

Introduction to Clinical Trials – Day 1

Session 1 - Background

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General comments

- Organizational...
 - UW netID: to be announced
 - Password: to be announced
- Assumed prior knowledge
 - Basis statistics
 - Basis study designs
- PLEASE ask questions at any time
- Includes slides/content from Scott Emerson, Tom Fleming

Overview – Introduction to Clinical Trials

- Primary Design Issues
 - Introduction / Background
 - Screening Studies
 - Fundamentals of Trial Design
 - Statistical Tasks in Trial Design
 - Elements of a Clinical Protocol
- Conduct and Implementation
 - Randomization strategies
 - Blinding
 - Specification of secondary endpoints
 - Handling of missing data
 - Conduct and monitoring of the study
 - Independent data monitoring committee
 - Reporting of the result

Clinical Trials

- Clinical trials in the context of other studies
- 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 / effectiveness
- Synthesis and quantification of evidence
- Adoption of new treatment indication

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Sections

- Intro
- Sci/Stats
- Phases
- Ethics & Oversight
- Protocol
- Summary

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Start at the end....

- Where do we want to be?
 - Find a new treatment that improves health of individuals
 - Find a new treatment that improves health of the population
 - Treatments administered to a community
 - Treatments tested on a population

Sections

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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

Sections

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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 / geographic 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 response 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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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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Scientific Setting

- 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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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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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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Kefauver-Harris Amendments (1962)

- required that manufacturers prove the effectiveness of drug products before they go on the market, and afterwards report any serious side effects
- required that evidence of effectiveness be based on adequate and well-controlled clinical studies conducted by qualified experts
- mandated that FDA conduct a retrospective evaluation of the effectiveness of drugs approved for safety—but not for effectiveness—between 1938 and 1962
- transferred to FDA control of prescription drug advertising, which would have to include accurate information about side effects

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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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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

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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

Sections

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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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Example – Design/Statistics

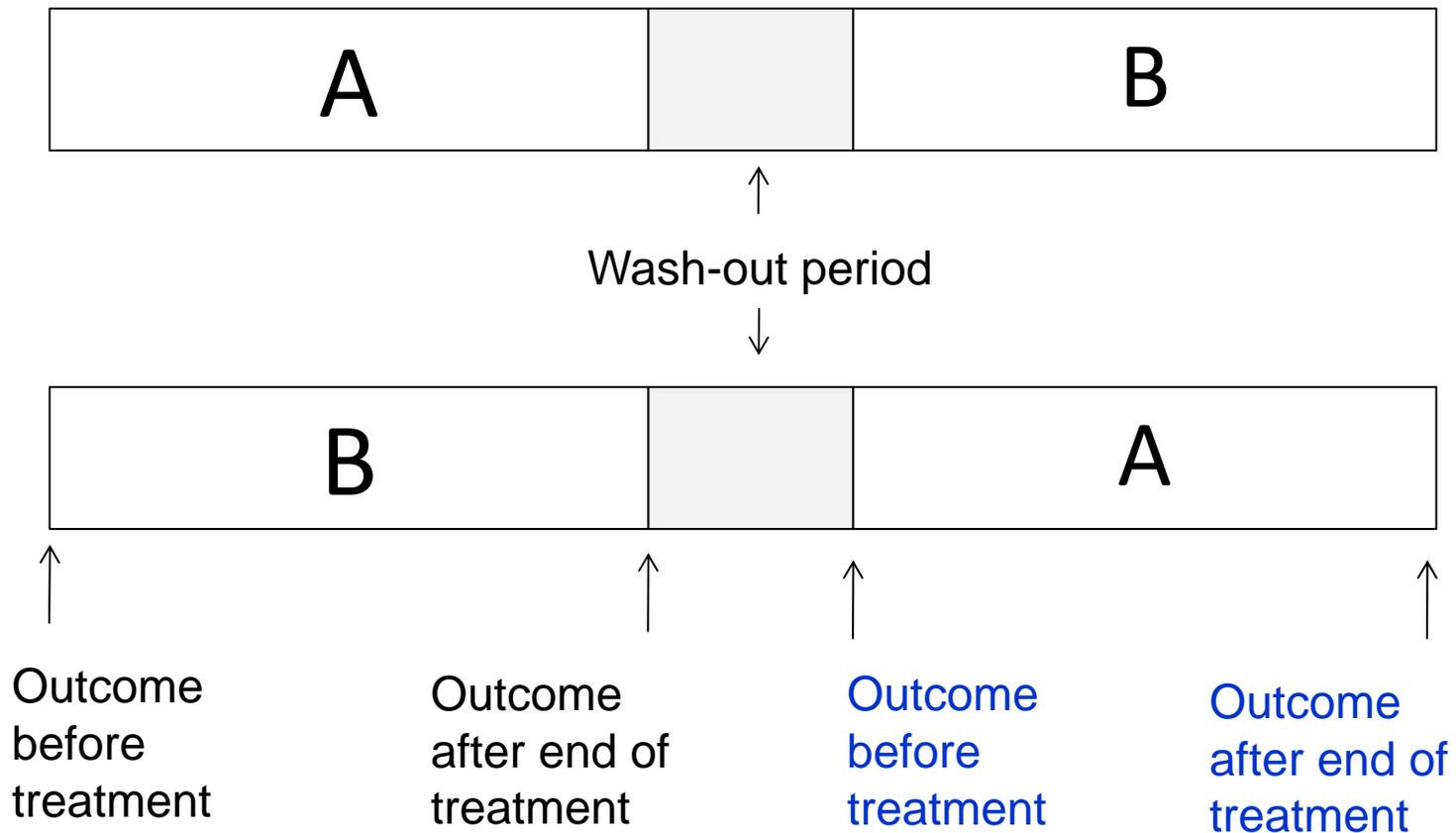
- Example
 - Double-blind placebo controlled cross-over trial
 - Completed
 - Needed help with statistical analysis and write-up

