing Requirements
• Safety Labeling Changes
• Risk Evaluation and Mitigation Strategies (REMS)
• Required Safety Reviews ("915" and "921")
• Active post-market Risk Identification and Analysis system
  – FDA Sentinel Initiative
**Active Risk Identification and Analysis (ARIA) System**

- Mandated creation in Section 905 of FDAAA 2007
- Linked to PMR in Section 901(3)(D)(i):
  - “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).”
Defining ARIA

• ARIA uses a subset of Sentinel System’s full capabilities to fulfill the FDAAA mandate to conduct active safety surveillance.

* Pre-defined, parameterized, and re-usable to enable faster safety surveillance in Sentinel (in contrast to protocol based assessments with customized programming).

† Electronic claims data, without manual medical record review.
What is Sufficiency?

• Adequate data
  – Drug/biologic of interest and comparator
  – Confounders and covariates
  – Health outcome of interest

• Appropriate methods

• To answer the question of interest
  – assess a known serious risk related to the use of the drug/biologic
  – assess signals of serious risk related to the use of the drug/biologic
  – identify an unexpected serious risk when available data indicate the potential for a serious risk

• To lead to a satisfactory level of precision
When are automated queries insufficient?

- 43 Drug-AE pairs sufficient^
- 51 Drug-AE pairs insufficient^  
- Reasons for Insufficiency*
  - Study population = 24
  - Exposure = 17
  - Outcome = 38
  - Covariate = 10
  - Analytic tool = 12

^1/2016-2/2018 – first 2 years of ARIA
*Total = 101 (some drug-AE pairs have more than one reason for insufficiency) - preliminary results
How do we improve sufficiency?

• Start “simple”
  – Add data partners (e.g. Medicare and HCA)
  – Create linkages (e.g. National Death Index and mother-infant)
  – Build new tools (e.g. Treescan for signal detection, distributed regression)
  – Add data to the Common Data Model (CDM) (e.g. physician specialty)
How do we improve sufficiency?

• When is “simple” not enough?
  – Outcomes with human expert-constructed algorithms, using data in the Sentinel CDM, resulting in insufficient PPV

  Acute pancreatitis
  Implant related complications (2)
  Osteosarcoma
  Suicidal ideation and behavior
  Opportunistic infections
  Outpatient neutropenia

  Stillbirth
  Fluoroquinolone-associated disability
  Neonatal enteroviral sepsis
  Nerve injury
  Anaphylaxis and serious hypersensitivity reactions (3)
How do we improve sufficiency?

• When is “simple” not enough?
  – Data not easily available for addition to CDM (e.g. lifestyle covariates in clinical narratives)
  – Data available but hard to standardize (e.g. laboratory, radiology, pathology results)
    • non-randomly missing so also need novel statistical methods
  – Cancer staging, severity, history, and therapeutic regimen
How do we improve sufficiency?

• When is “simple” not enough?
  – Direct linkage between claims and EHRs represents a small fraction of all patients in the Sentinel System
  – Many medical records only available as paper or PDF
  – 18 data partners in the Sentinel System don’t do everything exactly the same way
Might a machine-readable health record help?

• HOI algorithm identification and development
  – Apply machine learning to classified records to identify new algorithms from data already in CDM
  – Extract free-text fields from the machine readable health record, combined with claims, to create better algorithms

• Support epidemiologic studies via faster chart validation of outcomes, when a particular set of charts is needed
"Text in EMRs is accessible, especially with open source information extraction algorithms, and significantly improves case detection when combined with codes. More harmonization of reporting within EMR studies is needed, particularly standardized reporting of algorithm accuracy metrics like positive predictive value (precision) and sensitivity (recall)."

Authors also noted small sample that directly compared codes to narratives and variability in performance.
Health Outcome of Interest: Anaphylaxis Pilot project using OCR and NLP

• In the Sentinel System, most medical records only available as paper or PDF
• The human expert-constructed algorithm for anaphylaxis case identification has an “insufficient” PPV when using data in CDM
• Optical Character Recognition (OCR) of paper charts plus application of previously developed Natural Language Processing (NLP) and rule- and similarity-based algorithms for anaphylaxis case classification
Key Points

- The authors developed and validated an algorithm using administrative and claims data to identify cases of anaphylaxis.
- The PPV for the overall algorithm was 63.1% (95% CI: 53.9-71.7%). While this PPV improves on previous publications, it remains low.
- The authors were able to identify an algorithm that optimized the PPV but demonstrated lower sensitivity for anaphylactic events.
Key Points

- The authors developed an algorithm to extract key features from narratives of Vaccine Adverse Event Report System (VAERS) reports using natural language processing.
- The authors used those features to classify reports of possible anaphylaxis after vaccination based on the Brighton Collaboration definition using both a rule-based and similarity-based classifier.
Health Outcome of Interest: Anaphylaxis

Application of VAERS algorithm to MS charts

Key Points

- The previously developed natural language processing, rule- and similarity-based classification approaches demonstrated almost equal performance (F-measure: 0.753 vs. 0.729, recall 100% vs 100%, precision 60.3% vs 57.4%).
- These algorithms might improve recall but had similar precision (PPV) to claims only algorithms from MS.

