FDA's Sentinel Initiative: Current Status and Future Plans

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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

www.mini-sentinel.org

Harvard Pilgrim Health Care Institute

- Participation of all medical products Centers at FDA
- Developed the scientific operations needed for an active medical product safety surveillance system
- Created a coordinating center with continuous access to automated healthcare data systems, which has the following capabilities:
  - A "laboratory" for developing and evaluating scientific methodologies that might later be used in a fully-operational Sentinel System.
  - Provides 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.

Organizations

- America's Health Insurance Plans
- 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

Mini-Sentinel Year 1: Activities

- Data Core
  - Developed and implemented Mini-Sentinel Common Data Model
  - First version of Mini-Sentinel Distributed Database
- Methods core
  - Framework for safety surveillance methods and a prioritized list of gaps
  - Specific methods development
- Protocol core
  - Systematic reviews of 20 Health Outcomes of Interest (HOIs) to identify validated algorithms for identifying cases in claims data
  - Validated one HOI algorithm in source data
  - Developed active surveillance protocols

Mini-Sentinel Year 2

- Implemented active surveillance protocol for potential drug-related acute MI
- Evaluated emerging safety issues for
  - New molecular entities (newly approved drugs)
  - Drugs that have been marketed for >2 years
- Evaluated impact of regulatory actions (e.g., restricted distribution)
- PRISM2
  - A continuation of the active surveillance system developed for H1N1 vaccine safety surveillance by HHS, FDA, and CDC
  - Institute safety monitoring for a non-influenza vaccine
- Added laboratory and vital sign data to MSDD
- Continued methods development
- Broadened modular programs capabilities

There is more to Mini-Sentinel than just data

- Methods core
  - Framework for safety surveillance methods and a prioritized list of gaps
  - Specific methods development
- Protocol core
  - Systematic reviews of 20 Health Outcomes of Interest (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 protocols

Federal Partners Collaboration

- An active surveillance initiative via intra-agency agreements with CMS, VA, DoD
- All medical products Centers participate
- 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
- Assess interpretability of query findings resulting from a decentralized analytic approach and different patient populations

Current Sentinel Initiative Plans

- System should 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: currently, not doing signal generation
- How to incorporate registries and other data sources; matching non-personally identifiable data

