FDA's Sentinel Initiative — A National Strategy for Monitoring Medical Product Safety

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Sentinel Initiative

- Develop a national electronic safety monitoring system
  - Strengthen FDA's ability to monitor postmarket performance of medical products
  - Enable FDA to access existing automated healthcare data by partnering with data holders (e.g., insurance companies with large claims databases, owners of electronic health records, others)

- Will augment, not replace, existing safety monitoring systems

Potential Capabilities of Sentinel

- 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

Contracts

(reports on Sentinel Website)

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

- Scientific Operations

Defining and Evaluating Possible Database Models

Evaluation of Existing Methods for Safety Signal Identification

Evaluation of Timeliness of Medical Product Uptake in Healthcare Systems

- Data and Infrastructure

Evaluation of Potential Data Sources for Sentinel Initiative*

Evaluation of Potential Data Sources for Blood and Tissue Products

Evaluation of Potential Orthopedic Device Implant Registries

Evaluation of Potential Data Sources for Animal Drugs Used in Veterinary Medicine *

- Governance

Developing a Governance and Operations Structure for Sentinel Initiative

- Stakeholder Outreach/ Privacy Issues

Engagement of Patients, Consumers, and Health Care Professionals

Evaluation of State Privacy Regulations in Relation to the Sentinel Initiative

