ENGELBERG CENTER for
Health Care Reform
at BROOKINGS

Brookings Roundtable Webinar: Mini-Sentinel Accomplishments and Plans for Year 2

January 31, 2011

Housekeeping Points

- 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 opportunities for questions and discussion following today's presentations. 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 the Q&A session.
- Call the Brookings IT Help Desk at 202-797-6193 with technical problems.

Speakers

- Judy Racoosin, Sentinel Initiative Scientific Lead, U.S. Food and Drug Administration
- Richard Platt, Chair, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute
- Lesley Curtis, Associate Professor of Medicine, Center for Clinical and Genetic Economics at Duke University School of Medicine
- Deven McGraw, Director, Health Privacy Project at the Center for Democracy and Technology
- Bruce Fireman, Biostatistician and Research Scientist, Kaiser Permanente Northern California

Additional Sources of Information

http://www.brookings.edu/health/Projects/surveillance

http://www.fda.gov/Safety/FDAsSentinelInitiative

http://www.nejm.org

Setting the Stage for the Mini-Sentinel Update

Judy Racoosin, MD, MPH
Sentinel Initiative Scientific Lead
US Food and Drug Administration
January 31, 2011

FDA Amendments Act of 2007

Section 905: Active Postmarket Risk Identification and Analysis

- Establish a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including
  - at least 25,000,000 patients by July 1, 2010
  - at least 100,000,000 patients by July 1, 2012
- Access a variety of sources, including
  - Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs)
  - Private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data)

Sentinel Initiative

- Improving FDA's capability to identify and evaluate safety issues in near real time
- Enhancing FDA's ability to evaluate safety issues not easily evaluated with the passive surveillance systems currently in place
    - Expanding FDA's access to subgroups and special populations (e.g., the elderly)
    - Expanding FDA's access to longer term data
    - Expanding FDA's access to adverse events occurring commonly in the general population (e.g., myocardial infarction, fracture) that tend not to get reported to FDA through its passive reporting systems

**Will augment, not replace, existing safety monitoring systems

Mini Sentinel

Harvard Pilgrim Healthcare

- Develop the scientific operations needed for the Sentinel Initiative.
- 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 Initiative.
  - 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.

Scenarios included in signal refinement

- Concern emerges prior to marketing
  - Safety concern observed in premarket development program
  - Theoretical safety concern based on serious side effects of medical products
- Concern emerges after product has been marketed for a period of time

FDA's Mini-Sentinel Program
Status Report

Richard Platt, MD, MSc
Harvard Pilgrim Health Care Institute
and Harvard Medical School

