Use of electronic health data to support a Learning Health System: Lessons from several distributed networks in the US

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The Learning Health System in Europe
Brussels, Belgium
September 25, 2015
Some distributed networks in US

- CDC’s Vaccine Safety Datalink (VSD)
- Health Care Systems Research Network
- FDA’s post-market safety programs
- Meningococcal Vaccine Safety Study
- FDA Mini-Sentinel
- NIH Health Care Systems Collaboratory
- PCORI National Clinical Research Network (PCORnet)
- MDPHnet
Some distributed networks in US

- CDC’s Vaccine Safety Datalink (VSD)
- Health Care Systems Research Network
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Vaccine Safety Datalink

- Funded by US Center for Disease Control and Prevention
- Post-marketing safety of vaccines
- Integrated delivery systems and health insurers
- Data standardization via a common data model
- Often rely on chart review
- Data are updated frequently (can be weekly)
- Work has informed vaccination policy
Launched November 2012

Real time access to ambulatory EHR data to inform public health

Automatically identifies reportable and chronic diseases and enables flexible querying

Massachusetts Department of Public Health (MDPH) epidemiologists have submitted hundreds of queries

Now an operational suite of systems supported by MDPH
Welcome to Mini-Sentinel

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

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

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

Spotlight

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

Latest Postings

Ongoing Projects
- Decision Analysis for Surveillance and Health - Pandemic Influenza (PRISM)
- Quantifying Uncertainty in Protocol Based -
Sentinel History

- **2007:** FDA Amendments Act
  - A mandate to create an active surveillance system
  - Access data from **25 million** individuals by July 2010
  - Access data from **100 million** individuals by July 2012

- **2008:** FDA launched the Sentinel Initiative

- **2009:** Mini-Sentinel funded under Sentinel Initiative
  - 5-year pilot to create active surveillance system monitoring the safety of FDA-regulated medical products
  - Develop policies, processes, infrastructure, collaboration

- **2014:** Funding awarded for Sentinel
Collaborators

Lead – HPHC Institute

Data and scientific partners

Scientific partners

health care systems research network
Bringing multiple data partners together

- Centralized vs. Distributed

- Distributed data system is preferred because
  - Data sits behind data partner’s firewall
  - Data remains under local control
  - Only minimally necessary info is shared in a given analysis
  - Preserve patient privacy & proprietary interests
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
## Common Data Model

### Administrative

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Demographic</th>
<th>Dispensing</th>
<th>Encounter</th>
<th>Diagnosis</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
</tr>
<tr>
<td>Enrollment start &amp; end dates</td>
<td>Birth date</td>
<td>Dispensing date</td>
<td>Dates of service</td>
<td>Date</td>
<td>Dates of service</td>
</tr>
<tr>
<td>Drug coverage</td>
<td>Sex</td>
<td>National drug code (NDC)</td>
<td>Provider seen</td>
<td>Principal diagnosis flag</td>
<td>Procedure code &amp; type</td>
</tr>
<tr>
<td>Medical coverage</td>
<td>Race</td>
<td>Days supply</td>
<td>Type of encounter</td>
<td>Encounter type &amp; provider</td>
<td>Encounter type &amp; provider</td>
</tr>
<tr>
<td>Medical record availability</td>
<td>ZIP code</td>
<td>Amount dispensed</td>
<td>Facility</td>
<td>Diagnosis code &amp; type</td>
<td>Encounter ID</td>
</tr>
</tbody>
</table>

### Clinical Data Elements

<table>
<thead>
<tr>
<th>Lab Result</th>
<th>Vital Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person ID</td>
<td>Person ID</td>
</tr>
<tr>
<td>Dates of order, collection &amp; result</td>
<td>Date &amp; time of measurement</td>
</tr>
<tr>
<td>Test type, immediacy &amp; location</td>
<td>Height and weight</td>
</tr>
<tr>
<td>Procedure code &amp; type</td>
<td>Diastolic &amp; systolic BP</td>
</tr>
<tr>
<td>Test result &amp; unit</td>
<td>Tobacco use &amp; type</td>
</tr>
<tr>
<td>Etc.</td>
<td>Etc.</td>
</tr>
</tbody>
</table>

### Death Information

<table>
<thead>
<tr>
<th>Death</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person ID</td>
<td>Person ID</td>
</tr>
<tr>
<td>Death date</td>
<td>Cause of death</td>
</tr>
<tr>
<td>Source</td>
<td>Source</td>
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<tr>
<td>Confidence</td>
<td>Confidence</td>
</tr>
<tr>
<td>Etc.</td>
<td>Etc.</td>
</tr>
</tbody>
</table>

### Registry

<table>
<thead>
<tr>
<th>State Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person ID</td>
</tr>
<tr>
<td>Provider</td>
</tr>
<tr>
<td>Admission Type</td>
</tr>
<tr>
<td>Vaccine Code</td>
</tr>
<tr>
<td>Vaccine Code Type</td>
</tr>
<tr>
<td>Etc.</td>
</tr>
</tbody>
</table>
Impact / Dissemination

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

- 70 peer-reviewed articles

- 48 methods reports / white papers

- Thousands of unique queries and comparisons contributing to over 140 formal assessments

www.mini-sentinel.org
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 & Co., Inc.) and Rotarix (GlaxoSmithKline Biologics).

