BROOKINGS
Forum on Post-Market Evidence and Drug Safety

June 13, 2008

The University Club, Washington, DC

Agenda for Brookings Forum on Post-Market Evidence

June 13, 2008
The University Club, 1135 16th St NW, Washington, DC 20036

8:30-9:00 **Registration and Continental Breakfast**

9:00-9:15 **Welcome and Introductory Remarks**
Mark McClellan, Brookings Institution

9:15-9:45 **Overview of Recent FDA Drug Safety Activity**
Andrew von Eschenbach, FDA
Janet Woodcock, FDA

9:45-10:30 **Building a National Network for Drug Safety**
Panelists:
Rich Platt, Harvard University
Marcus Wilson, HealthCore
Janet Marchibroda, eHealth Initiative

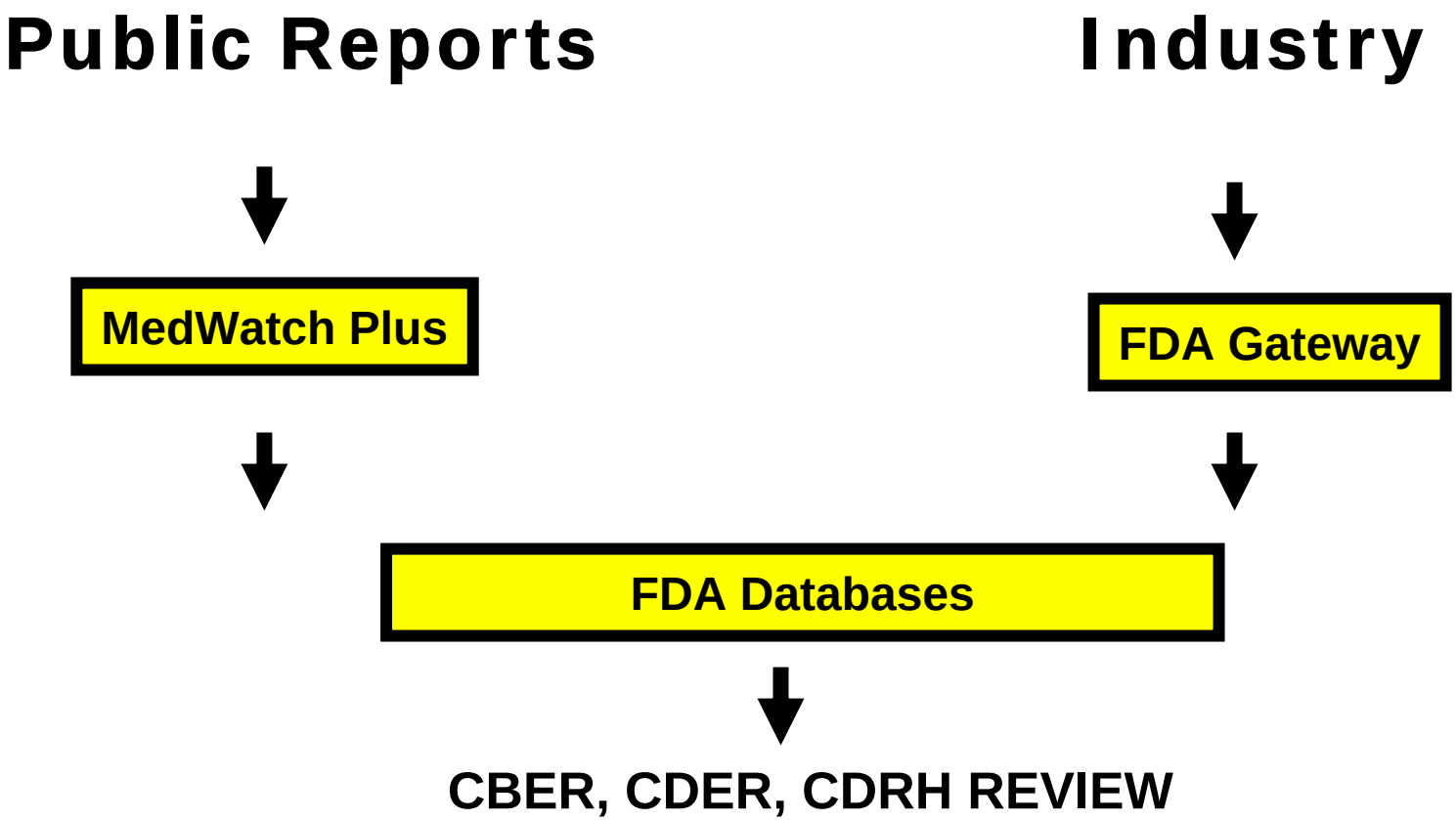
10:30-10:45 **Break**

10:45-12:15 **Key Challenges and Possible Solutions**
Moderated by Mark McClellan, Brookings Institution

