ENGELBERG CENTER for Health Care Reform at BROOKINGS

Overview of FDA's Mini-Sentinel Pilot

Richard Platt, Professor and Chair of the Department of Population Medicine at Harvard Medical School and the Harvard Pilgrim Health Care

September 15, 2011

Brookings Roundtable on Active Medical Product Surveillance

Some Initial Housekeeping

- To minimize feedback, please confirm that the microphone on your telephone is muted.
- To mute your phone, press the mute button or '*6'. (To unmute, press '*7' as well.)
- **There will be several opportunities for questions and discussion throughout today's session. Please use the Q&A tab at the top of your screen to submit your questions into the queue at any point and we will call upon you to state your question.**
- We will open up the lines for questions from those participating only by phone at the end of each Q&A session.
- Call the Brookings IT Help Desk at 202-797-6193 with technical problems.

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

September 15, 2011

Mini-Sentinel

www.mini-sentinel.org

- Develop the scientific operations needed for an active medical product safety surveillance system
- Create a coordinating center with continuous access to automated healthcare data systems, which would have the following capabilities:
  - Provide a "laboratory" for developing and evaluating scientific methodologies that might later be used in a fully-operational Sentinel System.
  - Offer the Agency the opportunity to evaluate safety issues in existing automated healthcare data system(s) and to learn more about some of the barriers and challenges, both internal and external.

Stages of postmarket surveillance

Aim = Identify excess risk	All (suspected and unanticipated) adverse events (AEs), all products	**Specific AE:product pairs of concern**	A highly suspected AE:product pair
Approach		**Repeated assessment of accumulating experience or one-time expedited assessment**	
Example		Active surveillance in Mini-Sentinel and VSD using coded electronic health information	

Sentinel prototype

- Develop a consortium of data partners and other content experts

Mini-Sentinel Partner Organizations

HealthCore
WELLPOINT
KAISER PERMANENTE
hmo research network
Aetna
Humana Pharmacy Solutions®
VANDERBILT SCHOOL OF MEDICINE
OUTCOME™
Penn Medicine
Cincinnati Children's change the outcome
DukeMedicine
CRITICAL PATH INSTITUTE Improving the Path for Innovative Therapies
UAB
PARTNERS HEALTHCARE
AHIP America's Health Insurance Plans
UIC
THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH
RUTGERS Institute for Health

Sentinel prototype

- Develop a consortium of data partners and other content experts
- Develop policies and procedures

Governance principles/policies

- Public health practice, not research
- Minimize transfer of protected health information and proprietary data
- Public availability of "work product"
  - Tools, methods, protocols, computer programs
  - Findings
- Data partners participate voluntarily
- Maximize transparency
- Confidentiality
- Conflict of Interest

Sentinel prototype

- Develop a consortium of data partners and other content experts
- Develop policies and procedures
- Create a distributed data network with access to electronic health data and full text records
  - Develop secure communications capability
- Evaluate extant methods in safety science
  - Develop new epidemiological and statistical methods as needed
- Evaluate FDA-identified medical product-adverse event pairs of concern

Data Core

Methods Core

Protocol Core

The Mini-Sentinel Distributed Database

Data Core Leaders:
Lesley Curtis
Mark Weiner

Agenda

- Overview of the Mini-Sentinel Distributed Database
- Generating useful information
- Future plans for the Mini-Sentinel Distributed Database

Why a Distributed Database?

- Data Partners maintain physical control of their data
- Local content experts maintain a close relationship with the data
- Eliminates the need to create, secure, maintain, and manage access to a complex, central data warehouse

Guiding Principles (selected)

- Data Partners have the best understanding of their data and its uses; valid use and interpretation of findings requires input from the Data Partners.
- Distributed programs should be executed without site-specific modification after appropriate testing.
- The Mini-Sentinel Common Data Model accommodates all requirements of Mini-Sentinel data activities and may change to meet FDA objectives.

