Using large linked healthcare databases for medical product safety assessment

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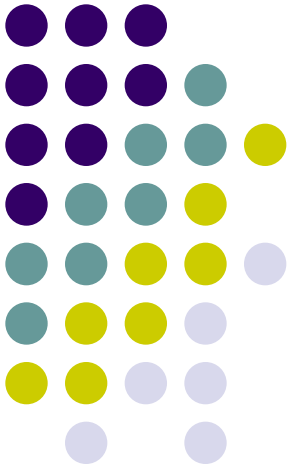


Potential Conflict of Interest

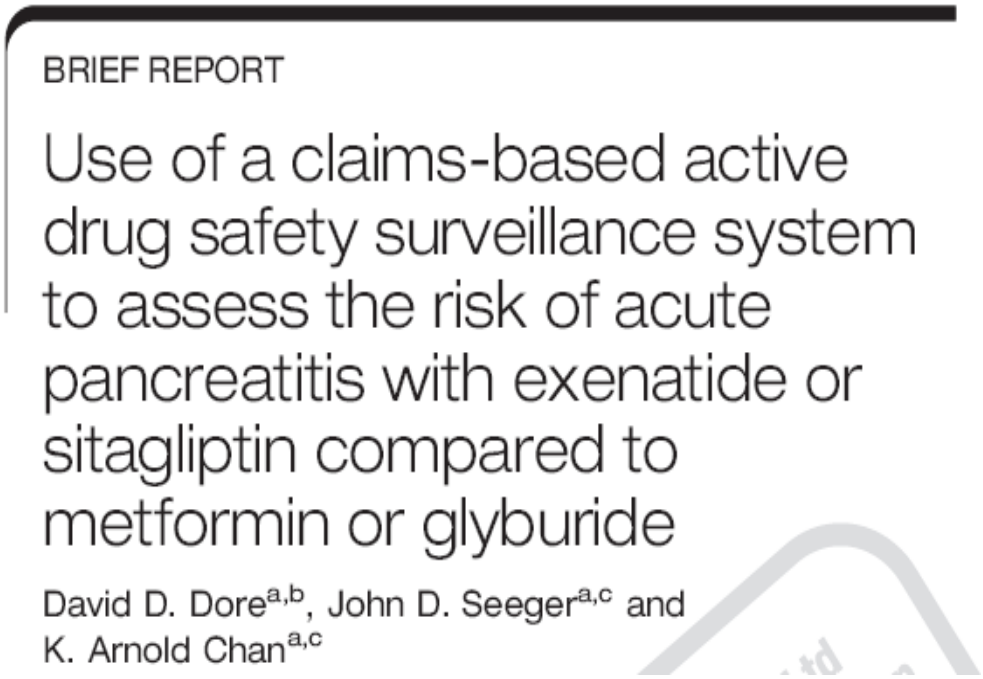
- Adjunct Associate Professor, Harvard School of Public Health
- Part time employee of i3 Drug Safety
- Co-editor of a book, no royalty received
- Public health worker

Outline

- Some examples of using large healthcare databases for public health research
- Ethical principles in biomedical research
  - Special considerations about observational studies conducted with large healthcare databases
- Using large healthcare databases
  - UK, Scandinavian countries, USA
- Scientific and practical issues

Current Medical Research and Opinion 2009; 25: 1019-27

- The report was sponsored by the manufacturer of exenatide



BRIEF REPORT

Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide

David D. Dore[a,b], John D. Seeger[a,c] and K. Arnold Chan[a,c]

- The exendatide vs. metformin/glyburide comparison was initiated after exenatide approval
- Data system allows evaluation of all potential outcomes that resulted in ICD-9 diagnosis codes
- Address an important public health question

Using databases for drug safety

FDA U.S. Food and Drug Administration — U.S. Department of Health and Human Services

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

FDA News

FOR IMMEDIATE RELEASE

September 17, 2007

Media Inquiries:
Sandy Walsh, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

AHRQ and FDA to Collaborate in Largest Study Ever of Possible Heart Risks With ADHD Medications

Two U.S. Department of Health and Human Services agencies will collaborate in the most comprehensive study to date of prescription medications used to treat attention deficit hyperactivity disorder (ADHD) and the potential for increased risk of heart attack, stroke or other cardiovascular problems.