Current Mini-Sentinel Distributed Database

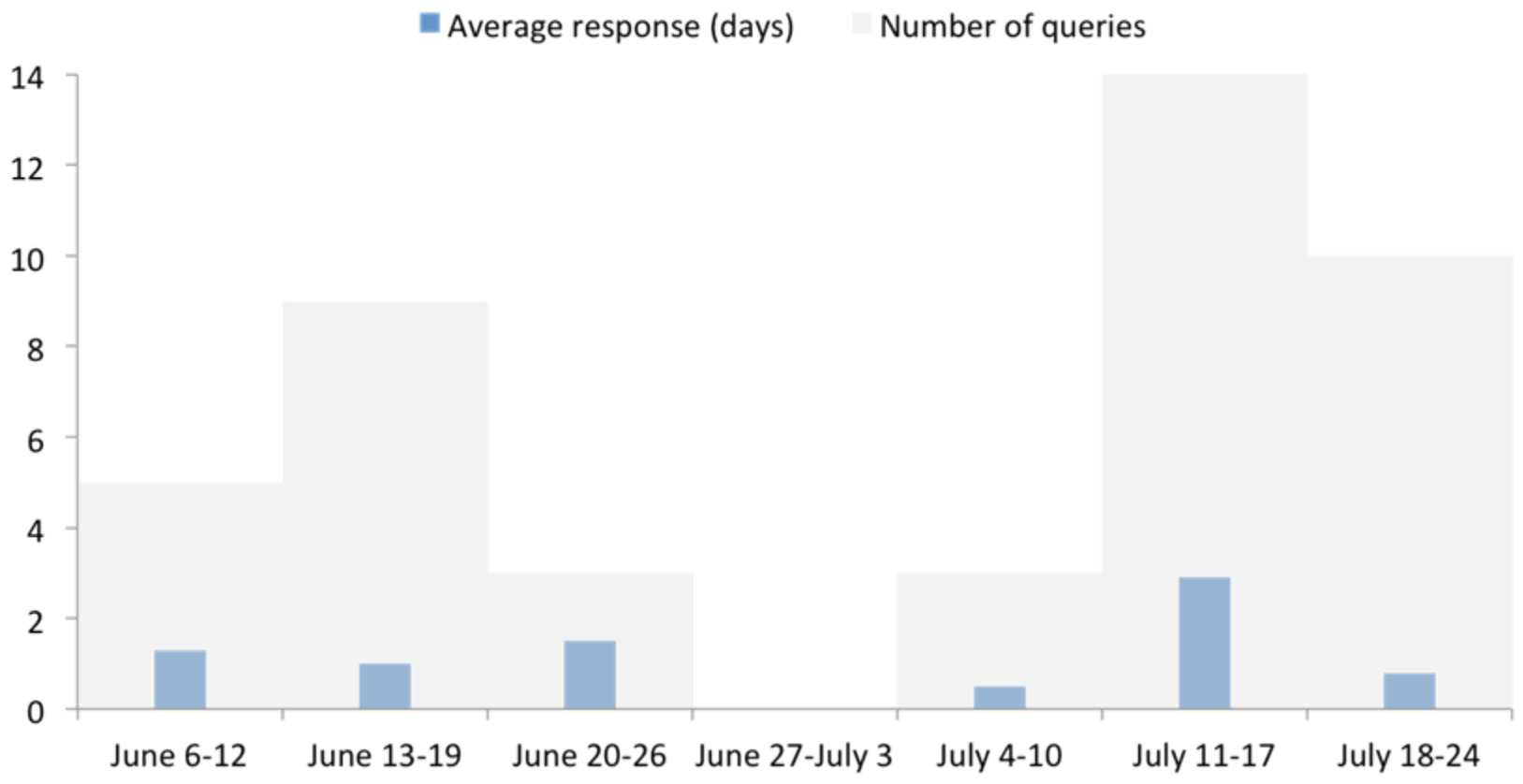
- Quality-checked data held by 18 partner organizations
- 125 million individuals
  - 316 million person-years of observation time (2000-2011)
  - 39 million individuals currently enrolled, accumulating new data
  - 24 million individuals have over 3 years of data
  - 20 million have eHRs

*As of 7 July 2011

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

Data Partner Response to Queries



Institutionalizing Sentinel Capabilities

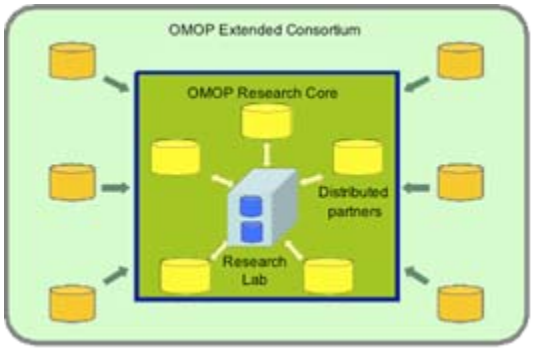
- Ensure effective collaboration between all CDER offices
- Integrate Sentinel into postmarket review process
- Develop policies and procedures around communication of Sentinel findings

OMOP Project

Active Surveillance
Observational Medical Outcomes Partnership OMOP Data Community