January 31, 2011

richard_platt@harvard.edu

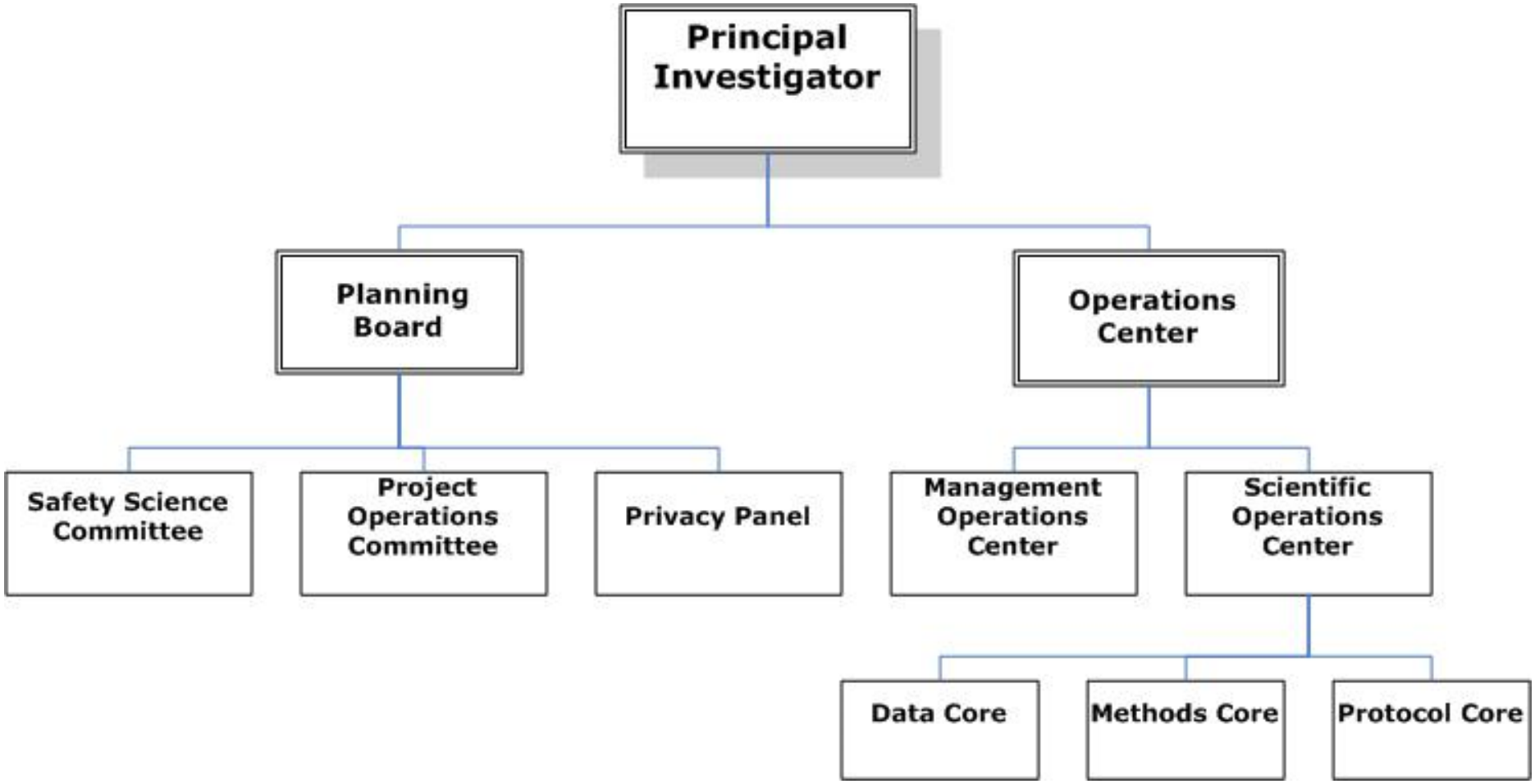
Mini-Sentinel

Areas of activity

- Coordinating center
- Governance
- Privacy policies – Deven
- Data development – Lesley
- Communications
- Methods development
- Active surveillance – Bruce

Mini-Sentinel

Coordinating Center



Mini-Sentinel

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 for individuals

Mini-Sentinel

Distributed data partners

Additional Partners

Secure Communications

- Portal for secure file transfer and storage
- Complies with Federal Information Security Management Act (FISMA)

Mini-Sentinel

Mini-Sentinel

Search

Welcome to Mini-Sentinel

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

New Postings

December 16, 2010

- Common Data Model v1.1

Public communications

- www.minisentinel.org
  - Results of completed evaluations
  - Ongoing and committed evaluations
  - Methods and tools
  - Policies and procedures
  - Protocols
  - Computer programs

Mini-Sentinel

Methods development

- Epidemiology methods
  - Taxonomy of study designs for different purposes
  - Literature review completed for algorithms to identify 20 outcomes using coded health data
- Statistical methods (under way)
  - Better adjustment for confounding
  - Case based methods
  - Regression methods for sequential analysis

Mini-Sentinel

Next steps – active surveillance

- Drugs
  - **Implement active surveillance protocol for acute MI related to new oral hypoglycemics**
  - Evaluate new safety issues for older drugs
  - Evaluate impact of regulatory actions, e.g., restricted distribution
- Vaccines (PRISM)
  - **Active surveillance of specific outcomes following rotavirus and human papilloma virus vaccines**

Mini-Sentinel

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

Mini-Sentinel

The Mini-Sentinel Distributed Database

Year 1 Accomplishments

Lesley H. Curtis
Duke University

January 31, 2011

Creating the Mini-Sentinel Common Data Model

- Develop guiding principles
- Review existing common data models
- Draft and revise specifications

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.

