FDA's Mini-Sentinel Program to Evaluate the Safety of Marketed Medical Products

Progress and Direction

Richard Platt
Harvard Pilgrim Health Care Institute
Harvard Medical School
for the Mini-Sentinel Investigators

January 31, 2013
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.
  - Offer FDA the opportunity to evaluate safety issues in existing automated healthcare data system(s) and learn more about barriers and challenges.
Initial needs

- Policies
  - Privacy
  - Governance

- Data model

- Procedures at FDA, at Coordinating Center, at Partner sites
  - White papers
  - Standard operating procedures

- Infrastructure at FDA, at Coordinating Center, at Partner sites
  - Personnel
  - Hardware
  - Software

Everything!
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
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!

info@mini-sentinel.org
“This assessment [...used...] FDA’s Mini-Sentinel pilot...”

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

Senghee 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 Shoailbi, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, PharmD, PhD
All drugs have adverse effects. The challenge for practicing physicians is to determine which medications have the fewest adverse effects for a given therapeutic benefit. Unfortunately, drugs with similar indications often have not been directly compared with one another because their approvals were based on comparison with placebo or with only one member of the same or a similar class. Moreover, the comparable risks for unusual adverse effects with a group of different medications having similar indications can be even more challenging because most phase 3 efficacy trials are not powered to accurately estimate or even detect the adverse effect that can be life-threatening. Using the Food and Drug Administration’s Mini-Sentinel program, Toh et al show that all the drugs acting on this system are not associated with the same incidence of angioedema. Specifically, the incidence was significantly higher for angiotensin-converting enzyme inhibitors and aliskiren than for angiotensin receptor blockers, and all the study drugs were associated with a greater incidence of angioedema compared with the reference category of β-blockers.

Beyond the content, we commend the Food and Drug Administration for developing the Mini-Sentinel Distributed Database; this analysis draws on medication use and

“...we commend the Food and Drug Administration for developing the Mini-Sentinel...”

RE-USE OF MINI-SENTINEL DATA FOLLOWING RAPID ASSESSMENTS OF POTENTIAL SAFETY SIGNALS USING CUSTOMIZABLE MODULAR PROGRAMS

Prepared by: The Mini-Sentinel Data Re-use Committee
MINI-SENTINEL METHODS

FRAMEWORK FOR ASSESSMENT
OF SIGNAL REFINEMENT POSITIVE RESULTS

Prepared by: David L McClure, PhD, Marsha A Raebel, PharmD, BCPS, FCCP, W Katherine Yih, PhD, MPH, Azadeh Shoaibi, MS, MHS, Jerry Mullersman, MD, PhD, MPH, Colin Anderson-Smits, MPH, Rita Ouellet-Hellstrom, PhD, Aloka Chakravarty, PhD, Clara Kim, PhD, Jason M Glanz, PhD

In theory there is no difference between theory and practice. In practice there is.

Yogi Berra

www.brainyquote.com/quotes/quotes/y/yogiberra141506.html#gsD0IBx3dytirLPX.99
Mini-Sentinel Distributed Analysis

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6 Results are aggregated
PopMedNet Architecture – Deployment Overview

- PMN Software – Supports multiple deployment models
  - Agnostic to data center infrastructure and complements existing network infrastructure
  - VM based deployments enabling ease of disaster recovery and planning
  - Seamless overlay of VPN Connections (Remote Access, Site to Site, Two Factor User Authentication)
  - Supports consolidation of remote sites into the data center for central management (Data Partner Components can be hosted in a central data center similar to the PMN Portal)
  - Secure End to End connection (Encrypted Transport using X.509 certificates)
  - Supports industry standard RBAC configuration for users
  - Supports Data Source provisioning based on RBAC and additional data source specific metadata
  - Queries distributed using a PULL model instead of PUSH model
Mini-Sentinel Distributed Analysis

1- User creates and submits query (a computer program)
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6 Results are aggregated
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Query tool development /use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development
A Mini-Sentinel week

- Distributed dataset development/maintenance
Data Refreshes: Data Partner

1. Create Data Update Work Plan
2. Review Data Update Work Plan
3. Verify Source Data Availability
4. Verify/Modify ETL Process
5. Extract Data from Source System
6. Transform & Load Data into CDM
7. Validate Data Load
8. Create Query Tool Files
9. Data Quality Checking & Profiling
10. Manage Data Update Process

MSOC  Data Partner
Data Refreshes

- 120 core data refreshes received since MS began

How long does it take to approve a refresh?

