FDA's Sentinel Initiative

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Overview

- Sentinel Initiative
- Mini-Sentinel Pilot Program
- Completed & Current Projects
  - Semi-Automated Routine Prospective Safety Surveillance System
- Future Steps

FDA Amendments Act of 2007

Section 905: Active Post-market Risk Identification and Analysis

- Establish a post-market 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 system 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)
    - Longer term data
    - 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

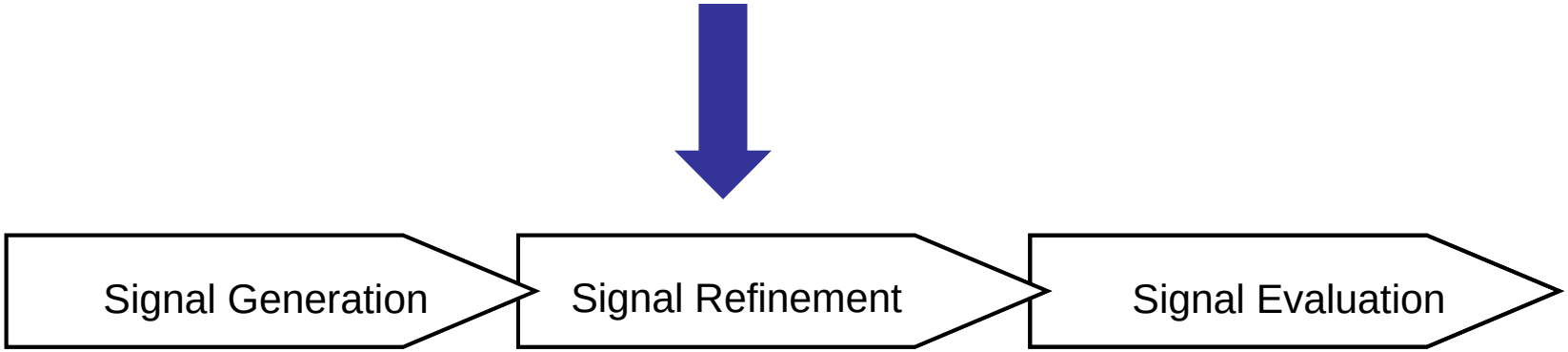
**Will augment, not replace, existing safety monitoring systems

A Collaborative Effort

- Collaborating Institutions (Academia and Data Partners)
  - Private: Mini-Sentinel pilot
    - **Harvard Pilgrim Health Care Institute**
  - Public: Federal Partners Collaboration
- Industry
  - Observational Medical Outcomes Partnership
- All Stakeholders
  - Brookings Institution cooperative agreement on topics in active surveillance