Ball et al, Evaluating automated approaches to anaphylaxis case classification using unstructured data from the FDA Sentinel System, under review
Key Points

- Reasons for misclassification included: the **inability** of the algorithms to make the **same clinical judgments as human experts** about the timing, severity, or presence of alternative explanations; the identification of terms consistent with anaphylaxis but present in conditions other than anaphylaxis.
Additional Challenges

• Solutions need to be implementable in a distributed data network
  – adaptable to run on native databases with very different formats
  – account for likely performance differences in different settings

• Potentially has implications for data governance and privacy preservation
Summary

• Many efforts to improve ARIA sufficiency underway
• “Non-simple” problems related to outcome validation might benefit from new technologies, such as NLP and machine learning
• Goal for workshop is to brainstorm ideas for 1, 3, 5 year projects and to know what to put into the 10 year bucket
• Solutions for improving ARIA sufficiency will likely also contribute to building Sentinel as a national resource for the learning healthcare system
Acknowledgements

• Michael Nguyen, Steve Anderson, Gerald Dal Pan, and Sentinel Team
• Jeff Brown, Judy Maro, Rich Platt, Sentinel Operations Center staff, and Sentinel Partners
• Adam Aten, Greg Daniel, Mark McClellan, and Duke Margolis staff
Thank you
Summary of Ongoing Projects and New Directions

Duke-Robert J. Margolis, MD, Center for Health Policy: Next Steps to Advance the Sentinel System

July 26, 2018
Jeffrey Brown, PhD
### Projects in Progress

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<tr>
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<tbody>
<tr>
<td>Data Partner Data Assets and Expertise Survey</td>
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<td>Data Partner Technical Assessment: Discovery and Planning</td>
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<tr>
<td>Data Sharing Guidance for Limited Datasets, patient profiles, and chart re-use</td>
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<tr>
<td>HOI 1.0 Validation (Serious Infections)</td>
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<td>HOI 1.0 Validation (Lymphoma)</td>
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<td>HOI 1.0 Validation (Stillbirth)</td>
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## Projects Slated to Start / Planned

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<tr>
<td>HOI 2.0 Validation (Anaphylaxis)</td>
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<td>HOI 2.0 Validation (Acute Pancreatitis)</td>
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<td>MITRE CASAE engagement to assess new technologies for distributed networking</td>
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<td>Chart Review Re-Engineering</td>
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<td>- Development of Chart Review Resource Intensity Score</td>
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<td>- Standardized SOPs for Chart Review</td>
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<td>- Discovery Phase for facility and provider SCDM fields</td>
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<td>Vertical Distribute Regression Demonstration with CMS and PCORI sites</td>
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Opportunities for Improving the Efficiency of Outcome Validation in the Sentinel System
Project Categories

1. Chart Review Improvement Activities
   – Includes laying the groundwork for later HOI 2.0 methods
2. Common Data Model Readiness for Expansion
3. Methods Activities
4. Sentinel Patient Identifier and Linkage Activities
# Chart Review Improvement Opportunities

<table>
<thead>
<tr>
<th>Data Sources</th>
<th>Proposal Description</th>
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<tbody>
<tr>
<td>Charts</td>
<td><strong>Scan Charts</strong>: Develop process to routinely scan charts at scale using optical character recognition tools</td>
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<tr>
<td>CDM</td>
<td><strong>Improve Case Classification</strong>: Using existing Common Data Model data to develop machine learning methods to improve case classification (requires validated cases for learning)</td>
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<tr>
<td>EHR, CDM</td>
<td>Use corpus of validated cases and machine learning to assess whether claims data alone, claims + structured EHR, claims + unstructured EHR best identify cases</td>
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Chart Review Improvement Opportunities: Issues to consider

- Identify production-level Optical Character Recognition software and assess implementation barriers
  - Data storage, privacy, access, costs
- Address legal and regulatory issues with re-use of existing charts for other public health activities
- Assess potential to amend the “Dear Healthcare Provider” letters to allow for multiple uses of charts and chart-derived data
## Common Data Model Infrastructure Opportunities

