ENGELBERG CENTER for Health Care Reform at BROOKINGS

Highlights from the Sentinel Initiative Public Workshop

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February 1, 2012

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

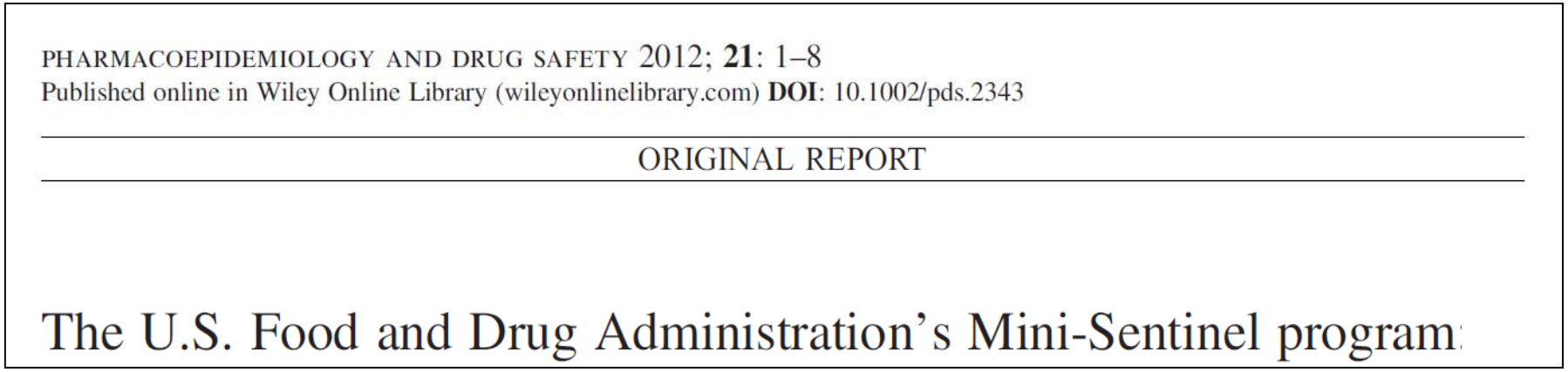
Richard Platt
Harvard Pilgrim Health Care Institute
Harvard Medical School
for the Mini-Sentinel Investigators

January 18, 2012

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.

The annotated Mini-Sentinel



PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**: 1–8
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2343

ORIGINAL REPORT

The U.S. Food and Drug Administration's Mini-Sentinel program:

- Supplement to Pharmacoepidemiology and Drug Safety
- 34 peer reviewed articles; 297 pages
- Goals, organization, privacy policy, data systems, systematic reviews, stats/epi methods, record retrieval and review, protocols for drug/vaccine studies...
- Open access!
- http://onlinelibrary.wiley.com/doi/10.1002/pds.v21.S1/issuetoc

www.mini-sentinel.org

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	

Mini-Sentinel goals

- Develop a consortium
- Develop policies and procedures
- Create a distributed data network
- Evaluate/develop methods in safety science
- Assess FDA-identified topics

Active surveillance activities

- Characterize populations, treatments, and health events
- For older products, assess concerns arising from any source
- Assess impact of FDA actions
- For new products, monitor accumulating experience for pre-specified potential adverse outcomes

Mini-Sentinel goals

- Develop a consortium of data partners and other content experts

Mini-Sentinel Partner Organizations

Leadership

- Planning board – principal investigators, FDA, public representative
- Operations center
- Cores: data, methods, protocols
- Policy committee
- Safety science committee
- Privacy board
- Workgroups

Mini-Sentinel goals

- Develop a consortium
- 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

Mini-Sentinel goals

- Develop a consortium
- Develop policies and procedures
- Create a distributed data network with access to electronic health data and full text records
  - Develop secure communications capability

Activities

Data capacity	Distributed methods	Signal alerting
• **Integrity** – **Common data model** – **Data completeness** – **Data validity** – **Health Outcome of Interest detection and validation** • **Environments** – **Claims** – **EHRs**	• **Distribution and retrieval**	

Applications

Mini-Sentinel's Evolving Common Data Model

- 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)

The Mini-Sentinel Distributed Database

- Populations with well-defined person-time for which medically-attended events are known
- 126 million individuals*
  - 345 million person-years of observation time (2000-2011)
  - 44 million individuals currently enrolled, accumulating new data
  - 27 million individuals have over 3 years of data

*As of 12 December 2011. The potential for double-counting exists if individuals moved between data partner health plans.