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 revised labeling for RotaTeq and Rotarix. Information for RotaTeq as a result of the new safety data includes an advisory and patient information for RotaTeq as a result of the changed labeling. This advisory was added to the Highlights, the existing intussusception subsection of the Warnings and Precautions section, and the Post-Marketing Experience section of the Full Prescribing Information, as well as to the Patient Information. The Mini-Sentinel PRISM study is the largest study of intussusception after rotavirus vaccines 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.

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm356758.htm
Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, Ph.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Martin Kulldorff, Ph.D., David Martin, M.D., M.P.H., Cheryl N. McMahill-Walraven, M.S.W., Ph.D., Richard Platt, M.D., Nandini Selvam, Ph.D., M.P.H., Mano Selvan, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Nguyen, M.D.
FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa

This update is a follow-up to the FDA Drug Safety Communication of 12/7/2011: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
References

Safety Announcement
[11-02-2012] The U.S. Food and Drug Administration (FDA) has evaluated new information about the risk of gastrointestinal bleeding (occurring in the stomach and intestines) and intracranial hemorrhage (a type of bleeding in the brain) for new users of Pradaxa compared to new users of warfarin. This assessment was done using insurance claims and administrative data from FDA’s Mini-Sentinel pilot of the Sentinel Initiative. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial).1 (see Data Summary). FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue.

“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.
Rate of gastrointestinal bleeding per 100k days at risk (8 scenarios)

# Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

<table>
<thead>
<tr>
<th>Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal hemorrhage</strong></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
</tr>
<tr>
<td><strong>Intracranial hemorrhage</strong></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
</tr>
</tbody>
</table>
Protocol-based assessment – Dabigatran

MINI-SENTEL MEDICAL PRODUCT ASSESSMENT

A PROTOCOL FOR ASSESSMENT OF DABIGATRAN

Prepared by: Alan S. Go, MD¹, Daniel Singer, MD², T. Craig Cheetham, PharmD MS³, Darren Toh, ScD⁴, Marsha Reichman, PhD⁵, David Graham, MD MPH⁵, Mary Ross Southworth, PharmD⁶, Rongmei Zhang PhD⁷, Monika Houstoun, PharmD⁵, Yu-te Wu, PhD⁷, Katrina Mott, MS⁵, Joshua Gagne, PharmD ScD⁸

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

**Data Summary**

**Olmesartan label change:**

sprue-like enteropathy

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, Apo-Benicar, and generics) can cause sprue-like enteropathy. This problem is also known as sprue-like enteropathy, sprue-like enteropathy, and idiopathic sprue-like enteropathy. The condition requires significant weight loss. The FDA recommends that physicians discontinue the drug if symptoms and no other cause can be identified.

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.
ARBs and celiac disease: all users

- ARBs: New users after >365 day washout; Celiac Disease: 1st dx code after >365 day without diagnosis.
ARBS and celiac disease: all users

<table>
<thead>
<tr>
<th>Cases</th>
<th>213</th>
<th>28</th>
<th>55</th>
<th>10</th>
<th>150</th>
</tr>
</thead>
<tbody>
<tr>
<td>New users</td>
<td>535,045</td>
<td>69,868</td>
<td>171,630</td>
<td>44,770</td>
<td>346,618</td>
</tr>
</tbody>
</table>
ARBs and celiac disease: 2+ years

<table>
<thead>
<tr>
<th>ARB</th>
<th>Cases</th>
<th>New users</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOSARTAN</td>
<td>9</td>
<td>25,045</td>
</tr>
<tr>
<td>IRBESARTAN</td>
<td>1</td>
<td>2,721</td>
</tr>
<tr>
<td>OLMESARTAN</td>
<td>5</td>
<td>4,419</td>
</tr>
<tr>
<td>TELMISARTAN</td>
<td>0</td>
<td>1,124</td>
</tr>
<tr>
<td>VALSARTAN</td>
<td>7</td>
<td>13,925</td>
</tr>
</tbody>
</table>
“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..
Key Contributors to Mini-Sentinel’s Progress

- **Tightly Coupled** network
- Frequent and coordinated interactions between FDA, data partners, content experts, epidemiologists, and statisticians
- Clear ownership and goals
- Established agreements and contracts
- Distributed data network (no central repository)
- Public health practice
- Focused on best understood and useful data for purpose
  - **First**: Claims and administrative data, plus access to full text records
    - Syntax and semantics are clear and understood
  - **Then**: electronic medical records, registries, ...
    - Much more complex to understand, standardize, and use for research
- Rapid cycle development of capabilities
Thank You

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For More Information

PopMedNet Website
popmednet.org

PopMedNet Wiki
popmednet.atlassian.net/wiki
Thank You

Links

- www.PopMedNet.org
- mehi.masstech.org/what-we-do/hie/mdphnet/about
- www.pcornet.org
- www.mini-sentinel.org
- nihcollaboratory.org/Pages/distributed-research-network.aspx

NIH Collaboratory Distributed Research Network Presentations

https://www.nihcollaboratory.org/Pages/Grand-Rounds-11-14-14.aspx
Selected references