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Example: Cross-over trial

- Typical design for two treatments



Sections

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Example: Cross-over trial

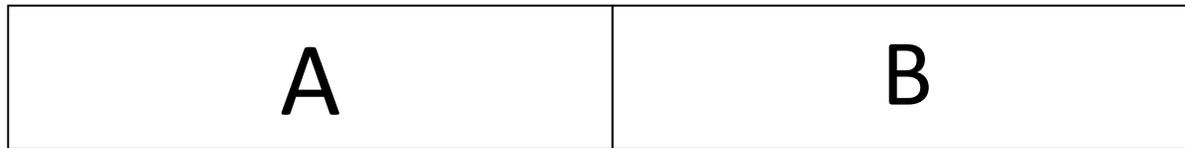
- Design for this study
 - Primary outcome
 - Hemoglobin level
 - Secondary outcome
 - Frequency and intensity of nose bleeds
 - Time points of evaluation
 - Before treatment initiation
 - 3 months
 - 6 months

Sections

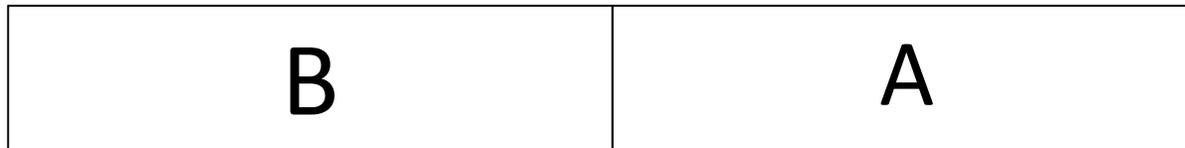
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Example: Cross-over trial

- Design for this study



No Wash-out period



↑
Outcome
before
treatment

↑ Outcome
after end of
treatment

↑ Outcome
before
treatment

↑ Outcome
after end of
treatment

Sections

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Example: Cross-over trial

- Potential issues
 - Last observation from first phase
= first observations last phase
 - No wash-out period ... justifiable?

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Example: Cross-over trial

- What if there is an effect under A?