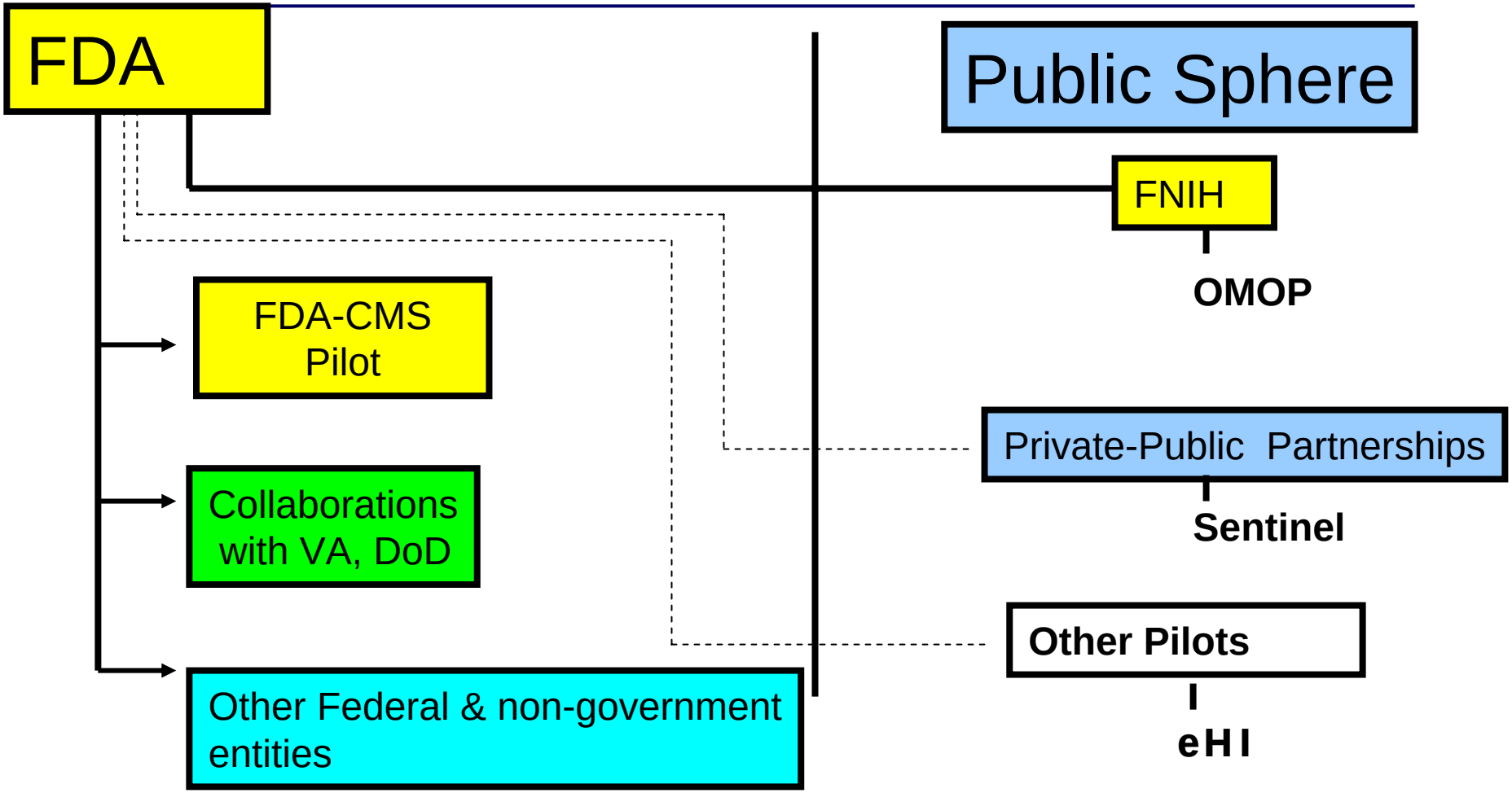
- Infrastructure and Governance
  - Janet Woodcock, FDA
  - Garry Neil, J&J
- Data and Methods Issues
  - Arnold Chan, i3 Drug Safety
  - Gigi Hirsch, MIT Center for Biomedical Innovation
- Legal and Privacy
  - Kristen Rosati, Coppersmith Gordon Schermer & Brockelman PLC
  - Judy Kramer, Duke University
- Communications and Impact on Practice
  - Marc Boutin, National Health Council
  - Lee Rucker, AARP
  - Sharon Levine, Kaiser Permanente

12:15-12:30 **Discussion and Next Steps**
Mark McClellan, Brookings Institution

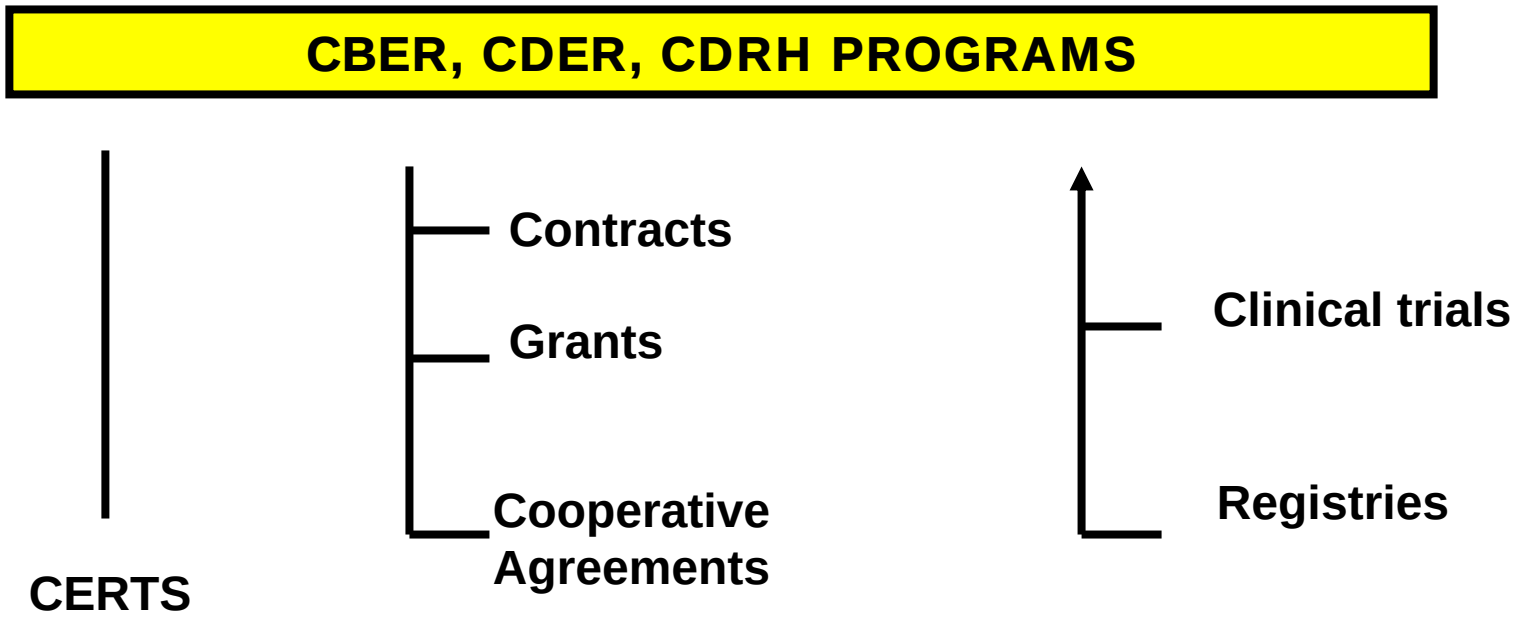
FDA Medical Product Surveillance: AE Reporting



