Society for Clinical Trials 34th Annual Meeting

Workshop P1
Essentials of Randomized Clinical Trials

Sunday, May 19, 2013
8:00 AM - Noon
Fairfax B Room
Part I: Introduction

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Essentials of Randomized Clinical Trials
SCT Pre-Conference Workshop – Boston, MA
May 19, 2013

Introduction to Randomized Clinical Trials
Outline I

• Historical perspective
• Rationale for randomized clinical trials
  – Rationale for randomization
  – The equipoise issue
  – To blind or not to blind?
• Key issues in the design of a RCT:
  – What is the study question? Defining hypothesis, objectives and end-points
  – Defining selection criteria: generalizability vs. homogeneity
  – Selecting the control group: the placebo vs. “usual care” issue
Introduction to Randomized Clinical Trials

Outline II

• The different phases of a RCT
• Basic RCT Designs
  – Parallel, cross-over, factorial and cluster designs
  – Large Simple Trials
  – Comparative Effectiveness trials
  – Superiority, Equivalence and Non-Inferiority trials
• Key elements of a RCT Protocol
• Some ethical considerations
  – Informed Consent Process
  – Patient safety issues

Historical perspective

I raised myself very early to visit them when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses.

Ambroise Paré (1510 – 1590)

Historical perspective

Lind’s Scurvy Study

Nb of Patients: 12

Test Treatments:
- Cyder, 1qt/day
- Elixir vitriol, 25 gutts, 3 times/day
- Vinegar, 2 tsp, 3 times/day
- Bigness of nutmeg 3 times/day
- Orange (2); lemon (1)/day

Control Treatment
- Sea-water, ½ pt/day

Follow-up: 6 days

Outcome: fit for duty

Lind’s Treaty on Scurvy, 1753
Historical perspective
Key Dates in the History of RCT

• 1747 Lind’s Scurvy experiment
• 1800 Waterhouse’s smallpox experiments
• 1863 Gull’s use of Placebo Treatment
• 1923 Fisher’s 1st application of randomization
• 1931 1st use of randomization (and blindness) in a clinical trial
• 1946 Nuremberg Code for Human Experimentation
• 1962 Hill AB Statistical Methods of Clinical and Preventive Medicine
• 1979 Society for Clinical Trials
• 2006 Clinical and Translational Science Awards (CTSAs) program
• 2009: The Recovery Act (ARRA) provides $1.1 billion for Comparative Effectiveness Research.

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Randomized Clinical Trials
Some Terminology

• Clinical Trial:
  – An experiment testing medical (e.g. drug, surgical procedure, device or diagnostic test) treatments on human subjects
    • Experiment: a series of observations made under conditions controlled by the scientist
    • Prospective (≠ case-control study)
    • Comparative (≠ cohort study)
    • Involves human subjects
  – A research activity that involves administration of a “test treatment” to some “experimental unit” in order to evaluate that treatment
Randomized Clinical Trials
Some More Terminology

• Randomization: the process of assigning patients to treatment using a random process (such as a table of random numbers)

• Randomized controlled clinical trial (or randomized clinical trial—RCT):
  – Clinical trial with at least one control treatment and one test treatment
  – In which the treatment administered are selected by a random process

Randomized Clinical Trials
Why Randomize?

“The goal of randomization is to produce comparable groups in terms of general participant characteristics, such as age or gender, and other key factors that affect the probable course the disease would take. In this way, the two groups are as similar as possible at the start of the study. At the end of the study, if one group has a better outcome than the other, the investigators will be able to conclude with some confidence that one intervention is better than the other.”

Friedman et al. Fundamental of Clinical Trials, Mosby Press

Randomized Clinical Trials
Why Randomize?

• To find out which (if any) of two or more interventions is more effective
• Produce comparable groups
  – Protect against both known and unknown/unmeasured confounders (prognostic factors)
  – Eliminate treatment selection bias
• Best to establish causality
• Can define “Time zero”
Randomized Clinical Trials

Why Randomize?

- Necessary to detect small but clinically important treatment differences
- Protect against possible time trends in:
  - Patient population and disease characteristics
  - Diagnostic methods and supportive care
- Provides a valid basis for statistical tests of significance

Randomized Clinical Trials

Why Randomize: The Hormone Replacement Therapy Story


METHODS. We followed 48,470 postmenopausal women, 30 to 63 years old... during up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

RESULTS. After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80).

CONCLUSIONS. Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke.

ESTROGEN FOREVER?

The prevailing medical view is that most should stay on estrogen for the long haul... At the turn of the century, women died soon after their ovaries quit.” Now they live to face heart disease, osteoporosis, increased fractures... problems that may be prevented in part by taking estrogen...

There may be other risks and other advantages of HRT, but what doctors know is limited by the type of research that has been done. Instead of setting up a group of women on HRT and a carefully matched control group that does not take hormones, studies like the Nurses trial simply look at populations of women who made their own choice whether to take estrogen. “the problem with this... is that women who take hormones go to doctors more, eat well, exercise and are in better health generally than women who don’t take hormones.” Thus it is hard to tell whether their lower rates of heart disease or colon cancer or fractures reflect HRT or these other healthy habits.

June 26, 1995
Randomized Clinical Trials
Why Randomize: The Hormone Replacement Therapy Story

A large, federally funded clinical trial, part of a group of studies called the Women’s Health Initiative (WHI), has definitively shown for the first time that the hormones in question—estrogen and progesterin—are not the age-defying wonder drugs everyone thought they were. As if that weren’t bad enough, the results, made public last week, proved that taking these hormones together for more than a few years actually increases a woman’s risk of developing potentially deadly cardiovascular problems and invasive breast cancer, among other things.

July 22, 2002

Is there equipoise?

- **Definition:** A state of genuine uncertainty on the part of the clinical investigators regarding the comparative therapeutic merits of each arm of the trial
- Trial options must be consistent with **standard of care:** if state of genuine uncertainty exists randomization is an acceptable option

Importance of the informed consent process

- Accept risk of new treatment
- Accept concept of randomization
- Informed about alternative treatment options
Randomized Clinical Trials

When Randomize?

- Finding “window of opportunity”
  - Too early
    - Not enough “preliminary” evidence: biological plausibility, epidemiologic studies
    - Intervention not “mature” enough (e.g. surgical technique)
  - Too late: intervention already established in clinical practice
- Changing Clinical Practice Guidelines

Randomized Clinical Trials

To Blind or not to Blind?