The Mini-Sentinel Distributed Database

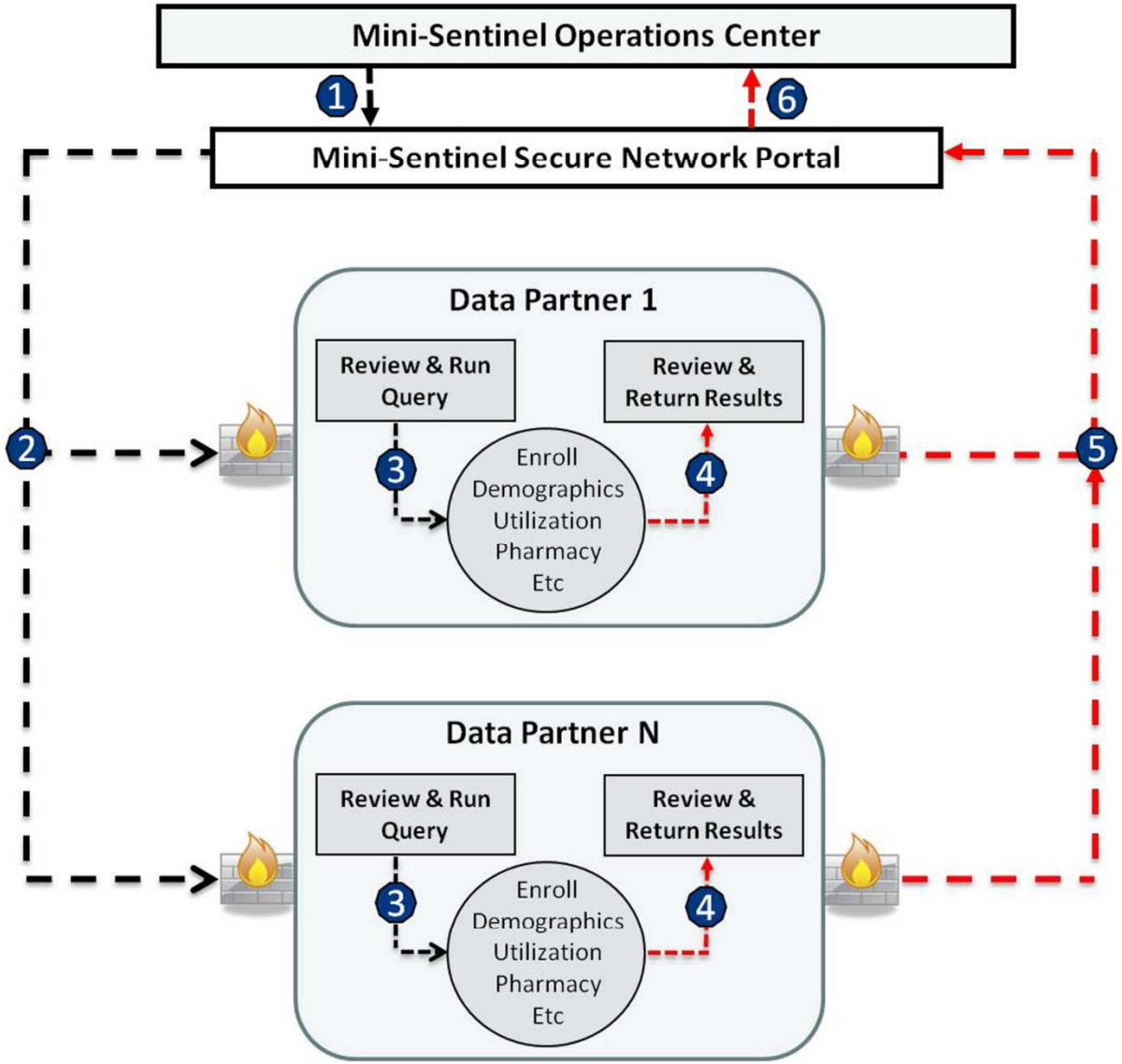
- 3 billion dispensings
  - Accumulating 37 million dispensings per month
- 2.4 billion unique encounters
  - 40 million acute inpatient stays
  - Accumulating 41 million encounters per month including over 400,000 hospitalizations
- 13 million people with ≥1 laboratory test result