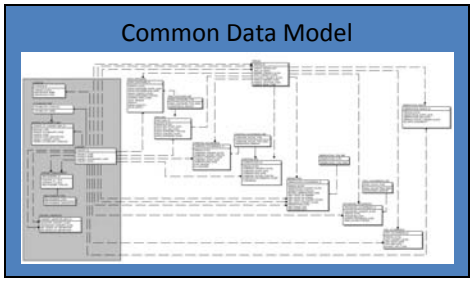
Data Source	Type of Data	Available Lives (millions)
GE Centricity EHR	Electronic health record	**11.2**
Thomson MarketScan Commercial Claims and Encounters	Subpopulation with administrative claims & laboratory results	**58**
Thomson Medicare Supplemental	Administrative claims	**4.4**
Thomson Multistate Medicaid	Administrative claims	**11.1**
Thomson Lab Supplement	Administrative claims	**1.5**
Regenstrief Institute	Health information exchange (administrative claims and EHR)	**9.4**
Partners Healthcare System	Electronic health record	**5.0**
Department of Veteran's Affairs MedSAFE	Electronic health record (at VA facilities)	**7.8**
Humana	Administrative claims (w/ Medicare advantage & prescription plans)	**6.5**
SDI Health	Administrative claims from point of care w/ EHR subset	**160**

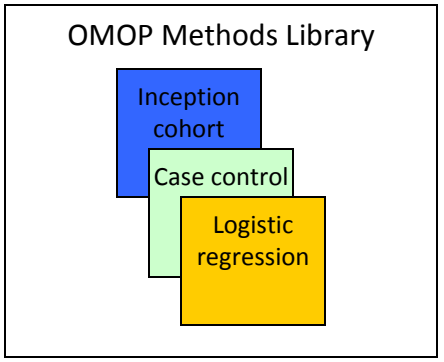
OMOP Research Experiment



- 10 data sources
- Claims and EHRs
- 200M+ lives

- Open-source
- Standards-based





- 14 methods
- Epidemiology designs
- Statistical approaches adapted for longitudinal data

Drug

Outcome	ACE inhibitors	Amphotericin B	Antibiotics: erythromycins, sulfonamides, tetracyclines	Antiepileptics: carbamazepine, ph enytoin	Benzodiazepines	Beta blockers	Bisphosphonates: alendronate	Tricyclican tidepressants	Typical antipsychotics	Warfarin
Angioedema										
Aplastic Anemia										
Acute Liver Injury										
Bleeding										
Hip Fracture										
Hospitalization										
Myocardial Infarction										
Mortality after MI										
Renal Failure										
GI Ulcer Hospitalization										

Legend	Total
True positive' benefit	2
True positive' risk	9
Negative control	44

OMOP Research Experiment

- Rigorously test various methods for detecting associations between drugs and “medical outcomes”, using well validated positive and negative controls
- Research lab allows characterization of datasets and investigation of impact of multiple “parameter settings” for each method