- Definition: concealment (masking) to the patient (single blind), investigator (double) and the monitors (triple) of the identity of the intervention.
  (Opposite = unblinded or open trial)
- Goal: avoid bias (systematic error = anything that does not occur by chance!)
  *The more subjective the intervention, the more important the blinding!*
  Bias can occur at any stage of the study: patient assignment, data collection, event ascertainment...

Randomized Clinical Trials

To Blind or not to Blind?

- Unblinded trial
  - May be the only option: strategies of treatment (drug vs. surgery) behavioral interventions...
  - “True” blinding may be hard: expected biological effect of intervention
  - Easier to carry out and less expensive but...
    *Risk of bias generally outweigh benefits!*
- Alternative to blinding intervention (if not possible): blind outcome assessment
Randomized Clinical Trials
What is Randomization?

From Furberg BD and Furberg CD. Evaluating Clinical Research. Springer Ed.

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Elements of a RCT
What is the Study Question (Who-What-When)?

• Primary question tests the hypothesis
• Hypothesis must include:
  – Population studied
  – Primary outcome of interest
  – Intervention studied
  – Period of observation
• Objective: phrase the research question in concise, quantitative terms
Elements of a RCT

Primary and Secondary Objectives

- Primary objective needs to be defined (determine sample size)
- Secondary objective needs to be:
  - Defined a priori (avoid post hoc "fishing expedition")
  - Chosen parsimoniously (avoid false positive)
- Primary vs. secondary:
  - Question of greatest interest/relevance
  - Consider feasibility (e.g. mortality vs. morbidity)

The Endpoints

- Quantitative measurement required by the objectives (= outcome, response variable)
- Event/condition the trial is designed to ameliorate, delay, prevent...
- Primary endpoint: need to be clearly and rigorously defined (what is survival?)
- Endpoints defined by type of measurement used:
  - Discrete, dichotomous (dead or alive?), count, time to event
  - Continuous (BP change), ordered (toxicity)

The Endpoints: what makes a good Primary Endpoint?

- Must answer the primary question (Co-primary?)
- Frequency of occurrence must be known in control (determine sample size)
- Must be able to estimate treatment effect: clinical relevance (minimum desired effect to change practice?)
- Must be assessed/evaluable in all participants
- Can be measured accurately/reliably/objectively
  - Blinded randomization
  - Blinded assessment (soft end point?)
- All patients must be evaluated (no post randomization exclusion/no lost to follow up)
Elements of a RCT

Composite Endpoints

• Considered to have occurred if any one of several different outcomes are observed (mortality, myocardial infarction and stroke)
  • ↑Event rate (↑power/↓sample size)
  • ↓Study duration
  • Overall “index” (risk/benefit)
  • Need to account for:
    • Correlation (causal pathway?)
    • Noise?
    • Missing data
    • Adjudication?

Elements of a RCT

Surrogate Endpoints

• “A test, measurement, score, or some other similar variable that is used in place of a clinical event in the design of a trial, or in summarizing results from it.”
  • Believed to be correlated with clinical event
  • Perceived utility in yielding detectable treatment difference

Elements of a RCT

Surrogate Endpoints Criteria

• Strong statistical association with clinical endpoint.
• Change in surrogate strongly correlated with change in clinical endpoint (but: correlation ≠ causality)
• Surrogate is in the biological pathway of the disease (but there may be > 1 pathway!)
• Short latency (↑surrogate followed by rapid onset of disease)
• Responsive to treatment (effect on surrogate may not equal effect on disease)
### Elements of a RCT

**Surrogate Endpoints**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Smaller sample size</td>
<td>• Not well correlated to ideal endpoint</td>
</tr>
<tr>
<td>• Endpoint earlier than ideal endpoint</td>
<td>• Mechanism of action unclear</td>
</tr>
<tr>
<td>• Easier</td>
<td>• Less acceptable</td>
</tr>
<tr>
<td>• Less costly</td>
<td>• Less clinical relevance</td>
</tr>
<tr>
<td></td>
<td>NO SURROGATE for Safety</td>
</tr>
</tbody>
</table>

### Elements of a RCT

**Surrogate Endpoints: Examples**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Definitive Endpoint</th>
<th>Surrogate Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>MI</td>
<td>Cholesterol level</td>
</tr>
<tr>
<td></td>
<td>CHD</td>
<td>Carotid IMT</td>
</tr>
<tr>
<td></td>
<td>Heart Failure</td>
<td>BNP</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Cancer</td>
<td>Mortality</td>
<td>Tumor size reduction</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>Overall Survival</td>
<td>PSA decline</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>AIDS/Death</td>
<td>CD4+ count</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Vision Loss</td>
<td>Intraocular pressure</td>
</tr>
</tbody>
</table>

### Elements of a RCT

**What is the Study Question?**

> = IS ANY EASY TO FIND THE REASON, THEN YOU DON'T KNOW WHAT YOU'RE LOOKING FOR.

From Furberg BD and Furberg CD. Evaluating Clinical Research. Springer Ed.
Elements of a RCT
Defining the Study Population

• Subset of population with disease/condition of interest
• Patients enrolled = subset of study population defined by
  the eligibility criteria
• Inclusion criteria: Define “at risk” population
  − Less inclusive (= more homogeneous population): potential for
    benefit increase
    • but need to understand mechanism of action of intervention
    • Cannot generalize to other “subgroups”
  − More inclusive (= more heterogeneous population):
    • Increase generalizability
    • But may dilute effect of intervention (increase sample size)
  − Select group more likely to benefit from intervention
    • Higher risk: increase number of events, decrease sample size
    • But: are results applicable to lower risk?

• Exclusion criteria:
  − Insure patient safety (risk/benefit in specific subgroups)
  − Assess competitive risk
  − Assess likelihood of adherence to protocol and intervention

Eligibility criteria will be defined by goal of trial:
  efficacy vs. effectiveness trial?

