

# **Evidence-Based Medicine: Problems and Methods**

A Short History

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# Problems of Clinical Research

- Human variation
- Therapeutic relationship: physician-patient roles and expectations
- Ethics of research: subject selection, subject compliance, continuance
- Multiple stakeholders: physicians, patients, policymakers, manufacturers

# Methods

- Comparative clinical trials
- Randomization => statistical analysis
- Blinding
- "Intention to treat"
- Meta-analysis
- Systematic review of evidence

# Comparative Trials: Precursors

- Work not accepted at the time
  - James Lind on scurvy (1753)
  - Pierre Louis on bloodletting (1835)
  - Ignaz Semmelweis on puerperal fever (1847)
- Work accepted at the time
  - John Snow on cholera (1854)
  - Walter Reed on yellow fever (1901)

# 1900: Calls for reform of patent medicine market

- 1905: the AMA's Council on Chemistry and Pharmacy – the need for “ a rational therapeutics”
- 1906: the Pure Food and Drug Act – the need for a scientific basis for regulation
- 1931: the Therapeutic Trials Committee of the Medical Research Council

# Borrowed Ideas: Randomization

- R.A. Fisher's work at Rothamsted Agricultural Station
- *The Design of Experiments* (1935)
- Randomization of assignment to experimental and control groups allows the investigator to calculate the statistical significance and likelihood of error of observed differences in effect.

# Borrowed Ideas: Blinding

- Blindfold Tests: widely used by advertisers and consumer groups in the 1930s and 1940s
- Torald Sollmann suggested a placebo control and blinded observer as a solution to investigator bias as early as 1930

# The Streptomycin TB Trials

- Feldman and Hinshaw's principles of design  
1944: "some procedure of chance"
- The VA 1946: problems of physician compliance
- The MRC 1947-48: drug scarcity ensures compliance to protocol
- The US Public Health Service 1947: replacing physician judgment with standardized criteria

# Working Guideline to Regulatory Law

- Explosion of new drugs in 1950s raised concerns over pricing and exploitation
- Thalidomide disaster of 1962 pushed passage of Kefauver-Harris Amendments
- FDA empowered to review efficacy of new and existing drugs; relied initially on expert clinical judgment – the Drug Efficacy Study panels 1966-69

# RCT As Evidentiary Standard

- FDA moved to withdraw drugs from market on DESI recommendations
- Pharmaceutical companies went to court, forcing FDA to define “substantial evidence.”
- May 1970 regulations specified:
  - Criteria for patient selection
  - Exclusion of bias
  - Comparability of variables
  - Use of control group
  - Statistical analysis of data

# 1970-1990: More Players, More Evidence

- Investigators produced much trial evidence of varying quality
- Limited resources for major definitive trials
- Who has the expertise to assess the evidence?
- How do we select the “best” evidence/determine where more is needed?
- What is the “answer” we are looking for?
  - Best fit to theoretical concepts
  - Comparative efficacy
  - User efficacy

# A Statistical Solution: Meta-Analysis

- First used in astronomy 1860s
- Karl Pearson's work on typhoid vaccine 1904
- Introduced into social sciences 1970s and then into medicine
- Do results correlate with those of large RCTs? (Not always – LeLorier et al, 1997)
- Does meta-analysis resolve problems of small, poor-quality trials? (No – Jüni et al, 1999)

# Evidence Review: Art => Science

- Cochrane 1972: collective ignorance of much of the available evidence
- Mulrow 1987: Selection bias, haphazard analysis found in literature reviews
- Oxman and Guyatt 1988: Guidelines for reading reviews
- McMaster method => Evidence-based Medicine 1990-95
- The U.K. Cochrane Centre 1992

# **But Systematic Review Projects Need Evidence to Review**

Factors of bias, subject recruitment, ethics, career incentives, data measurability lead to problems of experimental and publication selection:

Only certain trials are likely to be done and not all the results will be published.