Researchers supported by the Agency for Healthcare Research and Quality and the U.S. Food and Drug Administration will examine the clinical data of about 500,000 children and adults who have taken medications used to treat ADHD, to determine whether those drugs increase cardiovascular risks.

Using databases for drug safety

JAMA 2004; 292: 2585-90

Incidence of Hospitalized Rhabdomyolysis in Patients Treated With Lipid-Lowering Drugs

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Judy A. Staffa, PhD
Deborah Shatin, PhD
Susan E. Andrade, ScD
Stephanie D. Schech, MPH
Lois La Grenade, MD, MPH
Jerry H. Gurwitz, MD
K. Arnold Chan, MD, ScD
Michael J. Goodman, PhD
Richard Platt, MD, MSc

Context Lipid-lowering agents are widely prescribed in the United States. Reliable estimates of rhabdomyolysis risk with various lipid-lowering agents are not available.

Objective To estimate the incidence of rhabdomyolysis in patients treated with different statins and fibrates, alone and in combination, in the ambulatory setting.

Design, Setting, and Patients Drug-specific inception cohorts of statin and fibrate users were established using claims data from 11 managed care health plans across the United States. Patients with at least 180 days of prior health plan enrollment were entered into the cohorts between January 1, 1998, and June 30, 2001. Person-time was classified as monotherapy or combined statin-fibrate therapy.

Main Outcome Measure Incidence rates of rhabdomyolysis per 10000 person-years of treatment, number needed to treat, and relative risk of rhabdomyolysis.

Results In 252 460 patients treated with lipid-lowering agents, 24 cases of hospi-

Using large databases to evaluate the effectiveness of a black box warning

Contraindicated Use of Cisapride

Impact of Food and Drug Administration Regulatory Action

Walter Smalley, MD, MPH
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Jerry Gurwitz, MD
Susan E. Andrade, DSc
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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.

