



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



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## **Agenda**

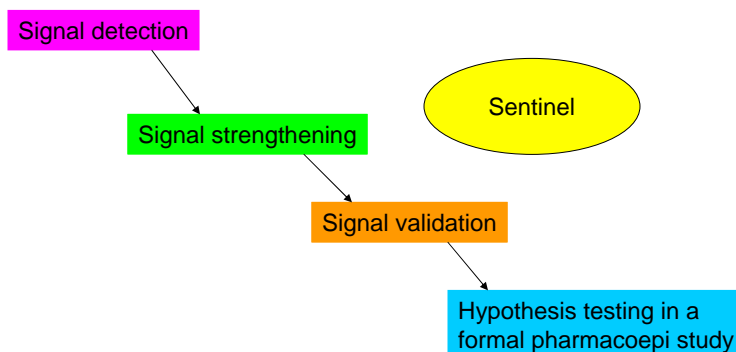
- Sentinel Initiative Overview
- Progress to date
- Next steps

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## Sentinel Overview

- Develop an active electronic safety monitoring system to
  - Strengthen FDA's ability to monitor postmarket performance of medical products
  - Augment, not replace, existing safety monitoring systems
  - 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)

## Evaluation of postmarket safety issues



## How may Sentinel complement what we are already doing?

- Safety issues may be identified and evaluated in near real-time
- Sentinel expands the capacity for evaluating safety issues
  - Improved access to subgroups, special populations
  - Improved precision of risk estimates due to expanded number of populations available for study
- Active surveillance may identify an increased risk of common AEs (e.g., MI, fracture) that health care providers may not suspect are related to medical products

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## A Work in Progress

May '08: Sentinel Initiative launched with release of initial report

- A long-term project; will be implemented in stages and will necessarily evolve
- Currently working on the “how and what”

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# Contracts

- **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

- **Governance**

Developing a Governance and Operations Structure for Sentinel Initiative

- **Stakeholder Outreach/ Privacy Issues**

Engagement of Patients, Consumers, and Health Care Professionals



## Evaluation of Existing Methods for Safety Signal Identification

*Group Health Cooperative Center for Health Studies*

### Objectives of contract:

- Identify/describe (statistically and clinically) existing signal detection methods that could be employed by the Sentinel System
- Address prior/current uses, what is known about its robustness for detecting signals across different types of data sources, what is known about flexibility for detecting different types of signals
- Recommendations for next steps for engaging most promising methods

## Methods reviewed in detail

- Continuous sequential monitoring methods
  - Sequential probability ratio test
  - Chart-based detection methods
  - Maximized sequential probability ratio test
- Group sequential monitoring methods
- Datamining methods
  - Proportional reporting ratio
  - Bayesian Confidence Propagation Neural Network
  - Multi-Item Gamma Poisson Shrinker
- Bayesian Updating

## Communication

- Efforts to provide information on status of initiative and obtain input from stakeholders
  - Website  
<http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm>
  - Public outreach
  - Internal meetings



## Federal Activities

- Collaborations with CMS, DoD, and VA
  - SafeRx project with CMS to develop near-real time active surveillance methods using Medicare data
  - Several ongoing projects within medical product Centers to evaluate potential medical product-adverse event signals and develop active surveillance methodologies as well as conduct more formal studies
- Federal Partners Working Group
  - Share information and discuss issues related to complementary efforts being carried out by the various Agencies within the Federal government
  - Participants include FDA, ONC, NIH, CDC, CMS, DoD, VA, AHRQ, IHS, HRSA, OHRP, and CPSC

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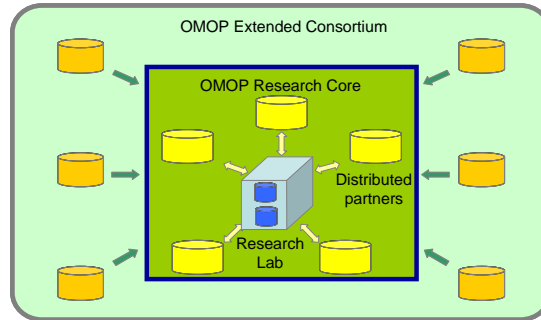
## Observational Medical Outcomes Partnership

<http://omop.fnih.gov>

- Public-Private Partnership with FNIH, FDA, and PhRMA
- Conducts experiments to assess value, feasibility, and utility of observational data to identify and evaluate the safety risks and potential benefits of prescription drugs
- Tests approaches for creating the infrastructure for accessing and managing required data
- Enables the evaluation of a possible governance model, consisting of an Executive Board, and Scientific and Technical Advisory Boards

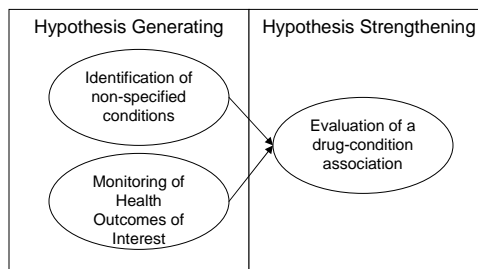
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## Overview of Partnership Design



- **OMOP Research Core** is responsible for designing, developing and managing the execution of the approved research proposals.
- **OMOP Research Lab** will be used to manage analysis process across all data sources within the Research Core.
- **Distributed Partners** implement the OMOP Common Data Model and execute protocols within their data environment
- The broader scientific community can voluntarily participate in the **OMOP Extended Consortium**

## OMOP analysis problems



**Identification of non-specified associations:** This exploratory analysis aims to generate hypotheses from observational data by identifying associations between drugs and conditions for which the relationships were previously unknown. This type of analysis is likely to be considered an initial step of a triaged review process, where many drug-outcome pairs are simultaneously explored to prioritize the drugs and outcomes that warrant further attention.