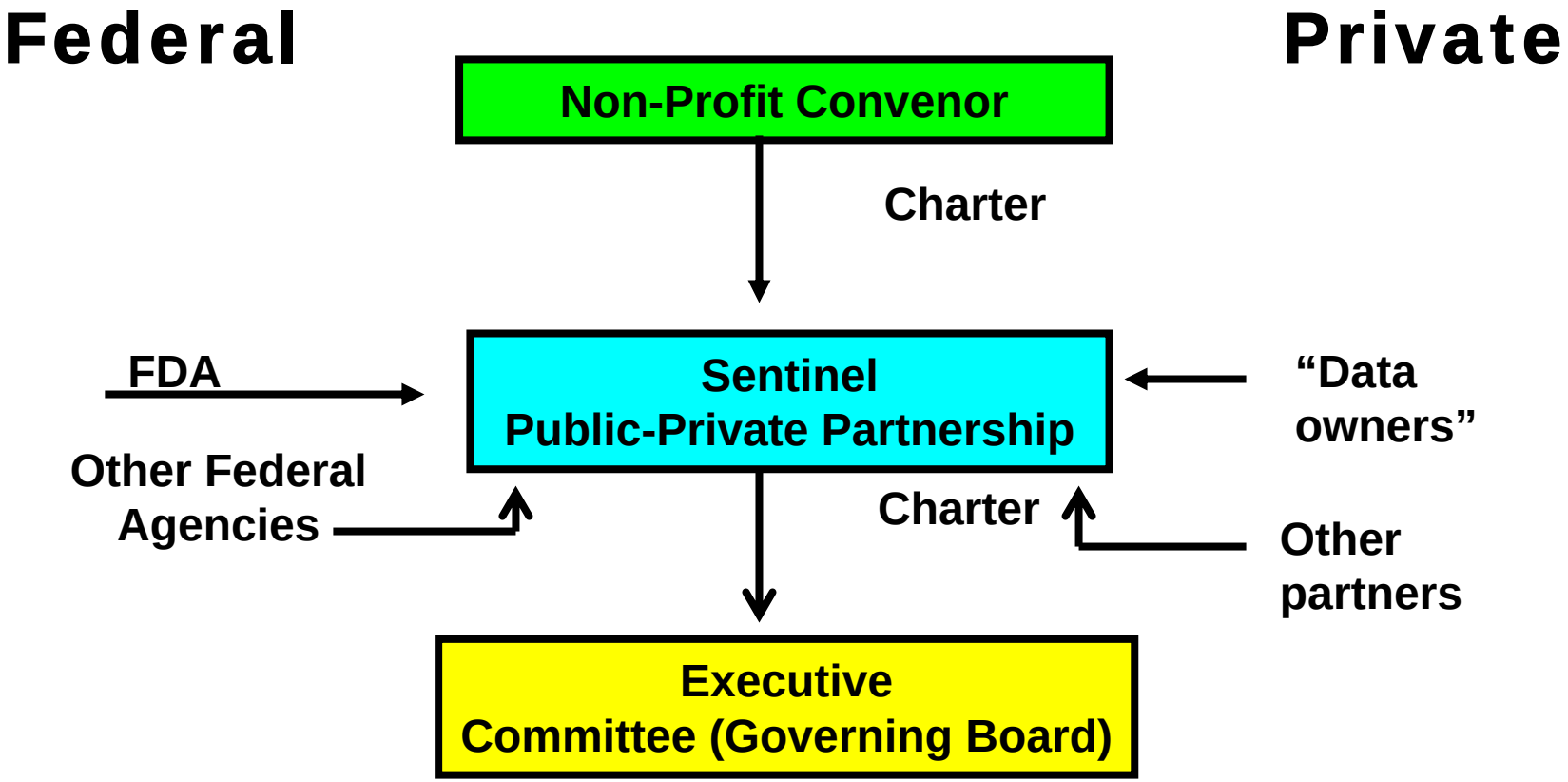
New Approaches to Surveillance



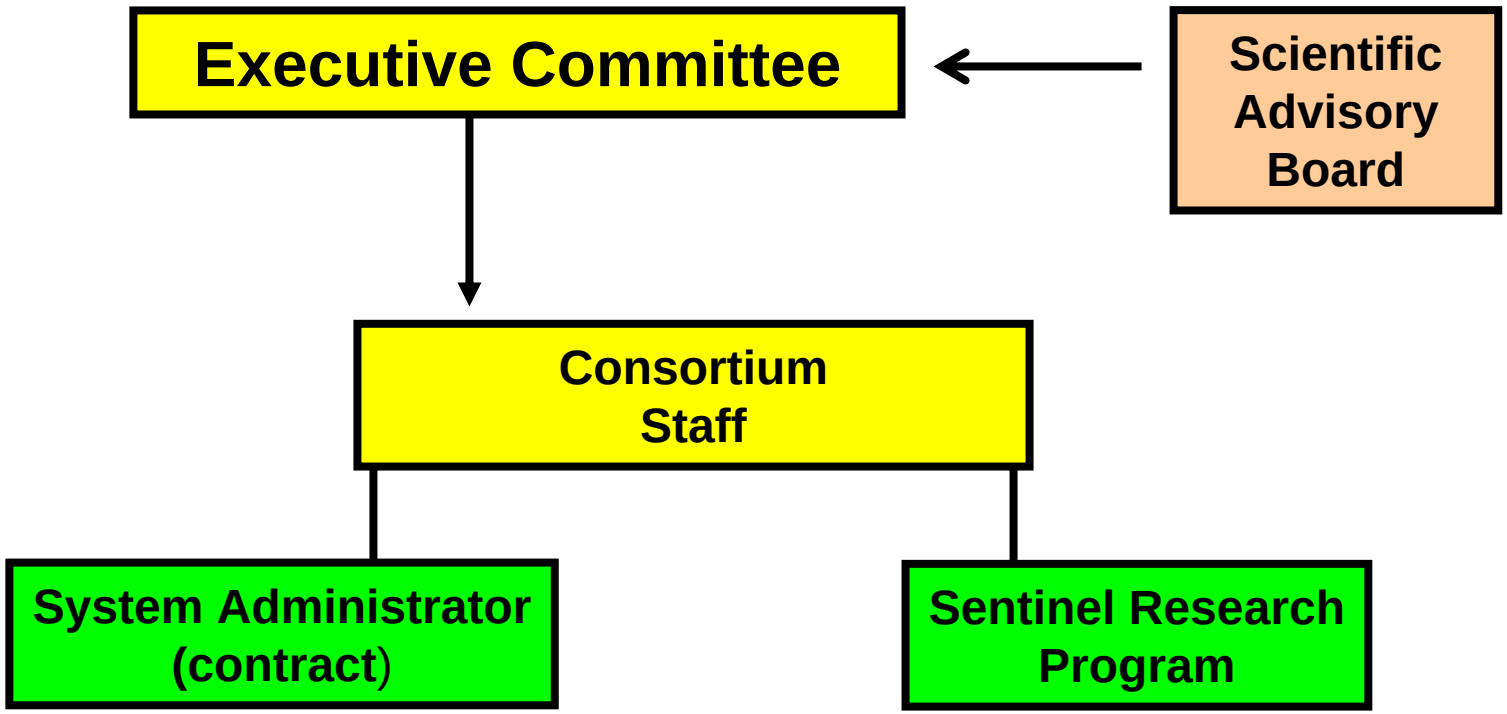
FDA Medical Product Surveillance: Additional Resources