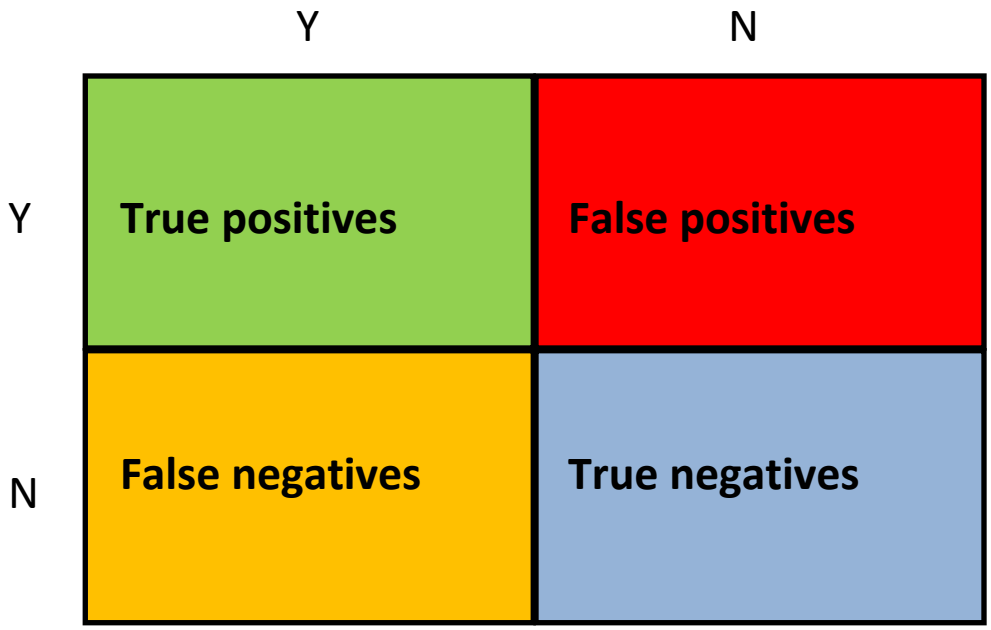
OMOP Research Experiment

- Does NOT test validity of “epidemiologist designed-by-hand” pharmacoepi study
- Tests validity of “button push” experiment after datasets analyzed and parameters set
- Relevant to Sentinel automated queries
