ENGELBERG CENTER for Health Care Reform at BROOKINGS

Overview of FDA's Sentinel Initiative

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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.

Update on FDA's Sentinel Initiative

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US Food and Drug Administration
September 7, 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 investigate safety issues in near real time
- Enhancing FDA's ability to evaluate safety issues not easily investigated 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

Sentinel Initiative Vision*

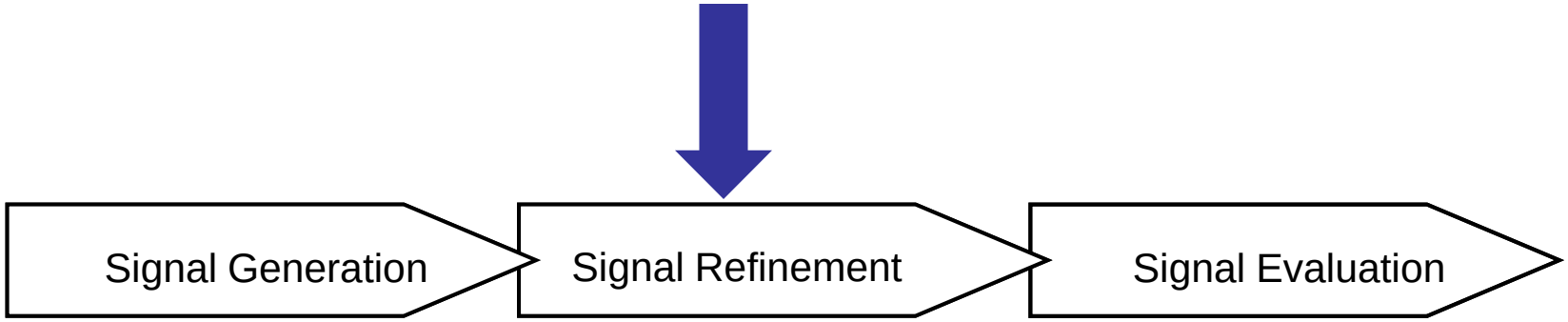
- System will be able to refine safety signals in near real-time. This will require the following capabilities:
  - rapidly defining exposed cohorts;
  - establishing algorithms to capture health outcomes of interest;
  - using sophisticated modular programs capable of running investigations with minimal input from epidemiologists and clinicians and limited or no ad hoc programming; and
  - developing a framework to guide methodological approaches for safety surveillance investigations that include confounding adjustment.
- Approaches for signal generation will be under development.

* Within the next 3 years

Sentinel Initiative: A Collaborative Effort

- Data Partners
  - Private: Mini-Sentinel pilot
  - Public: Federal Partners Collaboration
- Industry
  - Observational Medical Outcomes Partnership
- All Stakeholders
  - Brookings Institution cooperative agreement on topics in active surveillance

Phases of Active Surveillance



- Signal generation includes a collection of methods for identifying potential associations between medical products and health outcomes of interest (HOIs)
- Signal refinement is a process for evaluating the magnitude and clinical significance of a suspected association
- Signal evaluation consists of the implementation of a formal epidemiological analysis to establish or refute causality between exposure to a medical product and the health outcome of interest