- Calculations

- Change under A – Change under B

AB sequence

$$\begin{array}{r} \text{– hbA [t=0] – hbA [t=3]} \quad \text{– (hbB [t=3] – hbB [t=6])} \\ \quad 9 \quad \text{–} \quad 14 \quad \text{–} \quad (\quad 14 \quad \text{–} \quad 9 \quad) = -10 \end{array}$$

BA sequence

$$\begin{array}{r} \text{– hbA [t=6] – hbA [t=3]} \quad \text{– (hbB [t=0] – hbB [t=3])} \\ \quad 9 \quad \text{–} \quad 14 \quad \text{–} \quad (\quad 9 \quad \text{–} \quad 9 \quad) = -5 \end{array}$$

- Under this calculation they should be the same!!!

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Example: Cross-over trial issues

- Absence of carry-over effect – violated
- Basic premise underlying the design
- Misunderstanding – wash-out period
- “Wash-out” of drug in the system
- Sustained effect on hemoglobin

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Example: Cross-over trial

- N = 106 patients interested and contacted
- N = 34 examined
- N = 22 started drug intake
- N = 2 non-compliant

- 9 Female, 11 Male
- 52 mean age (range 34 – 72)

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Take home message

- “Bottom line” ?
- Statistician NEEDS to understand concepts of the application
- Investigator NEEDS to understand concepts of the statistical analysis

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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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Phase III Clinical Trials

- Common scenarios
 - Establish efficacy / effectiveness of new treatment
 - superiority over no intervention
 - superiority over existing treatment
 - Establish equivalence with current treatment
 - Two-sided equivalence: bioequivalence
 - establish response not markedly higher or lower
 - One-sided equivalence: noninferiority
 - establish treatment not markedly worse
 - perhaps superior on secondary endpoint
 - Establish harm of existing treatment

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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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Example

- Random high bias
- Fleming (2010, Ann Intern Med, 153, 400)
 - Exploratory analyses
 - Misleading *P values*
 - Overestimate of effect sizes

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Maternity Ward Example

- Fleming (2010)
 - Nursery, 22 infants
 - 2 boys
 - 20 girls

P-value: 0.0001

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Maternity Ward Example

- Performing second study based on promising results
(not part of the Fleming article)
 - Maternity unit 1, 22 infants (2 boys, 20 girls)
 - Maternity unit 2, 22 infants
 - 11 boys
 - 11 girls

Sections

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Maternity Ward Example

- Combining study data
 - Maternity unit 1, 22 infants (2 boys, 20 girls)
 - Maternity unit 2, 22 infants (11 boys, 11 girls)

Combined (13 vs 31)

P-value: 0.0096

Need to address the fact that these were two studies!
Even then, carrying the problem forward!

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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
 - 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?

Sections

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Intervention

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

Sections

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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