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Homogeneity
• Divergent subgroup of patients (i.e., “atypical” patients) can distort
  findings for the majority
• Restriction of population reduces “noise” and allows study to be done
  in a smaller sample size
  ⇒ Restrict population to homogenous group

Generalizability
• At the end of the study, it will be important to apply findings to the
  broad population of patients with the disease
• It is questionable to generalize the findings to those excluded from
  the study
  ⇒ Have broad inclusion criteria “welcoming” all
### Elements of a RCT

**Defining the Study Population: Efficacy vs. Effectiveness trial**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Efficacy Trial</th>
<th>Effectiveness Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal</td>
<td>Test biological question</td>
<td>Assess &quot;real life&quot; effect of intervention</td>
</tr>
<tr>
<td>No participants</td>
<td>&lt; 1,000</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>Cohort</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Data collection</td>
<td>Extensive</td>
<td>Limited</td>
</tr>
<tr>
<td>Focus of inference</td>
<td>Internal validity</td>
<td>Generalizability</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Strict</td>
<td>Broad</td>
</tr>
</tbody>
</table>


### Elements of a RCT

**Choosing an Effectiveness Design**

- **Define the question:** What is the purpose of the trial?
  - Does the intervention work when applied in usual practice?
- **Define the setting:** under which conditions will the trial results be applicable?
  - Ideal setting vs. normal practice?
- **How are participants selected?**
  - Eligibility criteria mostly defined by the condition of interest
- **Outcomes of interest?**
  - Direct relevance to practice
  - Will influence clinical decisions and/ or health policy decisions

### Randomized Clinical Trials

**Nature of “Intervention”**

- Drug (or drug regimen)
- Surgical procedure
- Medical device
- Therapeutic modality (radiation, biologic therapy, etc)
- Diet
- Behavioral intervention (education)
- Clinical approach to diagnosis, treatment, symptom management, palliative care, etc. (e.g. strategy)

The common denominator: there is a choice between two alternative approaches; uncertain which is preferable (e.g. equipoise)
Randomized Clinical Trials
Selecting the Control Group

- Four different types:
  - Placebo
  - No Treatment
  - Different doses or regimens of the treatment
  - Different active treatment (including usual care)

- Control group will be classified based on:
  - Type of treatment used
  - Method of assignment in control group
  - May be more than one control!

Randomized Clinical Trials
Selecting the Control Group: The Placebo Issue

- Definitions
  1. Clinical: “A substance having no pharmacological effect but given merely to satisfy a patient who supposes it to be a medicine”
     Goal: to distinguish pharmacological effects from the effects of suggestion
  2. Research: “A substance having no pharmacological effect but administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation.”
     Goal: to obtain an unbiased assessment of the result of an experiment

Randomized Clinical Trials
Placebo Control: Scientific Justification

- Minimize subject and investigator bias (when used with randomization and blinding)
- Maximize likelihood of establishing efficacy: encourage optimal conduct of the trial: decrease “incentive” for poor trial conduct (drop-outs, cross-overs, etc)
- Enable distinction between adverse effects of drug/intervention and disease
- Allow for measurement of true effect size: account for the “placebo effect”
Randomized Clinical Trials

The Active Control

- **Positive control**: new therapy compared to known active therapy (randomized, can be blinded)
  - Goal: effectiveness or non-inferiority
  - Based on assumption that previous treatment shown to be effective! (external validation needed)
- **Challenges**:
  - Effect size and safety assessment more difficult
  - Larger sample size
  - Many possible bias: non adherence, concomitant therapies, randomization of inappropriate patients

Randomized Clinical Trials

Usual Medical Care as Control Group

- State of equipoise: is there a “standard of care”?
- Potential advantages:
  - Increase relevance
  - Increase external validity
  - Increase practicality
- Interpretation of evidence:
  - Is usual care validated by research? Is there a consensus on what is “usual care”?
  - Adherence to guidelines/evidence-based care?

Introduction to Randomized Clinical Trials

Outline II

- **The different phases of a RCT**
- **Basic RCT Designs**
  - Parallel, factorial, cluster and cross-over designs
  - Large Simple Trials
  - Comparative effectiveness trials
  - Superiority, Equivalence and Non-Inferiority trials
- **Key elements of a RCT Protocol**
- **Some ethical considerations**
  - Informed Consent Process
  - Patient safety issues
The Different Clinical Trial Phases

Phase I
- First in humans
- Small, uncontrolled
- Healthy volunteers/failed conventional therapy
- Dose-escalation protocols
- Tolerability/toxicity study: Maximum Tolerated Dose (MTD)
- Dose-response models

Phase II
- Test biologic activity/effect
- Estimate rates of adverse events
- Performed in patients with disease/condition of interest
- With or without comparison group
- Strict eligibility criteria

Phase IIa
- Small scale feasibility studies
- Intermediate endpoints

Phase IIb
- Comparative, randomized
- Intermediate endpoints
### The Different Clinical Trial Phases
#### Phase III
- Determine the effectiveness (overall benefit/risk-cost assessment) of new therapies relative to standard therapy
- Large sample size
- Multicenter
- Superiority, equality, equivalence or non inferiority

### The Different Clinical Trial Phases
#### Descriptive Terminology
- **Early phase/development**:
  - Translational trials (e.g. from lab to clinic)
  - Mechanistic trials
    - Treatment mechanism
    - Dose finding/dose ranging studies
- **Middle development**
  - Safety and activity: probability of benefit?
  - May be randomized (remove selection bias, temporal trends)
  - Intermediate/surrogate outcomes
  - Small sample size

### The Different Clinical Trial Phases
#### Descriptive Terminology
- **Late development**
  - Comparative studies
    - Treatment efficacy (IIb/III)
    - "Pivotal" trials
    - Large scale/simple trials
    - Superiority or equivalence
  - Late Safety Studies
    - Estimate of incidence of rare serious side effects
    - Very large sample size
    - Causality inference?
The Different Clinical Trial Phases

**Phase IV**

- Long term surveillance studies (“post marketing”) for safety
- New dosing regimens/indications
- Look for rare side effects
- Often non randomized

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**The Different Clinical Trial Phases**

**Summary**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Features</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>First administration of new therapy in humans</td>
<td>Exploratory: determine if further investigation is possible</td>
</tr>
<tr>
<td>II</td>
<td>Early trials in patients</td>
<td>Dose-response relationship PK/PD Studies</td>
</tr>
<tr>
<td>III</td>
<td>Large scale comparative trials</td>
<td>Clinical efficacy/effectiveness Regulatory approval</td>
</tr>
<tr>
<td>IV</td>
<td>Monitoring in clinical practice</td>
<td>Post marketing surveillance Rare adverse events</td>
</tr>
</tbody>
</table>

From: Antman EM, Califf RM. Clinical Trials and meta-analysis Cardiovascular therapeutics. WB Saunders 1996

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Basic RCT Designs
Parallel Design

FREEDOM Design
Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease

Eligibility: DM patients with MV-CAD eligible for stent or surgery
Exclude: Patients with acute STEMI, cardiogenic shock

Randomized 1:1

- MV-stenting With Drug-eluting stents And abciximab
- CABG With or without CPB


Basic RCT Designs
Cross Over Design

- Participant = own control
- Randomize: order of treatment for each patient (e.g. AB vs. BA)
- Advantages
  - Reduce variability ➔ Reduce Sample Size
  - Detect difference in response in individual patient
- Disadvantages
  - Order of treatment should not matter
  - No carry over of effect ➔ test for interaction