*As of 12 December 2011

Why a Distributed Database?

- Avoids many concerns about inappropriate use of confidential personal data
- Data Partners maintain physical control of their data
- Data Partners understand their data best
  - Valid use / interpretation requires their input
- Eliminates the need to create, secure, maintain, and manage access to a complex, central data warehouse

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 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
- Data Partners can choose to evaluate queries before execution or queries can be run automatically.

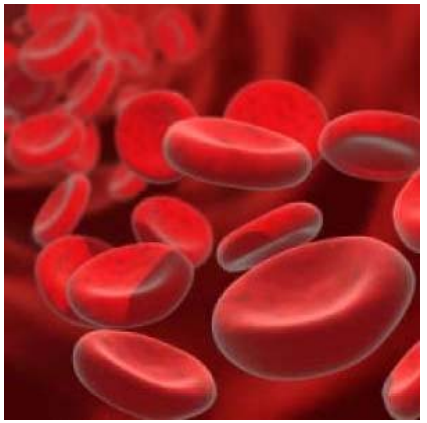
Mini-Sentinel Modular Programs

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

Detecting and Validating Health Outcomes

- Detecting potential cases using administrative data
  - 20 systematic reviews: algorithms to detect health outcomes of interest
- Validating cases using full text records
  - Acute myocardial infarction
    - 93% of charts retrieved (143/153)
    - 86% of cases confirmed by expert panel