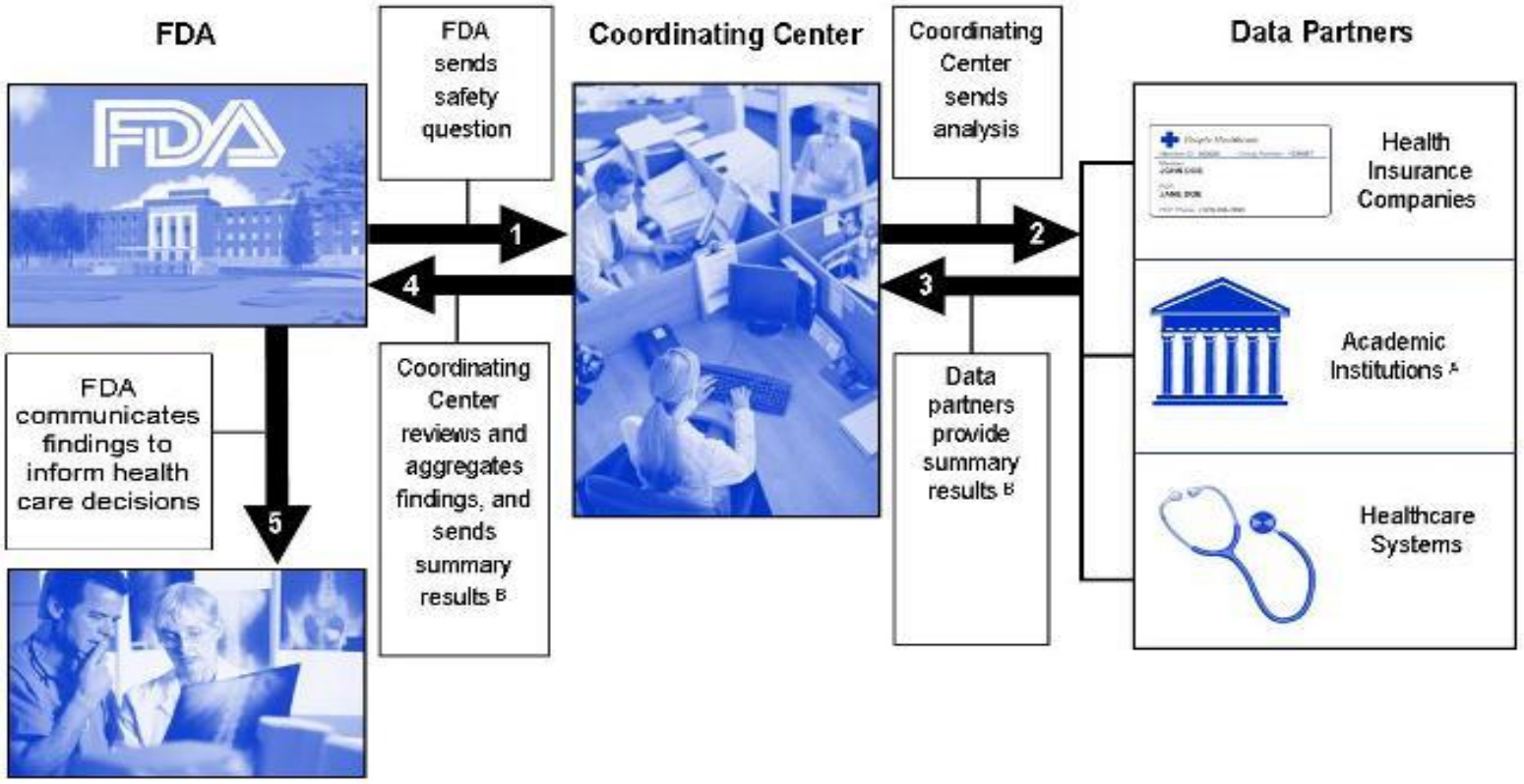
Mini-Sentinel

www.mini-sentinel.org

Harvard Pilgrim Health Care Institute

- 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 investigate safety issues in existing automated healthcare data system(s) and to learn more about some of the barriers and challenges, both internal and external.

Figure 1: Overview of the Mini-Sentinel Safety Question Evaluation Process



A. Only those academic institutions with electronic healthcare data will receive safety questions for evaluation.

B. Data partners will provide summary results from analyses conducted within their secure data environments. Those summary results will not include directly identifiable health information.