Basic RCT Designs
Cross Over Design
Standard two-sequence, two-period crossover design

Remedia Ed.
### Basic RCT Designs
#### Factorial Design

#### Intervention A

<table>
<thead>
<tr>
<th>Active</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Active</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>a= Active A + Active B</td>
</tr>
<tr>
<td>b= Control A + Active B</td>
</tr>
<tr>
<td>c= Active A + Control B</td>
</tr>
<tr>
<td>d= Control A + Control B</td>
</tr>
</tbody>
</table>

#### Analysis of a 2 x 2 factorial RCT

- Effect of A: ac vs. bd *
- Effect of B: ab vs. cd *

*If no treatment interaction

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**BP**

<table>
<thead>
<tr>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>1178</td>
<td>1193</td>
</tr>
</tbody>
</table>

**Lipid**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>5128*</td>
<td>5123*</td>
</tr>
</tbody>
</table>

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### Basic RCT Designs
#### Factorial Design

#### Advantages:
- Two trials for (almost) the price of one
- Design is best if: two intervention have different mechanisms of actions or different outcomes (e.g. cancer for A and CV disease for B)

#### Disadvantages:
- Need to test for possibility of interaction (e.g. A differs based on the presence or absence of B)
- Test for interaction not very powerful
- Need to consider gain in cost vs. increased complexity, recruitment and adherence issues and potential for adverse events

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Basic RCT Designs
Cluster Design

- Cluster design = group randomization
- Group = schools, clinics, villages...
- Sample size: based on number of groups (not individuals)
  - Need to be adjusted by factor \( N_m \) (where \( N \) = number of cluster each of size \( m \))
  - Need to take into account within-cluster correlation of response (correlation = loss of efficiency)
- Analysis:
  - Cannot use classic statistical methods (correlation)
  - Random effect model
  - Use sensitivity analyses

Basic RCT Designs
Cluster Design: The Public Access Defibrillation (PAD) Trial

Resuscitation. 2003 Feb;56(2):135-47

Basic RCT Designs
Large Simple Trials

- Provide a more reliable estimate of the effect of intervention
- Needed to uncover smaller treatment effects
  Those are important in common conditions
- Increase generalizability
  But limit data collection/subgroups and secondary analyses
- Decrease cost by simplifying design and management
  But need strong randomization procedures and reliable outcomes assessment
Basic RCT Designs

Large Simple Trials: The ISIS 3 trial

ISIS-3: a randomised comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction

**Comparative Effectiveness Trials**

Comparative effectiveness is a type of health care research that compares the results of one approach for managing a disease to the results of other approaches.

Usually compares two or more types of treatment, such as different classes of drugs, for the same disease. Can compare types of surgery or other kinds of medical procedures and tests.

CER is designed to inform health care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options.
Basic RCT Designs
Comparative Effectiveness Trials

Superiority, Non Inferiority and Equivalence Trials

- **Superiority trial**
  - Is (new) intervention better than no (placebo) intervention or standard intervention?
  - Goal: Demonstrate a difference!

- **Non inferiority trial**
  - Is new intervention not worse than standard? (not less effective, but safer, cheaper, etc.)
  - Goal: Demonstrate that new intervention is not worse than the standard by a prespecified $\Delta$ (minimum clinically significant difference)

- **Equivalence trial**
  - Are the effects of the two interventions very similar?
  - Goal: Demonstrate that the two interventions are not different by more than the prespecified $\Delta$

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- **Key elements of a RCT Protocol**
- **Some ethical considerations**
  - Informed Consent Process
  - Patient safety issues
Key elements of a RCT Protocol
Study Design: Preliminary Considerations

- Demonstrate need for trial
- Establish study objectives
- Choose best approach to problem/question
  - Small vs. large?
  - Less is more!
- Objectives ≠ study goals
  - Objectives: statement about question to answer
  - Goals: what you need to achieve to answer the question

Key elements of a RCT Protocol
Study Design: Framing the Question

- Toxicity? Efficacy? Effectiveness?
- Feasibility
- Proof of concept
- Pilot study

Why? How? Importance?
Outcome

Key elements of a RCT Protocol
Study Design: Key Steps to Follow

1. Establish study objectives
2. Choose basic study design
3. Determine primary and secondary outcomes
4. Choose type of control
5. Determine need/feasibility of blinding
6. Choose randomization procedure
7. Sample size and power
8. Determine screening, baseline, treatment and follow-up periods
9. Choose patient population
10. Establish treatment modalities
Elements of a RCT
Protocol: Table of contents (I/IV)

• Abstract
• I. STUDY HYPOTHESIS
• II. INTRODUCTION AND BACKGROUND
• III. OBJECTIVES OF THE STUDY
  – A. Primary objective
  – B. Secondary objective
• IV. STUDY ENDPOINTS
  – A. Primary Endpoint
  – B. Secondary Endpoints
• V. STUDY DESIGN
• VI. PATIENT SELECTION
  – A. Inclusion criteria
  – B. Exclusion Criteria
• VII. INFORMED CONSENT PROCEDURE

Elements of a RCT
Protocol: Table of contents (II/IV)

• VIII. RANDOMIZATION PROCEDURE
• IX. ADMINISTRATION OF STUDY DRUG
• X. DATA MANAGEMENT, QUALITY ASSURANCE & MONITORING PROCEDURES
  – A. Data collection and management
  – B. Monitoring reports
    1. Executive Committee
    2. Steering Committee
    3. Data and Safety Monitoring Board
  – C. Quality Assurance
• XI. STATISTICAL ANALYSES
  – A. Primary endpoint
  – B. Sample size and power
  – C. Subgroup and secondary analyses
  – D. Interim analyses

Elements of a RCT
Protocol: Table of contents (III/IV)

• XII. STUDY ORGANIZATION
  – A. Sponsor
  – B. Steering Committee
  – C. Clinical Trial Center
  – D. Data and Safety Monitoring Board
• XIII. SUBSTUDIES AND ANCILLARY STUDIES
  – A. Introduction
  – B. Ancillary studies
  – C. Databank studies
  – D. Application review process
  – E. Data storage and analysis
Elements of a RCT
Protocol: Table of contents (IV/IV)

• XIV. PUBLICATION POLICY
  – A. Data analysis and release of results
  – B. Review process
  – C. Primary outcome papers, abstracts and presentations

• XV. CLOSEOUT PROCEDURES
  – A. Interim
  – B. Reporting of Study Results

• XVI. REFERENCES

Appendices
  - Mode Informed Consent
  - Conflict of Interest Policies

Introduction to Randomized Clinical Trials
Outline II

• The different phases of a RCT
• Basic RCT Designs
  – Parallel, cross-over, factorial and cluster designs
  – Large Simple Trials
  – Comparative Effectiveness Trials
  – Superiority, Equivalence and Non-Inferiority trials
• Key elements of a RCT Protocol
• Some ethical considerations
  – Informed Consent Process
  – Patient safety issues