Mini-Sentinel Common Data Model v1.1

- Describes populations with administrative and claims data
  - Has well-defined person-time for which medically-attended events are known
- Data areas
  - Enrollment
  - Demographics
  - Outpatient pharmacy dispensing
  - Utilization (encounters, diagnoses, procedures)
  - Mortality (death and cause of death)

The Mini-Sentinel Distributed Database

- Quality-checked data held by 17 partner organizations
- 99 million individuals*
  - 316 million person-years of observation time (2000-2011)
  - 39 million individuals currently enrolled, accumulating new data
  - 24 million individuals have over 3 years of data

*As of 7 July 2011. The potential for double-counting exists if individuals moved between data partner health plans.

The Mini-Sentinel Distributed Database

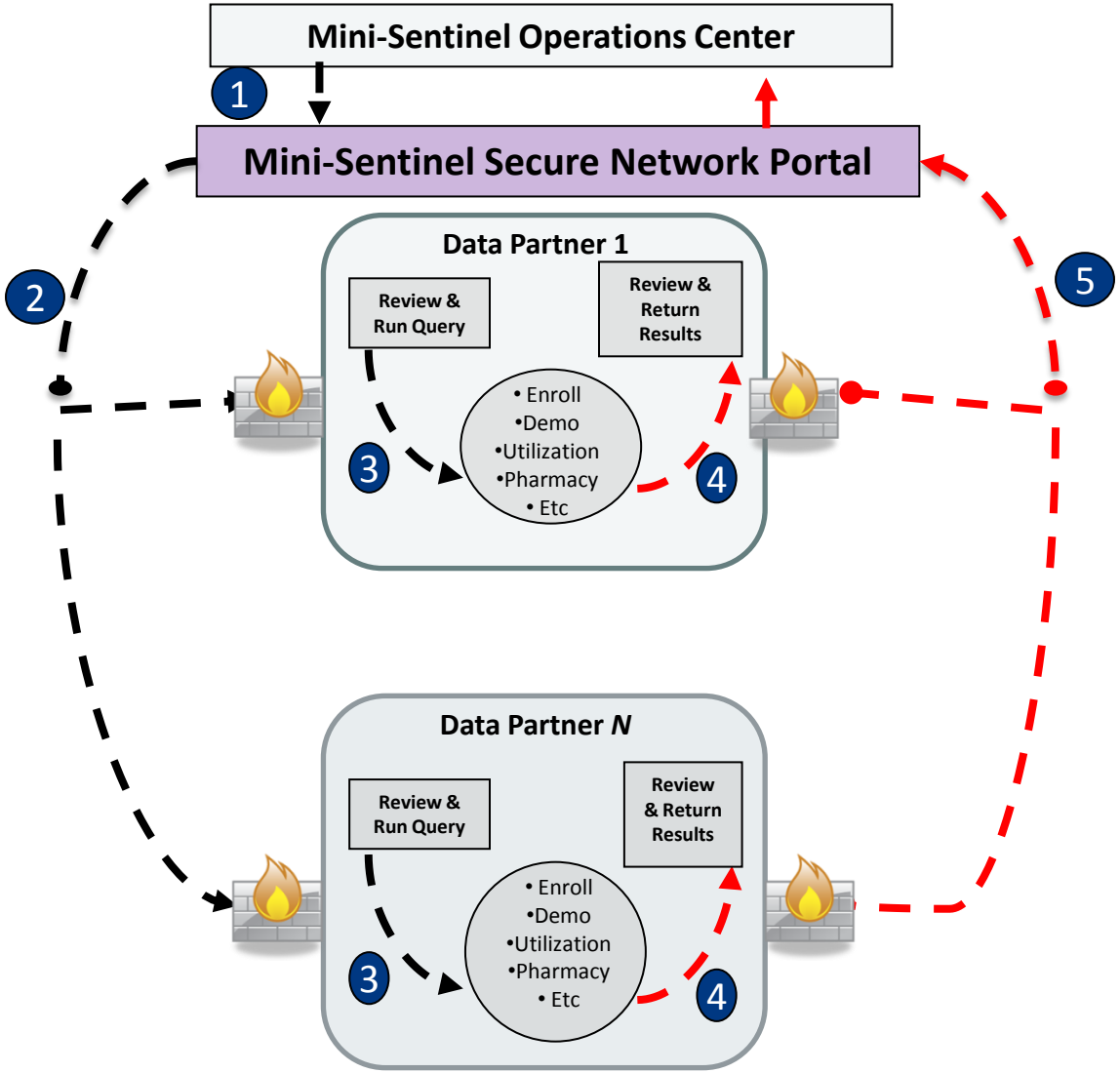
- 2.9 billion dispensings
  - Accumulating over 30 million dispensings per month
- 2.4 billion unique encounters; 38 million acute inpatient stays
  - Accumulating over 30 million encounters per month, including over 400,000 hospitalizations

