Overview of FDA's active surveillance programs and epidemiologic studies for vaccines

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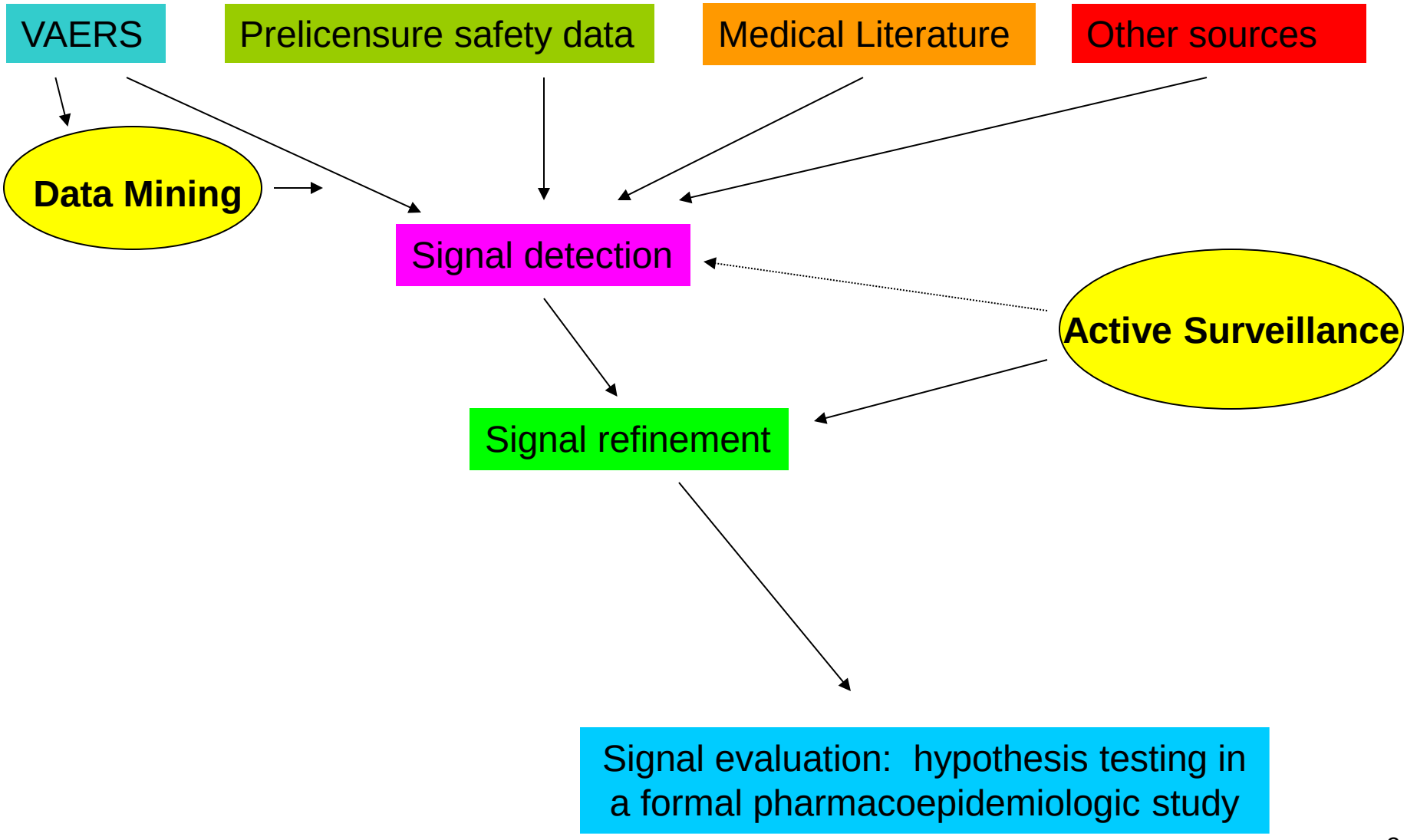
Application of Pharmacovigilance to
U.S. FDA Regulatory Decisions for Vaccines
June 3, 2012


VAERS
Prelicensure safety data
Medical Literature
Other sources
Data Mining
Signal detection
Active Surveillance
Signal refinement
Signal evaluation: hypothesis testing in a formal pharmacoepidemiologic study