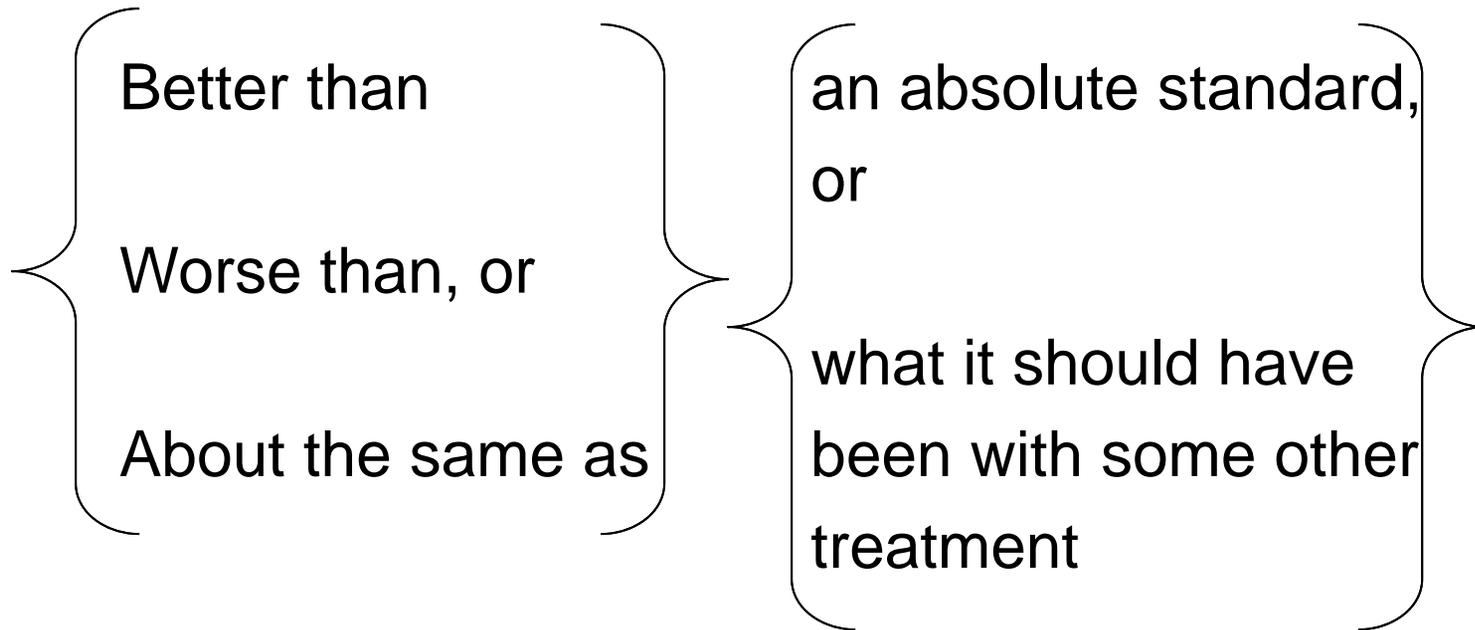
- Factors leading to efficacy trials
 - “Knowledge is good”
 - As pilot studies before prevention studies
- Factors leading to effectiveness trials
 - Serious conditions
 - Patients generally want to get better
 - Short therapeutic window for treatment
 - Waiver of informed consent
 - Do not withhold 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



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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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Review: Statistical Hypotheses Testing

- According to Karl Popper (Austrian Philosopher):
- 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 $1-\alpha$	Type II error Prob β
We reject H_0	Type I error Prob α	No error Prob $1-\beta$

- 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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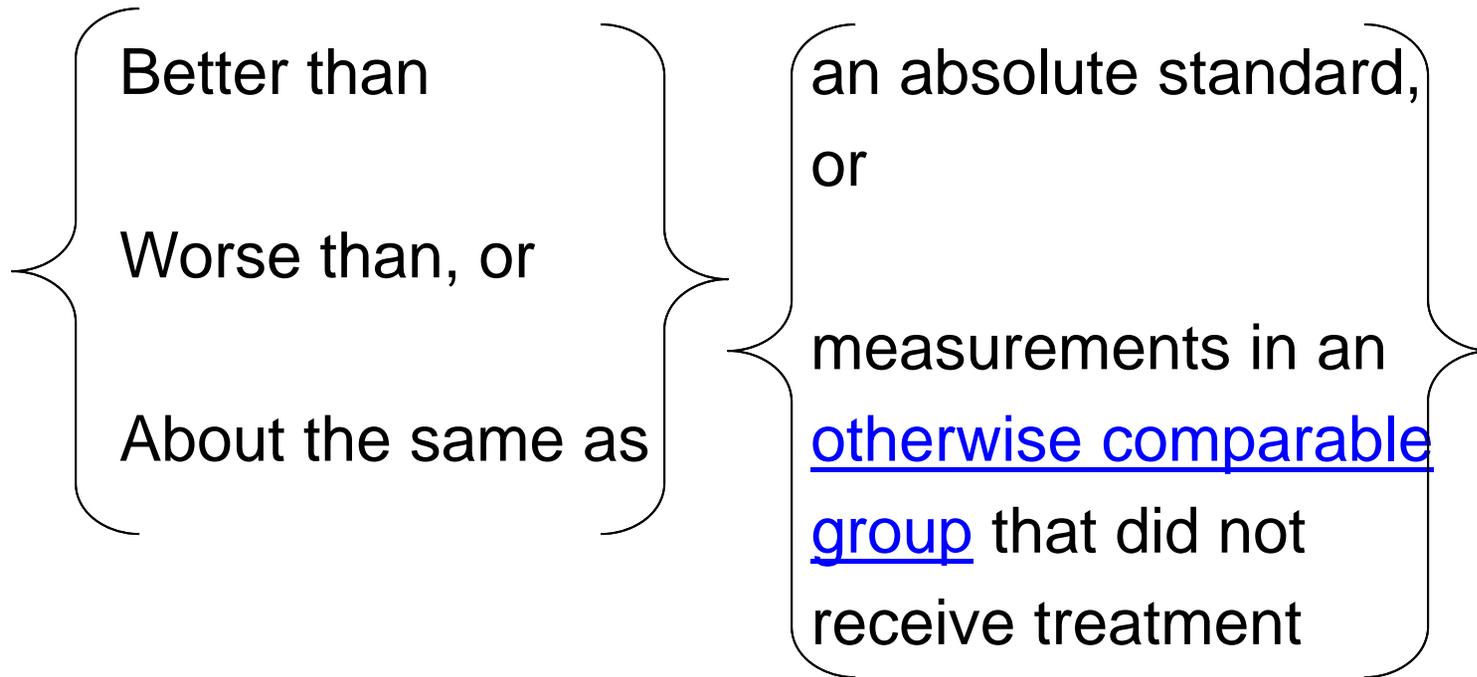
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First Statistical Refinement