*As of 7 July 2011

Generating Useful Information

- Quarterly refresh cycles
- Secure web portal for distributed analyses
- Capability for rapid querying
  - Query Tool
  - Modular Programs
- Protocol-based assessments

Mini-Sentinel Distributed Analysis



1- Query created and submitted by authorized user on the secure network portal

2- Data partners notified of query and retrieve it from the secure network portal

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

4- Data partners review results

5- Data partners securely return results to the secure network portal for review by requestor

Mini-Sentinel Query Tool

- Enhanced version of PopMedNet™ software application
- Queries summary counts of each table in the local implementation of the common data model.
  - Summary tables reside with the Data Partners
  - Software securely transmits queries and posts results
- Data Partners can choose to evaluate queries before execution or queries can be run automatically.

Mini-Sentinel Modular Programs

1. Drug exposure for a specific period
   - Incident and prevalent use combined
2. Drug exposure with a specific condition
   - Incident and prevalent use combined
   - Condition can precede and/or follow
3. Outcomes following first drug exposure
   - May restrict to people with pre-existing diagnoses
   - Outcomes defined by diagnoses and/or procedures
4. Concomitant exposure to multiple drugs
   - Incident and prevalent use combined
   - May restrict to people with pre-existing conditions

Current expansion

- Incorporate data from state and local immunization registries
  - 3 data partners and 8 state and local immunization registries
- Include selected clinical data including vital signs and clinical laboratory results
  - e.g., glucose, HBA1c, hemoglobin, INR, creatinine, ALT

On the Horizon

- Expand Mini-Sentinel common data model to include additional clinical data from Electronic Health Records and other sources
- Enhance existing modular programs
  - Automated confounder adjustment
  - Self-control designs
- Expand the library of summary tables and modular programs

Mini-Sentinel Methods Core:
Accomplishments and lessons learned

Methods Core Leaders:
Sebastian Schneeweiss
Jennifer Nelson

Map of methodologic domains

Data capacity	Distributed methods	Signal alerting
• **Integrity** – Common data model – Data completeness – Data validity – HOI validation • **Environments** – Claims – EHRs • Ambulatory • Inpatient – Registries – Other (blood banks, genetic data, etc.)	• **Distribution and retrieval** • **Anonymous linkage across sources** • **Distributed multivariable analysis** – Horizontal – Vertical	• **Design & validity** – Expedited design choice – Automated confounding adjustment • **Performance of** – Sequential testing – Non test-based – Decision analytic approaches • **Special aspects** – Drugs, vaccines, biologics, devices

Applications
• Oral antidiabetic agents and MI, rotavirus vaccine and intussusception, etc.