Routine Pharmacovigilance

- All-inclusive surveillance for all vaccines conducted by both the US FDA and sponsors
  - Continuous safety monitoring with passive surveillance
    - The Vaccine Adverse Event Reporting System (VAERS) is co-managed by FDA and CDC
  - Disproportionality analyses of spontaneous reports
  - Periodic safety update reports (PSURs)
  - Signal detection, issue evaluation, labeling updates
  - Medical literature review
- Contact with international public health and regulatory agencies

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COMMENTARY

The Growing Role of Epidemiology in Drug Safety Regulation

Margaret A. Hamburg

For the US Food and Drug Administration (FDA), having the capacity to monitor drug safety in the postmarket environment under conditions of actual use is as essential to ensuring patient safety as evaluating initial clinical trial data in the premarket setting. The increased availability of electronic health care data represents an opportunity to further develop this capacity. The role of FDA's epidemiologists, alongside other experts in pharmacovigilance, statistics, and clinical medicine, is critical in using these data for detecting, quantifying, and characterizing these serious drug safety concerns. Understanding the role of epidemiology, FDA has increased its investment in, and reliance on, this discipline over the past decade.

***Epidemiology*, Sept 2011**

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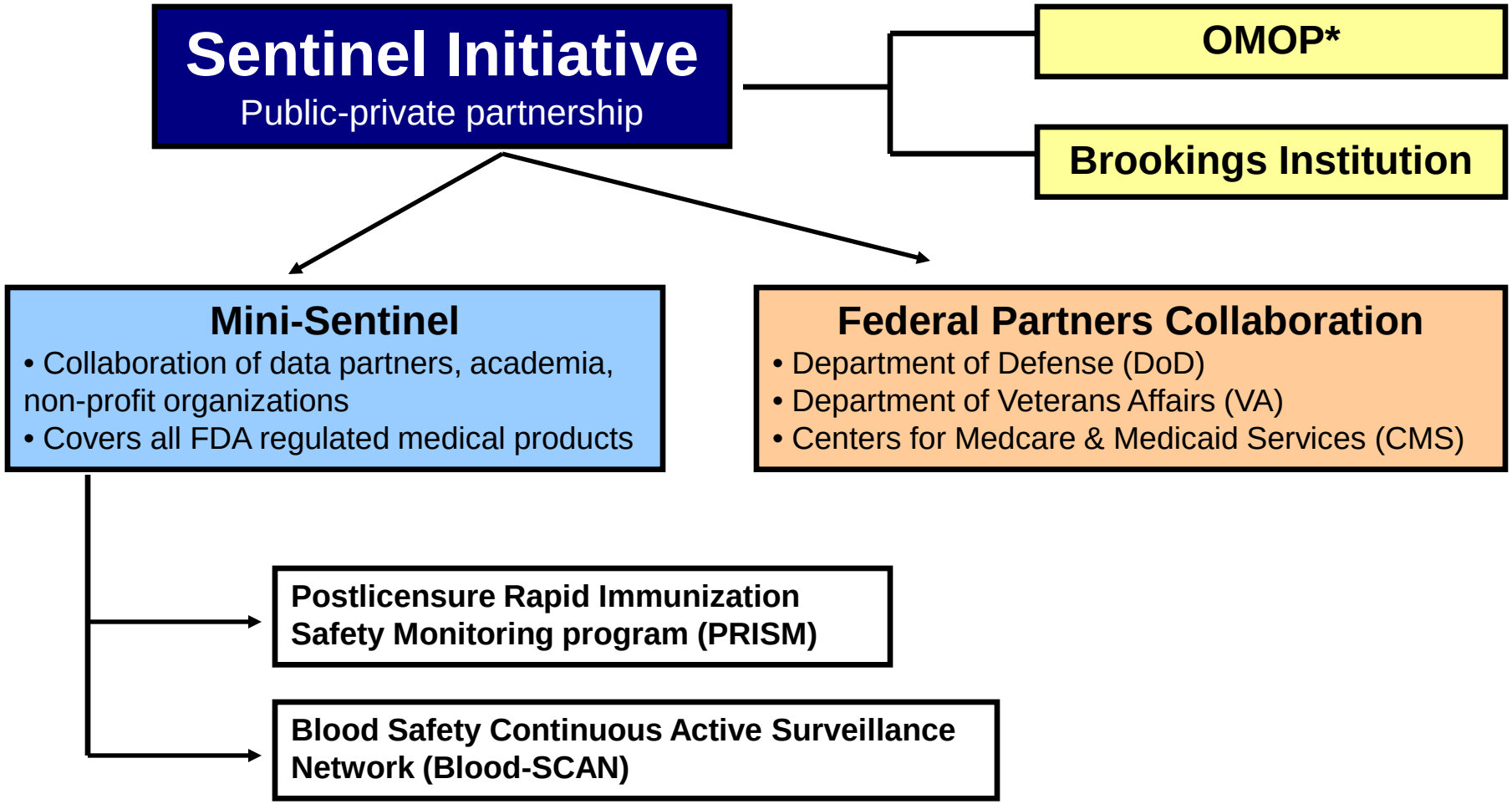
FDA Amendments Act of 2007