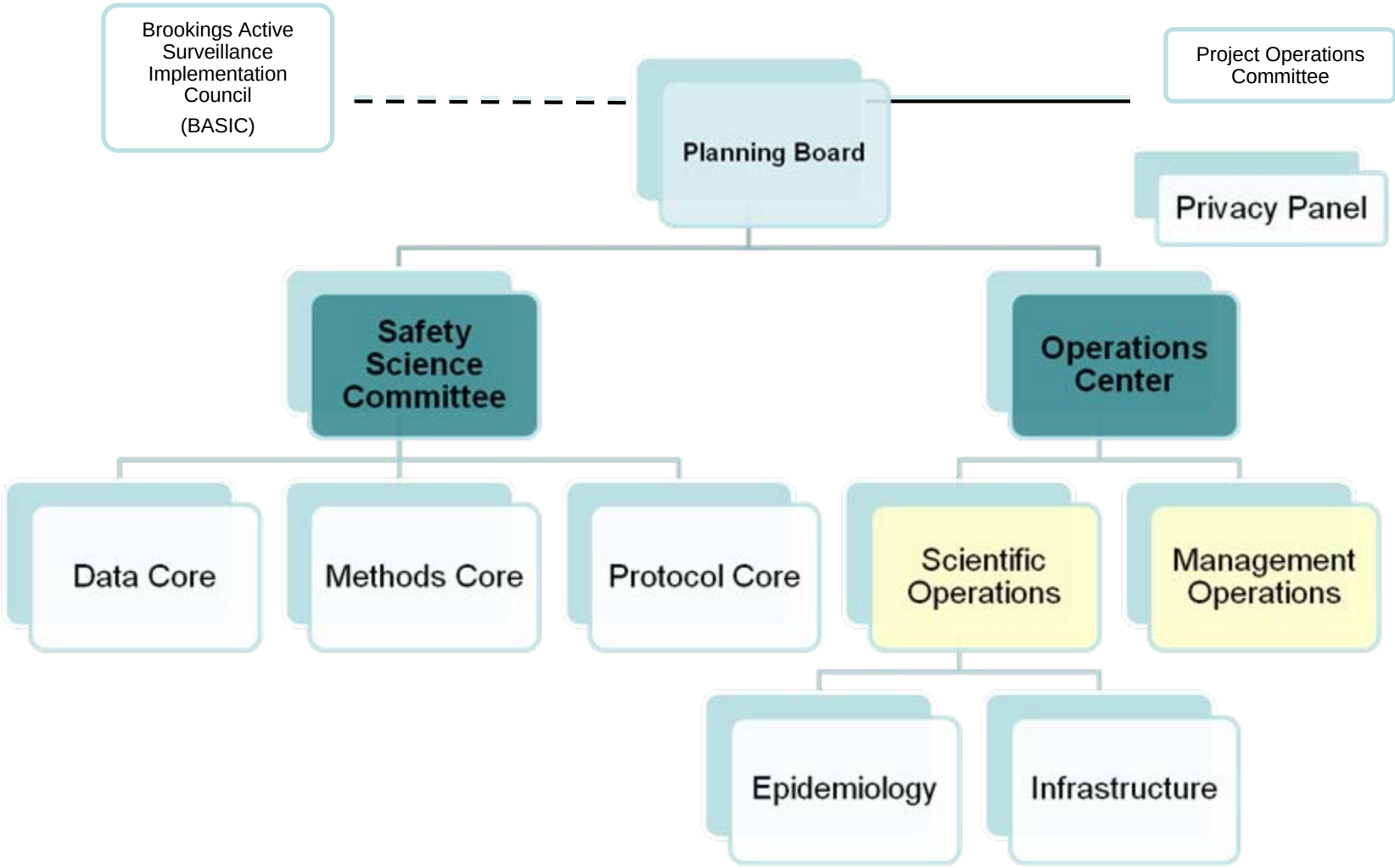
* Still in progress

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.

Mini-Sentinel Coordinating Center



Organizations

- America's Health Insurance Plans
- CIGNA Healthcare
- Cincinnati Children's Hospital Medical Center
- Critical Path Institute
- Brigham and Women's Hospital
  - Division of Pharmacoepidemiology and Pharmacoeconomics
  - Division of General Medicine
- Duke U School of Medicine
- HMO Research Network:
  Group Health Research Institute
  Harvard Pilgrim Health Care Institute
  Henry Ford Research Foundation
  HealthPartners Research Foundation
  Lovelace Clinic Foundation
  Marshfield Clinic Research Foundation
  Meyers Primary Care Inst(UMass / Fallon)
- HealthCore, Inc
- Humana - Miami Health Services Research Center
- Kaiser Permanente:
  Colorado, Georgia, Hawaii, Mid-Atlantic, N. California, Northwest, Ohio, and S. California regions
- Outcome Sciences, Inc
- Risk Sciences International
- Rutgers University Inst for Health
- U of Alabama at Birmingham
- U of Illinois at Chicago
- U of Iowa College of Public Health
- U of Pennsylvania School of Medicine
- Vanderbilt U School of Medicine
- Weill Cornell Medical College

Data Environments

- 60 million individuals (administrative & claims)
  - Kaiser, HMORN, Healthcore, Humana, CIGNA, Vanderbilt
- 10 million also have EMRs
  - Kaiser, HMORN
- 88 inpatient facilities
  - Kaiser, U Penn, Iowa, Cincinnati, U Illinois Chicago, Partners
- Device and disease registries
  - Outcome Sciences, Weill-Cornell, Duke, Kaiser