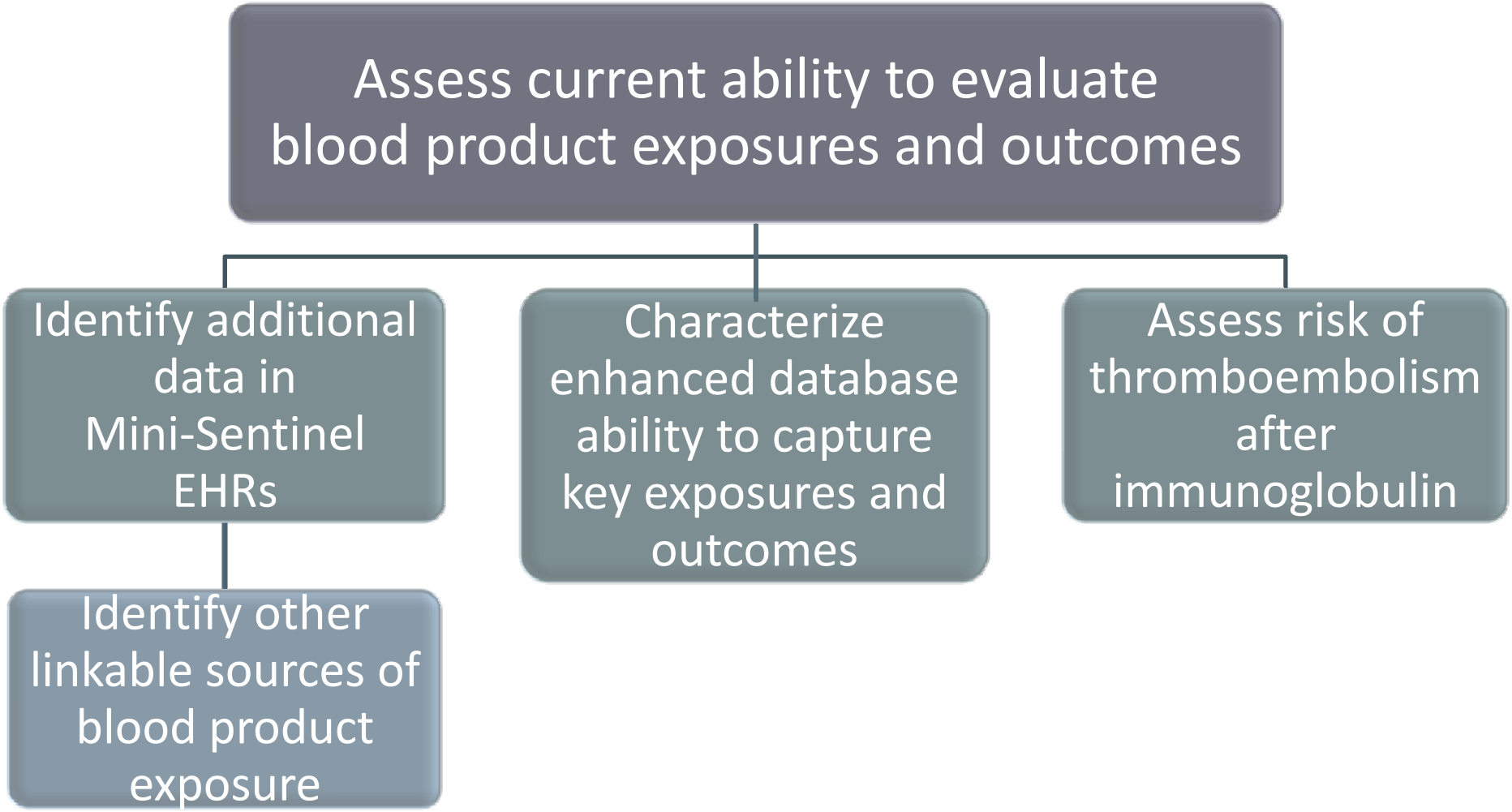
Blood Safety Continuous Active-Surveillance Network (Blood-SCAN)



http://www.newsrx.com/images/sized/uploads/topics/blood1-300x300.jpg

- Strengthen FDA's hemovigilance capabilities
  - Initial focus on recipient safety
  - Emphasis on non-infectious complications
- Create and characterize a Blood-SCAN distributed database
  - Develop an active surveillance system for regulated blood and blood-derived product use
  - Harmonize Blood-SCAN with existing US biovigilance efforts

Blood-SCAN Proposed Activities



Data development in progress

- Expand base population
- Incorporate data from immunization registries
- Develop capacity to assess blood products
- Completion of data checking of vital signs and laboratory data
- Outcome detection: 18 systematic reviews focused on outcomes of special interest for vaccine safety
- Outcome validation:
  Acute liver injury, acute renal failure, anaphylaxis, intussusception, venous thromboembolism

Data development: On the Horizon

- Additional data
  - Electronic Health Records
  - State birth registries
- Enhance/expand library of modular programs and summary tables
  - More kinds of pre-compiled data
  - More flexible exposure and outcome options
  - Automated confounder adjustment
  - Self-control designs

Mini-Sentinel goals

- Develop a consortium
- Develop policies and procedures
- Create a distributed data network
- Evaluate extant methods in safety science
  - Develop new epidemiological and statistical methods as needed

Activities

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**	• **Design & validity**
		– **Study design choice**
		– **Automated confounding adjustment**
		• **Performance of**
		– **Sequential testing**
		– Data mining

Applications

Design and validity

- Taxonomy:
  - Expedited choice of design and analytic monitoring approach
  - Identified generic attributes of exposure, outcomes, and relationships developed a decision table (Gagne et al, PDS supplement)
- Self-controlled designs:
  - Developed guidance on (Maclure, PDS supplement)
    - Strength/limitations, practicability in a monitoring setting
  - Tested a multivariate approach

