Biosimilar Collective Intelligence System: Utilizing Data Consortiums to Prove Safety andEffectiveness of Biosimilars

Reviewing current landscape of existing data consortiums: How they are being used, what they uncover, how they function—the Mini-Sentinel example

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November 12, 2013
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Outline

- Need for post marketing surveillance
- Why multisite studies
- Surveillance and sequential analysis
- Mini-Sentinel
At approval

- We know
  - Within a small, well-defined population in a controlled environment, and short-term exposure, the drug is
    - Relatively safe
    - More effective than placebo

- We don’t know
  - Real-world safety
  - Real-world effectiveness
  - Comparative effectiveness
  - Cost-benefit
At approval: What’s worse

We know that we don’t have a reliable system for actively monitoring and investigating what we don’t know.
Benefits of a surveillance system

If we had a reliable system to generate post marketing evidence

• Change the risk-benefit calculation for stakeholders and the FDA
• Improve use of medications via evidenced-based medicine
• Encourage drug development
Surveillance goals

“A principal goal of our post approval drug-safety system should be to minimize the delay between approval and the discovery of these serious risks.”

Sometimes multi-site studies are needed

- Rare exposures
- Rare outcomes
- Sample size (speed)
- Sub-group analyses
- Analytic flexibility
When multi-site studies are needed

Distributed networks aren’t far behind
Some distributed networks

- CDC’s Vaccine Safety Datalink (VSD)
- HMO Research Network
- FDA’s post-market safety programs
- Meningococcal Vaccine Safety Study
- EU-ADR
- Scalable PArtnering Network for CER: Across Lifespan, Conditions, and Settings (SPAN)
- Post-licensure Rapid Immunization Safety Monitoring (PRISM)
- FDA Mini-Sentinel
- NIH Health Care Systems Collaboratory
- PCORI National Clinical Research Network
Distributed network approach

- Standardize data
- Data partners maintain physical control of their data
- Data partners control all uses of their data
- Data partners control all transfer of data
- Computer programs should run at multiple sites without modification
Distributed network key success factors and characteristics

• Engagement with data partners
• Coordinating center support
• Analytic tools
• Data, epidemiologic, and statistical expertise
• Type of data source (insurer, delivery system)
• Data refresh frequency
• Self-aware learning system
• Operational efficiency
Approaches to surveillance

• **Epidemiologic** study after specified time or exposures
  – Signal detection and hypothesis generation
  – Hypothesis testing

• **Sequential analysis of accumulating data**
  – Signal detection and hypothesis generation

• **Data mining**
  – Signal detection and hypothesis generation
Sequential surveillance

- Extract, manipulate, and summarize data as they accumulate
- Conduct periodic analysis
- Repeated statistical testing of the same data requires special methods
  - Sequential probability ratio test; Maximized SPRT
  - Group sequential methods
Active Surveillance of Vaccine Safety

A System to Detect Early Signs of Adverse Events

Robert L. Davis,*† Margarette Kolczak,‡ Edwin Lewis,† James Nordin,§ Michael Goodman,§ David K. Shay,‡ Richard Platt,‡ Steven Black,† Henry Shinefield,† and Robert T. Chen‡

Background: There currently are no population-based systems in the United States to rapidly detect adverse events after newly introduced vaccines. To evaluate the feasibility of developing such systems, we used 5 years of data from 4 health maintenance organizations within the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink.

Methods: Within every year, each week’s vaccinated children were followed for 4 weeks, and rates of adverse events were compared with rates among children of similar ages before the introduction of the new vaccine. We assessed risks for intussusception after rotavi-

Conclusions: We conclude that it is feasible to develop systems for rapid and routine population-based assessments of new vaccine safety.

(Epidemiology 2005;16: 336–341)

Recent events in the United States have underscored the need for surveillance systems that detect adverse events as soon as possible after the introduction of new vaccines (eg,
Real-Time Vaccine Safety Surveillance for the Early Detection of Adverse Events

Tracy A. Lieu, MD, MPH,*† Martin Kulldorff, PhD,* Robert L. Davis, MD, MPH,‡
Edwin M. Lewis, MPH,§ Eric Weintraub, MPH,‡ Katherine Yih, PhD, MPH,* Ruihua Yin, MS,*
Jeffrey S. Brown, PhD,* and Richard Platt, MD, MSc,* for the Vaccine Safety Datalink Rapid Cycle Analysis Team

Background: Rare but serious adverse events associated with vaccines or drugs are often nearly impossible to detect in prelicensure studies and require monitoring after introduction of the agent in large populations. Sequential testing procedures are needed to detect vaccine or drug safety problems as soon as possible after introduction.