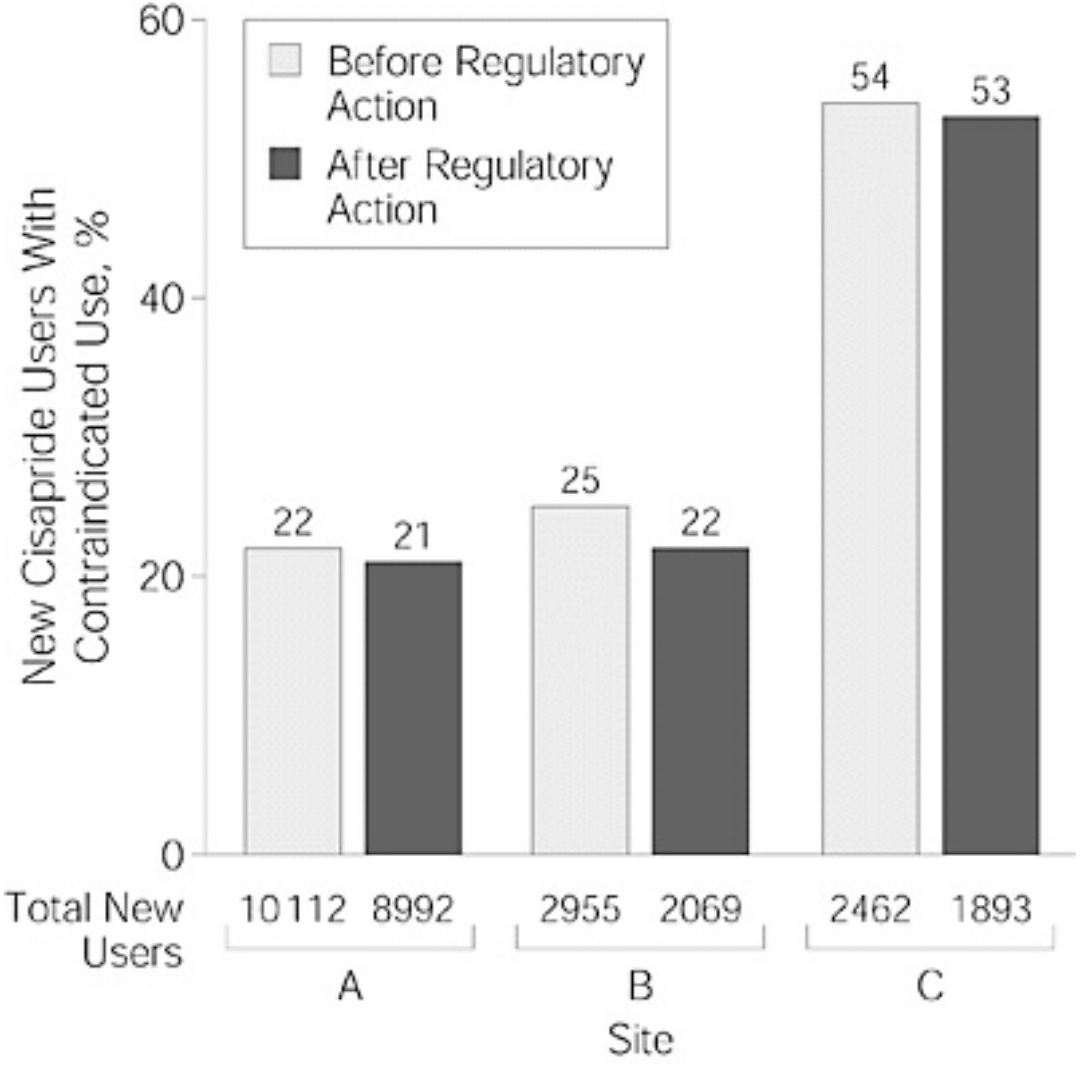
Results In the year prior to regulatory action, cisapride use was contraindicated for 26%, 30%, and 60% of users in study sites A, B, and C, respectively. In the year after regulatory action, use was contraindicated for 24%, 28%, and 58% of users, a reduction in contraindicated use of approximately 2 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 the cytochrome P450-3A4 enzymes

Black box warning did not work for cisapride (*JAMA* 2000; 284: 3036-9)



Using database for safety surveillance

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 1275–1284
Published online 22 October 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1509

ORIGINAL REPORT

Early detection of adverse drug events within population-based health networks: application of sequential testing methods[†,‡]

Jeffrey S. Brown PhD[1,2*], Martin Kulldorff PhD[1], K. Arnold Chan MD, MPH, ScD[3,4], Robert L. Davis MD, MPH[5], David Graham MD[6], Parker T. Pettus MS[1,2], Susan E. Andrade ScD[2,7], Marsha A. Raebel PharmD[2,8], Lisa Herrinton PhD[2,9], Douglas Roblin PhD[2,10], Denise Boudreau PhD[2,11], David Smith PhD[2,12], Jerry H. Gurwitz MD[2,7], Margaret J. Gunter PhD[2,13] and Richard Platt MD, MSc[1,2]

A recent article published online at Medical Care

- http://journals.lww.com/lww-medicalcare/Abstract/publishahead/Active_Influenza_Vaccine_Safety_Surveillance_.99875.aspx