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
  - A comprehensive approach to automated covariate adjustment is being developed for Propensity Score and Disease Risk Score methods (Rassen & Schneeweiss, PDS supplement)
- Simulation studies indicate theoretical biases (M-Bias and z-Bias) are not usually a problem (Myers et al. AJE 2011;174:1213)

Performance of signal alerting algorithms

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

Methods development: In progress / Future directions

- Sequential monitoring using inverse probability weighting
- Semi-automated or automated confounding control using propensity and disease risk scores
- Simulation framework for evaluating alerting algorithms
- Anonymous linkage across data sources
- Analytic approaches in a distributed data setting

Mini-Sentinel goals

- Develop a consortium
- Develop policies and procedures
- Create a distributed data network
- Evaluate/develop methods in safety science
- Evaluate FDA-identified topics

Activities

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** • **Analytic approaches in a distributed data setting**	• **Design & validity** – Expedited design choice – Automated confounding adjustment • **Performance of** – Sequential testing – Non test-based – Decision analytic approaches

Applications

- **Characterize exposures and health events, monitor accumulating experience**
- **Assess impact of FDA regulatory action**

Active surveillance activities

- Characterize exposures and health events

Rapid Queries of Exposures – Examples

- Drugs
  - Analeptics, Analgesics, Antihypertensives, Antiarrhythmics, Antiretrovirals, Antidepressants, Antipsychotics, Antibiotics, Bronchodilators, Cancer chemotherapy agents, Growth factor inhibitors, Intravenous iron, Smoking cessation drugs, Steroids
- Vaccines
  - Measles/mumps/rubella, rotavirus, human papilloma virus
- Devices
  - Hip replacement, Negative pressure wound therapy devices

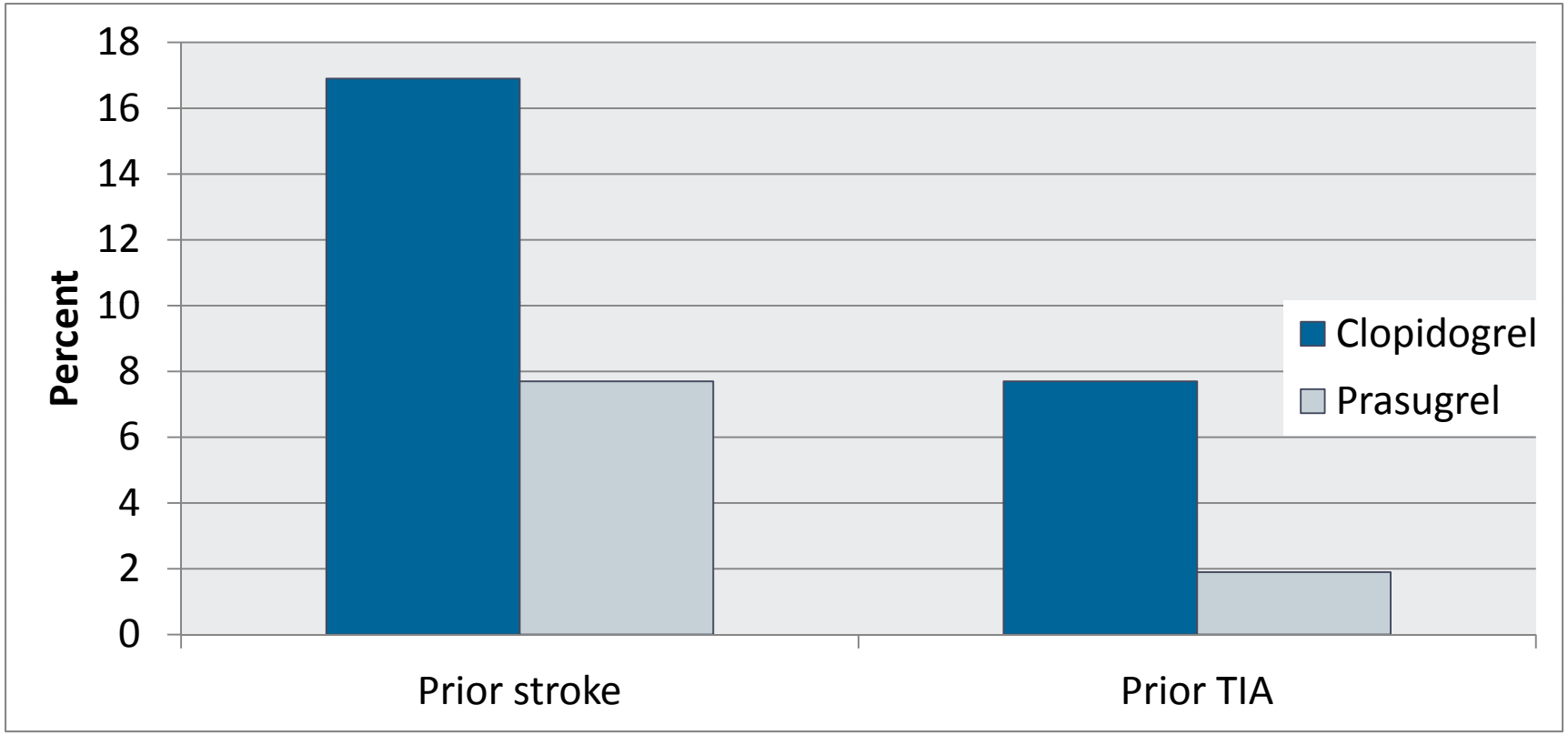
Rapid Queries of Health Events – Examples