	Pre-FDAAA	Post-FDAAA
Pharmacovigilance	• Passive surveillance • Ad hoc analytic studies • Voluntary commitments for postmarketing studies	• Active surveillance of 100 million individuals by 2012 • Authority to require postmarketing studies
Communication	• Negotiated label changes • Risk communication discretionary	• Authority to require label changes based on new safety information • Quarterly publication of potential safety signals • Published conclusions from an 18-month post-approval safety review
Risk Mitigation	• Negotiated RiskMAP (risk minimization action plan)	• Authority to require REMS (Risk Evaluation and Mitigation Strategies) to ensure that benefits outweigh risks

Components of the Sentinel Initiative



* Observational Medical Outcomes Partnership

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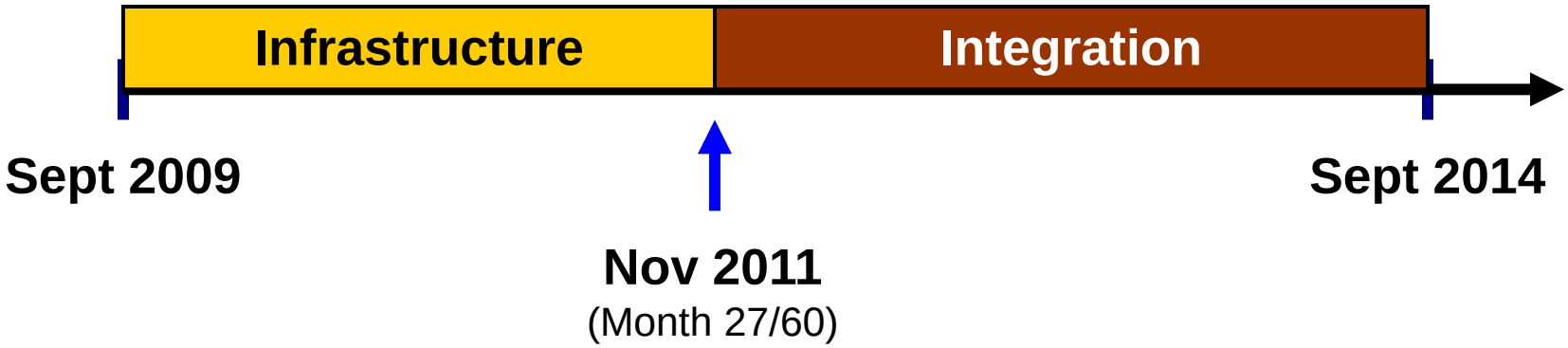
5 Year Mini-Sentinel Pilot



- Governance
- Common data model
- Data partnerships
- Distributed database
- Queries
- First protocols