- Validity of formal pharmacoepidemiology study has not been established
- Methods evaluated used in both types of studies—attempts to deal with confounding

Measuring method performance

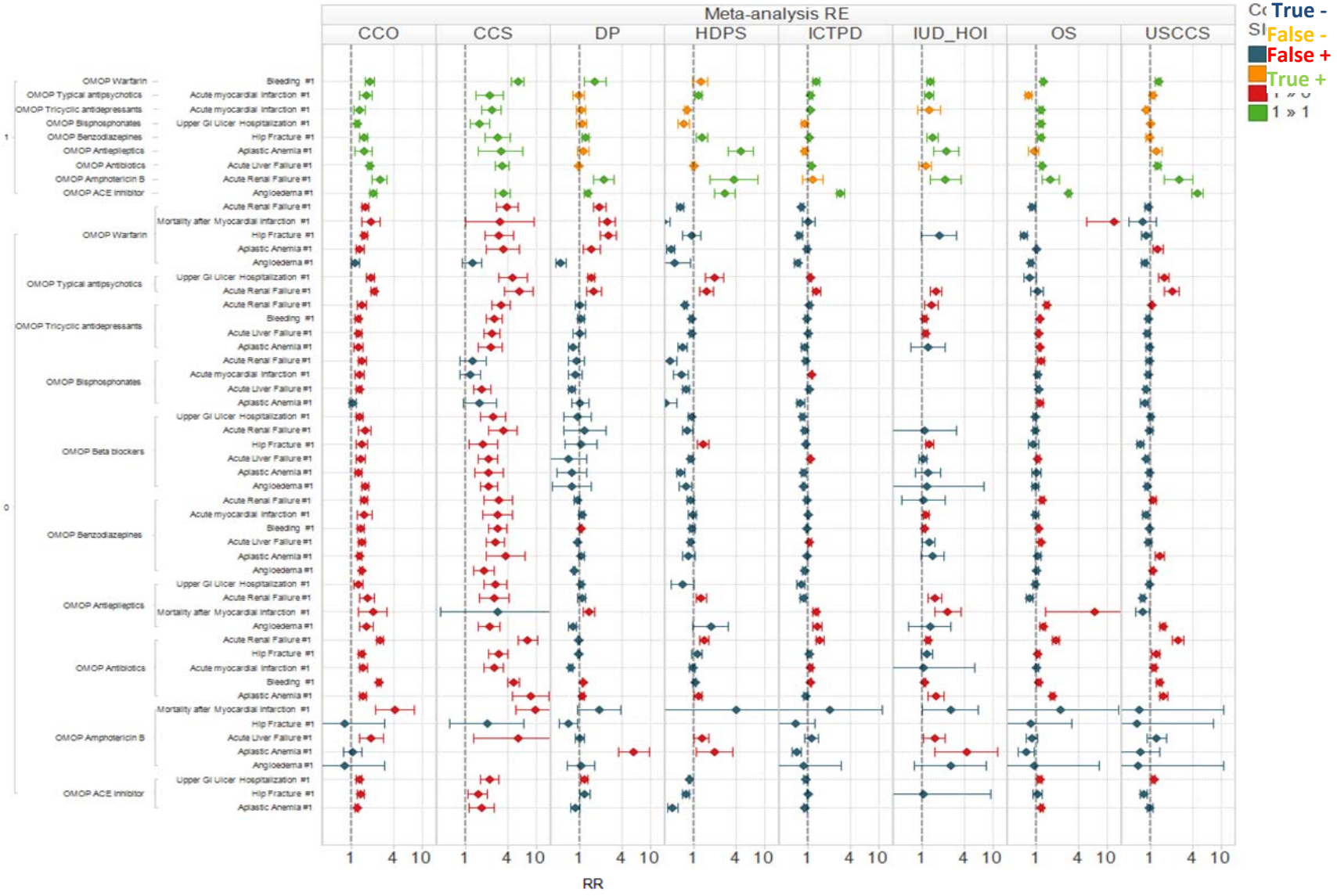
Drug-condition association status
Y – 'true association',
N – 'negative control'