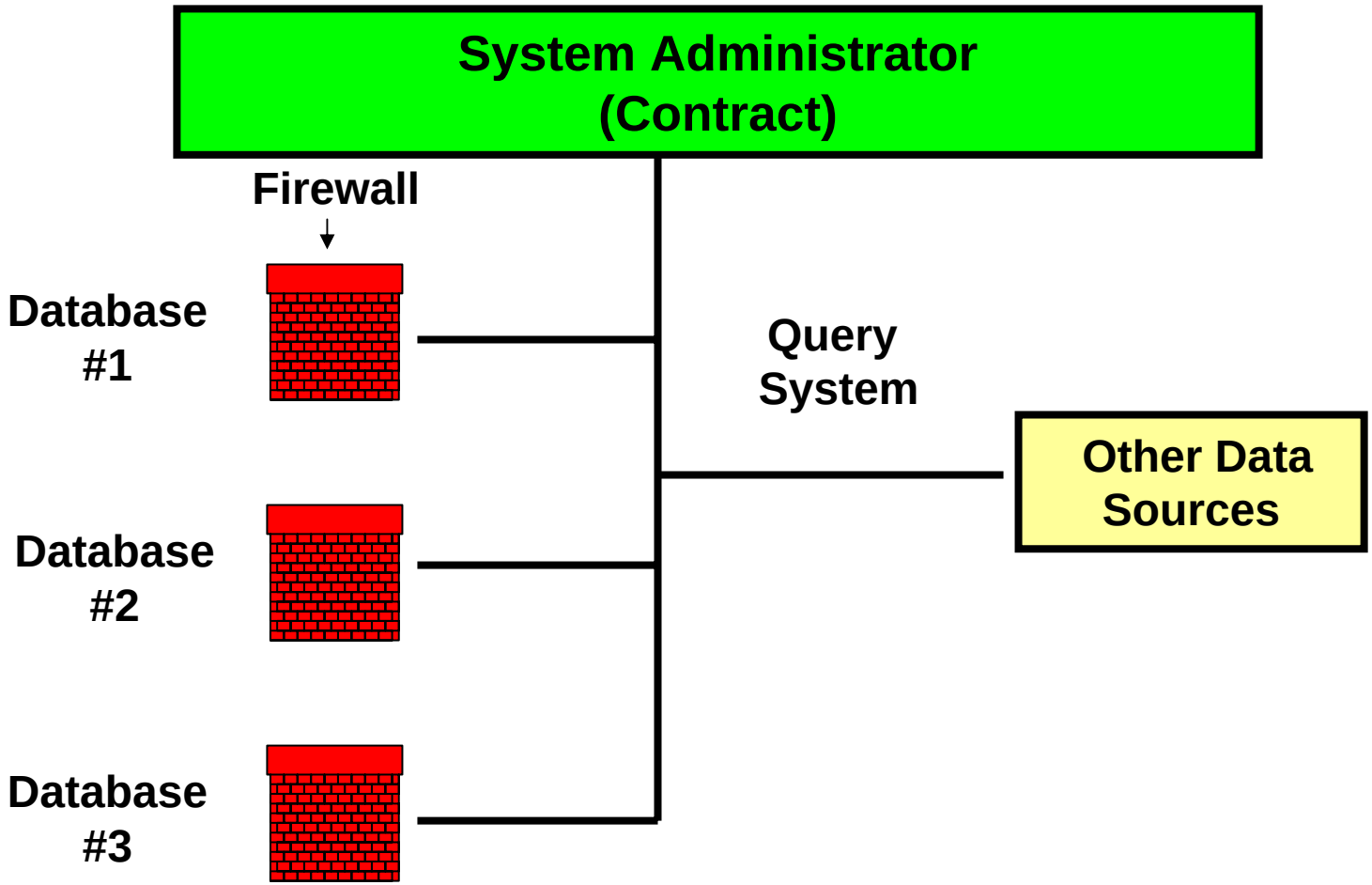
Sentinel: A Possible Model Structure



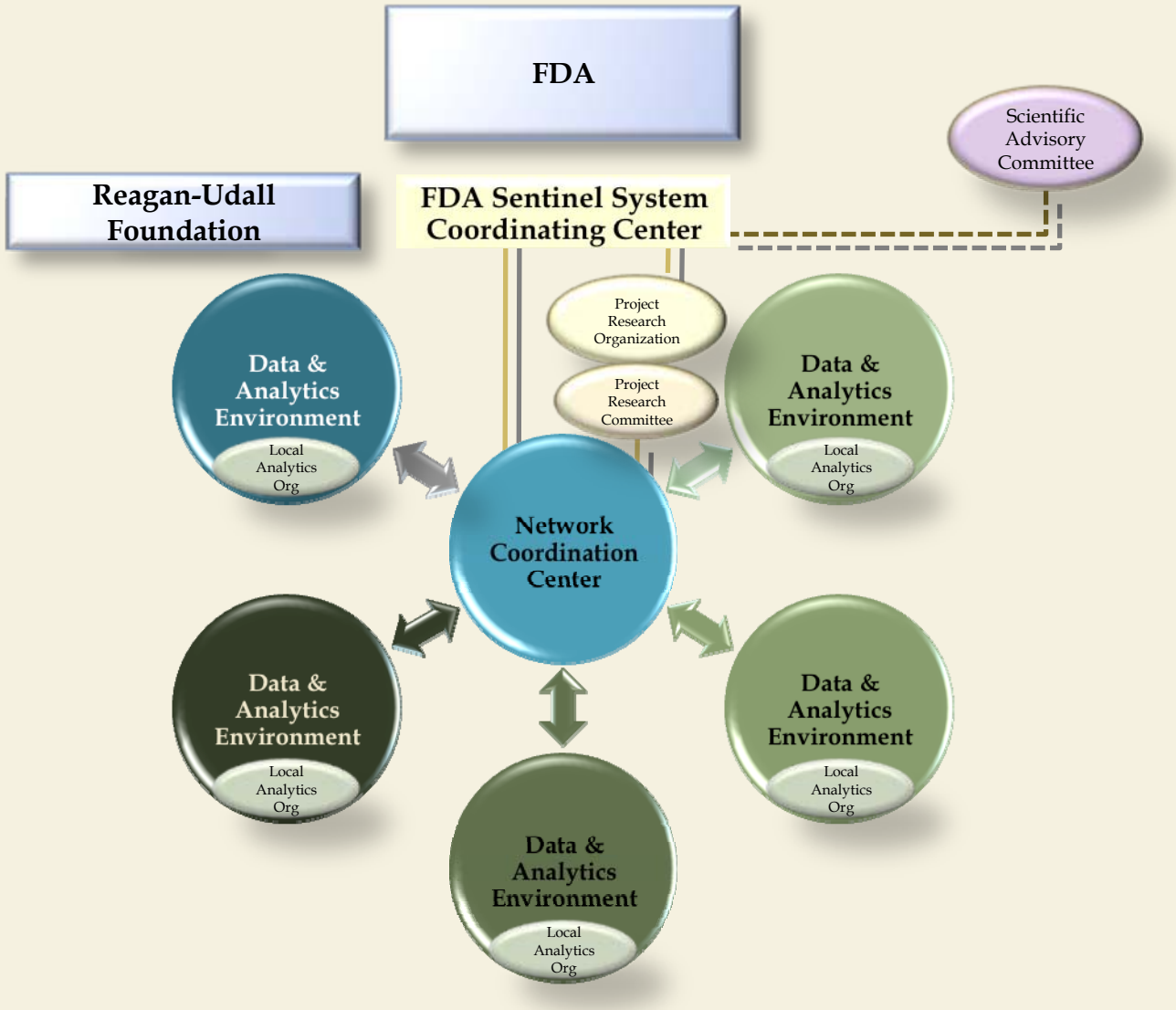
Sentinel Model Structure



Sentinel System Model



Proposed Sentinel System Structure



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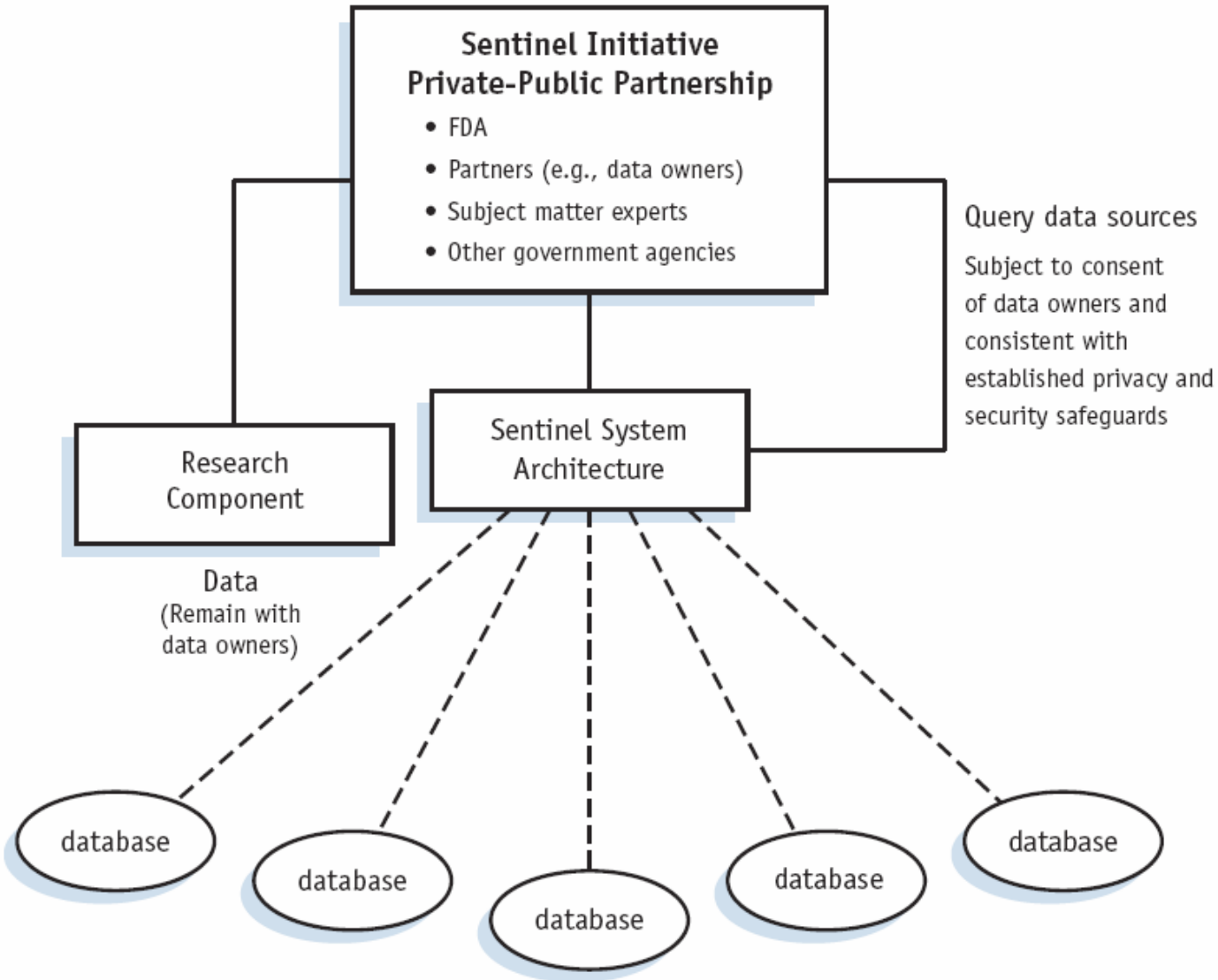
Data and Methods Issues

K. Arnold Chan, MD, ScD, FISPE

June 13, 2008

http://www.fda.gov/oc/initiatives/advance/reports/report0508.html

A Potential Organizational Structure for the Sentinel Initiative/System



g safety

Sentinel System: faster access to relevant data

Contraindicated Use of Cisapride

Impact of Food and Drug Administration Regulatory Action

Walter Smalley, MD, MPH
Deborah Shatin, PhD
Diane K. Wysowski, PhD
Jerry Gurwitz, MD
Susan E. Andrade, DSc
Michael Goodman, PhD
K. Arnold Chan, MD, DSc
Richard Platt, MD, MS
Stephanie D. Schech, MPH
Wayne A. Ray, PhD

Context Cisapride, a gastrointestinal tract promotility agent, can cause life-threatening cardiac arrhythmias in patients susceptible either because of concurrent use of medications that interfere with cisapride metabolism or prolong the QT interval or because of the presence of other diseases that predispose to such arrhythmias. In June 1998, the US Food and Drug Administration (FDA) determined that use of cisapride was contraindicated in such patients and informed practitioners through additions to the boxed warning in the label and a "Dear Health Care Professional" letter sent by the drug's manufacturer.