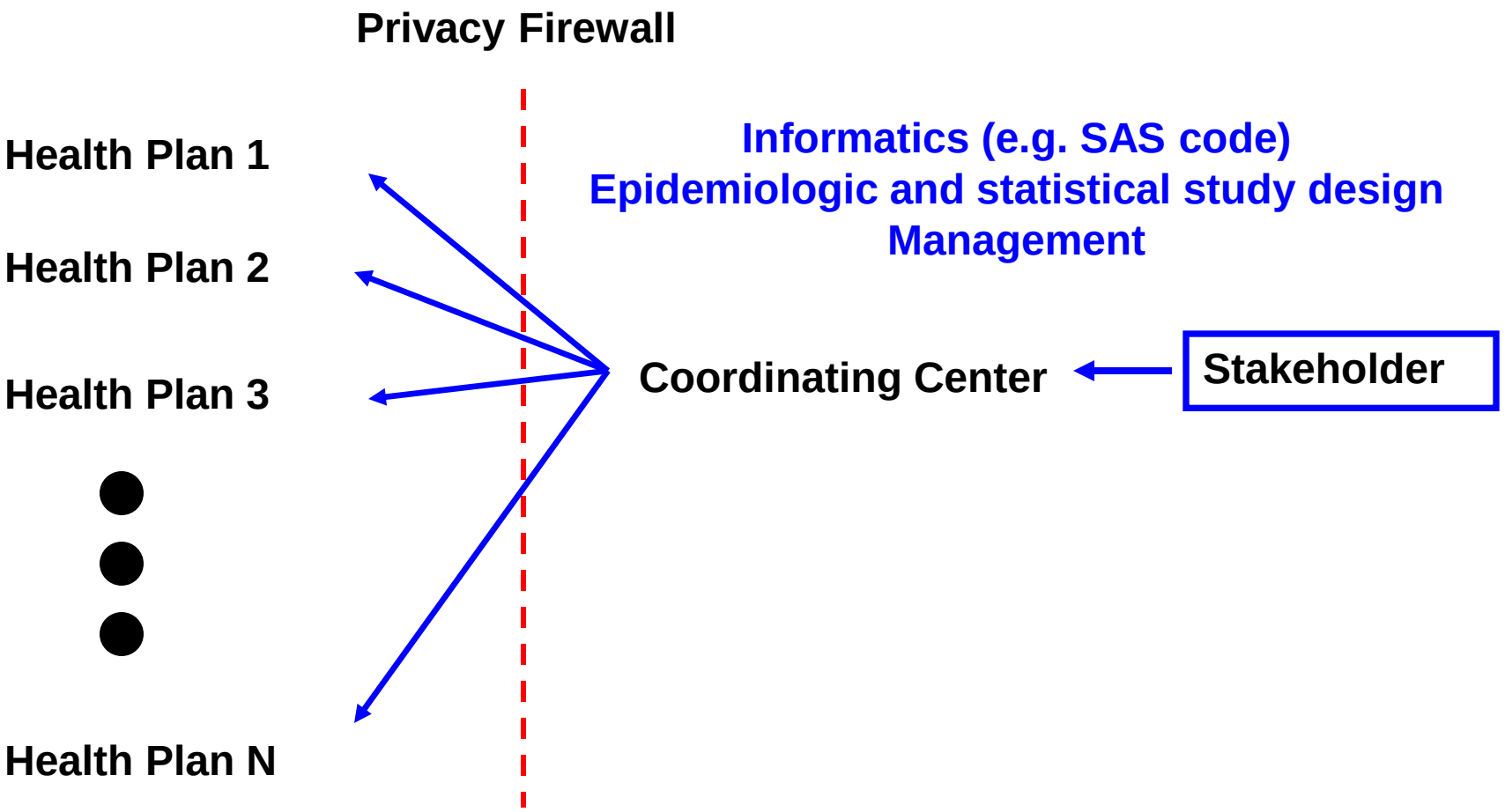
- "Augment not replace" existing systems
- Increase transparency of results
- Incorporate Sentinel into FDA routines