- Cardiovascular: Acute myocardial infarction, Hyperlipidemia
- Neurologic: Parkinson's disease, Progressive multi-focal leukoencephalopathy
- Gastrointestinal: Celiac disease, Ulcerative colitis, Crohn's disease
- Allergic: Severe cutaneous conditions, Anaphylaxis, Angioedema, Milk allergy
- Other: Osteonecrosis of the jaw

Prasugrel and Prior Stroke/TIA

- Prasugrel indicated to prevent thrombotic cardiovascular events in selected patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention.
- It is contraindicated in patients with a history of transient ischemic attack (TIA) or stroke
- Prasugrel and clopidogrel users' prior history compared

Clopidogrel and Prasugrel: Prior Stroke or TIA



Clopidogrel (153,191)*	25,820	11,815
Prasugrel (6,997)	540	134

* New users after ≥365 day washout

Conclusions / Limitations

- Some prasugrel users have a prior diagnosis of TIA or stroke
  - Fewer than for clopidogrel users
- ICD-9 codes used for TIA and stroke not validated in Mini-Sentinel
- Longest look back for event was 1 year, patients that had an event >1 year prior would be missed

Active surveillance activities

- Characterize population and treatments
- For older products, rapidly assess concerns arising from any source

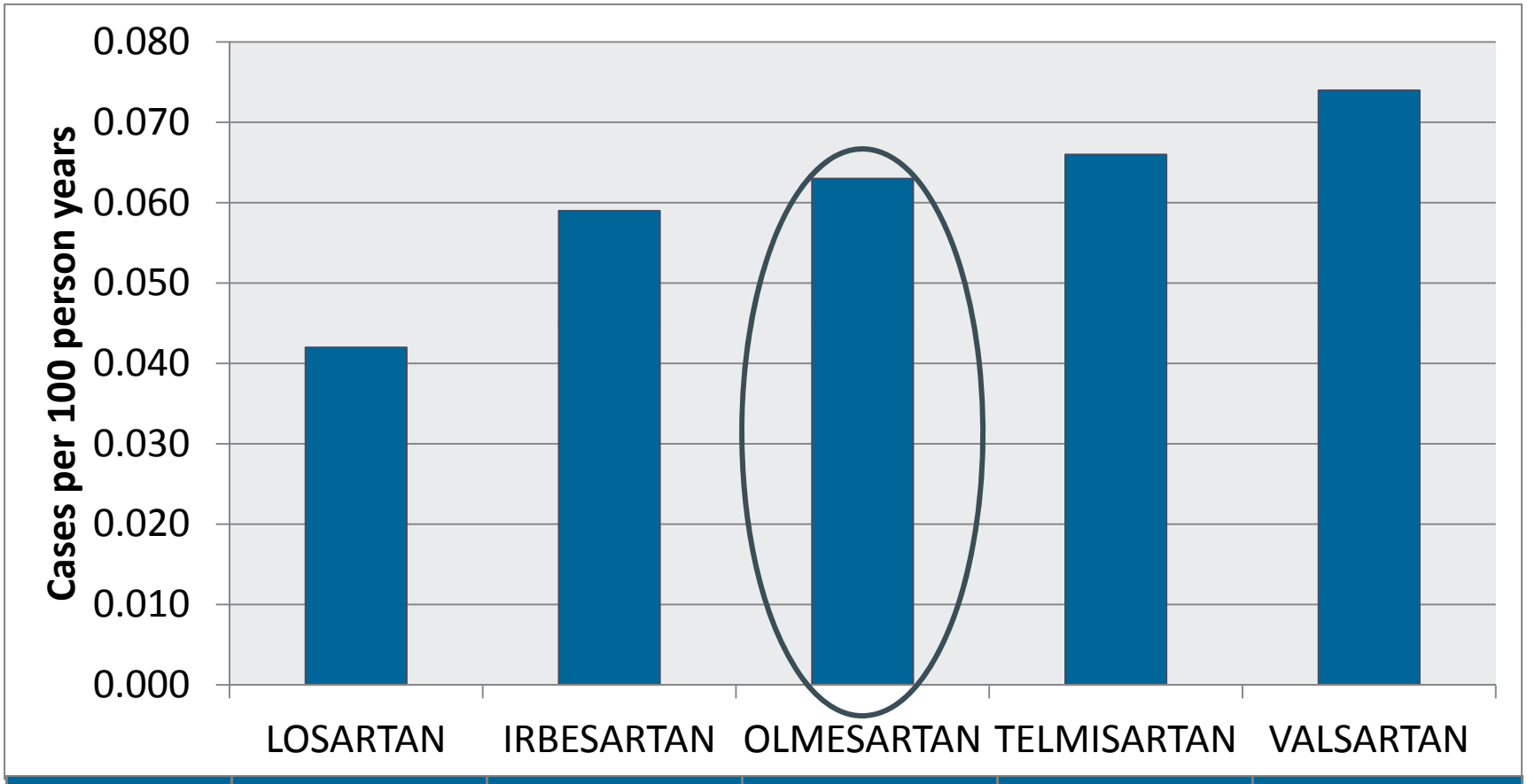
Rapid Queries of Exposure-Outcome Pairs

- 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

ARBs and celiac disease

- Potential olmesartan signal identified in AERS database
- Review of cases inconclusive

ARBs and celiac disease



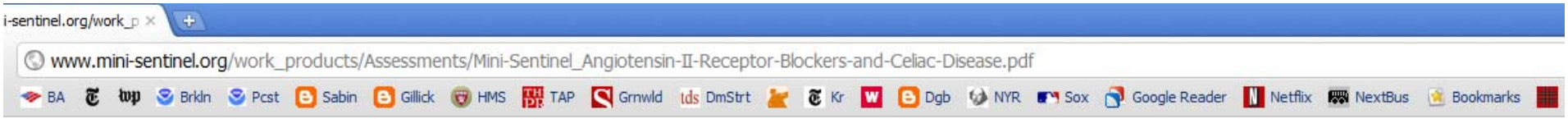
Cases	63	10	17	5	50
New users	235,630	40,071	81,560	24,596	153,159

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

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
(See online specification for details: http://www.mini-sentinel.org/data_activities/details.aspx?ID=111)

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

One-Time Protocol-based Assessments

- Rotavirus Vaccines and Intussusception
- Influenza Vaccine and Febrile Seizures
- Influenza Vaccine and Pregnancy Outcomes
- HPV4 vaccine and Venous thromboembolism
- ACEIs/ARBs/aliskiren and Angioedema
- Aripiprazole and Venous thromboembolism

Rotavirus Vaccines and Intussusception*

Vaccine doses in study	1.8 million
Individuals in study	715,000
Number of outcomes based on ICD9 codes	64 cases within 21d after any vaccine dose

* Numbers are for RotaTeq. Estimates are based on actual numbers from the first two data partners and inference for the third data partner.