Objective To evaluate the impact of the FDA's 1998 regulatory action regarding contraindicated use of cisapride.

Design and Setting Analysis of data for the 1-year periods before (July 1997-June 1998) and after (July 1998-June 1999) the regulatory action from the population-based, pharmacoepidemiology research databases of 2 managed care organizations (sites A and B) and a state Medicaid program (site C).

Participants Patients with at least 180 days of prior enrollment in 1 of the 3 sites who were prescribed cisapride at least once in the period before (n=24 840) or after (n=22 459) regulatory action. Patients could be included in both cohorts.

Main Outcome Measures Proportion of cisapride users in each period for whom cisapride use was contraindicated by the product label, based on computerized patient medical encounter records.

Results In the year prior to regulatory action, cisapride use was contraindicated for 26%, 30%, and 60% of users in study sites A, B, and C, respectively. In the year after regulatory action, use was contraindicated for 24%, 28%, and 58% of users, a reduction in contraindicated use of approximately 2 per 100 cisapride users at each site. When the analysis was restricted to new users of cisapride after regulatory action, only minor reductions in contraindicated use were found.

Conclusion The FDA's 1998 regulatory action regarding cisapride use had no material effect on contraindicated cisapride use. More effective ways to communicate new information about drug safety are needed.

JAMA. 2000;284:3036-3039 www.jama.com

CISAPRIDE IS A GASTROINTESTINAL tract promotility agent that was first marketed in the United States in August 1993 with a label indication for nocturnal heartburn.[1] Use grew rapidly so that in 1995 there were approximately 5 million outpatient cisapride prescriptions filled in the United States.[2] However, by this time, the Food and Drug Administration (FDA) had received 34 cases of torsade de pointes and 23 of prolonged QT interval in cisapride users, including 4 deaths.[3] Since many of these cases were in patients taking drugs that inhibited

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Data / Methods

- Databases A & B for Risk Identification and
  Databases C & D for Risk Analysis

  OR

- 50% of Databases A, B, C, D for Risk Identification and
  The other 50% of Databases A, B, C, D for Risk Analysis

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How to access data from disparate databases?

- Same protocol, uniform implementation in each database
- Same protocol, same (research) database structure
  - Same hardware platform or
  - Same database structure and format

- Ideally
  - Platform independent
  - Use data in primary format
  - Moderate hardware investment
  - No individual level data leave the data owner
  - Security and audit trail

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For example, January 2005

Managing Disclosure of Private Health Data with Hippocratic Databases

Rakesh Agrawal, Dmitri Asonov, Roberto Bayardo,
Tyrone Grandison, Christopher Johnson, Jerry Kiernan

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WHITE PAPER

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How to combine data from disparate databases?

- Aggregate data vs.
- Individual level data (de-identified)

- Meta-analysis
- Minimal dataset with individual level data for multiple regression
- Multiple regression across disparate databases(?)

Brookings Forum on Post-Market Evidence: Data and Methods

June 13, 2008

CBI provides a Safe Haven for academia, industry, and government to collaborate on research and educational programs designed to overcome barriers to innovation that will improve public health.

Priorities: Tools & Methods

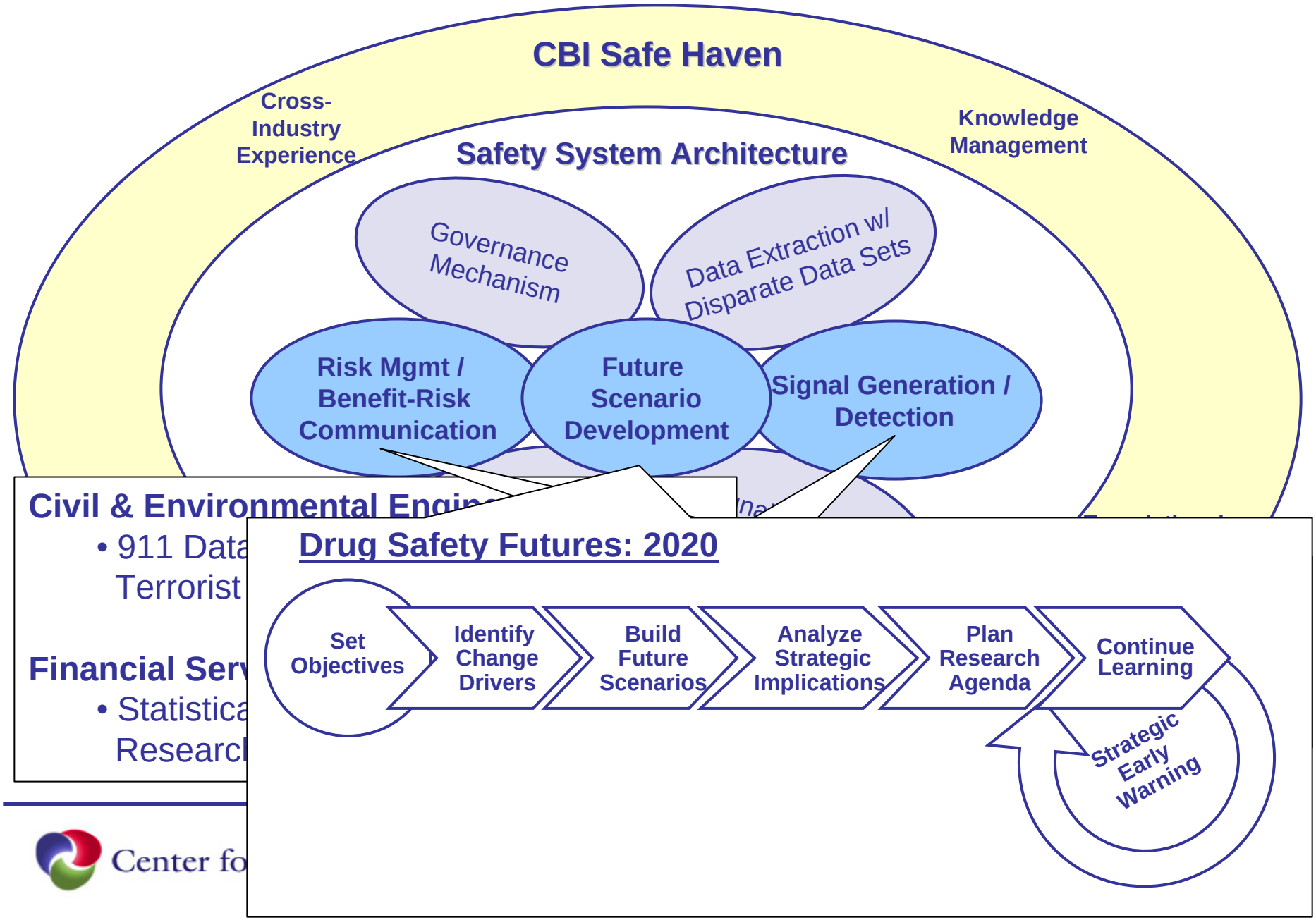
Short Term:

- **Best Practices – Tools and Methods**
  - Understand application of existing methods
  - Create new methods if necessary
  - Develop use guidance based on characterization of methods, as relates to types of data and questions
- **Research Funding**
- **Collaborative Research**

Long Term:

- **Talent Pipeline in Safety Science**
- **How to leverage new capabilities and knowledge from enhanced surveillance to improve R&D and patient care?**

Safety Surveillance Roadmap



Building the Talent Pipeline: Lessons Learned from the MIT Experience

- **Translational research requires sustained (multi-year) funding**
  - Justify “opportunity cost” of switching domains (senior faculty)
  - Competing opportunities (junior faculty)
  - Support PhD level research

- **Junior Faculty will consider tenure case**
  - Potential to draw talented graduate students
  - Interdisciplinary research has lower stature than traditional areas of academic expertise

For Additional Information, Contact:

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Forum on Drug Safety and Post-Market Evidence

Legal Issues in the Use of Electronic Health Information for Pharmacovigilance

Developed Through eHealth Initiative's Connecting Communities for Drug Safety Collaboration

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Coppersmith Gordon Schermer & Brockelman PLC
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(602) 381-5464

Overview of Legal Work for the eHI Connecting Communities for Drug Safety Collaboration

- Legal guidance evaluating the major legal issues involved in using electronic health information for drug safety
- Template agreements that will assist drug safety program collaborators
  - Template contract between an HIE or health system and pharmaceutical company partners
  - Template contract between the HIE and its participants (physicians, hospitals and others providing patient data to the HIE)

Legal Issues Examined

- Privacy compliance
- Common Rule compliance
- FDA reporting obligations for drug manufacturers
- FDA Amendments Act of 2007
- Tort liability under the common law for failure to warn

Overall conclusion: The legal risk is not high for health systems, health information exchange programs, and pharmaceutical companies using electronic health information for pharmacovigilance programs, as long as the program rigorously protects the privacy and security of individually identifiable health information and pharmaceutical companies communicate significant new findings of risk to the FDA and health care providers.

Privacy: A Maze of Laws

- HIPAA
- Federal Part 2 regulations (substance abuse treatment)
- Federal Privacy Act
- Federal Medicare Conditions of Participation
- State medical record confidentiality statutes: framework for analyzing categories of state laws that provide more protection for “special” health information, such as:
  - Genetic testing
  - Mental health information
  - HIV/communicable diseases

Privacy Compliance

- Important questions in privacy evaluation
  - What is the HIPAA status of the collaborators?
  - Who has access to individually identifiable information?
  - What type of information will be utilized?

- *Conclusion 1: The FDA is an essential partner in drug safety surveillance programs*
  - HIPAA (and many state laws) permit disclosure of health information for public health purposes to an entity regulated by the FDA for post-marketing surveillance and to an entity acting under a grant of authority from the FDA
    - Potential solution: FDA delegation of authority to/ partnership with entity governing distributed data network for pharmacovigilance

Privacy Compliance

- *Conclusion 2: A drug safety surveillance program structured as a research protocol will comply with federal and most state privacy laws*
  - Institutional Review Board waiver of HIPAA authorization likely where database research accesses large number of patient records and adequate privacy protection in place
  - Problems:
    - Regulatory uncertainty about the distinction between public health surveillance and "research"
    - The need to approach each HIE/health system IRB for approval and variability in IRB approaches and decisions
  - Potential Solutions:
    - Harmonization of regulatory approach
    - Creation of multi-center or central IRB at the national level to provide primary review

Implications of the Common Rule, FDA and Privacy Regulations to a Proposed Pharmacovigilance Program

Are we really protecting patients?

Brookings Forum on Post-market Evidence

Judith M. Kramer, MD, MS
Associate Professor of Medicine, Duke University Medical Center
Executive Director, Clinical Trials Transformation Initiative,
Duke Translational Medicine Institute

Assumptions

- **Goals of Pharmacovigilance:**
  1. As rapidly as possible detect previously unidentified, rare, serious and life-threatening adverse reactions to drugs, biological products, and devices
  2. Detect increased incidence of common serious or life-threatening conditions associated with the administration of drugs, biological products, and devices
- **Purpose: Preserve the Public Health**
- **Model:**
  - National system taking advantage of electronic claims and health records using distributed data
  - 100 million covered lives by 2012
  - Validation requires limited access to complete medical records by covered entity

Pharmacovigilance as public health surveillance or research under the Common Rule

- **45 CFR 46 (Common Rule)**
  - CDC[1]

    -If the primary intent is to protect the public health, activities are not "research"
  - OHRP[2] (Ivor A. Pritchard)

    -Primary intent should not be used as a basis to distinguish research from non-research

    -If the public benefit is so compelling as to require participation, the Common Rule should not apply

1. Guidelines for Defining Public Health Research and Public Health Non-Research; http://www.cdc.gov/od/science/regs/hrpp/researchDefinition.htm
2. Pritchard IA, Searching for "Research Involving Human Subjects": What is Examined? What is Exempt? What is Exasperating? IRB: Ethics & Human Research 23, no.3 (2001), 5-12

Other considerations regarding IRB review*:

- **Many institutions have internal policies requiring IRB review of *all research* conducted at the institution**
  - Even when research is not covered by either the Common Rule or FDA regulations
  - Even where research is exempt

From "An analysis of Legal Issues Related to the Use of eHI in Pharmacovigilance Programs"2008, Rosati, Fatica, Desai

Other Issues adding complexity

- **Applying confidentiality laws for 50 states in a national system**
- **FDA Reporting obligations**
  - Expedited reporting of individually identified SAEs would add administrative burden without informing
  - Aggregate information on SAEs derived from network (with numerator and denominator) would be more informative
  - Hypothesis-driven research is required to investigate putative signals
- **Possibility of false signals**
  - Limitations of observational data (e.g. confounding by indication)
  - Are we protecting patients if we misinform?

