Biost 524: Design of Medical Studies

Lecture 1:
Course Organization; Scientific Setting

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The Use of Statistics to Answer Scientific Questions Ethically and Efficiently

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Lecture Outline

- Course Structure
- Overview of Setting
  - Medical setting
  - Scientific setting

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Course Overview

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Course Structure

- Instructor: Scott S. Emerson, M.D., Ph.D.
- TA: Tanya Granston
- Time and Place:
  - Lectures: 8:00 - 9:20 am MW HSB T625
- Class web pages
  - www.emersonstatistics.com/b524/

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Assumed Prior Knowledge

- Scientific curiosity
- Statistical coursework
  - Introductory applied statistics
    - Biost 511 or 517
    - (Biost 512 or 518)

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Textbooks

- Friedman LM, Furberg CD and DeMets DL: *Fundamentals of Clinical Trials*
- Ellenberg S, Fleming TR and DeMets DL: *Data Monitoring Committees: A Practical Perspective*
- Pocock SJ: *Clinical Trials: A Practical Approach*

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Old Dogs, New Tricks

- Recording of Lectures: Camtasia
  - Audio and computer video on web
- No guarantees
  - "Mistakes happen"

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Computer Software

- Minimal use of software
  - Possibly of use for sample size calculation and evaluation of study design
- Students may use any program that will do what is required, however
    - I will make available a package in R for those who want to use it

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Grading

- 10% Three – four homeworks
  - Review of an article and answering questions
  - Written and / or in class
- 75% Group project
  - Design of a clinical trial
- 15% Protocol review committee
  - Critique of another group's project

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Topics

- Medical / scientific setting
- Design of clinical trials
  - Phases of investigation; types of studies
  - Specific aims; endpoints
  - Target population
    - Inclusion / exclusion criteria
  - Treatment
    - Intervention / comparison groups
  - Recruitment; informed consent
  - Retention; compliance
  - Protocol

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Topics

- Conduct of clinical trials
  - Data collection / management
  - Monitoring: QA / QC, safety
- Analysis of clinical trials
  - Statistical analysis plan
  - Reporting results

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Overview

Medical Setting

Where am I going?

- Ultimately, we perform clinical studies in order to address medical needs
- We thus want to be able to
  - classify the types of questions we answer in a clinical trial, and
  - understand the reasons one type of question might be more important than another.

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Overall Goal

- "Drug discovery"
  - More generally
    - a therapy or preventive strategy
      - drug, biologic, device, behavior
    - for some disease
    - in some population of patients
- Medical diagnosis / prognosis
  - Evaluation of methods

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Typical Chronology

- Observational epidemiology of disease, risk
- Preclinical experiments
  - Laboratory, animal studies of mechanisms, toxicology
- Clinical trials
  - Safety for further investigations / dose
  - Safety of therapy
  - Measures of efficacy
  - Confirmation of efficacy / effectivenesss
- Synthesis and quantification of evidence
- Adoption of new treatment indication

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The Enemy

- "Let's start at the very beginning, a very good place to start…"

- Maria von Trapp

(as quoted by Rodgers and Hammerstein)

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First Consideration

- Where do we want to be?
  - Find a new treatment that improves health of individuals
    - "Personalized medicine"
      - "Person" as fixed effects
      - "Person" as random effects
  - Find a new treatment that improves health of the population
    - Treatments administered to a community
    - Treatments tested on a population

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Treatment "Indication"

- Disease
  - Putative cause vs signs / symptoms
    - May involve method of diagnosis, response to therapies
- Population
  - Restrict by risk of AEs or actual prior experience
- Treatment or treatment strategy
  - Formulation, administration, dose, frequency, duration, ancillary therapies
- Outcome
  - Clinical vs surrogate; timeframe; measurement

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Disease

- A moving target heavily influenced by treatment
  - Then: "fevers"
  - Now: "MRSA-related pneumonia"
- Trends over place and time in definition because
  - Symptoms
    - Cultural effects, earlier recognition, symptomatic treatments, comorbidities
  - Signs
    - New diagnostic modalities, other prevention strategies (e.g., TB vaccine) and treatments
  - Unmet need
    - Effective treatment already discovered for subset

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Definition of Disease

- Specify the disease targeted by the therapy
  - Scientifically
    - Putative cause of constellation of symptoms
    - Symptoms / signs from multiple causes
  - Clinically
    - Diagnostic criteria
      - Incident vs prevalent
      - Symptoms
        - » Intensity, frequency, duration, response to treatment
      - Signs
        - » Method of measurement
        - » Magnitude, reproducibility
    - Prior treatment history

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Population

- Treatment indications may be restricted to a specific population
  - Demographics: age, sex
  - Genetics: drug metabolism
  - Comorbid conditions
    - Drug metabolism: renal, liver disease
    - Drug side effects: cardiovascular disease, bleeding
  - Prior treatment history: resistance to alternatives
  - Vulnerable populations
    - Pediatrics, pregnancy

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Definition of Treatments

- Full description
  - Formulation of treatment
  - Dose, administration, frequency, duration
    - Rules for responsive dosing (e.g., insulin)
    - Include plans for
      - Treatment of adverse events
      - Dose reduction
      - Dose discontinuation
  - Ancillary treatments
    - Prescribed vs allowed vs prohibited

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Outcomes

- The desired beneficial reponse from the treatment
  - Clinical outcomes
    - Prolonged survival
    - Quality of life
  - Surrogate outcomes
    - Improvement in some risk factor believed to be predictive of a good clinical outcome
- Definition
  - Method of measurement
  - Timeframe

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Diagnostic Test “Indication”

- Disease
  - Putative cause vs eventual outcomes
- Population
  - Identify risk factors (prevalence)
  - Eliminate known false positives, false negatives
- Test or testing strategy
  - Formulation, administration, method of measurement
- Outcome
  - Sensitivity, specificity
  - Predictive value of positive, negative

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Prognostic Test "Indication"

- Disease
  - Clinical diagnosis
- Population
  - Identify risk factors (prevalence)
  - Eliminate known false positives, false negatives
- Test or testing strategy
  - Formulation, administration, method of measurement
- Outcome: Clinical event or survival
  - Sensitivity, specificity
  - Predictive value of positive, negative

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Clinical Decision for Diagnosis

- What test provides the best information for a patient
  - Based on what we know about the patient?
  - Based on what we know about the test?

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Clinical Decision for Treatment

- What is the best treatment to give a patient
  - Based on what we know about the patient?
  - Based on what we know about the treatment?

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Second Consideration

- Synthesize and evaluate evidence for a therapy
  - Analysis and interpretation of clinical studies
- Evidence Based Medicine (PICO)
  - Patient population
    - Disease and population characteristics
  - Intervention
    - Precise description of treatment strategy
  - Comparator
    - Alternatives in the absence of the new treatment
  - Outcome
    - Both beneficial and adverse

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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-cntrl
    - **II-3:** Multiple time series with/without intervention; Dramatic results from uncontrolled tral
  - **Level III:** Opinions of respected authorities

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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 that 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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Types of Studies - 1

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

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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: A Moving Target

- 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

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Effectiveness: A Moving Target

- 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

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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

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

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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,	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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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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Phases of Investigation

- Series of studies support adoption of new treatment
  - Preclinical
    - Epidemiology including risk factors
    - Basic science: Physiologic mechanisms
    - Animal experiments: Toxicology
  - Clinical
    - Phase I: Initial safety / dose finding
    - Phase II: Preliminary efficacy / further safety
    - Phase III: Confirmatory efficacy / effectiveness
  - Approval of indication
    - (Phase IV: Post-marketing surveillance, REMS)

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