Current year activities

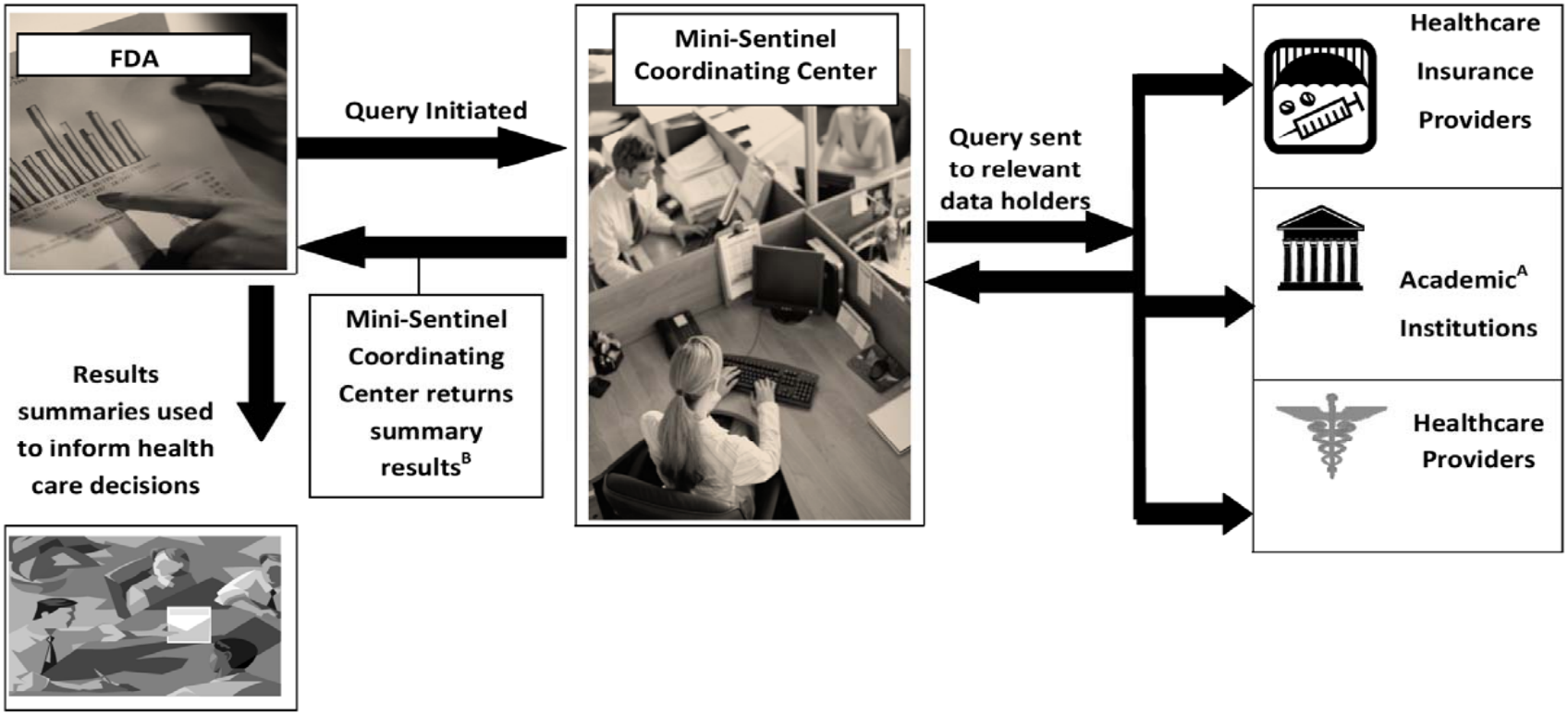
Data work

- Data inventory, plus a prioritized list of data needs
- Develop and implement Common Data Model
- First version of Mini-Sentinel Distributed Database, encompassing quality checked admin/claims data
  - Enrollment
  - Demographics
  - Utilization (diagnoses, procedures)
  - Outpatient pharmacy dispensing claims
- Capacity for timely response to queries

Distributed approach

- Distributed data model will be adopted
  - Data partners transform their local data to the Mini-Sentinel common data model
  - Coordinating center distributes analytic code via the distributed querying portal
  - Data partners securely return summary data to the coordinating center via the distributed query portal
  - Coordinating center reviews and analyzes data, provides detailed reports to FDA
- Methods for querying Mini-Sentinel
  - Rapid querying using standardized summary tables
  - Modular programs using the Mini-Sentinel Distributed Database
  - Ad-hoc SAS programs for evaluation protocols using the Mini-Sentinel Distributed Database

Overview of the Mini-Sentinel Query Process



A. Only those academic institutions with automated data will be recipients of queries.

B. No entities will have access to protected health information that they do not already hold. Instead, those whose queries are accepted by the **Mini-Sentinel Coordinating Center** for processing will receive results summaries from analyses conducted by each data holder that receives and agrees to respond to those queries. Results summaries will not include protected health information.