Method prediction: Drug-condition pair met a specific threshold

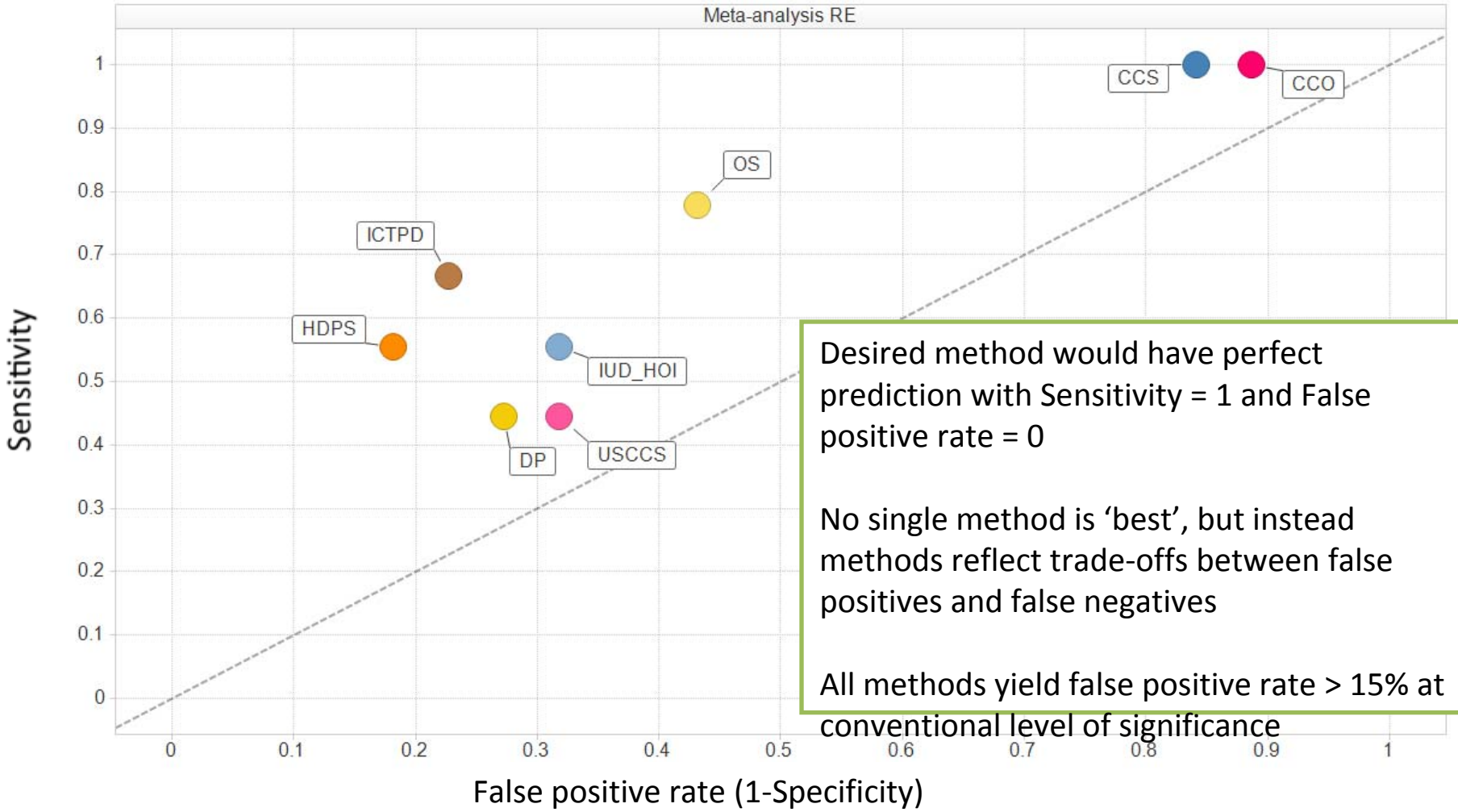


Question: For any method applied to any data source, what are the expected operating characteristics?

Distribution of estimates across all drug-outcome pairs



Comparing methods by sensitivity and specificity at alpha=0.05



Desired method would have perfect prediction with Sensitivity = 1 and False positive rate = 0

No single method is 'best', but instead methods reflect trade-offs between false positives and false negatives

All methods yield false positive rate > 15% at conventional level of significance

Current OMOP Efforts

- Add more pairs—positive and negative controls
- Look “under the hood” at results—can we figure out why the predictive values are so unsatisfactory?
- Compare results to setup via pharmacoepidemiologic “by hand” approach
- Contracts and grants to various groups around the country to work on these questions and methods

What is Next?

- Transition OMOP to be methodologic arm of Sentinel; setting up Sentinel data model
- Are considering setting up at Reagan-Udall Foundation, which is now getting started
- OMOP currently is set thru early next year at FNIH; plan would be that next fundraising effort would be for R-U.
- Funding for research fellows and research
- Computer lab may stay with FNIH