**Monitoring of Health Outcomes of Interest:** The goal of this surveillance analysis is to monitor the relationship between a series of drugs and specific outcomes of interest. These analyses require an effective definition of the events of interest in the context of the available data.



## Drug-HOI Pairs

Drug/class	Health Outcome of Interest
ACE inhibitors	Angioedema
ACE inhibitors	Hospitalization (including readmission and mortality)
Amphotericin B	Renal failure
Antibiotics: erythromycins, sulfonamides, and tetracyclines	Acute liver injury (symptomatic hepatitis)
Antiepileptics: carbamazepine, valproic acid, and phenytoin	Aplastic anemia
Benzodiazepines	Hip fracture
Beta blockers	Mortality after MI
Bisphosphonates: alendronate	GI ulcer hospitalizations
Tricyclic antidepressants	Myocardial infarction
Typical antipsychotics	Myocardial infarction
Warfarin	Bleeding



## International Discussions

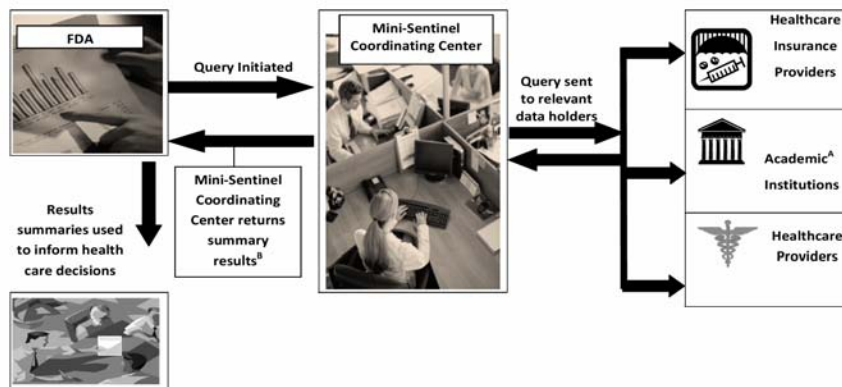
- **Europe**
  - **European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP)**
    - Create a "network of excellence" consisting of research and medical-care centers, healthcare databases, electronic registries and existing networks to strengthen postmarketing monitoring to facilitate the conduct of safety related postapproval studies
  - **IMI Topic 6/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

# Mini Sentinel

## Harvard Pilgrim Healthcare

- **Develop a coordinating center for a distributed system**
  - Access three or more health data environments with varied attributes to conduct analyses
  - Convene a Planning Board to develop governing documents and establish a Safety Science Committee charged with the day-to-day operations
  - Develop a means for secure communication with contracted data holders
  
- **Evaluate emerging methods in safety science**
  - Develop epidemiological and statistical methodologies for signal detection signal strengthening, and signal validation
  - Test such methodologies in the evaluation of FDA-identified medical product-adverse event pairs of concern

### 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.



## Federal Partners Collaboration

- An active surveillance initiative via intra-agency agreements with CMS, VA, DoD
- Identify medical product – AE pairs to evaluate
- Evolve active surveillance methodologies
- Evaluate interpretability of query findings resulting from a decentralized analytic approach

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## Engaging External Stakeholders: Convener on Active Medical Product Surveillance Brookings Institution

- Expert stakeholder conferences
  - Nov 23, 2009: Distributed Data Networks
  - March 2010: Privacy issues
- Public Workshop
  - Jan 11, 2010
- Medical Product Surveillance “Roundtables”
  - Update on Sentinel Initiative held Oct 30, 2009
  - “Learnings from H1N1 vaccine surveillance” scheduled for Dec 3, 2009
- Active Surveillance Implementation Meetings

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# Questions?

## Recommendations:

### Post-licensure hypothesis identification

- At time of product approval, review existing risk-benefit information to prioritize products and outcomes for post-licensure surveillance
- Determine whether active observational surveillance is the preferred surveillance method (vs. a formal pharmacoepi study or a large simple RCT)
- Use pre-licensure risk-benefit data to estimate expected event rates to inform post-licensure study power and samples size calculations



## Recommendations: Primary signal detection methods

- Active surveillance
  - Target specific medical product exposure- outcome pairs for routine post-licensure surveillance
  - Test target hypotheses with sequential analyses of automated healthcare data
    - Proven framework for evaluating pre-specified hypotheses at multiple points in time as data accrue, while controlling overall false positive error rate across all tests performed
    - Additional research needed to determine optimal approach (maxSPRT vs. group sequential methods)
  - Routine testing should be accompanied by routine descriptive analyses of safety data for full characterization



## Recommendations: Secondary and supplementary methods

- Continue to collect and analyze other supplementary post-licensure safety data
  - Spontaneous reports
  - Data mining for unanticipated adverse events in prospective cohorts
    - Adapt methods to explicitly control the overall false positive error rate
  - Develop meta-analysis methods to combine safety results across sites