MS Partner Organizations

Phases of Active Surveillance



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

Current Population Coverage

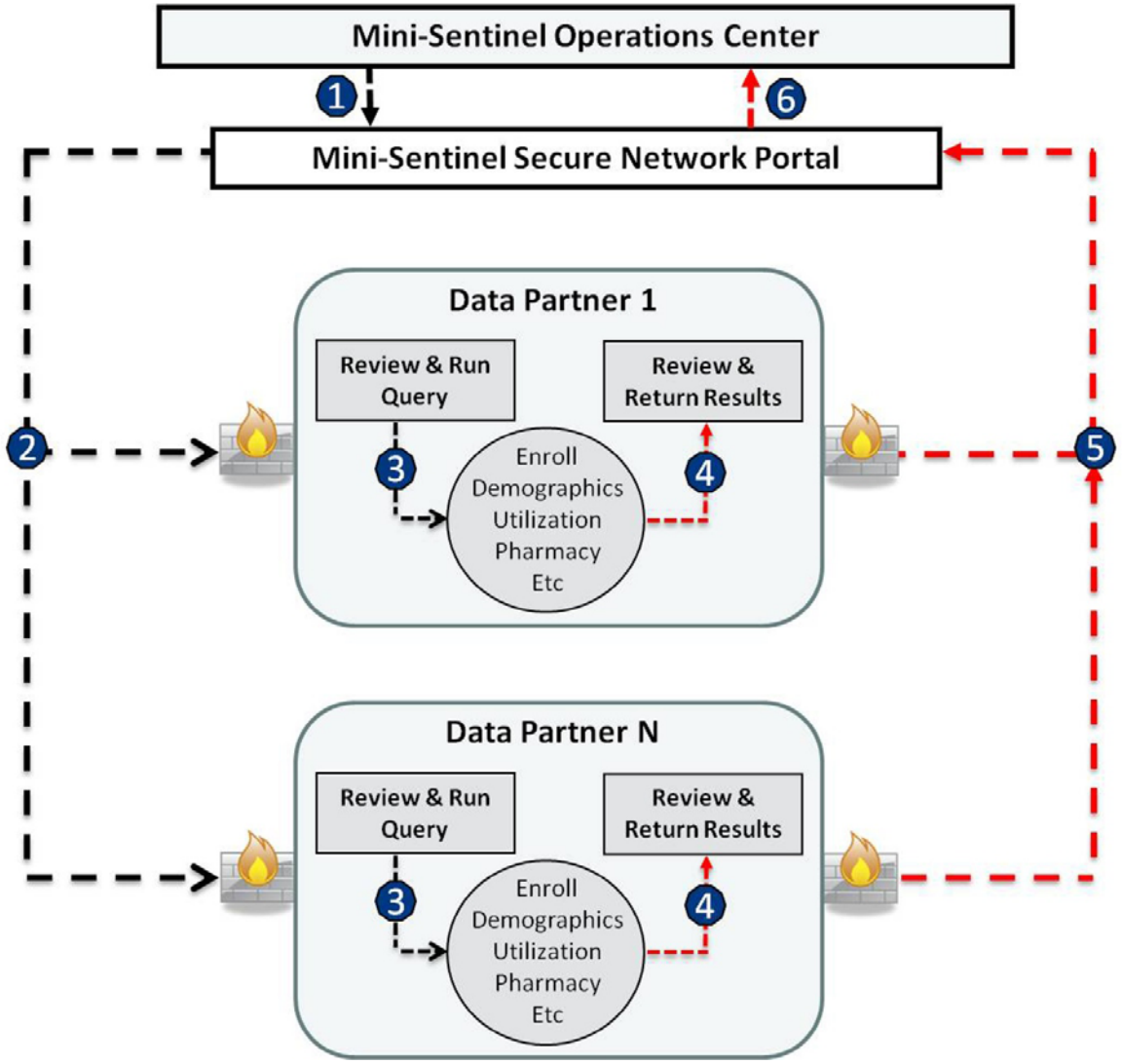
- Populations with well-defined person-time for which medically-attended events are known
- Over 130 million individuals*
  - 382 million person-years of observation time
- 3.7 billion dispensings
- 4.1 billion unique encounters
  - 46 million acute inpatient stays
- 24 million people with ≥ 1 lab test result

***As of December 2012. The potential for double-counting exists if individuals moved between data partner health plans.**

Why Distributed Database?

- Avoids many concerns about inappropriate use of confidential personal data
- Data Partners maintain physical control of their data
- Data Partners understand their data best
  - Valid use / interpretation requires their input
- Eliminates the need to create, secure, maintain, and manage access to a complex, central data warehouse

Mini-Sentinel Distributed Analysis



1- User creates and submits query (a computer program)

2- Data partners retrieve query

3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return summary results via secure network/portal