ORIGINAL ARTICLE

Active Influenza Vaccine Safety Surveillance

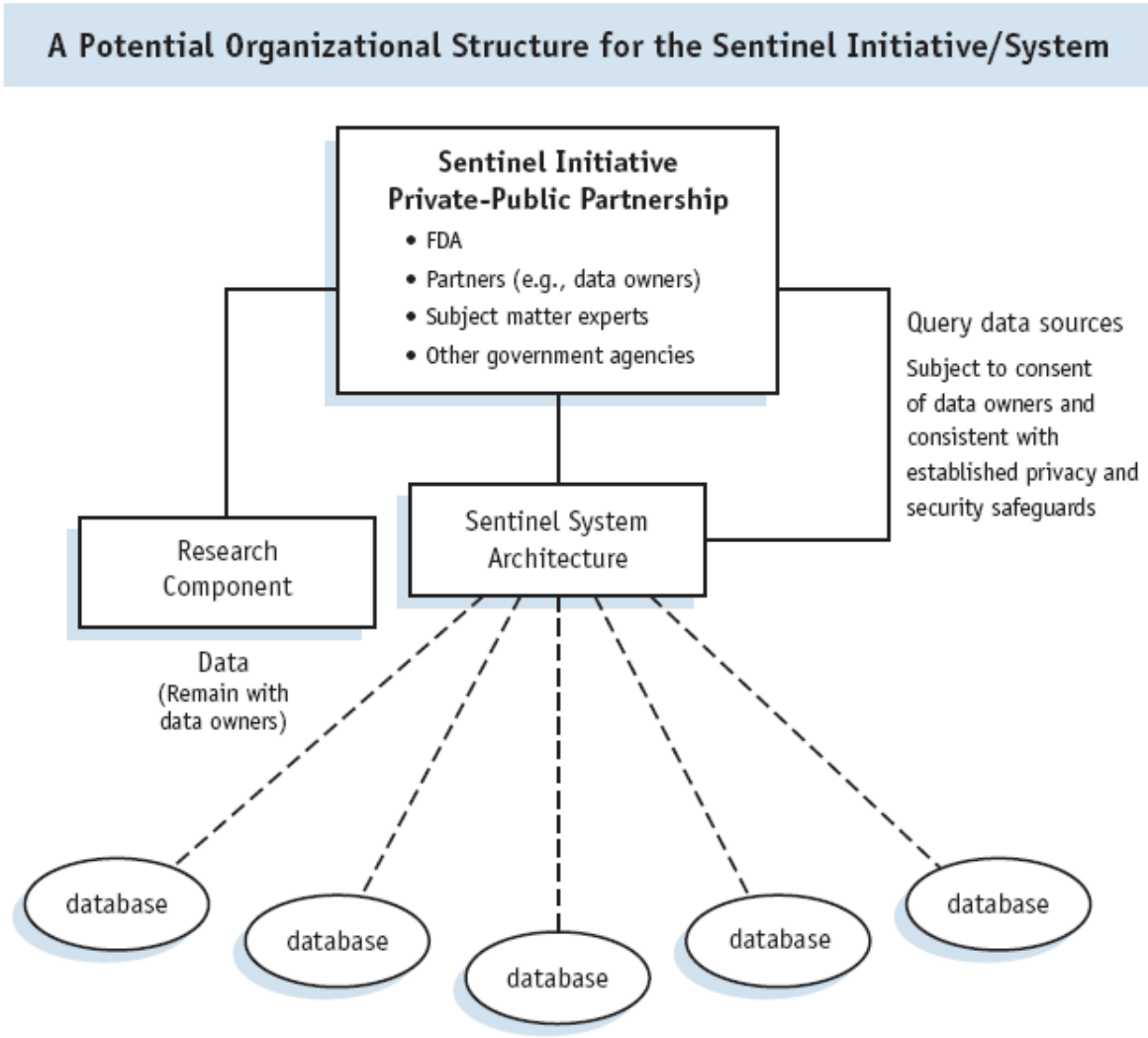
Potential Within a Healthcare Claims Environment