Mini-Sentinel Principles/Policies

- Public health practice, not research
- Minimize transfer of protected health information and proprietary data
- Data partners participate voluntarily
- Maximize transparency
  - Tools, methods, protocols, computer programs
  - Findings

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)

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

Distributed Querying Approach

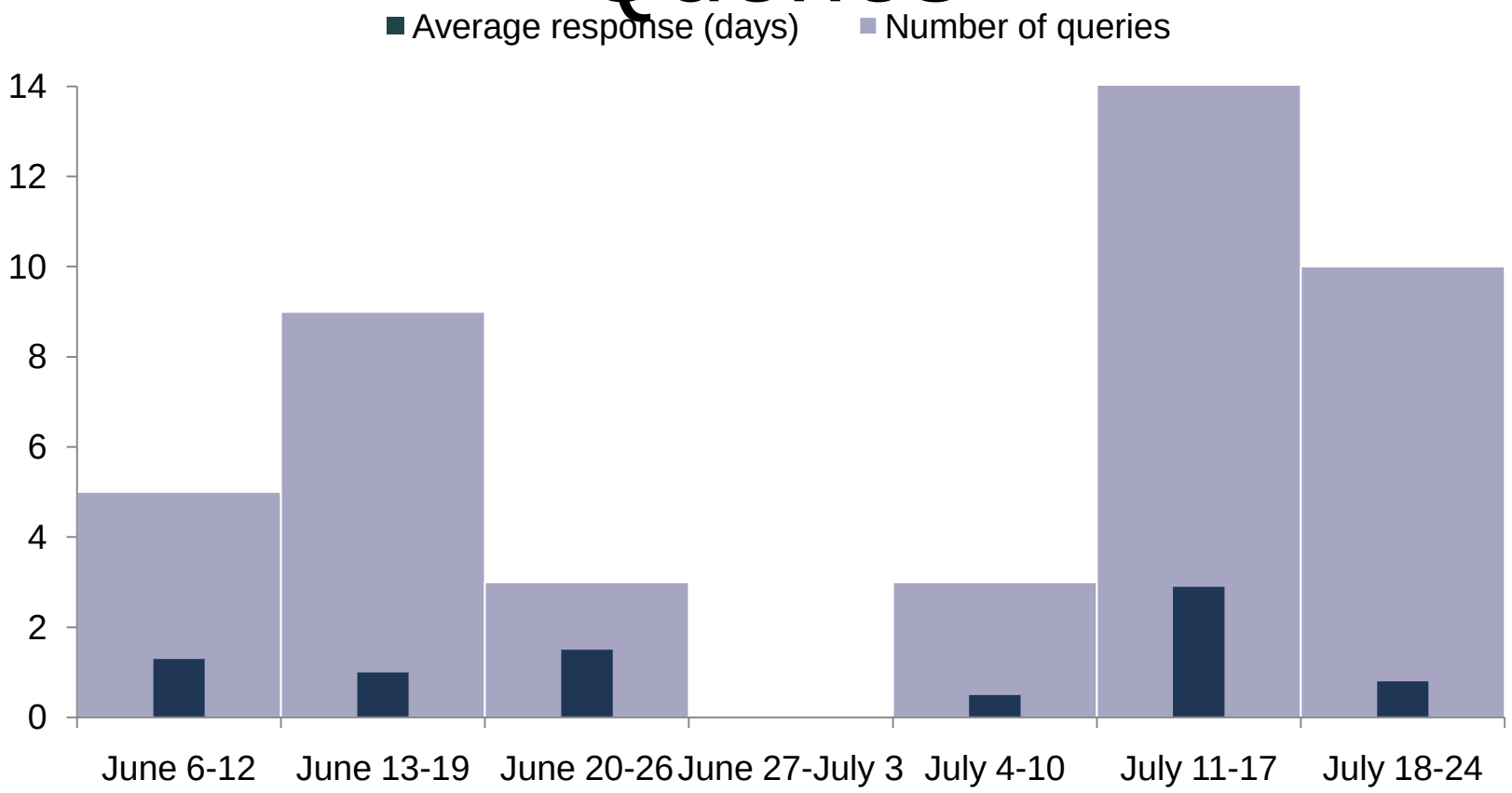
Three ways to query data:

1) Pre-tabulated summary tables
2) Reusable, modular SAS programs that run against person level Mini-Sentinel Distributed Database
3) Custom SAS programs for in-depth analysis