Current year activities

Methods development

- Framework for safety surveillance methods and a prioritized list of gaps
- Regression methods applicable for sequential surveillance programs
- Case only methods, e.g., cross-over designs, utilizing time-varying covariates
- Enhance methods for application of high dimensionality propensity score confounder adjustment

Current year activities

Protocol development

- Identify and characterize Health Outcomes of Interest (HOIs); prioritize 20 deserving evaluation via literature review and/or record review
- Select one HOI for full evaluation
  - Develop and test procedures for obtaining full text hospitalization records
  - Develop and test case identification and validation/adjudication process
- Develop protocol for active surveillance of drug-associated acute myocardial infarction

Safe Rx Project

- Collaboration between CMS and FDA
- Launched in 2008 at the time Medicare Part D data (prescription benefit) became available
- Evolved from earlier collaborations between CMS and FDA, primarily related to medical products covered by Medicare Part B
- Investigating ways to utilize Medicare and Medicaid medical product exposures and outcomes for active surveillance and full epidemiological studies

Federal Partners Collaboration

- An active surveillance initiative via intra-agency agreements with CMS, VA, DoD
- Small distributed system
  - Each Partner has unique data infrastructure
  - No common data model being utilized
- FDA proposes medical product – AE pairs to evaluate
- Develop a shared protocol
- Evaluate active surveillance methodologies
- Assess interpretability of query findings resulting from a decentralized analytic approach

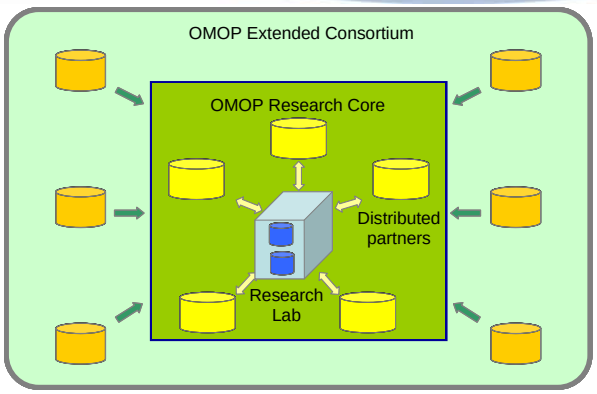
Planning template

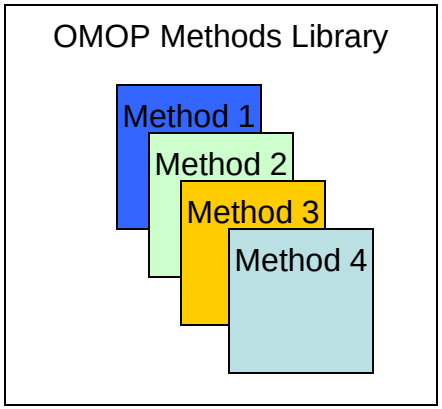
- CMS contractor Acumen developing a template for planning the active surveillance evaluations
  - Phase 1: Define treatments, outcomes, and related health circumstances and medical interventions for analysis
  - Phase 2: Describe analysis population
  - Phase 3: Compare populations for outcome events
- Template being refined through discussions with Federal Partners and by use in an active surveillance evaluation

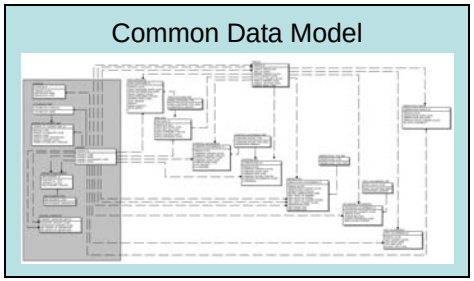
Observational Medical Outcomes Partnership
http://omop.fnih.org

- Public-Private Partnership with FNIH, FDA, and PhRMA
- OMOP is designed to provide and test:
  - Broad stakeholder participation
  - Transparency in an open innovation model
  - Development of reproducible processes in data and analyses
  - Standards for data models, terminologies, and methods
  - A public-private partnership governance structure with support from advisory boards
  - Empirical evidence that will inform appropriate use and best practices