Review of Existing Common Data Models: Lessons Learned

- It's feasible for multiple Data Partners to assemble patient-level files according to a common data structure.
- Data Partners can retain complete control of their data while working toward common objectives.
- It's necessary to evaluate carefully all coding schemes used by each Data Partner to ensure that variability is understood and addressed.
- Analytical imperatives can be met using a distributed model.

Development of Common Data Model

- Straw-man common data model
  - Minimal transformation to maintain granularity
  - Leverage prior experience
- Data Partner review and comment
  - Can your site implement these specifications?
  - Are definitions of tables and variables specific enough?
  - Are important data elements not included?
  - Are the requirements consistent with your expectations?
- FDA review and comment

Mini-Sentinel Common Data Model v1.0

- 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)

Developing the Mini-Sentinel Distributed Database

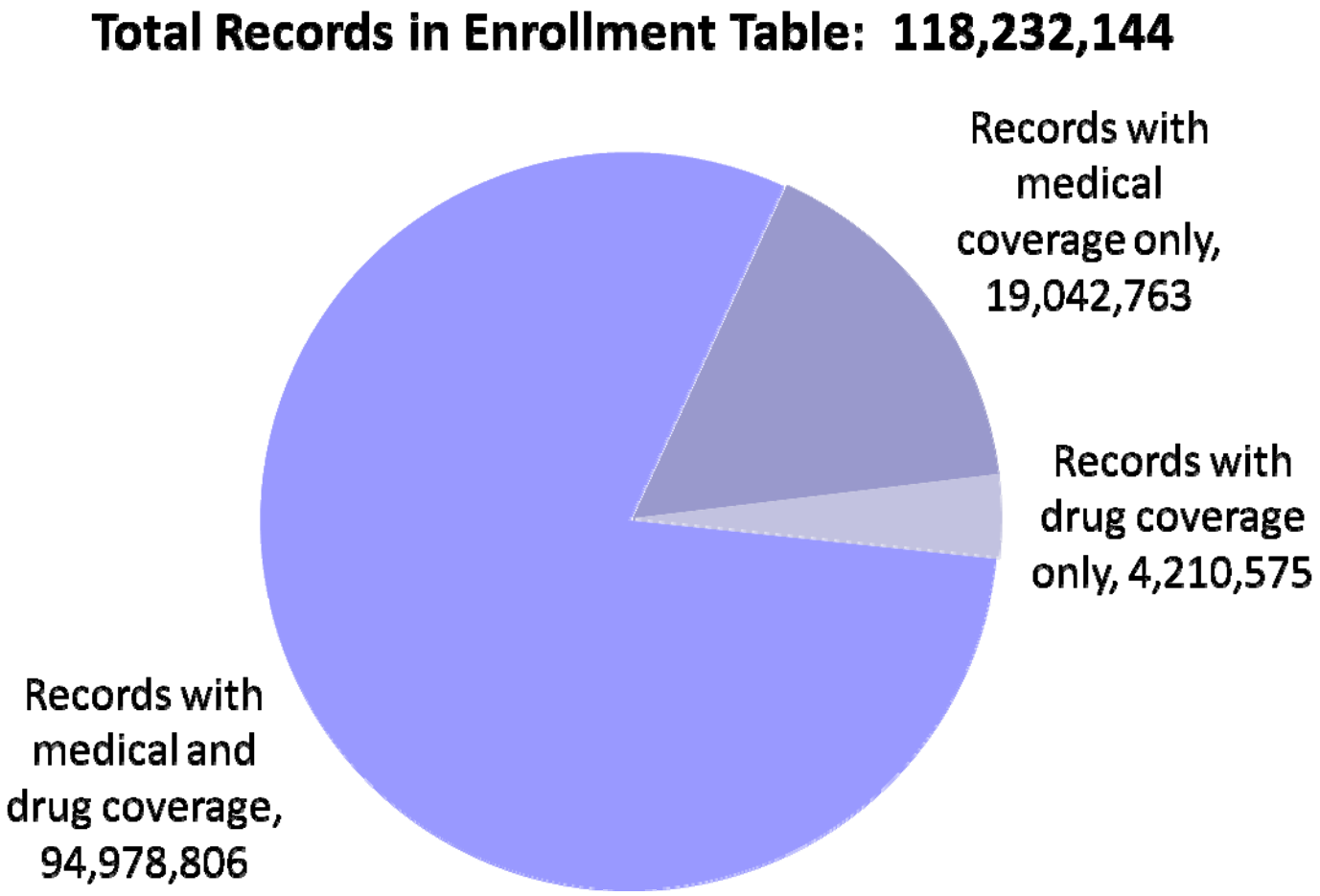
- Each Data Partner translated local source data to the common data model structure and format and documented the process in a detailed report.
- Questions and issues were discussed on weekly teleconferences.
- Transformed data were characterized using standard programs developed by the Mini-Sentinel Operations Center.