Conclusions: Real-time surveillance combining dynamic data files, aggregation of data, and sequential analysis methods offers a useful and highly adaptable approach to early detection of adverse events after the introduction of new vaccines.

Key Words: vaccine safety, active surveillance, sequential analysis, meningococcal vaccine, drug safety
Basic implementation steps

- Choose exposure and outcome
- Choose the comparator and comparison (historical, concurrent)
- Collect and summarize data
- Conduct sequential analysis and testing
  - Observed > than expected?
  - ...how about now?
  - ...now?
Surveillance for adverse drug events

- Apply methods and lessons from Vaccine Safety Datalink

- Unique drug-specific issues
  - Patterns of drug use: New (incident), chronic, and intermittent use
  - Accommodate misclassification of exposure (e.g., non-adherence, prior drug use, concomitant drug use)
  - Adjust for co-morbidities
Early detection of adverse drug events within population-based health networks: application of sequential testing methods†,‡

Jeffrey S. Brown PhD\textsuperscript{1,2,*}, Martin Kulldorff PhD\textsuperscript{1}, K. Arnold Chan MD, MPH, ScD\textsuperscript{3,4}, Robert L. Davis MD, MPH\textsuperscript{5}, David Graham MD\textsuperscript{6}, Parker T. Pettus MS\textsuperscript{1,2}, Susan E. Andrade ScD\textsuperscript{2,7}, Marsha A. Raebel PharmD\textsuperscript{2,8}, Lisa Herrinton PhD\textsuperscript{2,9}, Douglas Roblin PhD\textsuperscript{2,10}, Denise Boudreau PhD\textsuperscript{2,11}, David Smith PhD\textsuperscript{2,12}, Jerry H. Gurwitz MD\textsuperscript{2,7}, Margaret J. Gunter PhD\textsuperscript{2,13} and Richard Platt MD, MSc\textsuperscript{1,2}
Observed and expected events for rofecoxib versus naproxen users: 2000-2005

Signal after 28 events (16 expected) among new users of drug

Brown et al. (2007) PDS; Adjusted for age, sex, health plan. Outcome: AMI.
Observed and expected events for cetirizine users versus non-users: 2000-2005

Negative control; 6 observed and 6.1 expected. > 5 million exposed days.

Brown et al. (2007) PDS; Adjusted for age, sex, health plan. Outcome: Thrombocytopenia.
Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations†

Jeffrey S. Brown PhD1,2*, Martin Kulldorff PhD1, Kenneth R. Petronis PhD3, Robert Reynolds ScD3, K. Arnold Chan MD, MPH, ScD4,5, Robert L. Davis MD, MPH6, David Graham MD7, Susan E Andrade ScD2,8, Marsha A. Raebel PharmD2,9, Lisa Herrinton PhD2,10, Douglas Roblin PhD2,6, Denise Boudreau PhD2,11, David Smith PhD2,12, Jerry H. Gurwitz MD2,8, Margaret J. Gunter PhD2,13, and Richard Platt MD, MSc1,2

...alternative specifications tend to result in earlier signal detection by 10–16 months, a likely consequence of more exposures and events entering the analysis.
**Purpose:** Practical considerations for implementation of real-time drug safety surveillance using safety of generic versus branded divalproex as use case

**Methods:** Near real time surveillance at 4 health plans; monthly data extracts

**Results:** Data quality review process for each extract at each site is crucial. Data lags exists but can be accounted for.