Three weeks to three months
Standard data checks

- 100+ tables per data partner per refresh

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Data Visualization: After 7\textsuperscript{th} refresh, partner A
Data Visualization: After 8\textsuperscript{th} refresh, partner A

- New time period
- New data problem in old time period
Data Visualization: After 8\textsuperscript{th} refresh fixed
• “Eternal vigilance is the price of liberty”
  -- attributed to Thomas Jefferson

• “Eternal vigilance is the price of reliable data"  
  -- Mini-Sentinel

info@mini-sentinel.org
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Query fulfillment tools development /use
Typical Input to Modular Programs

- Look back XX days
- Inclusion/exclusion condition

Start of new treatment episode

- Outcome(s)
- Optional: blackout days
- Optional: extension days

Start Date

Index Date

End Date

Time
Mini-Sentinel Query Fulfillment Process

1. Request Query

2. Review Query & Log Request

3a. Design Query Tool or Modular Program Technical Specifications

3b. SAS Program Development

4. Review Query Technical Specifications

5. Develop & Test Query

6. Review & Approve Query

7. Distribute Query

8. Review Query

9. Run Query

10. Review Query Results

11. Aggregate Query Results

12. Create Final Query Report

13. Review Final Query Report


15. Receive Final Query Report via Secure Portal

16. Manage Query Request & Fulfillment Process
When existing programs aren’t enough

- Modify a modular program, or
- Create a new program
Uses of the distributed database

**Modular Programs**

- MP Queries
- MP Reports
- MP Scenarios

**Ad Hoc Programs**
A Mini-Sentinel week

- Distributed dataset development / maintenance
- Query tool development / use
- Protocol development / implementation
Protocols in the field now

- Impact of labeling change on use of long acting beta agonists
- Rotavirus vaccine and intussusception
- Human papillomavirus vaccine and thromboembolism
- Anti-diabetic drugs and acute myocardial infarction
Protocols under development

- Influenza vaccine safety
  (same season, sequential analysis)
- Metabolic effects of atypical antipsychotics in children and adolescents
- Influenza vaccine and febrile seizures
- Dabigatran and stroke / bleeding
- Influenza vaccine and birth defects, spontaneous abortion
- IV iron products and anaphylactoid reactions
- IV immune globulins and thromboembolic events
A Mini-Sentinel week

- Distributed dataset development / maintenance
- Query tool development / use
- Protocol development / implementation
- Methods development / implementation
Methods

- Improving confounder adjustment
- Validation of health outcomes of interest
- Data mining for vaccine adverse events
- Implementing routine prospective surveillance of new products using sequential methods
A Mini-Sentinel week

- Distributed dataset development / maintenance
- Query tool development / use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
Coming in 2013

- Prospective surveillance of new products
- New query tools
- New bandwidth to respond to more queries
- New data
  - Links to state birth and immunization registries
  - Explore use of inpatient data
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Query tool development /use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development
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 convening an ongoing series of discussions among stakeholders to address the near- and long-term challenges inherent in implementing the Sentinel System. In 2009, the FDA gave the Harvard Pilgrim Health Care Institute the lead role
Continue external engagements

- NIH Health Care System Collaboratory
- Observational Medical Outcomes Partnership (OMOP)
- Clinical Trials Transformation Initiative
- ONC Standards & Interoperability Framework (Query Health)
- IOM Roundtable on Value and Science-Driven Health Care
- Academy Health EDM Forum
- Other new partners as opportunities present
In conclusion
Key contributors to Mini-Sentinel’s progress

- Close, frequent, coordinated interactions between FDA, data partners, content experts, epidemiologists, and statisticians
- Distributed data network
- Public health practice
- Focus on defined populations with sufficiently complete data
  - First: Claims and administrative data, plus access to full text records
  - Then: electronic medical records, registries, ...
- Rapid cycle development of capabilities
- Ability to respond quickly to predefined needs
Success Of Program Linking Data Sources To Monitor H1N1 Vaccine Safety Points To Potential For Even Broader Safety Surveillance

ABSTRACT In response to the 2009 H1N1 pandemic and subsequent vaccination program, the Department of Health and Human Services and collaborators developed the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program as a demonstration project to detect rare plans and from public immunization registries that had originally not been designed to share data, and on a larger scale than had been previously attempted. The program generated safety data in two weeks rather than three to six montly 10ths—the standard time frame achievable using health plan data. PRISM substantially contributed to the understanding of the safety of H1N1 vaccines. Its use in the case of H1N1 highlights the necessity of proactive planning, scalable infrastructure, and public-private partnerships in

“...highlights the necessity of proactive planning...”

Salmon Health Affairs 2012; 31:2518
Costs and benefits

- Up to date distributed database + hundreds of rapid response queries
- Protocol based study
- Being prepared for pandemic or other crisis

~$10 million per year
$225,000+
Priceless!
Expectations confirmed

- Standard programs can help FDA quickly interpret signals from other sources:
  - Dabigatran and bleeding
  - Olmesartan and celiac disease
  - Varenicline and cardiac events

- Many sophisticated analyses do not require exchange of protected health information
Thank you!