Design and validity

- Taxonomy project:
  - Expedited choice of design and analytic monitoring approach
  - Identified generic attributes of exposure, outcomes, and relationships developed a decision table (Gagne et al, PDS submitted)
  - Year 2 Taxonomy working on refinements/analytic choices
- Self-controlled designs:
  - Came up with clear guidance on (Maclure et al, PDS submitted)
    - Strength/limitations, practicability in a monitoring setting
  - Tested a multivariate SCCS approach (Madigan et al, PDS submitted)

Decision Table:

64 drug-outcome pair scenarios are linked to two basic designs strategies

Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios

Monitoring scenario characteristics with implication for design choice[a]							Monitoring scenario characteristics with implication for analytic choice[a]		
	Characteristics of the (potential) exposure-HOI link								
			Strength of confounding						
Exposure persistence *(transient, sustained)*	**Onset of exposure risk window** *(Immediate, delayed)*	**Duration of exposure risk window** *(short, long)*	**Within-person** *(negligible, needs to be addressed)*	**Between-person** *(negligible, needs to be addressed)*	**HOI onset** *(abrupt, insidious)*	**Design choice[b]** *(self-controlled, cohort)*	**Background frequency of exposure** *(infrequent, rare)*	**Background frequency of HOI** *(infrequent, rare)*	**Analytic choice**
Transient (e.g. vaccine, *initiation* of a drug; including episodic drug use [e.g. triptans] to the extent that the question pertains to its transient nature)	Immediate	Short	Negligible	Negligible	Abrupt	1 self-controlled (or cohort)	Infrequent	Infrequent	1
								Rare	2
							Rare	Infrequent	3
								Rare	4
					Insidious	2 cohort (or self-controlled)	Infrequent	Infrequent	5
								Rare	6
							Rare	Infrequent	7
								Rare	8
				Needs to be addressed	Abrupt	3 self-controlled (or cohort)	Infrequent	Infrequent	9
								Rare	10
							Rare	Infrequent	11
								Rare	12
					Insidious	4 self-controlled or cohort	Infrequent	Infrequent	13
								Rare	14
							Rare	Infrequent	15
								Rare	16
			Needs to be addressed	Negligible	Abrupt	5	Infrequent	Infrequent	17

Design and Validity

- Automated covariate adjustment
  - Empirical covariate identification in claims data is essential
    - for improved confounding adjustment and rapid turn-around
  - Empirical approaches have been shown to be superior to investigator identified adjustment in claims
  - Simulation studies have shown that theoretical biases (M-Bias and z-Bias) are not relevant (Myers et al. AJE 2011 in press)
  - A comprehensive approach to automated covariate adjustment is developing for PS and DRS methods (Rassen & Schneeweiss, PDS submitted)

Performance of signal alerting algorithms

- Sequential testing
  - Developed guidance on sequential designs customized for observational safety settings (Nelson et al, submitted)
  - Reviewed methods 'state-of-the-art'
  - Simulation to compare performance (Cook et al, PDS submitted)
    - Type 1 error rate, power, time-to-signal detection
    - Varying outcome prevalence, exposure & confounder complexity
  - Using inverse probability weighting (ongoing Y2 activity)

Future directions

- Combining Propensity Score and Disease Risk Score to monitor NMEs
- Simulation framework for evaluating alerting algorithms
- Semi-automated or automated confounding control

FDA's Mini-Sentinel Program: Protocol Core

Protocol Core Leaders:
Sean Hennessy
Elizabeth Chrischilles
Ryan Carnahan

Overview of Protocol Core Activities

- Foundational Work
  - Systematic reviews of the literature
  - Validation of selected Health Outcomes of Interest
- Retrospective Assessments
  - Rapid queries of exposure-outcome pairs (modular programs)
  - One-time protocol based assessment
- Prospective Surveillance
- Assessment of FDA's Regulatory Actions

