Comparative Effectiveness Research: L'esperienza americana

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Background

- MD and residency in Italy
- MPH and DrPH in Pharmacoepidemiology at HSPH, Boston USA
- Instructor in Medicine at HMS, Boston USA
  - Comparative safety and effectiveness research (CER)
  - Methods for CER
  - Data linkage from multiple sources for CER

CER – Key US Milestones

Value for research of data routinely gathered in the process of delivering and paying for patient care

1988-89: "Effectiveness initiative" and Agency for Healthcare Policy and Research (AHCPR)

2003: Medicare Modernization Act (MMA) ($15 million per year)

2007: FDA Amendments Act (FDAAA) and Sentinel Initiative in 2008

2009: American Recovery and Reinvestment Act (ARRA) allocates $1.1 billion for CER

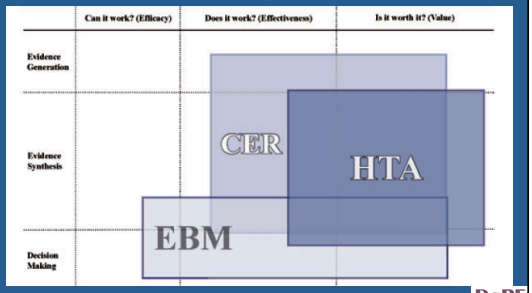
2010: Affordable Care Act (ACA) establishes PCORI to promote CER

CER in words

- Promotes studies comparing the effectiveness and safety of alternative ways of addressing common clinical problems in a "real world setting".
- Interventions to be evaluated include pharmaceuticals, devices, procedures, and diagnostic approaches.
- The ultimate goal is to support optimal decision-making by stakeholders in the healthcare system, including patients, physicians, provider organizations, etc.

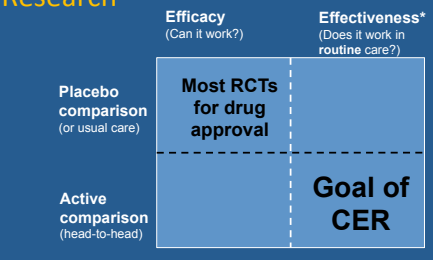
CER and its cousins

Evidence questions



Luce et al. The Milbank Quarterly. 2010

Objective of Comparative Effectiveness Research



Effectiveness = Efficacy X Adherence X Subgroup effects (+/-)

RCT — Reality of routine care

* Cochrane A. Nuffield Provincial Trust, 1972

As much as we all love randomized trials…

- It is an unrealistic expectation that we will have head-to-head randomized trials
  - for every intervention and
  - its combinations
  - in every patient subgroup
  - that exactly mimic routine care
- We need effectiveness evidence in a timely manner. Randomized studies may take some time to conduct
- About 85% of the CER evidence is from non-experimental (real-world) data!*

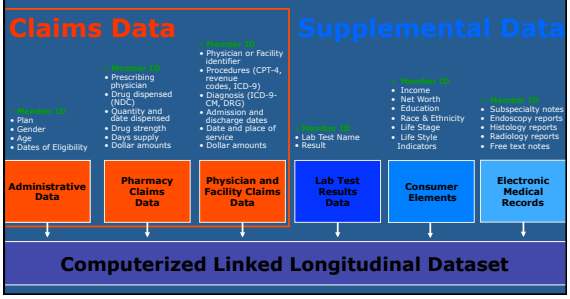
* Academy Health Report June 2009

Observational CER with US Electronic Healthcare Data

- Representative of routine care
  - Spectrum of disease severity
  - Spectrum of co-morbidities
  - Co-medications
  - Real world adherence
- Very large size
  - Infrequent exposure, recently marketed medications
  - Many subgroups to study treatment effect heterogeneity
- Long follow-up
  - With hard clinical endpoints
- Produce results fast at low cost

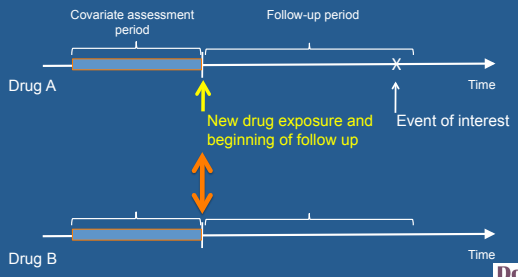
US Electronic health care information sources

- Constant flow of data with little delay and at low cost
- Millions of patients with defined person–time denominator
- Data reflect routine care
- Generalizable to large population segments
- HIPAA compliance protects patient privacy



Basic CER study design: Overview

Basic design for CER: New user cohort study with active comparison



Schneeweiss Pharmacoepi Drug Safety 2010

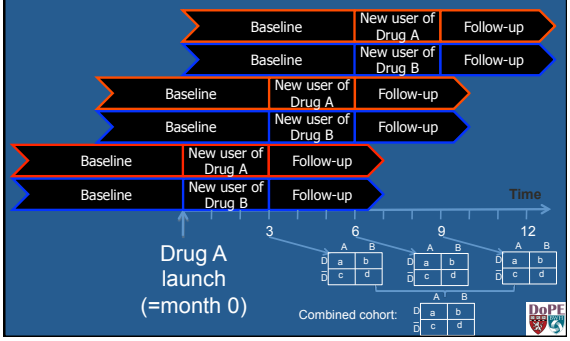
Recent applications of CER in US

Near-real-time monitoring

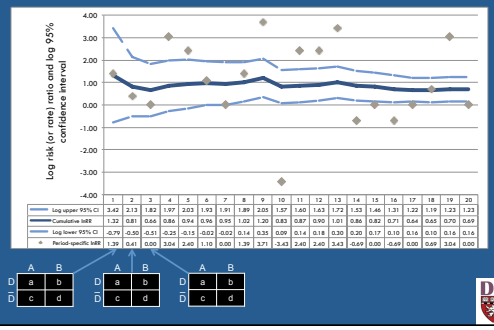
All stakeholders need CER information ASAP after marketing

- Growing interest in establishing a national infrastructure system to enable near-real-time monitoring of new medical products within the routine care setting.
- These systems of networked databases, such as the FDA's Sentinel System, may also serve as national resources for rapid generation of CE evidence.