Jeffrey S. Brown, PhD,† Kristen M. Moore, MPH,*† M. Miles Braun, MD, MPH,‡ Najat Ziyadeh, MA, MPH,§ K. Arnold Chan, MD, ScD,§¶ Grace M. Lee, MD, MPH,*‖ Martin Kulldorff, PhD,* Alexander M. Walker, MD, DrPH,¶** and Richard Platt, MD, MSc*†*

FDA Sentinel Initiative

- http://www.fda.gov/oc/initiatives/advance/sent

According to the FDA Sentinel Initiative



Using databases for surveillance

- New England Journal of Medicine 2009; 361: 645-647

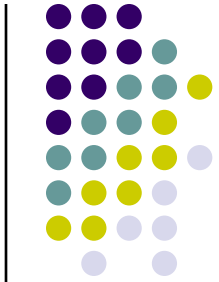
Perspective

AUGUST 13, 2009

The New Sentinel Network — Improving the Evidence of Medical-Product Safety

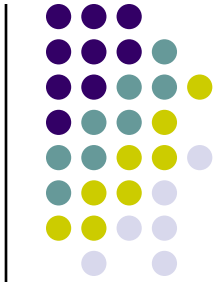
Richard Platt, M.D., M.Sc., Marcus Wilson, Pharm.D., K. Arnold Chan, M.D., Sc.D., Joshua S. Benner, Pharm.D., Sc.D., Janet Marchibroda, M.B.A., and Mark McClellan, M.D., Ph.D.

General ethical principles in human research (from a U.S. perspective)



- Respect for Persons / Autonomy
- Beneficence / Non-maleficence
- Justice
- Based on these principles, specific guidelines have been developed
  - Intervention studies
    - Good Clinical Practice and others
  - Observational studies
    - Primary data collection
    - Utilize secondary data

Different types of research, different types of ethical considerations



- Basic / mechanistic
  - Animal rights and welfare
- Clinical trials
  - Autonomy – informed consent
- Observational studies
  - Autonomy – authorization to use health records

- Is there a cultural component in ethical considerations?

The U.K. perspective

- Striking the right balance between privacy and public good. Lancet 2006; 367: 275

  "… the tension between the vital need to respect the privacy of patients and the important task of medical research using large population datasets."

  - Autonomy vs. Beneficence
  - Justice
    - Everyone, including study subjects, may benefit

A U.K. report in 2006

www.acmedsci.ac.uk/index.php?pid=99&puid=62

Personal data for public good: using health information in medical research

1. Interpreting the legal framework
2. Improving regulatory processes
3. Developing good practice in research using personal data, including issues related to anonymisation and consent
4. Harnessing the opportunities of the NHS National IT programme
5. Engaging the public

www.sciencemag.org/cgi/content/summary/sci;301/5630/163?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=denmark+epidemiology&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

- Science 2003; Vol. 301. no. 5630, p. 163

NEWS FOCUS

EPIDEMIOLOGY:

The Epidemiologist's Dream: Denmark

Lone Frank

Epidemiologists in Denmark finished enrolling a cohort of 100,000 pregnant women into a mother-and-child research project last September and expect to finish collecting data from the children over the next year. The entire survey--which is large for this country of 70,000 annual births--is to be completed in 2005 for about $15 million, a tiny fraction of what the cost would be in the United States.

Wettermark, Furu, Andersen, Martikainen, & Bergman

24th International Conference on Pharmacoepidemiology
& Therapeutic Risk Management
Copenhagen, Denmark
August 17-20, 2008

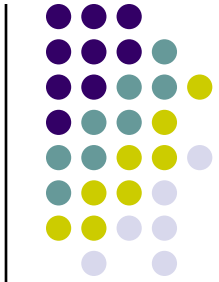
Symposium 19 August

The Nordic Countries as a cohort

ALS and statines:

Rapid Response analyses

Three related topics in database research in the U.S.A.