Next Steps for Sentinel

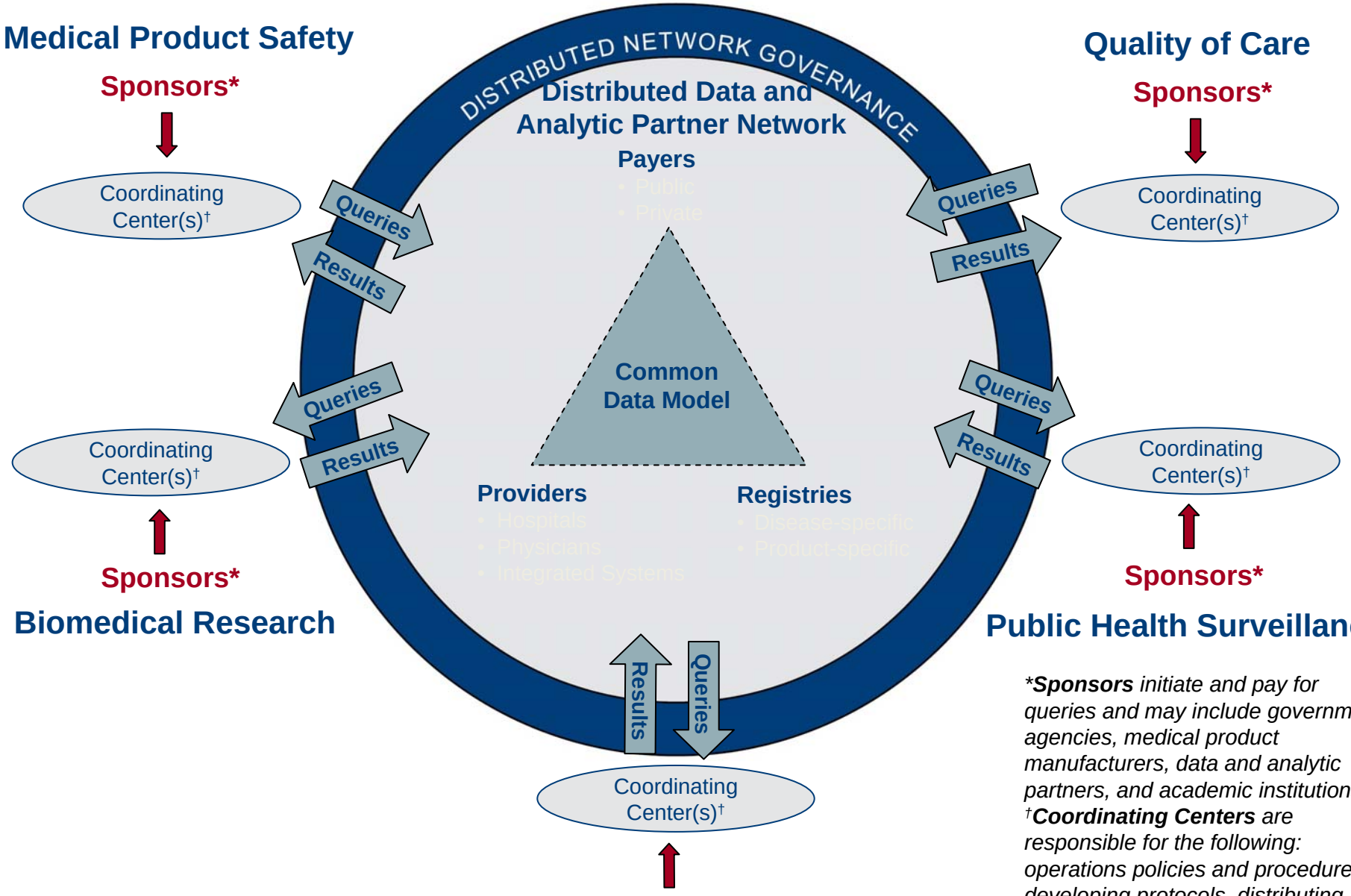
- Mini-Sentinel, and future Sentinel, are FDA projects funded Federally
- Would expect these to stay as “fully owned” FDA projects
- Envision a public-private partnership extension that would allow other parties to participate in research and studies using Sentinel Infrastructure
- Hope to establish at R-U

Next Steps for Sentinel

- Sentinel will gradually expand into eHR data
- “Secondary use” of such data will have many research purposes
- FDA would stick to medical product safety issues
- Expect R-U to work on similar projects with outside parties
- But others could use the data infrastructure for other research purposes

Future Steps

- The “data partners”, e.g., those who manage the claims data or who hold the eHR (for example, health care systems) do not wish to transform their data into multiple common data models
- The cost of transformation and maintenance of these data are one of the major costs for Sentinel
- Therefore, it makes sense that one transformed dataset be used for multiple research purposes



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.

Current Uncertainties

- Multiple efforts-most of much small scale than Sentinel—are going on to combine electronic health data for various research purposes
- Unclear if all will be able to work together
- Multiple competing data structures will be costly and perhaps distract from long-term goal of better data standardization in eHR
- FDA is trying to work with the various parties to develop an overall plan

Summary

- Sentinel is a going concern: use by FDA to better understand safety signals is ramping up
- Current plans are for further expansion of data sources via mini-Sentinel; continued research, and ongoing utilization
- Longer term plan is to develop PPP research arm and data utilization capability
- Long term hope is to establish a national secondary use data resource to be shared by many parties with disparate research needs