Biost 524: Design of Medical Studies

Lecture 1 continued:
Medical and Scientific Setting

March 30, 2011

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Summary from Monday

- Note: No TA
- MaFDA – see web site
- Medical Setting
  - Address medical needs
  - Drug, devices, biologics, diagnostic, prognostic
  - Treatment indication: Disease, Population, Treatment, Outcome
  - Evidence based Medicine: Patient population, intervention, comparator, outcome
  - Perspectives: Patients, Clinicians, FDA, NIH, other funding agencies, companies

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Level of Evidence

- U.S. Preventive Services Task Force
  - **Level I:** At least one properly designed RCT
  - **Level II:**
    - **II-1:** Well-designed, nonrandomized CT
    - **II-2:** Well-designed, multicenter cohort/case-control
    - **II-3:** Multiple time series with/without intervention; Dramatic results from uncontrolled trial
  - **Level III:** Opinions of respected authorities
    = Eminence based (not their wording!)

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Third Consideration

- Where do we get the data to be synthesized?
  - Well designed clinical interventional studies
- Clinical trials
  - Experimentation in human volunteers
  - Investigates a new treatment/preventive agent
    - Safety:
      - Do adverse effects outweigh potential benefit?
    - Efficacy:
      - Does treatment beneficially alter the disease process
    - Effectiveness:
      - Would adoption of the treatment improve morbidity / mortality in the population?

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Overview

Scientific Setting

Where am I going?

- The goal of medical science is to produce the evidence that can be used to
  - Gain approval of new treatments and diagnostic tests
  - Provide evidence to be used in applying those treatments and tests.

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Goals of Medical Research

- Identify methods to diagnose disease
- Identify risk factors for disease
- Identify treatments for disease
- Identify methods for disease prognosis
- Identify strategies for prevention of disease
- Basic science

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Legal Requirements for Good Science

- Wiley Act (1906)
  - Labeling
- Food, Drug, and Cosmetics Act of 1938
  - Safety
- Kefauver – Harris Amendment (1962)
  - Efficacy / effectiveness
    - " [If] there is a lack of substantial evidence that the drug will have the effect ... shall issue an order refusing to approve the application. "
    - "...The term 'substantial evidence' means evidence consisting of **adequate and well-controlled investigations, including clinical investigations**, by experts qualified by scientific training"
- FDA Amendments Act (2007)
  - Registration of RCTs, Pediatrics, Risk Evaluation and Mitigation Strategies (REMS)

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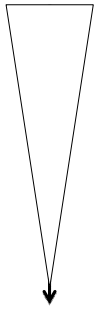
Typical Chronology



- Observational
- Preclinical
- Clinical trials
  - Safety / dose
  - Efficacy signal / further safety
  - Confirm efficacy / effectiveness
- Synthesis
- Adoption of new treatment indication

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Types of Studies - 1

- Anecdotal observations
  - Case report
  - Case series
  - Hypothesis generation

That's not an experiment you have there, that's an experience.
Sir Ronald A. Fisher (1890 - 1962)

The plural of anecdote is not data.
Roger Brinner

(note, cartoons and citations are from <www.causeweb.org>)

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Types of Studies - 2

- Designed observational study: Case - control
  - Sample diseased and nondiseased
  - Examine rates of exposures
  - Efficient for rare diseases
  - Can look at multiple risk factors
  - Limitation: Cannot infer cause and effect
    - Correlations with other factors
    - Protopathic associations

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Types of Studies - 3

- Designed observational study: Cohort study
  - Sample exposed and nonexposed
  - Examine rates of disease
  - Efficient for common diseases
  - Can look at multiple diseases
  - Can identify “retrospective cohort”
  - Limitation: Cannot infer cause and effect
    - Correlations with other factors
    - Protopathic associations

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Types of Studies - 4

- Designed interventional study: Clinical trial
  - Assign subjects to treatments
  - Examine outcomes
  - Can look at multiple diseases
  - Can infer cause and effect

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Clinical Trials

- Experimentation in human volunteers
- Investigation of a new treatment or preventive agent
  - Safety: Do adverse effects outweigh any benefit?
  - Efficacy: Can treatment beneficially alter disease?
  - Effectiveness: Would adoption of the treatment help population's health?
- Investigation of existing treatments
  - Relative benefits: Is one treatment clearly superior?
  - Harm: Should a therapy currently in use be removed?
- Some questions cannot be answered by a clinical trial
  - E.g., establishing harm of a new substance

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Efficacy

- Definition of efficacy can vary widely according to choice of endpoint and magnitude of importance
  - Basic science
    - Does treatment have any effect on the pathway?
  - Clinical science
    - Does treatment have a sufficiently large effect on a clinically relevant endpoint in some subpopulation of the target population?
- Moving target

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Effectiveness

- A treatment is "effective" if its introduction improves health in the population
  - Considers the net effect of safety and efficacy in the population as a whole
  - Takes into account such issues as
    - Noncompliance
    - Off-label use
- Moving target

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Effectiveness vs Efficacy

- A treatment can be both efficacious and ineffective depending on such factors as
  - Target population
    - Restricted eligibility due to toxicity, compliance
  - Intervention
    - Training, quality control, compliance
  - Comparison treatment
    - No treatment, active treatment, ancillary treatments
  - Measurement of outcome(s)
    - Clinical disease vs subclinical markers
  - Summary measure of outcome distribution
    - Effects on mean, median, outliers