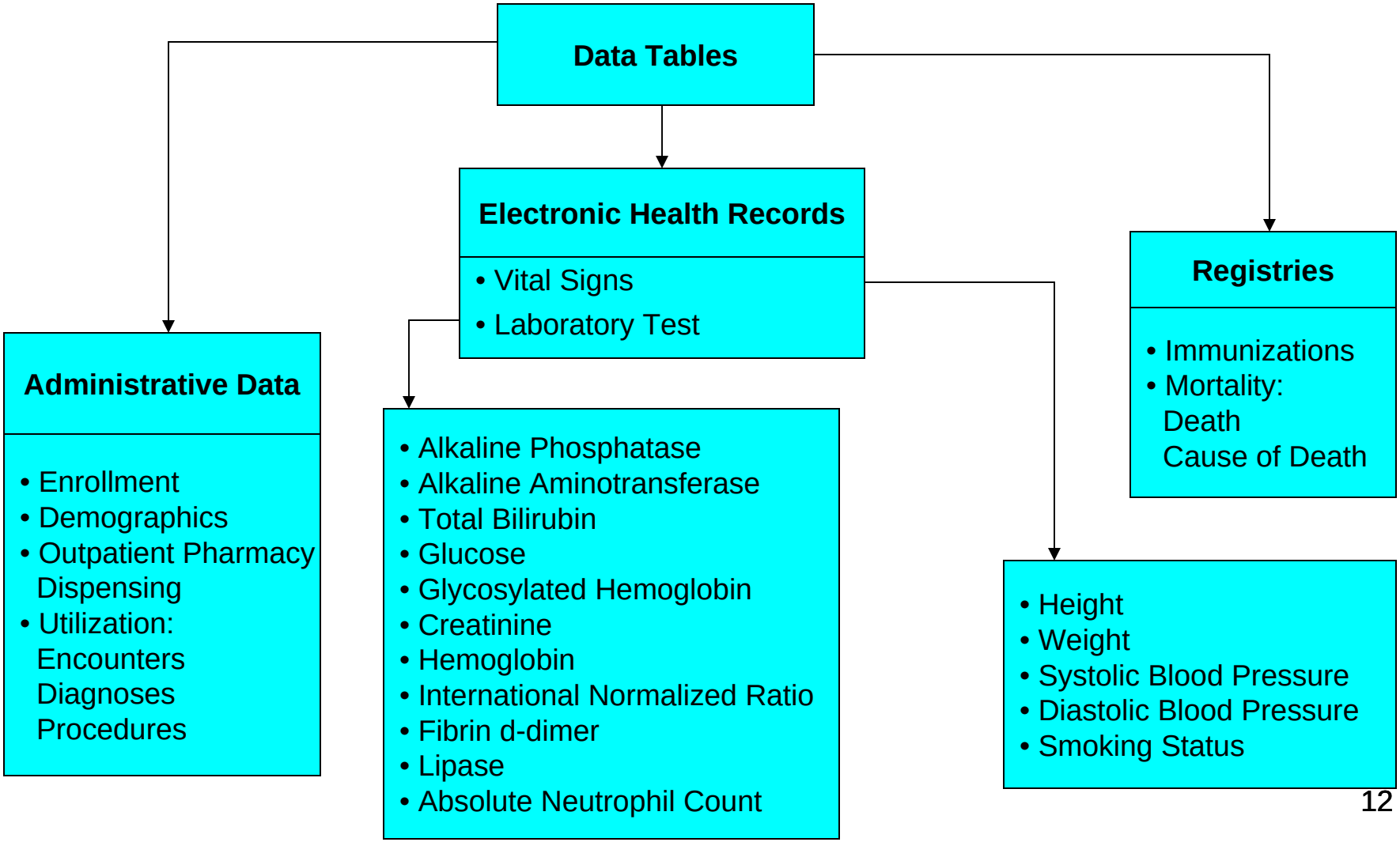
6 Results are aggregated

Common Data Model

- Standard data structure used by all MS Data Partners
- Allows MS Operations Center to build standardized programs and other tools to be run against patient-level data stored locally at each Data Partner site
- Current version

http://www.minisentinel.org/data_activities/distributed_db_and_data/default.aspx

Common Data Model



Distributed Querying Approach

Three ways to query data:

1) Pre-tabulated summary tables
2) Reusable, modular SAS programs
3) Custom SAS programs for in-depth analysis

Summary Tables

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

Modular Programs

- SAS programs flexible enough to allow for efficient analysis of events that follow a particular type of pattern
  - Use input datasets to specify analysis parameters and to customize the analysis for specific types of events
  - Rapid access to information
- Designed to run against datasets in MSCDM
- 9 MPs developed so far

Current Modular Programs

1. Use of outpatient pharmacy medication and/or medical procedure at defined time period
2. Use of drugs/procedures at defined time period among members with/without pre-existing condition
3. Frequency of selected events following new exposure to drugs/procedures among members with/without pre-existing condition
   - Stratified by Charlson Comorbidity Index, no. of medical utilization visits, change in Body Mass Index
   - Calculate Incidence Rate and Incidence Rate Ratio, 95% confidence Interval
4. Concomitant exposure to multiple drugs/procedures among members with/without pre-existing condition at defined time period

Current Modular Programs (cont.)