Ethical Issues
Specific to Clinical Trials

• Special ethical concerns because treatment is determined by chance

• The arms of the clinical trial must be in clinical equipoise

• Principle of non maleficence, withholding proven treatment from control group

• Periodic analysis of interim data by independent Data and Safety Monitoring Board
Some Ethical Considerations
Informed Consent Process

- Purpose of the trial
- Nature of the trial
- Procedures of the trial
- Risks and potential benefits and alternatives to participating
- Procedures to maintain confidentiality
- Assurances and contact information

Some Ethical Considerations
Informed Consent Issues

- Withdrawal
  - Participant is free to withdraw at any time
- New findings
  - Obligation to tell participant of any significant new findings that may affect his/her willingness to continue
- Potential for coercion
- Undue inducement/Exploitation

Some Ethical Considerations
Health Information Portability and Accountability Act (HIPAA)

- Research subjects must sign an authorization form that describes the use and disclosure of their protected health information (PHI) for research purposes
- HIPAA authorization wording may be part of informed consent document or a separate form
- Subject must be given signed copy of form with HIPAA disclosure information
- http://privacyruleandresearch.nih.gov/
Some Ethical Considerations
Responsibilities of Individual Investigators

• Handling and reporting adverse events promptly, completely and accurately
• Taking personal responsibility for the veracity of all reports in which the investigator is mentioned
• Being objective and evenhanded when reporting results and problems to colleagues
• Maintaining scientific detachment and caution when reporting to the public
• Reporting malfeasance and misconduct (data fraud e.g. fabrication or falsification of data)

Some Ethical Considerations
Summary Principles of Ethical Clinical Trials

• Collaborative partnership
• Scientific value
• Scientific validity
• Fairness of subject selection
• Favorable risk – benefit
• Independent Review
• Informed consent
• Respect for enrolled subjects

Emanuel et al. JAMA 2000: 283:2701

Some Ethical Considerations
Where to Go for More Info

• Human Subjects Research Protection
  – http://www.hhs.gov/ohrp/
  – Training: http://phrp.nihtraining.com/user/login.php
• Registry of clinical Trials and Background:
  – http://clinicaltrials.gov/
• Regulations and Ethical Guidelines:
  http://ohsr.od.nih.gov/guidelines/index.html
  – 45 CFR 46 Protection Of Human Subjects
  – Guidelines for Conduct of Research Involving Human Subjects at NIH
  – The Belmont Report Ethical Principles and Guidelines for the Protection of Human Subjects of Research
  – Nuremberg Code Directives for Human Experimentation
  – World Medical Association Declaration Of Helsinki
• NIH bioethics Resources: http://bioethics.od.nih.gov/index.html
Randomized Clinical Trials

Some Key Points

• Important
  – in evaluating interventions for the prevention, diagnosis, and treatment of disease
  – Important to obtain unbiased comparisons of interventions

• Ethical
  – in the presence of uncertainty (equipoise)
  – present the best choice of therapeutic options to the patients

• Robust
  – large trials recommended to increase reliability

• Applicable to studies of efficacy and of effectiveness

• Can answer more than one question at a time
  (factorial trials and other designs)

• In some situations, can randomize entire groups
  (e.g., communities, medical practices)

Randomized Clinical Trials

Some Key References

• Fundamental of Clinical Trials. Lawrence M Friedman, Curt D Furberg, David L DeMets. Springer Verlag Editors


• Successful randomized trials. A Handbook for the 21th Century. Michael Domanski, Sonja McKinlay. Lippincott Williams & Wilkins


Randomized Clinical Trials

Why Randomize?

“Mind you, only one dollar out of one hundred is.”
Part II: Basic Statistical Concepts

Michele Melia, Sc.M.
Senior Statistician
Jaeb Center for Health Research
Tampa, FL
SCT Pre-Conference Workshop
Essentials of Randomized Clinical Trials

Outline
- Randomization
- Blinding (masking)
- Hypothesis testing
- Confidence intervals
- Sample size
- Intention to treat

What is randomization?
A process by which subjects are randomly assigned to a treatment in a clinical trial
- Neither the participant nor the investigator knows what treatment the participant will receive
Why is randomization used?

- Problems arising with treatment assignment in clinical practice:
  - Individuals with certain disease characteristics are generally more likely to receive certain treatments (confounding by indication)
  - Inability to characterize why individuals were assigned to a particular treatment, leading to non-homogeneous groups with different (and unquantifiable) underlying risk
  - Wide variation in outcomes relative to the magnitude of differences due to treatments; treatment differences easily obscured by bias

How does randomization work?

- Randomization does:
  - Reduce bias in assigning patients to treatments
  - Ensure valid statistical tests
  - Reduce unwanted variation resulting in improved power for statistical tests
- Randomization does not:
  - Guarantee equal distribution of prognostic factors among treatment groups
    - For large studies, the chance of imbalances is small
    - For small studies, the chance of imbalances is larger

When is randomization used?

<table>
<thead>
<tr>
<th>Phase</th>
<th>Rarely</th>
<th>Not generally necessary to achieve phase I goals of establishing toxicity/maximum tolerated dose/dose response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II</td>
<td>Sometimes</td>
<td>When comparison group is helpful in defining possible biologic and adverse effects, e.g. for highly subjective endpoints. When required by FDA.</td>
</tr>
<tr>
<td>Phase III</td>
<td>Almost always</td>
<td>&quot;Gold standard&quot; for reducing bias in assignment of patients to treatment and estimation of treatment effects</td>
</tr>
</tbody>
</table>

Other methods of (non-random) treatment allocation are also sometimes used in CTs:

- Single group with or without historical controls
- Non-random allocation of 2 or more groups
Non-random methods of treatment allocation

- Alternating treatments (1st patient gets A, 2nd gets B, 3rd gets A, etc.)
- Alternating assignment by date or day of week (patient gets A if enrolled on even date, B if odd date)
- Using patient initials to determine assignment
  A-K → treatment 1
  M-Z → treatment 2

Basic types of randomization

- Simple
- Block
- Stratified / stratified block

Simple Randomization

A sequence from a random number table or generator is used to assign sequential patients to a study treatment using a pre-defined rule. E.g. Even number → A and Odd number → B.