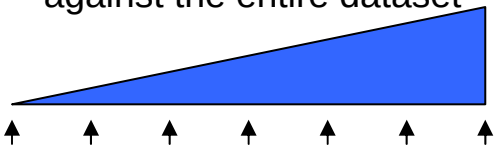
OMOP Experiment Research Workflow







Testing in each source:
-accumulating over time
-against the entire dataset



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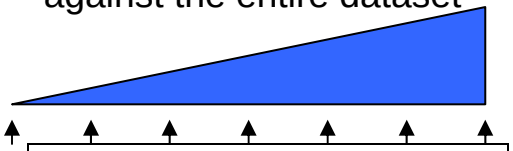

Health Outcomes of Interest
Angioedema
Aplastic Anemia
Acute Liver Injury
Bleeding
GI Ulcer Hospitalization
Hip Fracture
Hospitalization
Myocardial Infarction
Mortality after MI
Renal Failure

Drugs
ACE Inhibitors
Amphotericin B
Antibiotics
Antiepileptics
Benzodiazapines
Beta blockers
Bisphosphonates
Tricyclic antidepressants
Typical antipsychotics
Warfarin

Non-specified conditions

-All outcomes in condition terminology

-'Labeled events' as reference
-Warning
-Precautions
-Adverse Reactions
-Postmarketing Experience

OMOP Research Phases

- **Phase 1:** FEASIBILITY OF DATA INFRASTRUCTURE (Feb – July 2009)
  - Establish a consistent framework to use across disparate observational data sources
  - Establish OMOP Research Community
- **Phase 2:** FEASIBILITY OF ANALYSES (Aug – Dec 2009)
  - Develop and test analysis methods within the OMOP Research Lab and other data environments
  - Establish standard data characterization procedures
  - Implement health outcomes of interest definitions
  - OMOP to facilitate comparisons across databases
- **Phase 3:** PERFORMANCE MEASUREMENTS (Jan – July 2010)
  - Evaluate performance of methods and data in identifying drug safety issues
  - OMOP to facilitate comparisons across databases
- **Phase 4:** UTILITY OF ANALYSES & PROCESS (July – Dec 2010)
  - Assess the effectiveness and usefulness of how the results and comparisons contribute to decision-making

Convener on Active Medical Product Surveillance

Brookings Institution

- Expert stakeholder conferences
  - November 2009: Distributed Data Networks
  - March 2010: Legal issues
- Public Workshop
  - January 2010
- Medical Product Surveillance “Roundtables”
  - Update on Sentinel Initiative: October 2009
  - Learnings from H1N1 vaccine surveillance: December 2009
  - South Carolina Health Information Exchange: March 2010
  - Learning from DELTA System and Massachusetts Interventional Cardiology Device Safety Surveillance Pilot Project: May 2010
  - Learnings from OMOP: July 2010
- Active Surveillance Implementation Meetings
  - First meeting June 2010

International Discussions

- **Europe**
  - **European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP)**
    - Create a "network of excellence" consisting of research and medical-care centers, healthcare databases, electronic registries and existing networks to strengthen postmarketing monitoring to facilitate the conduct of safety related postapproval studies
  - **IMI/PROTECT**
    - To develop and validate tools and methods that will enhance AE data collection, active signal detection, create standards for pharmacoepi studies, and means to integrate all data know about a product for evaluation of risk:benefit
  - **EU-ADR**
    - Design, develop and validate a computerized system that exploits data from electronic healthcare records and biomedical databases for the *early detection of adverse drug reactions;* complementary to existing systems, have more power and detect signals earlier
- **Canada**
  - **Drug Safety and Effectiveness Network (DSEN)**
    - Enable research by linking researchers through a new virtual network, creating a national agenda of research based on priorities identified by decision-makers, provide funding for research to assess the risks and benefits of drug products that are on the market.
- **Japan**
  - **Utilization of Electronic Medical Records and Claims Data in Pharmacovigilance**
    - Secure access to EMR database including claim data to assess drug safety through ADR incidence survey and using a pharmacoepi approach

Lessons Learned to Date

- Clear articulation of scope is critical
- Broad, inclusive process is vital
- Managing expectations is key (aka patience)
- Build what we can today with a constant focus on what we will need, and can achieve, in the future