Foundational Work: Summary

Title	Leader	Status
Systematic reviews of validity of health outcomes of interest associated with medical products	Ryan Carnahan, PharmD, MS	Complete; Posted on Mini-Sentinel website; to be published in PDS supplement
Systematic reviews of validity of health outcomes of interest associated with vaccines	William Cooper, MD, MPH Melissa McPheeters, PhD, MPH	Proposal under development
Validation of myocardial infarction	Sarah Cutrona, MD Jerry Gurwitz, MD	Complete, posted on Mini-Sentinel website; to be published in PDS supplement
Validation of severe liver injury	Vincent Lo Re, MD, MSCE	Pending
Validation of anaphylaxis	Kathleen Walsh, MD, MSc	Pending

Rapid Queries of Exposure-Outcome Pairs

Objective: Rapid assessment of incident outcomes among new users of specified drugs

Topics:

1. Drugs to treat Parkinson's disease and acute myocardial infarction or stroke
2. Angiotensin receptor blockers and celiac disease
3. Drugs for smoking cessation and cardiac outcomes

Design: Modular programs

Status: Completed

One-Time Protocol-based Safety Assessments

Intussusception after Two Rotavirus Vaccines

(Leaders: Katherine Yih, PhD, MPH; Edward Belongia, MD; Thomas Buttolph, MD)

Objective: Assess the risk of intussusception following rotavirus vaccination

Design: Retrospective cohort design with multiple analysis methods; validation of intussusception algorithm

Status: Protocol drafted and nearly final; preliminary analyses underway

One-Time Protocol-based Safety Assessments

HPV4 Vaccination and Venous Thromboembolism (VTE)

(Leaders: Michael Nguyen, MD; Sharon Greene, PhD, MPH)

Objective: Assess the risk of VTE following HPV4 vaccination

Design: Self-controlled risk interval; will include validation of VTE algorithm

Status: Protocol drafted; programs being written

Prospective Active Surveillance

Antidiabetic Drugs and MI

(Leaders: Bruce Fireman, MA; Darren Toh, ScD)

Objective: Repeated evaluation of acute MI risk in users of saxagliptin compared to comparator agents, based on accumulating prospective data in population-based clinical and claims databases

Design: Inception cohort of saxagliptin vs. four comparator antidiabetic drugs

Status: Protocol complete; programs being written and tested

Assessments of FDA's Regulatory Actions

Long Acting Beta Agonists

(Leader: TBD)

Objective: Evaluate the impact of labeling change advising against long term use of LABAs as a single agent on changes in use and health outcomes of interest

Design: TBD

Status: Workgroup being formed

Mini-Sentinel:
A Rapid Query Example

Rapid Queries of Exposure-Outcome Pairs

Objective: Rapid assessment of incident outcomes among new users of specified drugs

Topics:

1. Drugs to treat Parkinson's disease and acute myocardial infarction or stroke
2. Angiotensin receptor blockers and celiac disease
3. Drugs for smoking cessation and cardiac outcomes

Design: Modular programs

Status: Completed

Example:

Rapid evaluation of drugs for smoking cessation and cardiac outcomes

Smoking Cessation Drugs and Cardiac Outcomes

7/4/2011 7/5/2011 7/6/2011 7/7/2011 7/8/2011

Smoking Cessation Drugs and Cardiac Outcomes

FDA indicates intent to query Mini-Sentinel

7/4/2011 7/5/2011 7/6/2011 7/7/2011 7/8/2011

Smoking Cessation Drugs and Cardiac Outcomes

FDA indicates intent to query

4PM FDA provides final specs

7/4/2011 7/5/2011 7/6/2011 7/7/2011 7/8/2011

Smoking Cessation Drugs and Cardiac Outcomes

FDA indicates intent to query

4PM FDA provides final specs

6PM Programs distributed to 17 data partners

7/4/2011 7/5/2011 7/6/2011 7/7/2011 7/8/2011

Smoking Cessation Drugs and Cardiac Outcomes

FDA indicates intent to query

4PM FDA provides final specs

6PM Programs distributed to 17 data partners

9AM Report delivered*

7/4/2011 7/5/2011 7/6/2011 7/7/2011 7/8/2011

* High level summary with data from 13 data partners; complete report on 7/12

Query Specifications

- Population: New users of varenicline or bupropion (comparator)
  - First dispensing of bupropion or varenicline (180 day look back)
  - No cardiac outcome (below) or more general cardiac/atherosclerosis diagnosis (ICD-9 code 414.0x) in prior 180 days
  - Cohorts
    - All
    - Tobacco use disorder code (305.1), any setting, in prior 180 days
- Exposure: First treatment course
  - Bridge gaps ≤7 days to create treatment episode
  - Extend "treatment effect" for 7 days after presumed last exposure
- Outcome: Composite cardiac outcome codes
  - Diagnosis code in inpatient or ED setting during treatment course
    - Acute MI (410.xx) OR Intermediate coronary syndrome/unstable angina (411.1) OR Acute coronary occlusion without MI (411.81)

Results from 17 data partners

	New users	Person-time (years)	Cardiac outcomes
All			
Varenicline	261,000	32,000	109
Bupropion	746,000	210,000	452
With tobacco code			
Varenicline	90,000	11,000	56
Bupropion	113,000	23,000	118

Results from 17 data partners

	New users	Person-time (years)	Cardiac outcomes
All			
Varenicline	261,000	32,000	109
Bupropion	746,000	210,000	452
With tobacco code			
Varenicline	**90,000**	**11,000**	**56**
Bupropion	**113,000**	**23,000**	**118**

Incidence rates and ratios – with tobacco code

Adjusted for	Varenicline rate	Bupropion rate	Rate Ratio*	95% CI
None	5.00 Per 1,000 person-yrs	5.14	0.97	0.69-1.35
Age			0.96	0.70-1.31
Sex			0.94	0.69-1.30
Age/Sex			0.94	0.68-1.29
Age/Sex/ Health Plan			1.02	0.71-1.47

* Mantel Haenszel Incidence Rate Ratio

Caveats

- Intended to be a quick look, not a final answer
- Result doesn't exclude excess risk
- Exposures may be missing or have misclassified indication
  - Smoking cessation meds may not be covered
    - Potential missing exposures
    - Intentional misclassification of indication
- Cohort may be unrepresentative
  - Tobacco code identified a minority of smokers, presumably not typical
- Outcomes may be misclassified
    - No verification of coded diagnoses
- Potential for residual confounding
    - Smoking intensity
    - Comorbidities, including depression; other

Summary

- Demonstrated ability to rapidly query 300 million person years of experience
  - Defined population with complete eligibility and claims
  - Data quality checked in advance
  - Results evaluated for consistency by age, sex, year, site, dispensings, and amounts dispensed
- Distributed network approach required no transfer of Protected Health Information

Mini-Sentinel: Directions

The NEW ENGLAND JOURNAL of MEDICINE

February 10, 2011. Volume 364: 498-9

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.[3] In 2009, the FDA gave the Harvard Pilgrim Health Care Institute the lead role

Challenges

- Develop reliable approaches to different types of:
  - Medical products
  - Outcomes
  - Patients
  - Data that are new to safety science (EHRs, inpatient settings, laboratories, …)
- Make the system operational
  - Need for timeliness in detection and followup
- Avoid false alarms

Next steps

- Expand the covered population
- Include additional types of data
- Address most pressing methodologic needs
- Improve ability to for rapid performance of recurring types of analyses
- Increase ability to address multiple requests in parallel
- Increase collaborations
- Increase bi-directional communications

Next steps

- Long-term, complex initiative
  - Implement in stages as scientific methodologies and data infrastructure evolves
  - Ensure maintenance of privacy and security within the distributed system
  - Continue to address the concerns of stakeholders including patients and the public
- Address how the eventual Sentinel System will function as a national resource and complement other HHS initiatives using distributed systems for comparative effectiveness and quality assurance

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Roundtable Discussion and Questions

View this and past Active Medical Product Surveillance webinars at:
http://www.brookings.edu/health/Projects/surveillance/roundtables.aspx