Innovation & collaboration → **Transition & reconfiguration**

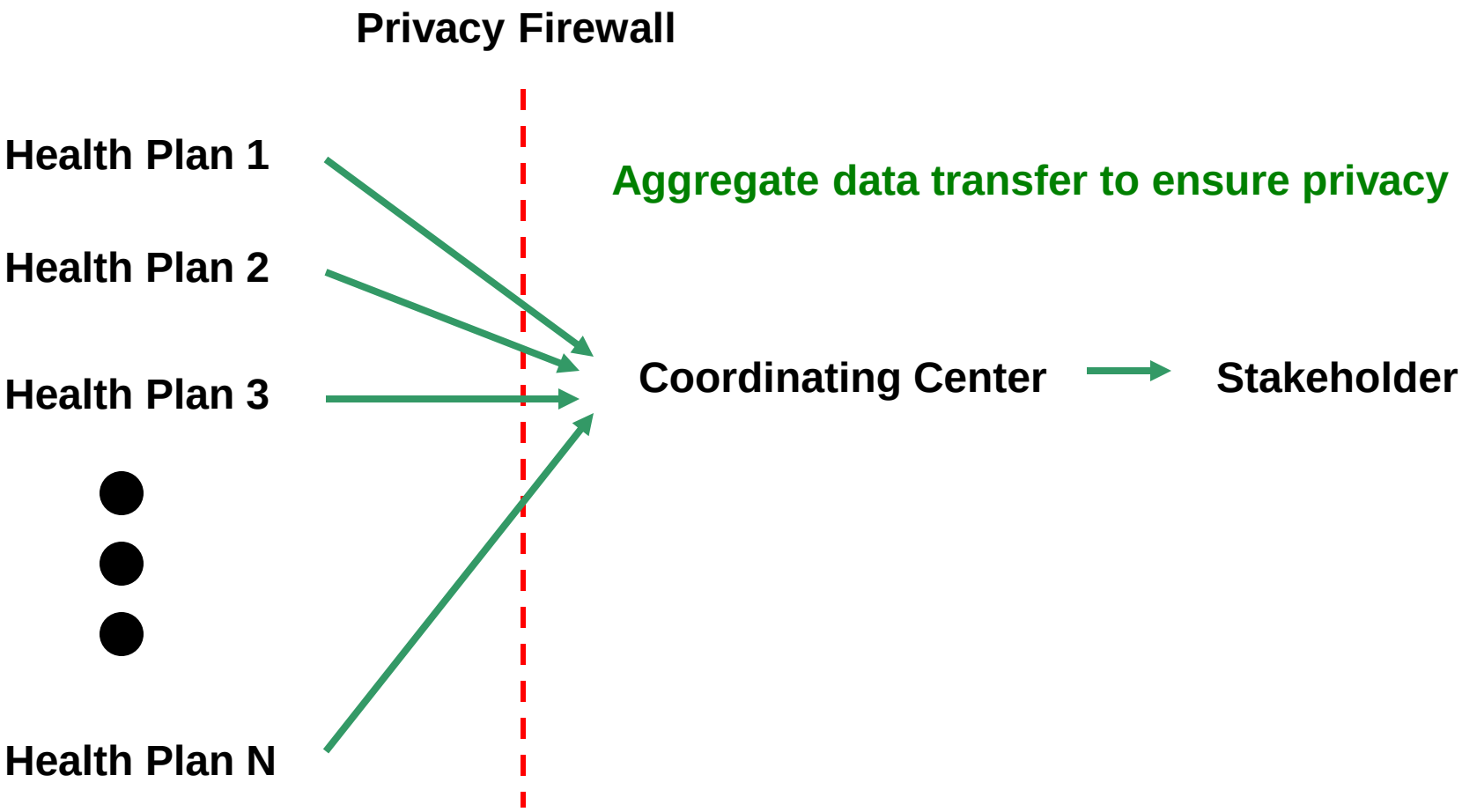
Mini-Sentinel

- Comprised of quality-checked data held by 17 partner organizations
- 99 million individuals (July 2011) accessible through a distributed database
- Provides FDA with the capability to address potential safety concerns with most regulated medical products in a timely fashion
  - Summary tables: prevalence information for products and diagnoses
  - Modular programs: produce crude rates in order to refine signals
  - Protocol based evaluations: Predefined algorithms to identify exposures, outcomes, comparators with standardized confounding control
- Advantages
  - Helps prioritize safety signals, informs “next step” (full epi study)
  - Conserves finite resources for protocol development, programming, and chart review
  - Decreases start up time (no customized protocol/programming)