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



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)

Sections

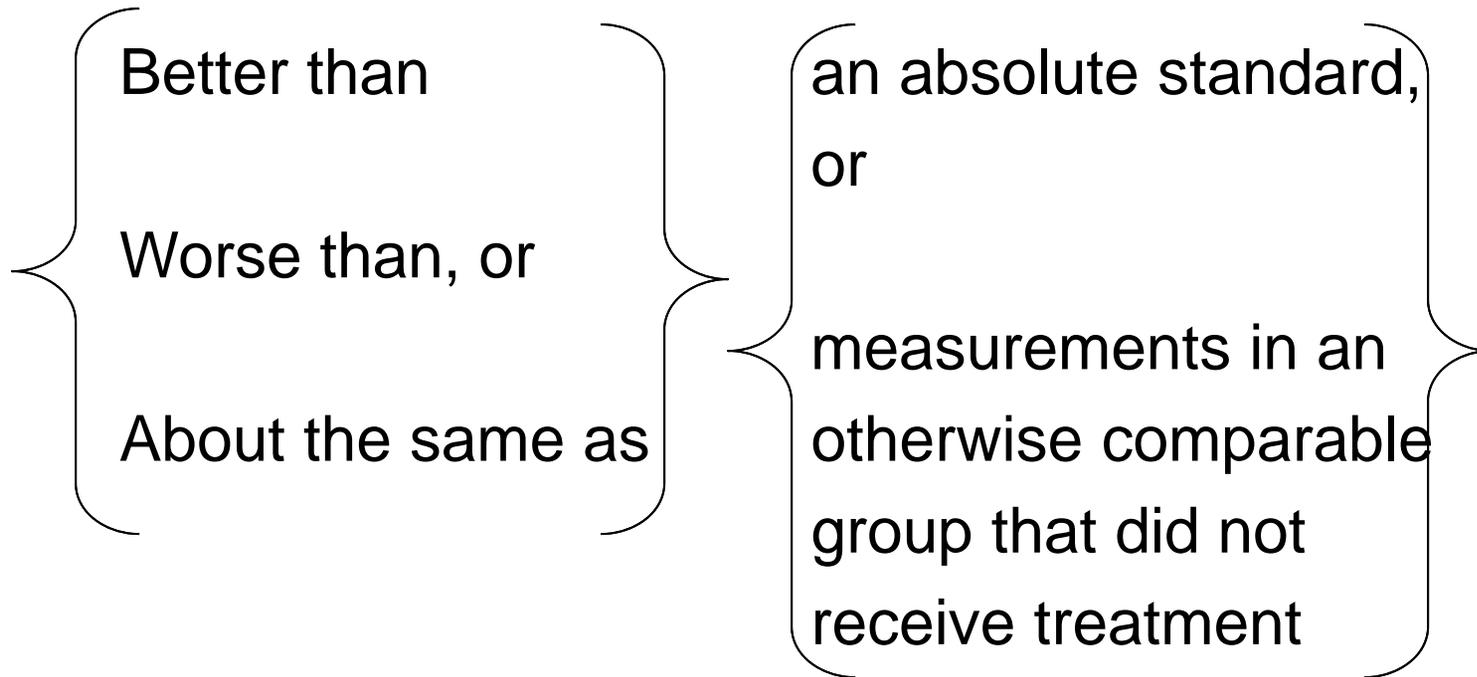
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Second Statistical Refinement