Summary Tables Overview

- Summarize utilization information using pre-defined concepts (disease, age groups, exposure)
- Created via distributed programs
- Held by the Data Partners
- Benefits:
  - Potential for blanket data sharing approval
  - Rapid access to information
  - No protected information shared
- Limitations:
  - No linkage across tables
  - Cannot add individuals across periods (double-count)
  - No temporal relationships

Data Partner Response to Queries



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

Custom Programs

- Users can work with Mini-Sentinel Operations Center (MSOC) to develop custom programs to run against the Mini-Sentinel Distributed Database (MSDD)
  - Summary tables and modular programs are limited and may not be appropriate for all types of queries
  - Project-specific code will become part of the Mini-Sentinel library
- The MSOC will
  - Distribute programs to the Data Partners
  - Receive/collate the output
  - Provide it to the requestor

Methods Core

- Framework for safety surveillance methods and a prioritized list of gaps
- Completed methods projects
  - 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
- Ongoing methods projects
  - White paper on methods to evaluate the impact of FDA regulatory actions
  - Evaluating Strategies for Data Sharing and Analyses in Distributed Data Settings
  - Developing a framework for validating the results of protocol-based assessments

Protocol core

- Systematic reviews of 20 HOIs to identify validated algorithms for identifying cases in claims data
- Validate HOI algorithms in source data
  - Develop and test procedures for obtaining full text hospitalization records
  - Develop and test case identification and validation/adjudication process
- Develop active surveillance protocol-based assessments

Mini-Sentinel Task Orders- Sentinel Core Team

- Add laboratory and vital sign data to MSDD
- Continue methods development and HOI validation
- Develop anonymous linking between data partners (e.g., device registry and claims)

Mini-Sentinel Task Orders- CDER

- Evaluation of emerging safety issues with new molecular entities
  - Sequential analyses over time or one time looks
  - Single outcome or multiple outcomes
- Evaluation of emerging safety issues with drugs on market > 2 yrs
  - Issues that emerged after approval
  - Single molecular entity or drug class
- Evaluation of Impact of FDA Regulatory Actions
  - Drug use under specific conditions
  - Monitor changes before and after FDA action
- Drug Use
  - Comparison of Sentinel Initiative pilots to proprietary nationally projected databases
  - In conjunction with outcomes evaluations

Mini-Sentinel Task Orders- PRISM (CBER)

- Create an operational framework
  - A guide to the key operational and methodologic decisions for designing surveillance projects in PRISM
- Evaluate 2 vaccine-event pairs
  - Gardasil vaccine and venous thromboembolism (VTE)
  - Rotavirus vaccines (Rotateq and Rotarix) and intussusception
- Identify and evaluate complementary data sources
  - E.g., state immunization registries
- Develop methods to detect non-prespecified events
- Develop improved methods for causal inference in sequential analysis

Mini-Sentinel

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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

May 27, 2011

- HOI Evidence Review - ABO Incompatibility Reactions
- HOI Evidence Review - Infections Due to Blood Products, Tissue Grafts, or Organ Transplants
- HOI Evidence Review - Lymphoma

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 – adverse event pairs to investigate
- Develop a shared protocol
- Assess interpretability of query findings resulting from a decentralized analytic approach and different patient populations

Convener on Active Medical Product Surveillance

Brookings Institution

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

- Expert stakeholder conferences
- Medical Product Surveillance “Roundtables”
- Active Surveillance Implementation Meetings
- Annual Public Workshop