<table>
<thead>
<tr>
<th>Sequence from random number table</th>
<th>Treatment assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
</tr>
<tr>
<td>0</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>A</td>
</tr>
</tbody>
</table>
Simple Randomization

- **Advantages**
  - Simple
  - Each new assignment made without regard to previous assignments
- **Disadvantages**
  - No guarantee of equal or approximately equal sample size in each treatment group at any stage of the trial (including at the end)
    - Imbalance reduces statistical power
    - Estimates of treatment effect are not affected; only precision
  - No protection against long runs of one treatment

Block randomization

- Block size that is an integer multiple of the number of treatments is chosen (integer≥2)
- Equal numbers of patients are assigned to each treatment within a block
  - Numbers are proportional rather than equal in the case of unequal allocation
- Overcomes some disadvantages of simple randomization

Example: Block Randomization for 2 Treatments

- Possible block sizes are 4, 6, 8, etc.
- For block size of 4, there are 6 treatment-balanced permutations
  - ABAB, AABB, ABBA, BABA, BBAA, BAAB
- These may be chosen at random with replacement

<table>
<thead>
<tr>
<th>Sequence from random number table</th>
<th>Treatment assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>AABB</td>
</tr>
<tr>
<td>1</td>
<td>ABAB</td>
</tr>
<tr>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>BAAB</td>
</tr>
</tbody>
</table>
Block randomization – cont’d

- Large block size does not protect as well against long runs as small block size
- Small block size makes it easier to guess next treatment
- To make it harder to guess the next allocation when small block sizes are used, block size can be chosen at random from a pre-defined list of block sizes, e.g. 4, 6, 8
- Simple and block randomization do not guarantee balance of treatment groups on important prognostic factors

Stratification

- With stratification, a separate, independent randomization sequence is used for each prognostic group (or strata)
- To guarantee treatment balance within strata at all stages of the trial, stratification is combined with blocking
  - Use of simple randomization within strata will not guarantee treatment balance within strata
  - Consequence of imbalance on a prognostic factor is bias in the estimated treatment effect (unless analysis is adjusted for the factor)

Example – Blocked and stratified randomization

- A randomized trial comparing near versus distance activities while patching for amblyopia (lazy eye) in children 3 to <7 years old
  - Pilot study data suggested that near activities might be less effective in moderate as compared to severe amblyopia
  - Randomization was stratified by amblyopia severity; random block sizes of 4 and 6 also were used
Example - continued

- If even, use block size=4; otherwise block size=6
- Use a random shuffle of the block elements

### Moderate amblyopia

<table>
<thead>
<tr>
<th>Random No.</th>
<th>Block size</th>
<th>Random sequence</th>
<th>Treatment assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>6</td>
<td>7 9 2 1 6 6</td>
<td>0 1 2 6 7 9</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>8 5 1 3 5 7</td>
<td>0 1 3 5 7 8</td>
</tr>
</tbody>
</table>

### Severe amblyopia

<table>
<thead>
<tr>
<th>Random No.</th>
<th>Block size</th>
<th>Random sequence</th>
<th>Treatment assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4</td>
<td>6 3 1 2 A A B B</td>
<td>1 2 3 6 B B A A</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0 9 5 7 3 4 A A B B</td>
<td>0 3 3 5 7 9 A B A A</td>
</tr>
</tbody>
</table>

Stratified randomization – cont’d

- Chance of imbalance on prognostic factors is small with large sample size
  - Stratification is more important when sample size is small
- As number of stratification factors increases, the number of strata grows very fast, and efficacy with respect to achieving desired balance may decrease
  - Think of case where # strata = sample size
- Be judicious in choice of stratification factors

Stratified randomization – cont’d

- If many prognostic factors must be controlled:
  - Consider combining them into an overall index and stratifying on index
  - Consider minimization
- When analyzing data, it is important to account for stratification
  - If ignored, variability due to the stratification factor is included with error variance
  - If included, variability due to stratification factor is removed from error term, increasing precision
Unequal Treatment Allocation

- With unequal treatment allocation, the study is designed to have unequal numbers of patients on the treatments
- Treatment groups of equal size are desirable from a statistical perspective for making treatment group comparisons
  - Maximizes power for a given sample size
  - However, loss of power may not be too severe as long as imbalance is not severe, e.g. 2:2:1

Unequal Treatment Allocation – cont’d

- Some reasons to consider unequal allocation:
  - More information is needed on effect of a new treatment (e.g. adverse effects, effect of dose)
  - Patients may be unwilling to be randomized if probability of assignment to control or placebo is high
  - To reduce study cost when one treatment is a lot more expensive than the other
- Principles of basic randomization regarding use of blocking and stratification still apply

Cluster Randomization

- Clusters of patients are randomized rather than the individual patients
  - Example: In trial of vitamin A supplementation for prevention of mortality in preschool children in Nepal, administrative wards were randomized to supplement or placebo (West KP, Lancet 1991)
- Cluster randomization reduces statistical efficiency (i.e., it requires more patients)
- Usually used when it is not feasible to randomize individual patients, or treatment contamination is a concern
Crossover Randomization

- Each patient is randomized to a sequence of treatments
  - Example: Effect of low-fat versus high-fat meal on AUC180 in type I diabetes (AUC180 = area under the 180 mg/dl line of the blood glucose over time curve)
  - Patients randomized to low-fat then high-fat meal or vice versa
- Crossover randomization increases statistical efficiency (reduces sample size); each patient acts as his/her own comparator providing control for all patient-level factors
- Crossover randomization is suitable only in certain circumstances: chronic disease with stable course; treatments with rapid and short-acting effects

Adaptive Allocation (aka Adaptive Randomization)

- Information on previously enrolled patients is used to modify (or adapt) the allocation ratio, i.e. the probability of being assigned to each treatment
- Information used typically is one of:
  - Treatment
  - Covariates (prognostic factors)
  - Response (outcome)
- Other terms:
  - Biased-coin design
  - Urn design
  - Play-the-winner design

Summary

- Randomization is the primary means for controlling bias in allocation of patients to treatment in a clinical trial
- Randomization helps to generate comparable groups of patients on each treatment
- Randomization enables valid statistical tests for the evaluation of the treatments
- Judicious use of stratification with appropriate analysis can improve statistical power
Blinding (Masking)

- What is it?
  - Concealment of the treatment assignment
- Who can/should be masked?
  - Trial dependent
  - Patient, treating clinician, possibly other clinical personnel, outcome assessor
- Purpose? Avoid bias in:
  - Delivery of treatment / other care
  - Compliance
  - Outcome assessment …
- The more subjective the outcome, the more important it is to mask