5. Use of drugs/procedures/diagnoses during a defined time period
6. Use of drugs/procedures after diagnoses/procedures during a defined time period among members with/without pre-existing condition
7. Patient characterization (top X drugs, procedure and diagnosis codes) before/after index date (first use, anniversary, etc.)
8. Assessment of uptake rate, persistence, patterns of use of drugs
9. Background rate and use of drugs/procedures among members with/without pre-existing condition

- Overall for entire period
- Stratified by year, month, age group, sex
- Incident and prevalent cohorts

Scientific Operational Units

- Methods Core
  - Develop a framework for safety surveillance methods, identify and fill gaps
- Protocol Core
  - Validate HOI algorithms in source data (medical charts)
  - Develop active surveillance protocol-based assessments
- Data Core
  - Expand and maintain Common Data Model
  - Perform data queries
  - Direct interactions with Data Partners

Completed Methods Projects

- Case-based analytic methods
- Statistical approaches for group sequential monitoring of post-market safety surveillance data
- Taxonomy for monitoring methods within a medical product safety surveillance system
- Enhanced methods for application of high dimensional propensity score confounder adjustment
- Methods to evaluate impact of FDA's regulatory actions
- Evaluating strategies for data sharing and analyses in distributed data settings
- Framework for assessment of signal refinement positive results

Current Methods Projects

- Using supplemental information for improved confounder adjustment
- Methods to improve confounder adjustment for emergent treatment comparisons
- Demonstrate feasibility of new sequential methods in a distributed data setting by implementing them in practice using MS data
- Develop anonymous linking between data partners (e.g., device registry and claims)
- Taxonomy framework
- Semi-automated routine prospective safety surveillance system

Completed Protocol Core Projects

- Systematic review of 20 HOIs to identify validated algorithms for identifying cases in claims data
- Validation of myocardial infarction, anaphylaxis, severe acute liver injury, acute kidney injury algorithms using medical charts
- Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system (Toh et al. Arch Intern Med 2012)
- HPV Gardasil vaccine and venous thromboembolism protocol-based assessment