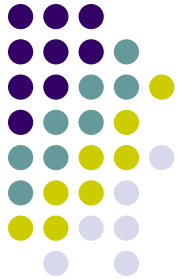


- Privacy
  - Right to be left alone
  - Derived from the Autonomy Principle
- Confidentiality
  - Legal requirement
  - Breach of confidentiality may result in substantial damage to individuals
    - Financial
    - Social stigma and discrimination
- Data security
  - Information Technology standard to prevent breach of data

U.S. legislations

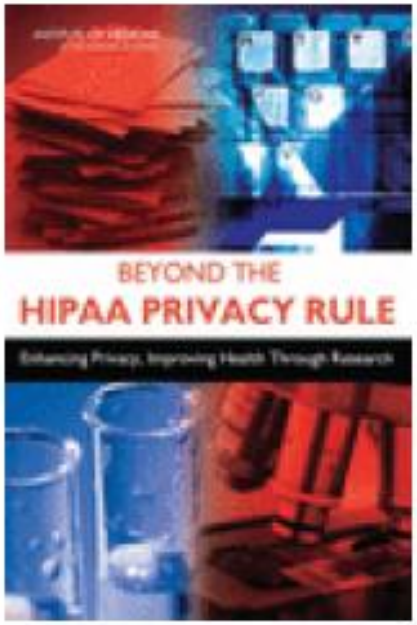
- Health Insurance Portability and Accountability Act (HIPAA)
  - Provisions for public health research with large linked health care databases
- American Recovery and Reinvestment Act (ARRA)
  - Security standard for electronic records

The consumers' view?



- U.S. Consumer Reports 2000 Aug issue, P 26
  - "Patients are well served if doctors and hospitals have fast access to accurate records."
  - "With proper safeguards against re-identification, analysis of government, hospital, and health-related databases yields a gold mine of information on public-health trends and the effectiveness of various types of care."
- Lancet 2006; 367: 275
  - "The Academy's report points to a paucity of evidence about patients' preferences for and attitudes towards participating in research, and calls for more involvement with the public to get a fuller and more accurate picture of their views."

Institute of Medicine Report in 2009



Sharyl J. Nass, Laura A. Levit, and Lawrence O. Gostin, *Editors*

Committee on Health Research and the Privacy of Health Information:
The HIPAA Privacy Rule

Board on Health Sciences Policy

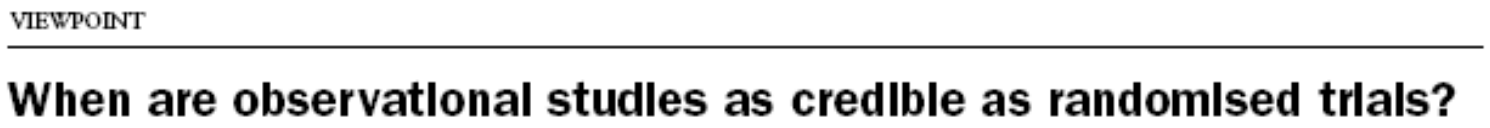
Board on Health Care Services

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

- The committee's conclusion is that the HIPAA Privacy Rule does not protect privacy as well as it should, and that, as currently implemented, the Privacy Rule impedes important health research.
- Privacy Rule in the U.S. is a work in progress.

A common misconception – data quality

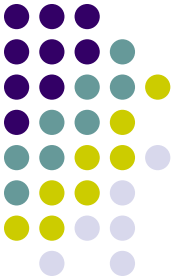
- Desire for perfect data may become the enemy of public good
  - Do not throw away the baby with the bathwater
- Jan P Vandenbroucke. Lancet 2004; 363: 1728-31


VIEWPOINT

When are observational studies as credible as randomised trials?

- What is the hierarchy of evidence?

My own thoughts on how to put ethical principles into practice



- Competent Privacy Board / Institutional Review Board / Human Subjects Committee review
- Legislation to provide the legal framework
- Training of investigators and research staff
- Utilize Information Technology to protect confidentiality without losing efficiency
- Open dialogue with all stakeholders
  - Investigators
  - Patients / consumers