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



Ethics and Roles of Oversight Committees

- IRBs (REBs) Institutional Review Board
- PRC Protocol Review Committee
- DMC / DSMB Data Monitoring Committee
Data Safety Monitoring Board
- SMC Study Monitoring Committee

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Equipoise

- A state of equilibrium
- A state of balance
- Counterbalance
- Individual / collective / on average ??????

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IRB – Protection of Human Subjects

- Review and approval by the Institutional Review Board (IRB) or the Human Subjects Division (HSD) is required before starting research involving human subjects.
- Authority to determine:
 - activity IS or IS NOT research and/or involving human subjects, or
 - that research qualifies for exemption
 - approve
 - conditionally Approve
 - require Modifications
 - defer
 - disapprove
 - terminate or suspend some or all parts of a study

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PRC – Protocol Review Committee

- Typically, established for network studies otherwise not peer reviewed
- tasked with assessing the scientific and design merit of each protocol including:
 - Importance of the question to be addressed
 - Merit of experimental design, including appropriate controls
 - Availability of adequate resources
 - Adequacy of patient population and number of patients, including appropriate representation of minorities and women

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PRC – Protocol Review Committee

- Appropriate recruitment strategies
- Adequacy of proposed plans for data acquisition, transfer, management and analysis
- Adequacy of quality control of data collection and monitoring and overall coordination of protocol management
- Description of appropriate plans to train center personnel to accomplish proposed research goals

Once protocols are finalized through the PRC process, DSMB members may still subsequently vote for approving the protocol but their responsibilities are for data quality and safety assurance.

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DMC / DSMB

- To protect the interests of the study participants
- To preserve trial integrity and credibility in a manner that will enable the clinical trial
- To provide timely and reliable insights to the broader clinical community
- This requires
 - Judgement
 - ... well informed
 - ... independent
 - ... scientifically objective
- Motivates fundamental principles for membership and function

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DMC / DSMB

- Multidisciplinary representation
 - Clinical trialist
 - (Bio)statistician
 - Ethics
 - Specific area(s) of research in question
- Freedom from apparent significant conflicts of interest... financial, professional, regulatory
- Sole Access to Interim results on relative efficacy & safety of interventions

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NHLBI policy regarding blinded data

- Note that as a general rule, the representative of the investigators is not permitted to receive blinded data or participate in discussions of blinded data that are collected during the investigation. This is particularly important if the representative is involved with seeing participants or is otherwise involved in a major way with running a clinic.

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DMC / DSMB – more specifics

- monitor the data from the clinical trial regularly, review and assess the safety and performance of its operations, safeguard the interests of study participants,
- And make recommendations with respect to:
 - Participant Safety
 - Efficacy of the study intervention
 - Benefit/risk ratio of procedures and participant burden
 - Selection, recruitment, and retention of participants
 - Adherence to protocol requirements

Sections

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DMC / DSMB – more specifics continued

- And make recommendations with respect to:
 - Data and Statistical Analysis plan
 - Adequacy of measured and collected data
 - Possible amendments to the study protocol and consent forms
 - Performance of individual centers and core labs
 - Impact of proposed ancillary studies and sub-studies on participant burden and overall achievement of the main study goals
- Open and closed (and closed closed) sessions
- Summary of deliberations are reported to IRBs

- ⇒ Module 5 (tomorrow)

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Relative Responsibilities/Relationships