Characterization of the Mini-Sentinel Distributed Database

- Overall, the Mini-Sentinel Distributed Database spans from 2000-2010
  - Most HMORN and Kaiser sites have data beginning in 2000
  - HealthCore has data going back to 2004
  - Humana has data going back to 2006

*As of 7 Jan 2011

Data Characterization: Enrollment*



* As of 7 Jan 2011

Data Characterization: Enrollment *

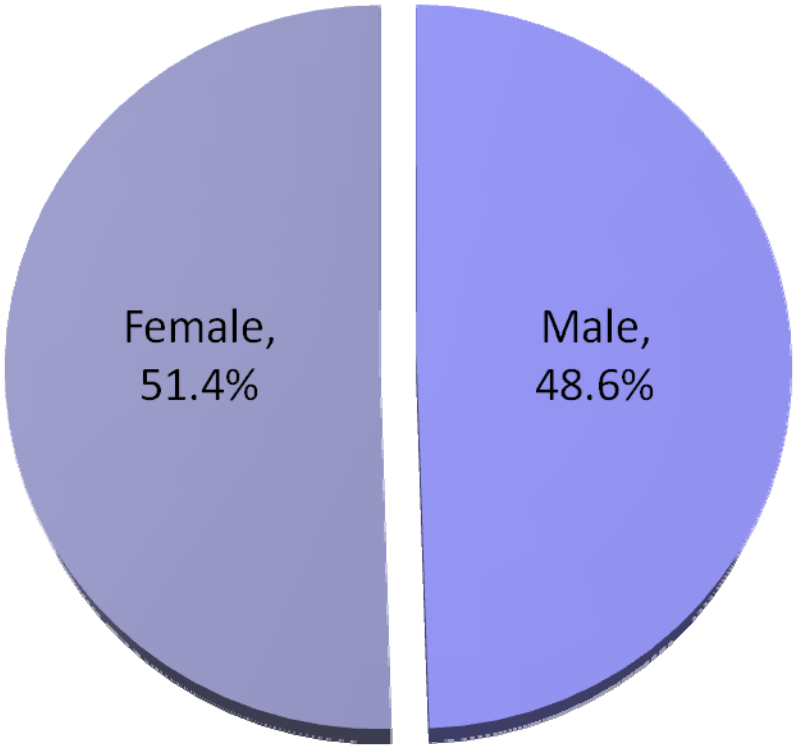
Unique members	71,152,385
Current† unique members with medical *and* drug coverage	22,482,689
Total person-years of observation time	167,295,216
Average person-months of observation time per member	28.2