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<tr>
<td>CDM, EHR</td>
<td>Assess governance barriers and feasibility of populating CDM with unstructured free text notes</td>
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<tr>
<td>CDM</td>
<td>Add Sentinel and non-Sentinel funded chart validation information (i.e., case status) to Common Data Model</td>
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<tr>
<td>CDM</td>
<td>Assess barriers to using charts obtained for other reasons (e.g., audits) to populate the Common Data Model with chart-extracted information</td>
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<tr>
<td>EHR</td>
<td>Evaluate value of EHR-only datasets for claims-compatible algorithm development</td>
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Common Data Model Infrastructure
Opportunities: Issues to consider

- Ongoing data assets and methods expertise survey will inform data discovery projects for enhancement of the Common Data Model
  - Some partners may have data that could be incorporated into the data model quickly
- Expect substantial regulatory and legal hurdles related to re-use of chart-derived data
- Use of standardized versus unstructured information for rapid querying
  - Use of unstructured data requires time to make usable
  - Issues with patient privacy with unstructured data
# Methods and Other Opportunities

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<tr>
<td>Implement machine learning for causal inference (i.e., substitute investigator-driven propensity score model with machine learning methods)</td>
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<td>Develop methods to use Missing Not-at-Random (MNAR) data; example: laboratory data values</td>
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<tr>
<td>Adapt doubly robust causal inference methods to a distributed database</td>
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<tr>
<td>Develop a process for rapid late-binding QA (example: lab data)</td>
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<tr>
<td>Partner with Health Information Exchanges to allow for rapid, focused chart retrieval</td>
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<tr>
<td>Develop alternatives to SAS-based querying infrastructure</td>
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Methods and Other Opportunities:
Issues to consider

- Methods projects (e.g., Missing Not-at-Random information, doubly robust causal inference) require workgroup creation and appropriate data
- Regulatory, legal, and technical issues with working with Health Information Exchanges
- Software and technical barriers for using alternative to SAS-based distributed querying
  - Positive experience with PCORnet can be leveraged
## Sentinel Patient Identifier and Linkage Opportunities

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<tr>
<td>CDM</td>
<td>Develop Sentinel Patient ID to identify same person across sites; assess overlap and proportion with enrollment transitions between existing partners</td>
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<tr>
<td>CDM, EHR</td>
<td>Demonstrate vertical distributed regression between sites to supplement claims data</td>
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<tr>
<td>CDM, EHR</td>
<td>Create a pilot claims-EHR linkage between Sentinel and PCORnet Data Partners</td>
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Classes of Methods for Linkage

- **Identifiable**: Use direct identifiers (like health information exchanges) or clear text identifiers
  - Example: PCORnet ADAPTABLE Clinical Trial. Patients will be individually consented for their participation anyway.

- **Anonymized or Privacy Preserving Record Linkage (PPRL)**: Use anonymous hash identifier with secure transmission of the random seed (i.e. salt)
  - Personally Identifiable Information (PII) is converted into “tokens” and recombined using hashes and encryption
  - Could use trusted third party or exchange hash tables
  - Example: PCORnet Antibiotics Observational Study
EXTENDING COMPARATIVE EFFECTIVENESS RESEARCH AND MEDICAL PRODUCT SAFETY SURVEILLANCE CAPABILITY THROUGH LINKAGE OF ADMINISTRATIVE CLAIMS DATA WITH ELECTRONIC HEALTH RECORDS: A SENTINEL-PCORnet COLLABORATION

Prepared by: Kevin Haynes, PharmD, MSCE,1 Nancy D. Lin, ScD,2 Paul Avillach, MD, PhD,3,4 Thomas W. Carton, PhD, MS,5 Jeffrey R Curtis, MD, MS, MPH,6 Kevin Fahey, MA,7 Crystal Garcia, MPH,8 Thomas Harkins, MA, MPH,9 Wenke Hwang, PhD,10 Cheryl N. McMahl-Walraven, MSW, PhD,11 David Meltzer, MD, PhD,12 Eliel Oliveira, MBA, MS,5 Pamala A. Pawloski, PharmD,13 Micah Prochaska, MD,14 Jon Puro, MPA:HA,14 Nandini Selvam, PhD, MPH,1 Richard Platt, MD, MSc8

https://www.sentinelinitiative.org/sites/default/files/data/ComplementaryData/Sentinel_Sentinel-PCORnet-White-Paper_0.pdf
White Paper: Major Linkage Options

- Study-specific linkage
- Many-to-many linked dataset of identifiers to understand overlap
- Creation of a general purpose, persistent analyzable linked dataset

Take-home: Resolving governance policies is more challenging than technical challenges.
Summary

- Sentinel working on expanding analytic and surveillance capabilities across a range of areas
  - Chart Review Improvement Activities
  - Common Data Model Readiness for Expansion
  - Methods Activities
  - Sentinel Patient Identifier and Linkage Activities

- Regulatory, legal, and technical barriers exist

- Actively seeking partnerships with technology experts, new data sources, and other to address capability gaps
Closing Remarks