Examples of Masking in Practice

- Collaborative Ocular Melanoma Study (COMS) trial for medium-sized tumors
  - Eyes with melanoma randomized to enucleation (removal of the eye) or radiation (eye is retained)
  - Impossible to mask patient or clinical staff
  - Primary outcome: all-cause mortality (objective)
  - Secondary outcome: melanoma-related mortality (subjective; cause of death assignment made by masked mortality coding committee)

- Patching versus Atropine for Amblyopia (lazy eye)
  - Patients randomized to patching or atropine drops in good eye
  - Not possible to mask patient or treating clinician
  - Primary outcome: visual acuity at 17 weeks
  - Visual acuity examiner is masked (by patching good eye)

- Levodopa for Residual Amblyopia (lazy eye that did not fully respond to conventional treatment)
  - Patients randomized to levodopa or placebo (2:1)
  - All patients patch good eye 2 hours/day
  - Primary outcome: visual acuity at 18 weeks
  - Patients and clinical personnel are masked by using placebo
Hypothesis Testing

A primary objective of most clinical trials is to demonstrate the effectiveness and safety of a treatment under investigation.

The purpose of such trials is to:

- Find out which (if any) of the treatments are more effective
- Convince others of the results

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Hypothesis Testing

Hypothesis testing involves:

- Collecting a sample and using the sample to estimate unknown population parameters.
- Comparing the sample estimate(s) to some hypothesized population value to see if the sample came from the specified population.

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Null and Alternative Hypotheses

Hypothesis: Statement about a population parameter

Null Hypothesis ($H_0$): A hypothesis of no difference or status quo; often what we would like to disprove

$H_0$: $\mu = 0$

Alternative Hypothesis ($H_A$): A statement which contradicts the null hypothesis

$H_A$: $\mu \neq 0$

The goal of hypothesis testing is to collect a sample and determine which hypothesis is 'more likely' to have generated the observed sample.

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Test Statistic

Test Statistic: A quantity computed from the data used to measure the plausibility of the alternative hypothesis relative to the null hypothesis.

Acceptance Region: The range of values for which $H_0$ is not rejected.

Rejection Region: The range of values for which $H_0$ is rejected.

The test statistic must fall into one of these regions.

Calculating the Test Statistic

Does performing near activities while patching for amblyopia result in more improvement in visual acuity (VA) among children age 3 to < 7 yrs as compared to distance activities?

- $H_0$: between group difference in mean change in VA = 0
- Test statistic: $t$-score =
  \[
  \frac{\text{sample mean} - \text{hypothesized population mean}}{\text{std(mean)}}
  \]
- Mean VA change difference (Near - Distance) = -0.03
  Std = 0.16
  $t$-score = (-0.03 - 0) / 0.16 = -0.19  df=391

Evaluating the statistical significance of the test statistic

The $t$-score falls in the rejection region, indicating statistical significance at the 0.05 level.
Rejecting the Null Hypothesis

- If the test statistic falls into the rejection region, the test is said to be statistically significant.
- If we don't reject $H_0$, we can't claim to 'accept $H_0$'.
  - Suppose one makes a statement 'all swans are white'.
  - To examine this statement, a sample of swans is drawn.
  - Two things can happen:
    a) All swans in the sample are white.
    b) At least one swan in the sample is not white.
  - The event (b) establishes the falsehood of statement.
  - However, the event (a) does not prove the statement!

Acknowledgment to Chris Coffey

Defining type I and II errors

<table>
<thead>
<tr>
<th>Study conclusion</th>
<th>Truth</th>
<th>Treatments not different ($\Delta = 0$)</th>
<th>Treatments differ ($\Delta \neq 0$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments not different ($\Delta = 0$)</td>
<td>True negative</td>
<td>False negative</td>
<td>Type II error ($\beta$)</td>
</tr>
<tr>
<td>Treatments differ ($\Delta \neq 0$)</td>
<td>False positive</td>
<td>True positive</td>
<td>Type I error ($\alpha$)</td>
</tr>
</tbody>
</table>

P-values

- Statistical tests quantify the probability of a type I error (false positive result).
  - $P(\text{observed data}^* | \text{null hypothesis is true}) = p$-value
- For example, an observed difference with $p \leq 0.01$ implies that the probability of obtaining a difference this extreme (or more so) by chance alone is less than or equal to 1%.
  - Example: you toss a coin 10 times and get 9 heads. What are the chances of 9 or more heads with a fair coin?
    - $P(\text{nine or more heads} | \text{true proportion}=0.5) = 0.0107$
    - Or data more extreme
Clinical Trial versus Jury Trial

Clinical Trial (statistical testing) | Jury Trial (criminal law)
---|---
• Assume the null hypothesis | • Presume innocent
• Goal: Detect a true difference (Reject the null hypothesis) | • Goal: Convict the guilty
• “Level of significance” | • “Beyond reasonable doubt”
• Requires evidence: Adequate sample size | • Requires evidence: Convincing testimony
• Mistake: False positive (Type I error) | • Mistake: Convict an innocent person

Acknowledgment to Susan Hilsenbeck and Sylvan Green

95% Confidence Interval

A 95% CI is generated by a statistical procedure that captures the population parameter (µ) in 95% of its applications.

Confidence Intervals

- Provides information about uncertainty in the estimate of the population parameter (Ex: Mean difference in VA) by including lower/upper bounds around the sample estimate
  • COMET2: 0.28 D (95% CI: 0.01 – 0.55 D)
- Express how certain (confident) we are that the procedure used to generate the interval includes the population parameter
  • Increasing length of confidence interval (90% → 95%) improves likelihood of capturing the population parameter
Relationship with Hypothesis Testing

What is the relationship between confidence intervals and hypothesis testing?

- Decision to reject/fail to reject the null hypothesis depends on whether the confidence interval includes value(s) consistent with the null hypothesis
  - If CI includes null hypothesis → Fail to reject
  - If CI excludes null hypothesis → Reject

Sample Size

- Sample size should be assessed as early as possible during the design phase
  - Do not want to waste time designing a study with a sample size that is not feasible

Basis of Sample Size Determination

- In all clinical trials, we are selecting a sample from a target population
- The possibility exists that the sample we select will not be representative of the outcome rate or treatment effect
- Goal is to select sample size to:
  - ensure high chances of getting the correct answer
  - AND
  - enroll as few subjects as possible
What information is needed?