Semi-Automated Routine Prospective Safety Surveillance System

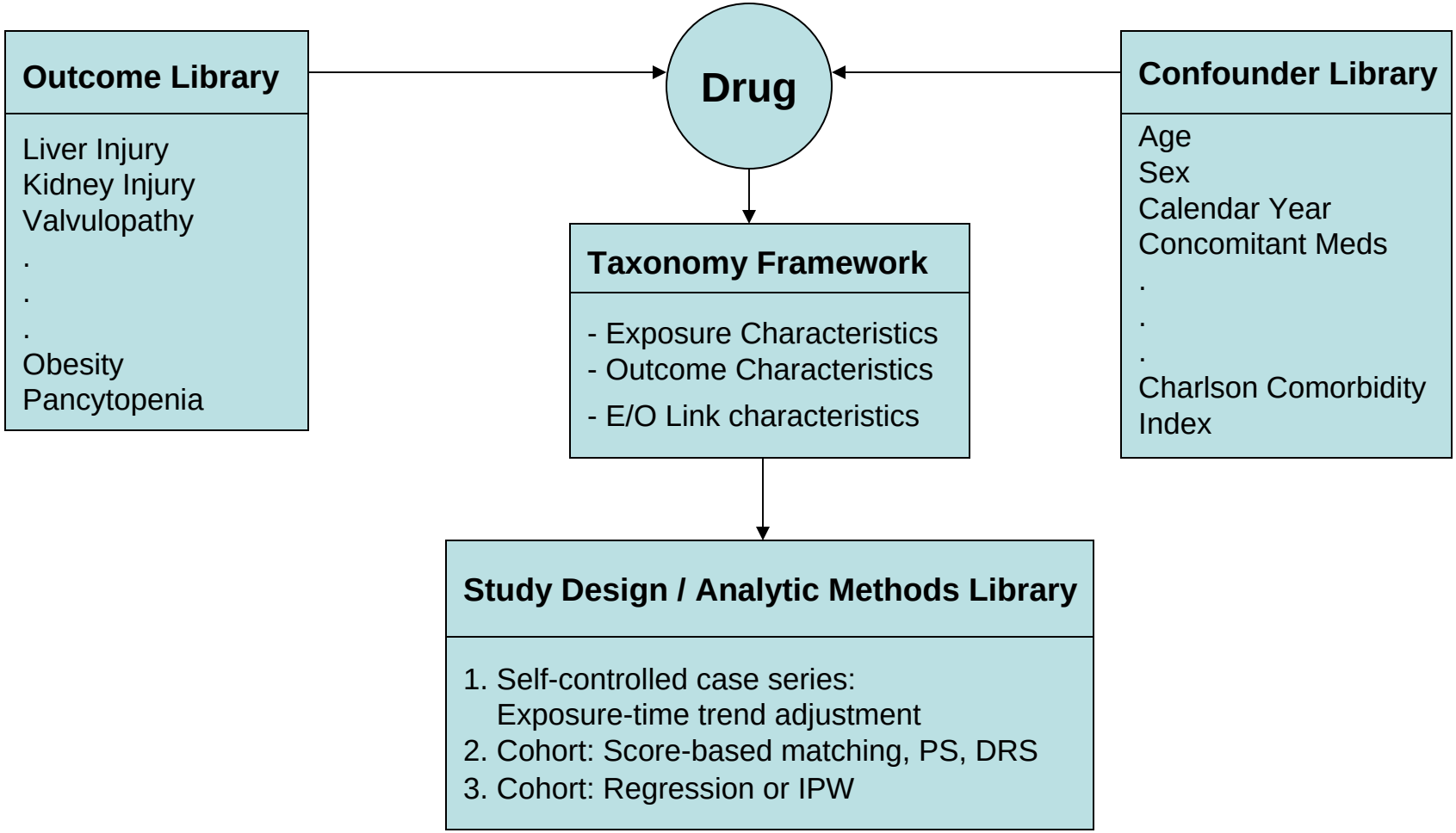
- Active, near real-time surveillance
- To increase the speed and throughput for monitoring while applying the systematic analytic process
- Library of outcome & confounder algorithms
- Library of study designs & analytic methods
- Systematic process for method selection

Routine Surveillance MP Study Design & Analytic Method

Module 1	Module 2	Module 3
Self-controlled case series Parameters: -Exposure time trend adjustment -… Maclure et al. PDS 2012 Whitaker et al. Stat Med 2006 Wang et al. Epidemiology 2011 Musonda et al. Vaccine 2008	**Cohort approach 1** Parameters: -Score-based matching (PS, DRS) -fixed/variable ratio -… Rassen et al AJE 2011, PDS 2012; Schneeweiss et al. Epidemiol 2009; Glynn et al PDS 2012; Austin et al Stat Med 2011	**Cohort approach 2** Parameters: -Regression -Weighted or unweighted -… Cook et al. PDS 2012 Austin et al. Stat Med 2007, 2010 Robins et al. Epid 2000 Cole et al. AJE 2008

Sequential Monitoring

Semi-automated Routine Prospective Safety Surveillance System



Federal Partners Collaboration

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

Future Steps

- Add additional laboratory and vital sign data to MSCDM
- Continue methods development
- Develop simulation framework for evaluating alerting algorithms

Future Steps (cont.)

- Long-term complex initiative
  - Implement in stages as scientific methodologies and data infrastructure evolve
  - Ensure maintenance of privacy and security within the distributed system
  - Continue to address the concerns of stakeholders including patients and the public
- To move forward from the MS pilot to the full Sentinel system with more capabilities and tools for safety surveillance of medical products

Thank you!

Any Questions?

www.mini-sentinel.org