FDA's Mini-Sentinel Program

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NIH Health Care Systems Research Collaboratory Grand Rounds
February 15, 2013
Mini-Sentinel

- Congress mandated FDA develop electronic record based safety surveillance system

- Mini-Sentinel is a five year pilot project to:
  - Develop operational capacity for active medical product safety surveillance in existing automated healthcare data systems
  - Develop and evaluate scientific methods
  - Offer FDA the opportunity to evaluate safety issues
  - Assess barriers and challenges
Mini-Sentinel’s key features – 1

- Governance – patient privacy, organizational expectations, etc.
- Focus on safety of marketed medical products
- Operates under FDA’s public health authority – no IRB oversight
- Distributed network – no central data repository
  - Pooled analysis file are created as needed
- Coordinating center – technical expertise, libraries of protocols/programs
- Data sources
  - Administrative data, EHR, registries
  - Access to full text records to confirm exposures, outcomes, risk factors
Mini-Sentinel’s key features – 2

- **Evaluations**
  - Safety of established products
    - Rapid assessment of new questions
    - In depth assessment of persistent questions
  - Response to regulatory action
  - Prospective assessment of accumulating experience with new products

- **Methods development**
  - Statistics, epidemiology, performance of detection algorithms, linkage between data sources
Mini-Sentinel’s key components

- Policies
  - Privacy
  - Governance

- Data

- Infrastructure and procedures for their use
  at FDA, at Coordinating Center, at Partner sites
  - Standard operating procedures
  - Personnel
  - Hardware
  - Software
Mini-Sentinel partner organizations
Mini-Sentinel Distributed Database*

- Populations with well-defined person-time for which most medically-attended events are known
  - 382 million person-years of observation time
  - 3.7 billion dispensings
  - 4.1 billion unique encounters
    - 46 million acute inpatient stays
- 24 million people with \( >1 \) laboratory test result

*As of January 2013
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 Distributed Analysis

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Mini-Sentinel’s Data Sources

- Administrative data
  - Enrollment
  - Demographics
  - Outpatient pharmacy dispensing
  - Utilization (encounters, diagnoses, procedures)

- EHR data
  - Height, weight, blood pressure, temperature
  - Laboratory test results (selected tests)

- Registries
  - Immunization
  - Mortality (death and cause of death)
### Mini-Sentinel’s Common Data Model

#### 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.

#### 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
- 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.
Standard data checks for each refresh cycle

- 120 core data refreshes received through 2012
- ~400 data checks per refresh
- 100+ tables per data partner per refresh

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Rapid Queries of Exposure-Outcome Pairs

- Angiotensin receptor blockers (ARBs) and celiac disease
- Drugs for smoking cessation and cardiac outcomes
- Drugs for Parkinson's disease and acute myocardial infarction or stroke
- Analeptics and severe cutaneous adverse reactions
- Oral hypoglycemics and hypersensitivity reactions
- Atypical antipsychotics and hypersensitivity reactions
- Vascular endothelial growth factor (VEGF) inhibitors and osteonecrosis of the jaw
- Direct thrombin inhibitors / warfarin and hemorrhage
- Aspirin antagonists and stroke or transient ischemic attack
Typical Input to Modular Programs

Start Date

- Look back XX days
- Inclusion/exclusion condition

Start of new treatment episode

Index Date

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

End Date

Time
Angiotensin Receptor Blockers and Celiac Disease

- Potential signal identified in FDA’s spontaneous report database (AERS)
- Review of cases inconclusive
### ARBs and celiac disease

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**ARBs:** New users after ≥365 day washout; **Celiac Disease:** 1st dx code after >365 day without diagnosis.

info@mini-sentinel.org
Limitations

- Capture of relevant GI events may be incomplete
- Potential inclusion of irrelevant events
- Patients exposed to different agents may differ with respect to risk of GI symptoms
- Majority of exposures limited to a few months duration
- Observed risk doesn’t exclude excess
ARBs and Celiac Disease