HPV4 vaccine and Venous Thromboembolism*

Vaccine doses in study	2.4 million
Individuals in study	987,000
Number of outcomes based on ICD9 codes	119 cases within 28d after any vaccine dose

*HPV4 vaccine is Gardasil. Estimates are based on inferences from preliminary data characterization analyses.

Influenza Vaccines and Febrile Seizures*

Vaccine doses in study	860,000 first doses
Individuals in study	860,000
Number of outcomes based on ICD9 codes	91 cases within 1d after a vaccine dose

* Estimates are for 6-59 mo olds, based on inferences from preliminary data characterization analyses.

Active surveillance activities

- Characterize population and treatments
- For older products, rapidly assess concerns arising from any source
- Monitor impact of FDA actions

Assessments of FDA's Regulatory Actions

Long Acting Beta Agonists

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

Status: Workgroup developing protocol

Active surveillance activities

- Characterize population and treatments
- For older products, rapidly assess concerns arising from any source
- Monitor impact of FDA actions
- For new products, monitor accumulating experience for pre-specified potential adverse outcomes

Antidiabetic Drugs and Acute MI

- Repeated evaluation of acute MI risk in new users of saxagliptin vs. comparator antidiabetic drugs
- Case mix adjustment via disease risk scores and propensity scores
- 280,745 eligible new users Aug, 2009 – Dec, 2010:

Antidiabetic drug	New users
Saxagliptin	5,877
Sitagliptin	31,425
Pioglitazone	55,134
Long-acting insulin	72,024
2nd generation sulfonylureas	116,285

Challenges

- Many different exposures
- Many different outcomes
- Many patient types
- Many and diverse data environments

- Need for timeliness in both detection and followup
- Need to avoid false alarms
- Need for multiple simultaneous activities
- Need for surge capacity

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

Thank you!

Communicating Findings from FDA's Sentinel Program

Ed Staffa, R.Ph.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Communications

Sentinel Progress

- From an *idea* in 2007… to a working "active surveillance" model with access to data for **100 million patients** from 17 data partners today
  - "Mini-Sentinel," the Sentinel pilot program
- We're well ahead of goals set by the *Food and Drug Amendments Act (FDAAA)* of 2007

Sentinel Surveillance

- Sentinel is a tool designed to enable safety scientists to have access to medical product data that they can analyze to help them assess complex safety issues.

Sentinel provides data, not "yes/no" answers

Sentinel Surveillance

- Sentinel *adds* to FDA's existing tools for gathering and analyzing data.
- Sentinel will not replace other tools FDA uses to assess safety of medical products.
- Findings from **all** of FDA's safety tools are used by FDA to make decisions on safety.

Sentinel will be a new and important "tool" in FDA's "tool box"

Communicating Sentinel Findings

- Communicating FDA's safety findings often involve varying degrees of uncertainty. Sentinel findings will not be different.
- To help ensure transparency, FDA is posting findings of Sentinel activities online.
- FDA uses Drug Safety Communications (DSCs) and other notifications to alert the public to new safety issues. http://www.fda.gov/drugs/drugsafety/ucm199082.htm

Communicating findings is different than communicating risk based on those findings

In Conclusion

- Sentinel continues to make great progress
- Like all scientific data, Sentinel findings will include uncertainty
- FDA will keep the public informed of Sentinel progress and findings

More Information

- FDA's Sentinel Web Page
  http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm
- Mini-Sentinel Web Page
- http://mini-sentinel.org/
- Sentinel Summary Booklet
- http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf

Questions?

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