**Conclusions:** Near real-time sequential safety surveillance is feasible, but several barriers warrant attention. …differential accrual between exposure and outcomes could bias risk estimates towards the null, causing failure to detect a signal.
Sequential surveillance in distributed networks

- Sequential drug safety surveillance is possible
- Makes best use of routinely collected data
- Simple data requirements allow combining data from multiple sources
  - Dispensing, diagnoses, demographics, eligibility
  - Stratified counts for analysis
  - Distributed data model → no transfer of PHI
- Requires strong coordinating center
  - Data checking and coordination is complex
  - Range of expertise needed
Mini-Sentinel

- Develop scientific operations for active medical product safety surveillance
- Create a coordinating center with continuous access to automated healthcare data systems, and the following capabilities:
  - Develop and evaluate scientific methods that might later be used in a fully-operational Sentinel System.
  - Evaluate safety issues
  - Identify and address barriers
- Operate under FDA’s public health authority
Safety issues

- Exposure-outcome relationships
  - Retrospective
  - Prospective
- Medical product utilization
  - Age, sex, calendar time
- Disease burden
- Response to FDA’s regulatory actions
Post-Market Safety Surveillance

Passive Surveillance (FAERS)

Signal identification: Potential safety concern identified

Data Mining

Summary Tables
Modular Programs
PROMPT

REMS and other assessments

Signal Refinement: Initial evaluation of safety concerns

Signal evaluation: Formal assessment of potential safety concerns

Rapid response querying and surveillance

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Mini-Sentinel Partner Organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners
Mini-Sentinel Distributed Analysis

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

2- Data partners retrieve query

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

4- Data partners review results

5- Data partners return results via secure network

6- Results are aggregated

ONC Query Health Compliant
The Mini-Sentinel Coordinating Center
Data Group
Structure of the data group

Cross functional staff of programmers, research associates, analysts, research assistants and vendors support the Data Group and workgroups.
# Mini-Sentinel Common Data Model

## Lab Results
- **Person ID**
- Dates of order, collection & result
- Test type, immediacy & location
- Procedure code & type
- Test result & unit
- Abnormal result indicator
- Ordering provider
- Department
- Facility
- Etc.

## Enrollment
- **Person ID**
- Enrollment start & end dates
- Drug coverage
- Medical coverage
- Etc.

## Demographics
- **Person ID**
- Birth date
- Sex
- Race

## Dispensing
- **Person ID**
- Dispensing date
- Dispensing MD
- National drug code (NDC)
- Days supply
- Amount dispensed

## Encounters
- **Person ID**
- Dates of service
- Provider seen
- Type of encounter
- Facility
- Department
- Etc.

## Vital Signs
- **Person ID**
- Date & time of measurement
- Encounter date & type when measured
- Height
- Weight
- Diastolic & systolic BP
- Tobacco use & type
- BP type & position
- Etc.

## Death
- **Person ID**
- Date of death
- Cause of death
- Source
- Confidence

## Procedures
- **Person ID**
- Dates of service
- Procedure code & type
- Encounter type & provider
- Etc.

## Diagnoses
- **Person ID**
- Date
- Primary diagnosis flag
- Encounter type & provider
- Diagnosis code & type
- Etc.

**Immunization registries**
- Birth and fetal death registries
- Inpatient data model

info@mini-sentinel.org
Data QA and characterization

1. Develop QA Package*
2. Execute QA Package
3. Review Output & Submit to MSOC
4. Track Receipt & Metadata
5. Execute Internal Programs
6. Review Output
7. Create Report
8. Execute Internal Programs
9. Review Output
10. Annotate Report
11. Review Report & Finalize
12. Review Report & Investigate Issues
13. Comment on Report
14. Review Report & Comment
15. Approve ETL
16. Track Approval & Metadata

*Program Development Team Follows MS SAS Program Development SOP to Create QA Package

Data Partner

MSOC
Data checking and characterization

- Hundreds of tables per data partner per refresh
- 4 levels of data checks
- > 1400 checks

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<td>4.6128</td>
</tr>
<tr>
<td>10</td>
<td>1.0 75+ Yrs</td>
<td>1324183</td>
<td>3.3928</td>
</tr>
</tbody>
</table>
New program development
Testing process and environments

- Among the 18 data partners there are 10 different environments
  - SAS versions (9.2, 9.3, 9.4; different versions of each)
  - Computing environments (Windows, Unix, Linux)
- 18 unique local hardware settings and systems
- Each distributed program must run in all environments
Query fulfillment process
Mini-Sentinel infrastructure systems

- Operations are all based on SOPs
- Tools are treated like software
  - Bug tracking system for all changes to code and code development
- FISMA compliant secure portal
- Activity tracker
- Secure distributed query tool
Mini-Sentinel querying tools