* As of 7 Jan 2011

†Total number of unique members enrolled in the month of January 2009

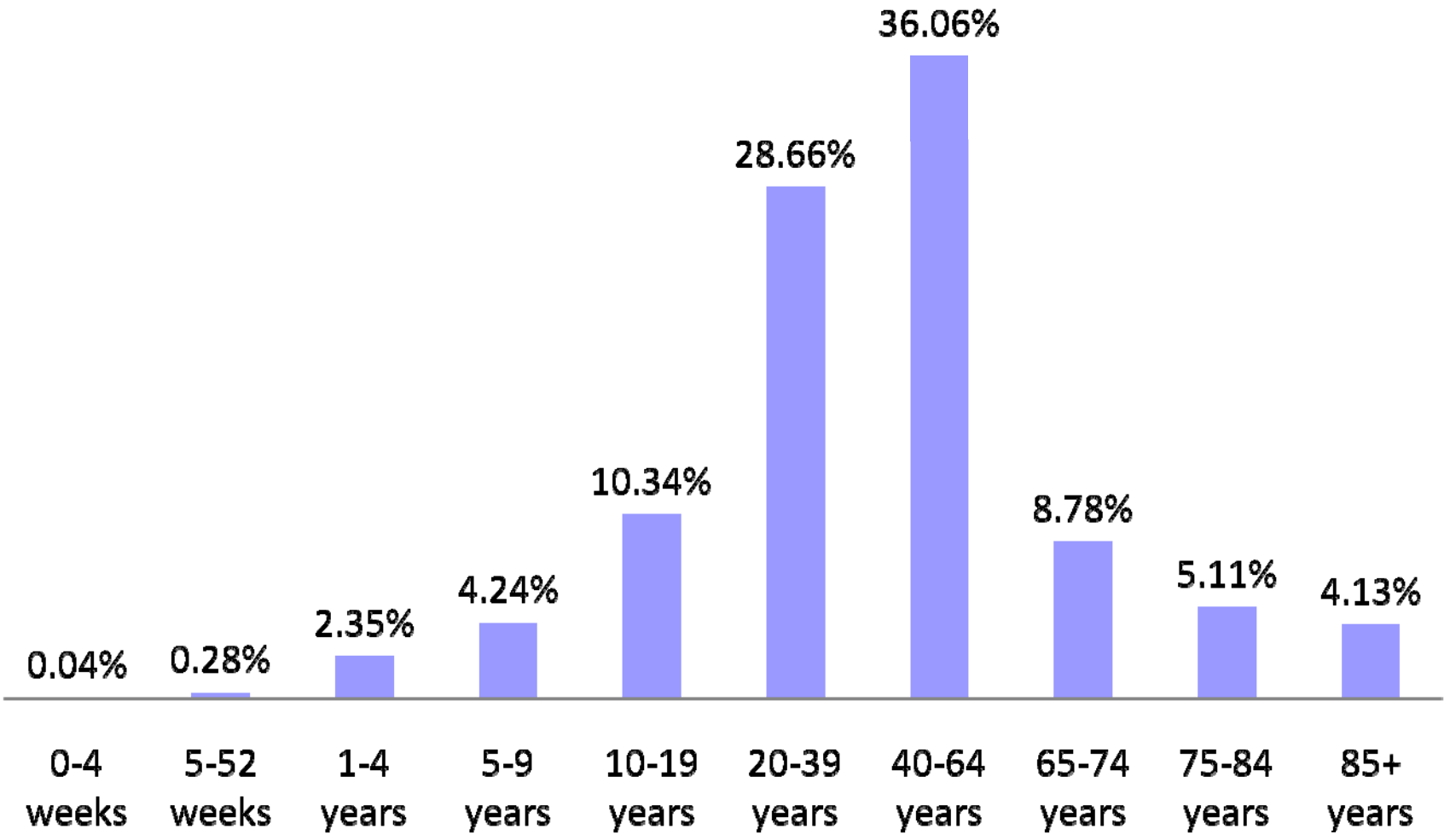
Contact: info@mini-sentinel.org

Data Characterization: Sex *



* As of 7 Jan 2011

Data Characterization: Age *

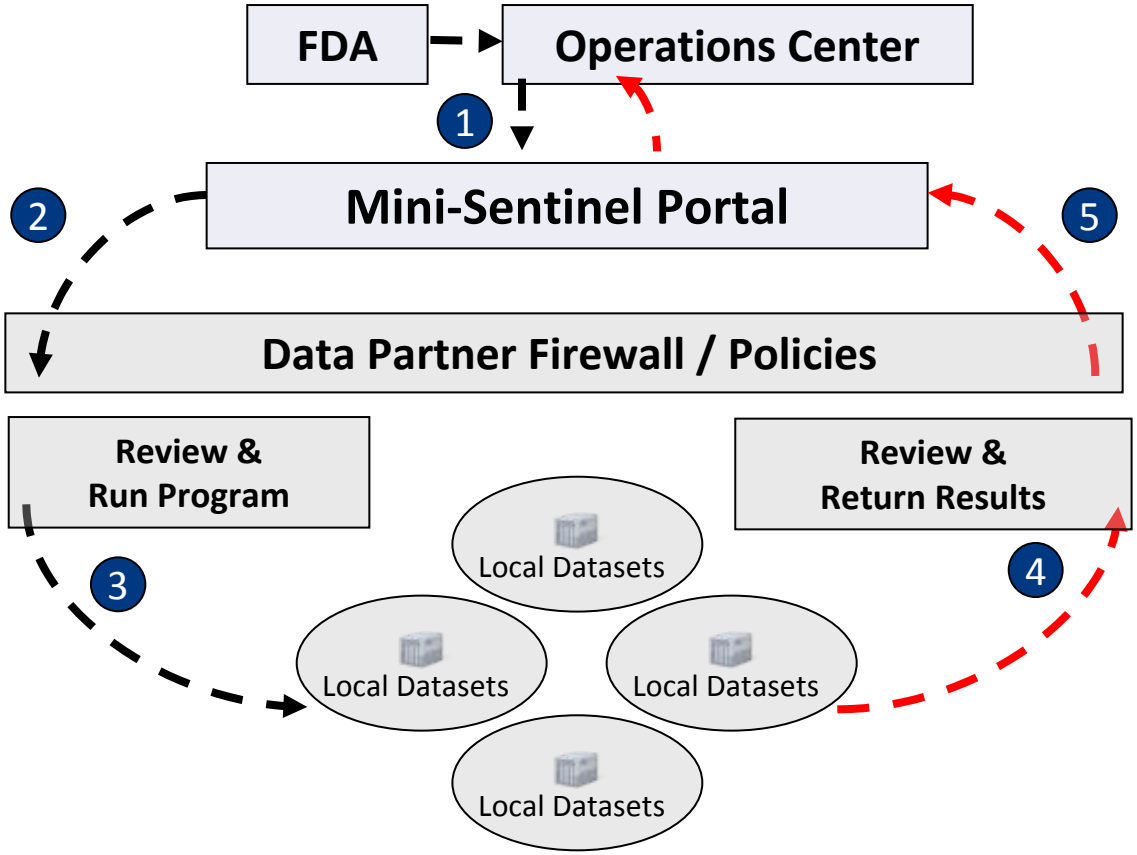


* As of 7 Jan 2011

Building the MS Infrastructure

- Standard programs to characterize and check quality of the Mini-Sentinel Distributed Database
- Formal assessment of Data Partners' technical environments
- Preparation for quarterly refresh cycles
- Empirical assessment of data latency
- Secure web portal for distributed analyses