A sequential drug monitoring system with healthcare databases, PS matched



Output of cumulating data in a monitoring system



Challenges in observational CER

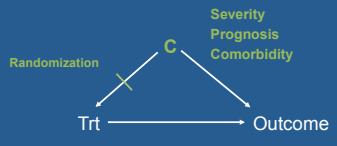
Challenges that come to mind

- **Can we handle confounding by indication?**
- Can we identify relevant subgroups?
- Can we really study long-term outcomes?
- Can we reliably assess the relevant outcomes?

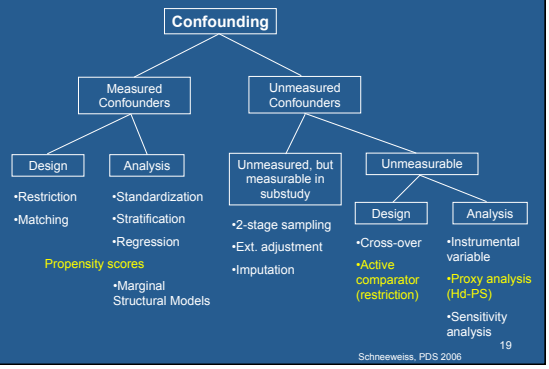
- …and don't forget the basics

Confounding

Patient factors become confounders (C) if they are associated with treatment choice and are also independent predictors of the outcome:



Dealing with confounding



Schneeweiss, PDS 2006

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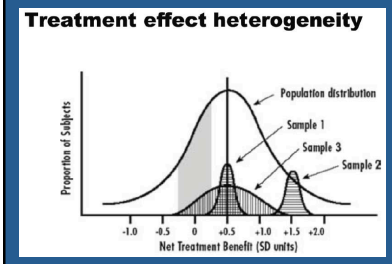
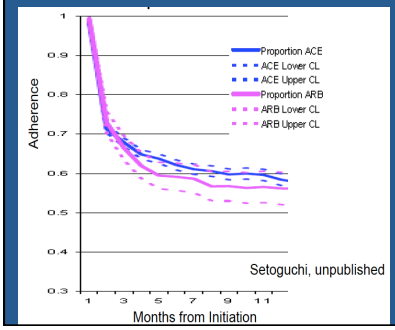
Can we identify relevant subgroups?



- Average treatment effect may not be the best estimate for some subpopulations
- Large population-based databases will allow us to assess treatment effect in subpopulations

Kravitz Milbank 2004

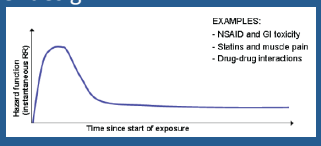
Assessing long-term outcomes in real-world settings



Adherence to ACE or ARB in Patients with Heart Failure Drops in the first 6 months

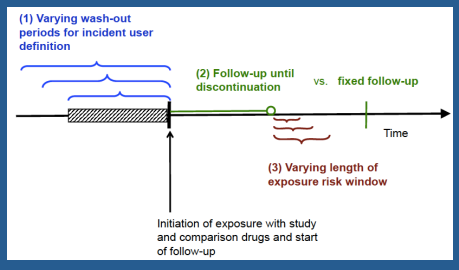
Attention to basic epidemiology principles is paramount

- Basic new user design

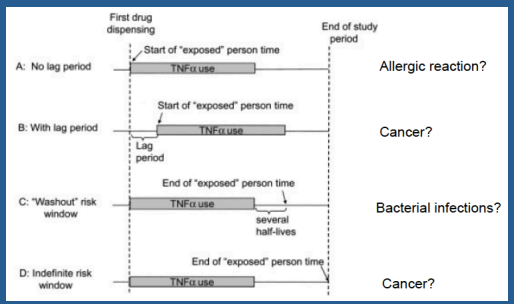


- Validate outcomes or at least use validated outcomes
- Sensitivity analyses will help you put results in perspective

Basic design sensitivity analyses

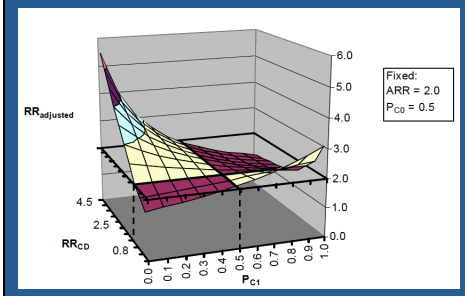


Exposure risk window



There is no right and no wrong. You need to argue your case based on event of interest, the biology, PK and PD

Residual confounding (array approach)



Schneeweiss PDS 2006

Conclusions

- Yes
  - Observational CER has many challenges
- But
  - Great needs and opportunities for observational CER
  - Advancement in methods and data sources is bringing more valid observational CER

Thanks!