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Disease Related Issues

- Efficacy and effectiveness study populations may differ with respect to
  - Certainty of diagnosed disease
  - Subgroups with more (less) severe disease

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Target Population

- Efficacy and effectiveness study populations may differ with respect to
  - Properly diagnosed disease
  - Subgroups with more (less) severe disease
  - Tolerance of treatment
  - Willingness to comply with treatment
  - Ancillary treatments
  - Different risk factors

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Ex: Desensitization in Allergy

- Efficacy trial might consider
  - Patients with proven allergy who have shown "response" in open label study (perhaps due to genetic profile?)
  - Exclusion criteria for safety in trial
    - Cannot tolerate oral food challenge
    - Patients likely to be noncompliant
  - Exclusion criteria to ensure adequate data
- Effectiveness populations might include
  - All patients with reported allergy

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Control Treatment

- Efficacy and effectiveness study populations may differ with respect to
  - Use of existing alternative treatments
  - Allowed ancillary treatments

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Ex: Control Treatment in Allergy

- Efficacy trial might consider
  - Placebo
  - Careful control of diet
- Effectiveness populations should be best current standard of care
  - Will patient's behavior differ when they know their treatment assignment?

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Intervention

- Efficacy and effectiveness populations may differ with respect to
  - Dose
  - Administration
  - Duration
  - Training
  - Quality control

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Ex: Insulin Dependent Diabetes

- Efficacy trial might consider
  - Glucose monitoring according to protocol
  - Lengthy training
  - Close monitoring and retraining when necessary
- Effectiveness trial should strive for realistic setting
  - What would instructions and training, monitoring be if treatment were efficacious
  - What if treatment fails (use another)

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Measurement of Outcome

- Efficacy and effectiveness populations may differ with respect to
  - Clinical measurement
  - Timing of measurement

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Ex: Hypercholesterolemia

- Efficacy trial might consider
  - Lowering of serum cholesterol
  - Means
- Effectiveness trial should strive for relevant outcome
  - Proportion exceeding acceptable thresholds
    - Normal cholesterol levels
  - Time of survival

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Which: Efficacy or Effectiveness

- Factors leading to efficacy trials
  - "Knowledge is good"
  - As pilot studies before prevention studies
- Factors leading to effectiveness trials
  - Serious conditions
    - Patients generally want to get better
  - Short therapeutic window for treatment
  - Waiver of informed consent
    - Do not withhold beneficial treatments in order to establish mechanisms
  - High cost of clinical trials (time, people, $$)

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Typical Scientific Hypotheses

- The treatment will cause an individual's outcome to be

{ better than, worse than, or about the same as } { an absolute standard, or what it would have been with some other treatment }

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Counterfactual

- The statement of the hypotheses assumed that it is possible to know what would have happened under some other treatment
  - Generally we instead have to measure outcomes that are observed
    - in another place (patient),
    - at another time, and / or
    - under different circumstances

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Causation vs Association

- Truly determining causation requires a suitable interventional study (experiment)
  - Comparisons tell us about associations
  - Associations in the presence of an appropriate experimental design allows us to infer causation
    - But even then, we need to be circumspect in identifying the true mechanistic cause
      - E.g., a treatment that causes headaches, and therefore aspirin use, may result in lower heart attack rates due entirely to the use of aspirin

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Investigating the Unknown

- We must acknowledge that we might be wrong
  - It will be impossible to prove something that is not true
  - The treatment might not work as we had hoped

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First Statistical Refinement

- Determine whether the group that received the treatment will have outcome measurements that are

{ higher than, / lower than, or / about the same as } { an absolute standard, or / measurements in an otherwise comparable group (that did not receive the treatment) }

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Variation in Response

- There is, of course, usually variation in outcome measurements across repetitions of an experiment
  - Variation can be due to
    - Unmeasured (hidden) variables
      - In the process of scientific investigation, we investigate one "cause" in a setting where others are as yet undiscovered
      - E.g., mix of etiologies, duration of disease, comorbid conditions, genetics when studying new cancer therapies
    - Inherent randomness
      - (as dictated by quantum theory)

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Second Statistical Refinement

- Determine whether the group receiving the treatment will tend to have outcome measurements that are

higher than,	an absolute standard, or
lower than, or	measurements in an otherwise comparable group (that did not receive the treatment)
about the same as	

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Review: Statistical Hypotheses Testing

- Karl Popper (1902 – 1996) Austrian Philosopher

from: www.univie.ac.at/science-archives/ popper/pict

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Review: Statistical Hypotheses Testing

- According to Popper:
- We can NOT prove that a hypothesis is true
- We can ONLY falsify a hypothesis

- Thus, "if we want to show" that a treatment "works" compared to a control, we start out by assuming that it has the same effect as the control, and try to disprove it.

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Review: Statistical Hypotheses Testing

- The truth can only be: either H_0 true, or H_A true

	H_0 is true	**H_A is true**
We fail to reject H_0	No error Prob 1-α	Type II error Prob β
We reject H_0	Type I error Prob α	No error Prob 1-β

- Type I error: falsely rejecting H_0
- Type II error: falsely not rejecting H_0
- Yogi Berra (slightly misquoted): Don't make the wrong mistake!

(Yogi Berra said: "I made a wrong mistake")

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Lecture 1

- Medical Setting
- Scientific Setting

- Questions ?

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