Mini-Sentinel Distributed Analysis



1- Query (an executable program) is submitted by FDA or Operations Center to the Mini-Sentinel Portal
2- Data Partners retrieve the query on the Distributed Querying Portal
3- Data partners review query and perform analysis locally by executing the distributed program
4- Data partners review results
5- Data partners return results to Distributed Querying Portal for review by FDA and\or Operations Center

Contact: info@mini-sentinel.org

Current 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

Privacy and Security in Mini-Sentinel: Ensuring Public Trust through Respectful Use of Health Information

Deven McGraw

Director, Health Privacy Project, CDT

January 31, 2011

Health Insurance Portability and Accountability Act (HIPAA)

- HIPAA permits disclosure of protected health information (PHI) to a "public health authority" for public health surveillance (which includes the safety of FDA-approved products)
  - FDA is a public health authority
  - Public health authority also includes a "person or entity acting under a grant of authority from or contract with such public agency" – Mini-Sentinel Operations Center and its subcontractors are acting under a grant of authority from the FDA
- Release of PHI (if any) to the Data Partners, the Operations Center and the FDA is not for "research" that requires approval by an Institutional Review Board

Federal Substance Abuse Treatment Regulations (the "Part 2 Regulations")

- Part 2 regulations protect information generated by a federally-assisted alcohol or drug abuse treatment program, if the information identifies a patient as an alcohol or drug abuser or someone who has applied for or received that type of treatment
- Part 2 regulations are unlikely to affect Sentinel, but covered data sources will need to evaluate release of original source data to Data Partners for analysis

State Confidentiality Laws

- State health information confidentiality laws often provide more protection for "special" health information, such as:
  - Genetic testing
  - Mental health information
  - HIV/communicable diseases
  - Most state laws regulate external disclosure, but not internal use of health information
  - Many state laws permit release for public health activities
  - No state laws (to my knowledge) regulate the release of aggregated, non-identifiable information
- Each data source will need to confirm compliance with its own state laws

Policies Comply with Fair Information Practices

- Distributed data model: drug safety questions are brought to the data
- All direct identifiers are removed from information provided to the Operations Center or the FDA
- Any identifiable information received by Data Partners to confirm drug safety signals may be used only for Mini-Sentinel purposes
- Operations Center may use information it receives only for Mini-Sentinel purposes
- Operations Center manages security in accordance with the HIPAA Security Rule and the Federal Information Security Management Act

Plans for Surveillance of Acute Myocardial Infarction in users of Oral Anti-Diabetes Drugs

Bruce Fireman
Kaiser Permanente, Oakland

January 31, 2011

Aims

- Develop and assess a framework and infrastructure for monitoring drug safety in large populations using distributed databases.
- For this pilot effort :
  - monitor acute MI in users of anti-diabetes drugs, and more specifically:
    - examine the association of AMI risk with saxagliptin, a recently approved DPP-4 inhibitor used for treatment of diabetes.

Type 2 Diabetes Study Population

- Adults with a diabetes diagnosis and an oral anti-diabetes drug in 12 month baseline period.
- Members for 12+ continuous months in Humana, Health Core, Kaiser Permanente, other HMO_RN.
- Few exclusions: recent AMI (<30 days), age<18, patients who have been taking only insulin.
- Study period: July 2009 through June 2013 (with baseline data back to July 2007)
- 1.3 million with T2DM now, 5.2 million person years to be monitored, 47,000 AMIs expected.

New-users of Saxagliptin compared with new users of 4 comparator drugs

- The comparators:
  - sitagliptin
  - pioglitazone
  - sulfonylurea (glyburide, glipizide, glimipiride)
  - long-acting insulin
- Follow-up for AMI begins at 1st Rx of a study drug.
- Follow-up ends when user quits drug or health plan
- Inference only from users followed since 1st use.
  No inference about the drug-AMI association from
  - prevalent users of study drugs
  - within-person change in MI risk: on-drug versus off-drug

  due to possible bias from unmeasured confounders.