Observational Medical Outcomes Partnership

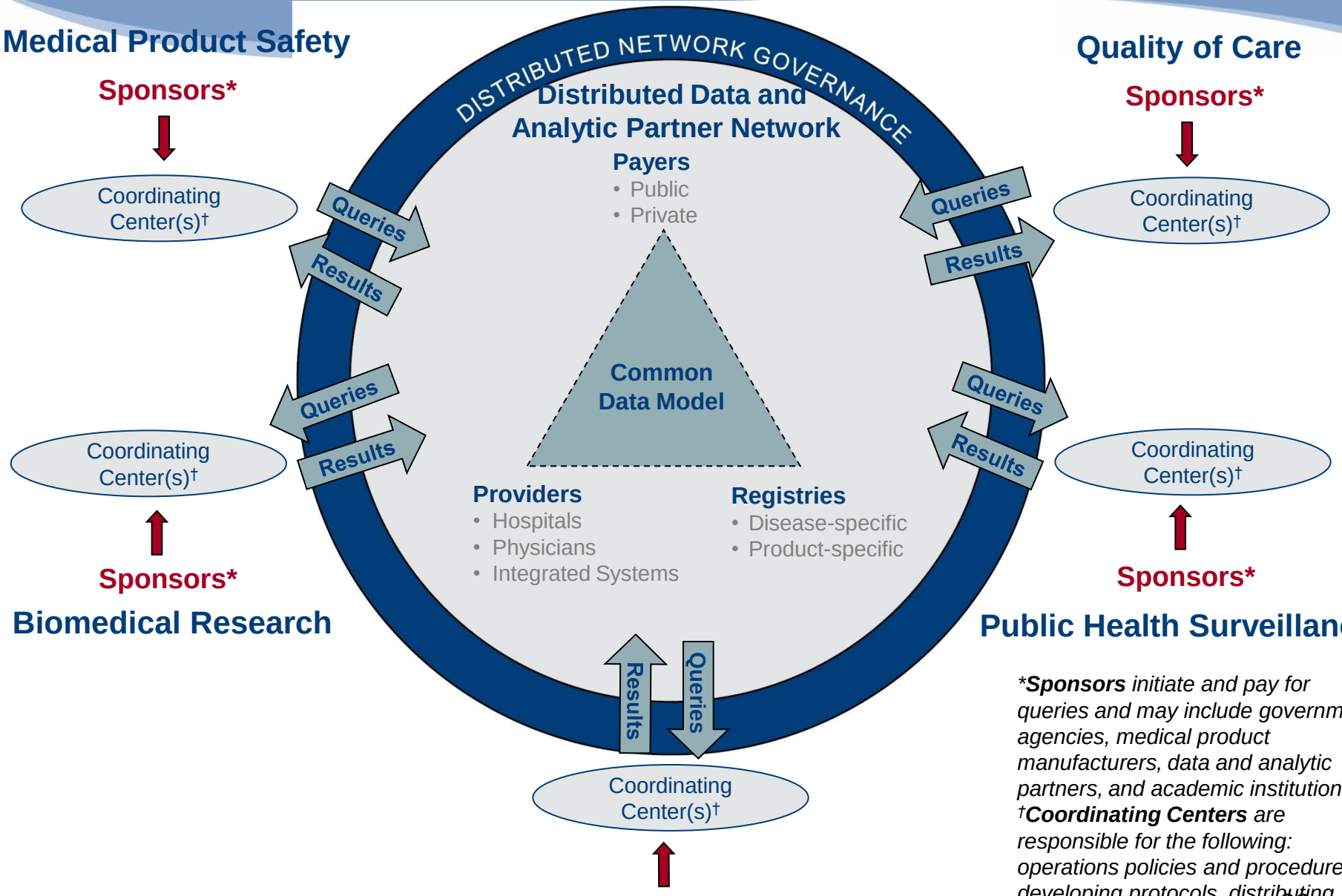
http://omop.fnih.org

A public-private partnership between industry, FDA and FNIH to inform the appropriate use of observational healthcare databases for active surveillance by:

- **Conducting methodological research** to empirically evaluate the performance of alternative methods on their ability to identify true drug safety issues
- **Developing open source tools and capabilities** for transforming, characterizing, and analyzing disparate data sources
- **Establishing a shared resource** so that the broader research community can collaboratively advance the science

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



**Sponsors* initiate and pay for queries and may include government agencies, medical product manufacturers, data and analytic partners, and academic institutions.*

*†**Coordinating Centers** are responsible for the following: operations policies and procedures, developing protocols, distributing queries, and receiving and aggregating results.*

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Roundtable Discussion and Questions

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