- Sponsors, Investigators, Care Givers
 - Decision making responsibilities for design, conduct, & analysis of the trial
 - Primary patient care responsibilities
- IRBs and Regulatory Authorities
 - Approval of Ethics/Science of the Trial Design
 - Real time Monitoring of Safety (SAEs)
- Data Monitoring Committees
 - Sole access during conduct of the clinical trial to: aggregated efficacy/safety data across the trial unblinded by treatment group

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Study Monitoring Committee

- **Internally** reviewing the conduct of studies with respect to
 - quality assurance of protocol implementation and data collection
 - proposing standards for acceptable adherence to protocols and data collection/data entry
 - development of performance reports
 - regular review of the reports of study progress and (site) performance
 - interacting with sites necessary to develop plans for addressing any particular areas of concern.
 - reporting to investigators etc. on study progress, adherence to study protocols, and adherence to standards for data completeness, timeliness, and quality
 - Potentially advise on sites readiness for starting enrollment on RCTs

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Elements of a Clinical Protocol

1. Background
2. Objectives
3. Study Design
4. Materials and Methods
5. Assessment of Safety
6. Investigator Requirements
7. Human Subjects Concerns

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Sections

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Elements of a Clinical Protocol

1. Background

1.1 Introduction

1.2 Investigational treatment A

1.2.1 Description of treatment

1.2.2 Prior clinical experience

1.2.2.1 Safety profile

1.2.2.2 Evidence of effectiveness

1.3 Investigational treatment B

...

1.4 Combined therapy A & B

...

1.4.2.1 Safety profile

Subadditive, additive, supraadditive effects

1.4.2.1 Evidence of effectiveness

Subadditive, additive, supraadditive effects

Sections

- Intro
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Elements of a Clinical Protocol

2. Objectives

2.1 Primary Objectives

State in terms of

- targeted population
- treatments being compared
- the clinical measure of outcome
- summary measure of that outcome

2.2 Secondary Objectives

List of each secondary objective stated similar to above

Sections

- Intro
- Sci/Stats
- Phases
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Elements of a Clinical Protocol

3. Objectives

3.1 Description of the study

3.2 Rationale for the study design

3.3 Outcome measures

- Primary effectiveness outcome measure
- Secondary effectiveness outcome measure
- Safety outcome measures
- summary measure of that outcome

3.4 Safety Plan

3.5 Ethical Issues

3.6 Administrative Structure

3.7 Regulatory oversight

Sections

- Intro
- Sci/Stats
- Phases
- Ethics & Oversight
- Protocol
- Summary

Elements of a Clinical Protocol

4. Materials and Methods

4.1 Patients

4.1.1 Patient selection

4.1.2 Inclusion criteria

4.1.3 Exclusion criteria

4.2 Method of treatment assignment and blinding

4.3 Study Treatment(s)

4.4 Concomitant and excluded therapies

4.5 Study assessments

4.6 Patient withdrawal from study

4.7 Study termination

4.8 Statistical Methods

Sections

- Intro
- Sci/Stats
- Phases
- Ethics & Oversight
- Protocol
- Summary

Elements of a Clinical Protocol

4. Materials and Methods...

4.8 Statistical Methods

4.8.1 Timing of analyses

4.8.2 Monitoring of study conduct

4.8.3 Analysis populations

4.8.3.1 Safety population

4.8.3.2 Primary effectiveness population

4.8.3.3 Secondary effectiveness population

4.8.4 Assessing comparability of treatment arms

4.8.5 Efficacy Analyses

4.8.6 Safety Analysis

4.8.7 Pre-specified exploratory analyses

4.8.8 Determination of sample size

4.8.9 Safety monitoring plan

Sections

- Intro
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Elements of a Clinical Protocol

5. Assessment of safety

- Any further information on specific safety variables
- Definition of methods and timing for assessing adverse events, serious adverse events
- Reporting requirements for SAEs
- Data safety monitoring board

6. Investigator requirements

6.1 Study initiation

6.2 During conduct of the study

6.3 Study completion

7. Human Subjects Concerns

Sections

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Summary

- Devil is in the details..... !!!
- Have to think through all aspects of project development – taylorred designs

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