Outcomes

- Primary: AMI identified from
  - Hospitalization, principal dx: 410.x0 or 410.x1, (PPV≈95%)
  - Emergency department diagnosis code of 410 plus death in ER or within 24 hours.
- Secondary: Acute Coronary Syndrome, including
  - AMI, or
  - Hospitalization with principal diagnosis: 411.1 or 411.8, or
  - Hospitalization with principal diagnosis: 414 plus secondary diagnosis: 411.1 or 411.8
- Measures of drug-outcome association (over time):
  - Relative risk
  - Risk difference

Adjustment for possible confounders

- Prior Cardiovascular Disease
- Demographics
- Co-morbid conditions
- Concurrent Medication Use
- Use of health services
- Site, health plan
- Time

Several adjustment strategies/methods

- Restriction to new users, stratification by site and prior cardiovascular disease, covariate adjustment
- Propensity score (PS), matching 1:1
- Disease risk score (DRS), stratification by decile

PS matching and DRS stratification permit adjustment for covariates *without pooling patient-level data*

- Advantages of PS matching
  - Balances comparisons of new-users of comparator drugs with new-users of saxagliptin, intuitive as in RCT
  - 1:1 matching restricts to best matches, simplifies analysis
- Disadvantages of PS matching
  - Separate PS needed for each pair of study drugs, each site
  - Not much data available for deriving PS at outset of study
- Advantages of DRS stratification
  - A single DRS can be used to compare all study drugs
  - Even if saxagliptin uptake is slow at first (or throughout), there will be enough data to derive the DRS
  - Intuitive implications for confounding, interactions
- Disadvantages of DRS stratification
  - Less feasible with rare outcomes, multiple outcomes
  - Less familiar

Sequential surveillance

- 1st analysis planned for 3/2011, examining study population since the 2009 licensure of saxagliptin.
- Then 9 quarterly analyses monitoring accumulating data, with final analysis planned for 6/2013.
- Sequential statistics adjusted for multiple “looks”, each “look” includes all available data.
- Threshold p-value required for a signal is 0.0144, to ensure that the overall chance of a false signal (about a safe drug) is below 0.05 across all ten quarterly analyses.

Power and reassurance: the size of the relative risks that can be detected or ruled out

- Assuming that
  - we accumulate 23,000 person-years in saxagliptin users and 23,000 in PS-matched users of a comparator, and
  - we expect 9 MIs/1000 person-years in the comparator-users
- then we have
  - 61% power to detect a relative risk of 1.25
  - 81% power to detect a relative risk of 1.33
  - 91% power to detect a relative risk of 1.40
- If we accumulate only half as much person-time then we have 80% power to detect relative risk of 1.5
- If signals do not arise, confidence intervals will be informative about the size of the relative risk (and risk difference) that can be "ruled out", and the reassurance that is appropriate.

AMI surveillance is designed to be worthwhile even if saxagliptin is not used much

- Analyses stratified by the proposed MI risk score can be used for comparisons among all anti-diabetes drugs that are commonly used in the study population.
- Comparisons of MI risk in users of anti-diabetes drugs can yield
  - worthwhile reassurance (or safety signals),
  - lessons about statistical methods
  - evidence of the value of Sentinel's data and infrastructure

  regardless of saxagliptin uptake.
- This outcome-centered surveillance is especially promising for outcomes – such as MI – that are important to examine in relation to many drugs.

Summary: Mini-Sentinel has developed plans to

- Examine AMI risk in saxagliptin users versus users of four comparator drugs: sitagliptin, pioglitazone, sulfonylurea, and long-acting insulin.
- Assess the feasibility and value of AMI surveillance in users of anti-diabetes drugs, using the distributed databases of Sentinel's data partners.
- Evaluate statistical methods for monitoring drug safety in large dynamic populations.