- Summary table queries
- Modular programs
  - Utilization patterns and cohort identification
  - Rate of adverse events following exposure
  - Background rates
- “macro” library
- Prospective Routine Observational Monitoring Program Tools (PROMPT)
  - Self-controlled design (exposure indexed)
  - Cohort design, with propensity score (exposure) matching
  - Cohort design, with regression adjustment (GEE)
  - Cohort design, with IPT weighted regression adjustment
Multiple networks sharing infrastructure
Multiple networks sharing infrastructure

- Each organization can participate in multiple networks
- Each network controls its governance and coordination
- Networks share infrastructure, data curation, analytics, lessons, security, software development
Thank you
this assessment [...] fda’s mini-sentinel pilot...
"In the months following the approval of the oral anticoagulant dabigatran ... in October, 2010, the FDA received through the FDA Adverse Event Reporting System many reports of serious and fatal bleeding events associated with use of the drug."

FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil

View and print full Drug Safety Communication (PDF - 54KB) en Español

Safety Announcement

[7-3-2013] The U.S. Food and Drug Administration (FDA) is warning that the blood pressure drug olmesartan medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy. FDA has approved changes to the labels of these drugs to include this information.

Symptoms of sprue-like enteropathy may include diarrhea with substantial weight loss. The enteropathy may develop gradually or quickly, and sometimes requires hospitalization. Although sprue-like enteropathy has not been previously reported in patients taking olmesartan, patients who develop these symptoms and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive started. Discontinuation of olmesartan has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients.

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) approved for the treatment of high blood pressure, alone or with other antihypertensive agents, and is one of eight marketed ARB drugs. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan.

FDA will continue to evaluate the safety of olmesartan-containing products and will communicate again if additional information becomes available.
FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception

FDA Safety Communication — June 13, 2013

FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception

FDA Approves Required Revised Labeling for RotaTeq Based on the Study Results

Purpose: To inform the public and healthcare providers that FDA is releasing final study results from a Mini-Sentinel postlicensure observational study of intussusception (a form of bowel obstruction) after vaccination with RotaTeq (Merck and Co., Inc.) and Rotarix (GlaxoSmithKline Biologicals).

RotaTeq and Rotarix are vaccines for the prevention of rotavirus gastroenteritis in infants 6 weeks to 32 weeks of age (RotaTeq) and infants 6 weeks to 24 weeks of age (Rotarix). The study was conducted in Mini-Sentinel’s Postlicensure Rapid Immunization Safety Monitoring (PRISM) program, the largest vaccine safety surveillance program in the United States.

FDA has approved required revisions to the Prescribing Information and Patient Information for RotaTeq as a result of the new safety data from this Mini-Sentinel PRISM study. New information was added to the Highlights, the existing intussusception section, the Post-Marketing Experience Information section of the Full Prescribing Information, and the Patient Information. The Mini-Sentinel PRISM study is the largest study to date and identified an increased risk of intussusception in the 21-day time period after the first dose of RotaTeq, with most cases occurring in the first 7 days after vaccination. No increased risk was found after the second or third doses. These findings translate into 1 to 1.5 additional cases of intussusception per 100,000 first doses of RotaTeq.

The data from the Mini-Sentinel PRISM study regarding the risk of intussusception following the use of Rotarix were inconclusive. Based on this study, no changes were made to the Prescribing Information or to the Patient Information for Rotarix. However, based on data from an observational study previously conducted in Mexico, it is estimated that 1 to 3 additional cases of intussusception would occur per 100,000 vaccinated infants in the United States within 7 days following the first dose of Rotarix. In September 2012, FDA announced that it had approved revisions to the Prescribing Information and to the Patient Information for Rotarix to include these results from the study in Mexico.

Label change
ORIGINAL INVESTIGATION

Online First

Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

Sengwee Toh, ScD; Marsha E. Reichman, PhD; Monika Houstoun, PharmD; Mary Ross Southworth, PharmD; Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn McCloskey, MD, MPH; Azadeh Shoai, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, PharmD, PhD
Mini-Sentinel Journal Supplement

- Supplement to Pharmacoepidemiology and Drug Safety
- 34 peer reviewed articles
- Goals, organization, privacy policy, data systems, systematic reviews, stats/epi methods, record retrieval and review, protocols for drug/vaccine studies...
- Open access!
Dabigatran and Postmarketing Reports of Bleeding
Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

“In the months following the approval of the oral anticoagulant dabigatran ... in October, 2010, the FDA received through the FDA Adverse Event Reporting System many reports of serious and fatal bleeding events associated with use of the drug.”

Thank you