**Modular Program Type:** MP 3 - Drug Use – Incident Outcomes

**Date Posted:**

**Medical product exposures of interest:**

This Modular Program execution included 7 unique exposures, all in the Angiotensin II Receptor Blocker (ARB) drug category. The exposures were defined using National Drug Codes (NDCs identified by FirstDataBank), limited to the oral formulations, identified in the Mini-Sentinel outpatient dispensing file. The 7 drugs included were:

- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan
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 […] used […] FDA’s Mini-Sentinel pilot…”

One-Time Protocol-based Assessments

- ACEIs/ARBs/aliskiren and Angioedema
- Rotavirus Vaccines and Intussusception
- Influenza Vaccine and Febrile Seizures
- Influenza Vaccine and Pregnancy Outcomes
- Human Papilloma Virus Vaccine and Venous Thromboembolism
ORIGINAL INVESTIGATION

**Online First**

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

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Mini-Sentinel distributed analysis

1 Workgroup creates and submits query (a computer program)

2 Data partners retrieve the 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 and returned
Cohort creation

Total population in Mini-Sentinel as July 2011
~99,000,000

Applying eligibility criteria *
(age, medical history, etc)

- ACEIs 1,845,138
- ARBs 467,313
- Aliskiren 4,867
- β-blockers 1,592,278

* New users with no recent exposure to any of the 4 classes and no prior angioedema
Statistical analysis

- Propensity score approach
  - Condensing information from a large number of variables
- Case-centered approach and meta-analysis
  - Needing only aggregated data to complete the analysis
Results

Adjusted relative risk

ACEIs

* Beta-blockers as the common reference group

Toh et al, Arch Intern Med 2012;172:1582-1589
Results

![Adjusted relative risk chart]

* Beta-blockers as the common reference group

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Results

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* Beta-blockers as the common reference group
Timeline

- Kick-off meeting: Mar 11
- Protocol finalized: Aug 11
- 1st workplan sent: Sep 11
- Analysis complete: Jan 12
- Draft final report: Feb 12

Total time from start to completion: ~11 months
Conclusions

- Largest assessment on this topic to date
- Replicated known ACEIs–angioedema association
  - With much more precise risk estimates
- Provided new information on angioedema risk for
  - Aliskiren (caveat: based on 7 exposed cases)
  - ARBs
Conclusions

- Time and cost efficient study
- Robust statistical analysis did not require sharing of person-level data
An aside on distributed data analysis

MINI-SENTINEL METHODS

EVALUATING STRATEGIES FOR DATA SHARING AND ANALYSES IN DISTRIBUTED DATA SETTINGS

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More results can be found here

- **Report:**

- **Manuscript:**

- **Presentation:**
“…we commend the Food and Drug Administration for developing the Mini-Sentinel…”

Risks and Benefits of Medications in Real-World Practice

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 inverse 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

Protocols in the field now

- Electronic data only
  - Impact of labeling change on use of long acting beta agonists
  - Anti-diabetic drugs and acute myocardial infarction

- Electronic data plus chart review
  - Rotavirus vaccine and intussusception
  - Human papillomavirus vaccine and thromboembolism
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
Key contributors to Mini-Sentinel’s progress

- Strong collaborations between investigators and data partners
  - Creation of a community of trust with shared goals, backed by clear governance policies
  - Data partners’ participation as collaborators
  - Data partners’ voluntary participation on a case-by-case basis

- Distributed data network

- Focus on a relatively few well defined types of assessment

- 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
Welcome to Mini-Sentinel

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated products.

Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance.

Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise.
Perspective

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...
NIH Health Care Systems Collaboratory

Home of the NIH Distributed Research Network
Millions of people. Strong collaborations. Privacy first.

A Virtual Home for Knowledge about Pragmatic Clinical Trials using Health Systems

The Collaboratory
Thank you!