Basic Distributed Database Model



Basic Distributed Database Model



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Modular Programs

- Examples
  - Frequency of incident events among members (with or without a pre-existing condition) exposed to a product
  - Concomitant product use among members (with or without a pre-existing condition) exposed to a product
- Potential uses
  - Immediate “next step” after passive surveillance/data mining findings
  - Estimate incidence rates of health outcomes of interest
  - Provide reassurance by analyzing trends over time
  - Enables FDA to prioritize safety issues

Framework Needed for Modular Programs

Positive Predictive Value of Administrative Codes

Exposure–Outcome Complexity*

	High	Low
High	Trends over time	Not feasible
Low	Incorporate into routine pharmacovigilance	Trends over time

* Numerous factors affect level of complexity including ease of measuring and controlling for confounding, availability of medical records, accuracy of documentation in medical records, etc.

Postlicensure Rapid Immunization Safety Monitoring System (PRISM)

- Integral part of Mini-Sentinel dedicated to vaccine safety
- Claims based system with over 40 million individuals
  - Four national health plans: Aetna, HealthCore (Wellpoint), Humana, OptumInsight (United Healthcare)
  - Linkages to eight vaccine registries: Florida, Michigan, Minnesota, New York, Pennsylvania, Virginia, Wisconsin, New York City
  - Limited access to medical records
- Infrastructure and methods development
  - Evidence reviews for key health outcomes
  - Operational framework
  - Identification of signals without pre-specified outcomes
  - Sequential analysis of data using propensity scores to control for confounding

PRISM Surveillance Evaluations

- Three vaccine safety evaluations underway
  - Rotavirus vaccines and intussusception
  - Human papillomavirus vaccine and venous thromboembolism
  - Seasonal trivalent influenza vaccine and febrile seizures

- Methodological highlights
  - Self controlled risk interval design developed in the Vaccine Safety Datalink
  - Vaccine exposure data enhanced by vaccine registry data
  - Exposures and outcomes will be chart validated

- An evaluation of pregnancy outcomes after trivalent influenza vaccine is currently being planned

CMS.gov
Centers for Medicare & Medicaid Services

- Medicare beneficiaries
  - 38 million persons age ≥65 years
  - 8 million persons age <65 with disability or end stage renal disease
- Near real-time surveillance
  - Active surveillance for signal detection
  - Conducted for GBS after influenza vaccination in 2009, 2010, and 2011
- Epidemiologic studies
  - Evaluation of GBS after 2009-10 H1N1 vaccine using medical record review data
- Methodological studies
  - Refinement of methodologies to conduct vaccine safety assessment
  - Examples: Alpha spending to take into account multiple testing, adjust for delay in claims

Other Federal Partners

- Address populations that might be under-represented in other systems
  - US Department of Defense
    - H1N1 end of season analysis
    - Planned study of Idiopathic Thrombocytopenic Purpura following live vaccines
  - US Department of Veterans Affairs
    - H1N1 end of season analysis
    - 2010-11 seasonal influenza vaccine end of season analysis
    - Planned study of Zoster vaccine
  - Indian Health Service
    - H1N1 end of season analysis
- Access to medical records for diagnosis verification and hypothesis confirmation
- Over 1,000,000 beneficiaries in each dataset

U.S. CDC Vaccine Safety Datalink

- Ten geographically diverse health maintenance organizations that participate in a large linked database representing approximately 3% of U.S. population

- Surveillance and Hypothesis testing studies can be conducted
  - Vaccination (exposure)
  - Outpatient, emergency department, hospital and laboratory coding data (health outcomes)
  - Demographic variables (confounders)
  - Accessible medical chart review

Summary

- Routine pharmacovigilance is currently performed for over 70 US licensed vaccines
- FDAAA 2007 prioritizes safety throughout the product lifecycle by placing additional emphasis on postmarketing data acquisition and use in the regulatory decision making process
- Population-based surveillance and epidemiologic study capabilities have expanded significantly
  - Mini Sentinel and the federal partners cover a large segment of the US population
- The volume and variety of FDA medical products exceeds the resources available for pre-planned evaluations; MiniSentinel modular programs are a general purpose risk refinement tool designed to address this gap
- Infrastructure and methods development for population based pharmacovigilance/pharmacoepidemiologic tools is ongoing

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