Other Issues (continued)

- **Application of duty to warn using the "learned intermediary doctrine" may need to change**
  - Practicing physicians not trained to interpret quantitative findings from observational research
  - May need an interdisciplinary team to interpret signals prior to communication to practitioners and patients

Summary of *likely* requirements under existing regulations and interpretations

- **IRB review of pharmacovigilance programs; expedited review by IRBs; ? central IRB**
- **Waiver of consent for large observational studies**
  - i.e. minimal risk; impractical; waiver will not adversely affect patients' rights and welfare
- **Public health exception in HIPAA (45CFR 164.512) likely for designated medical events; waiver of authorization for observational research in large datasets**
- **Use of full medical records for validation best done by covered entity in a distributed data network**

Seeking protection of patients through rapid detection of drug risks

- **Imagine a structure and regulatory framework that recognizes:**
  - Public health benefit of pharmacovigilance
  - Current and possible future states of health information technology
  - Need for rapid hypothesis-driven studies to evaluate possible associations of SAEs with a product
  - Need for rationalization of state and federal requirements for confidentiality in pharmacovigilance programs
- **The best minds should collaborate on how to facilitate pharmacovigilance and how best to communicate with patients and practitioners**

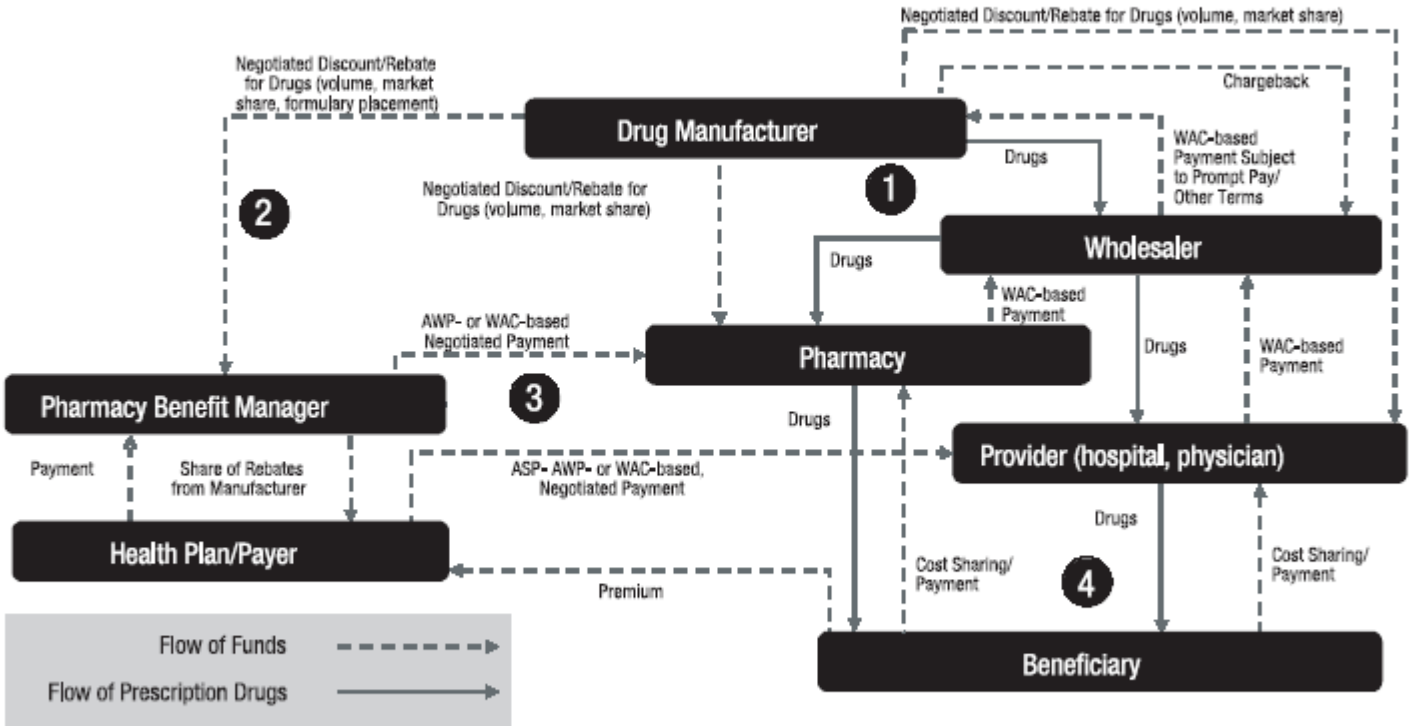
A Consumer Perspective on Post-Market Evidence: Mirage, Oasis, Opportunity

N. Lee Rucker, M.S.P.H., lrucker@aarp.org

June 13, 2008 Brookings Forum Washington, DC


SILBERS PHARMACY
PRESCRIPTIONS DRUGS
EX-LAX

EXHIBIT 1 Drug Distribution Model



Assumptions (Mirage)

We trust:

- Our physicians (and other prescribers)…
- Our pharmacists…
- The Food and Drug Administration…

Balance Between Benefits and Risks (Oasis)

Balance is a perpetual motion proposition

Communication (Opportunity)

"Our relationship [with patients]
must be built on trust,
and that trust comes from
communication and dialogue….
It's not important what we say,
it's what they hear."

Andrew von Eschenbach, M.D., Opening comments to the FDA Advisory Committee on Risk Communication, Feb. 28, 2008

"Shades of Safety"

"In this age of freely available information, drugs cannot easily be parsed into 'safe' and 'unsafe' categories. Instead, there will be shades of safety that must be graded against shades of efficacy."

Drazen JM, Morrissey S, Curfman GD, ***New England Journal of Medicine***, July 5, 2007, p. 63-64