- Basic trial design features:
  - Comparative type (equality, equivalence, non-inferiority)
  - Randomization design (parallel group, crossover, cluster)
- Number of treatment groups
- Primary outcome, outcome rate or variance in control group, analysis method for primary outcome
- Size of treatment effect to be detected
- Risk we are willing to take that study will “miss” a true treatment difference ($\beta$=type II error; $1-\beta$ is the study power)
- Risk we are willing to take that study will erroneously conclude treatments are different (α=type I error)

Effect of basic trial design elements on sample size

<table>
<thead>
<tr>
<th>Randomization Design</th>
<th>Relative Effect on Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel Group</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Crossover</td>
<td>Smaller</td>
</tr>
<tr>
<td>Cluster-randomized</td>
<td>Larger</td>
</tr>
</tbody>
</table>

Comparative Type

<table>
<thead>
<tr>
<th>Comparative Type</th>
<th>Relative Effect on Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy ($rx$ difference $\neq 0$)</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Equivalence</td>
<td>Larger</td>
</tr>
<tr>
<td>Non-inferiority</td>
<td>Smaller or larger</td>
</tr>
</tbody>
</table>

Outcome variable

- What is the most important outcome variable?
- What is the expected proportion with the outcome (or variance of the outcome if continuous) in the control and treatment groups?
  - Continuous outcomes usually have smaller SS than a proportion using the same measurement, but may be less clinically interpretable
  - E.g. % with systolicBP<120 and diastolic<80 versus mean reduction in mean arterial blood pressure
- Accurate estimate of control group outcome is key
- Analysis method for the primary outcome
  - Method for sample size calculation parallels the method for analysis
Outcome Variable

The smaller the treatment effect to be detected, the larger the required sample size.

- Sample size increases exponentially as the effect size decreases, regardless of the type of outcome

How to estimate outcome in the control group?

- Previous randomized trials
- Previous prospective studies
- Retrospective studies
- Pilot study

How to determine alpha ($\alpha$) and beta ($\beta$)

Although $\alpha$ often is set at 0.05 and $\beta$ at either 0.10 or 0.20, they should be study-specific
  - Seriousness of disease and impact of treatment
  - Public health importance of disease and treatment
  - Availability of other treatments
  - Cost of treatment

Sample size increases as $\alpha$ and $\beta$ decrease
Choosing $\alpha$ and $\beta$

Example*: It has been suggested that a certain hospital has lower birthweight babies than the national average.

- To see if a special care nursery is needed, a sample of birthweights from the hospital are collected and used to test:
  - $H_0$: $\mu \geq$ national average
  - $H_A$: $\mu <$ national average


Choosing $\alpha$ and $\beta$

- If $H_0$ is rejected, the hospital will add a special care nursery.
- If a type I error is made, the extra cost of adding a special care nursery will be recommended when it is not needed.
- If a type II error is made, a needed special care nursery will not be funded.
  - As a result, some low-birthweight babies may not receive the special attention that they need

Effect of Variance of Outcome on Sample Size

Larger variance $\rightarrow$ larger sample size

- For a proportion, variance is function of the outcome rate in the treatment groups:
  - $\text{Var} = P(1-P)$, which is largest for $P=0.5$
  - $P$ is the average of the control and treated group outcome proportions

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Sample size according to absolute difference in proportion of events between treatments

Adjustments to sample size estimate
- Losses to follow up
- Treatment group crossovers
- Poor treatment adherence
- Ineligible patients enrolled
- Misclassification of outcome

Presence of any of these increases sample size.

Your statistician can adjust the sample size accordingly, but this does NOT address possible bias that may be introduced.

Ways to decrease sample size (for dichotomous outcome)
- Increase the number of outcomes in control group (assumes events per group are proportional, e.g., 2:1)
  - Lengthen follow up
  - Change primary outcome or widen outcome criteria
  - Switch to a surrogate outcome
  - Limit enrollment to higher risk patients
- Increase magnitude of treatment effect to be detected
- Minor: increase alpha or beta; change to one-sided
Ways to decrease sample size (for continuous outcome)

- Reduce variance of outcome measure
  - Change to more precise measurement method
  - Measure more than once and use average
  - Limit enrollment to patients with less variability
- Increase magnitude of treatment effect to be detected
- Minor: increase alpha or beta; change to one-sided hypothesis test

Number of treatment groups

- Increasing the number of treatment groups will increase the sample size
- Increase depends on # of specific group comparisons planned
- Increase depends on sizes of the detectable treatment effects

Example: For $\alpha=0.05$ and $\beta=0.20$,

<table>
<thead>
<tr>
<th>No. of groups</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of comparisons</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>List of comparisons</td>
<td>$P_c=0.5$ v. $P_t=0.3$</td>
<td>$P_c=0.5$ v. $P_{t1}=0.3$</td>
</tr>
<tr>
<td>$P_{t1}=0.2$ v. $P_{t2}=0.3$</td>
<td>$P_{t}=0.3$ v. $P_{t1}=0.3$</td>
<td>$P_{t}=0.3$ v. $P_{t2}=0.3$</td>
</tr>
<tr>
<td>Sample size</td>
<td>103 per group</td>
<td>123 per group</td>
</tr>
</tbody>
</table>

Sample Size - Summary

- Sample size and other scientific demands usually must be balanced with practical limitations of available funds and number of eligible patients
- Finding a satisfactory balance frequently involves modifying aspects of the study design
- Given the close link between study design and sample size, it is advisable to evaluate sample size requirements as early as possible in the planning process
**Intention to Treat (ITT)**

- Patients should be included in the group to which they were randomized for analysis, regardless of the treatment actually received.
  - Failure to adhere to or complete the assigned treatment is often due to side effects, perceived lack of efficacy, disease progression, i.e., it is at least partly an outcome of the assigned treatment.
  - Failure to attribute these outcomes to the assigned treatment can introduce bias into the treatment comparison.

- ITT can be viewed as a test of treatment policy, i.e. a test of outcomes given an intention to treat each patient using a particular therapy.

**Example – Veterans Administration Cooperative Study of Coronary Artery Bypass Surgery**

- Medical therapy versus bypass surgery for CAD
  - 55% of medical therapy group received bypass surgery at some time during 14 years of follow up.
  - Small % of surgery group refused surgery.

- Compare 5 analysis methods:
  1. ITT (‘as-randomized’)
  2. Exclude treatment crossovers from analysis (‘adherers-only’)
  3. Include crossovers in alternate group (‘treatment-received’)
  4. Censor crossovers at time of treatment change (‘censored’)
  5. Transfer crossovers to alternate group at time of treatment change (‘transition’)


**Results of ITT Analysis**

![Graph showing cumulative survival rate over years on study.](graph.png)
**Summary – Intent to Treat (ITT)**
- ITT is the preferred analysis method in clinical trials as it avoids potential biases related to failure to adhere to assigned treatment.
- ITT tests treatment strategy, rather than treatment received.
  - Effect of following a treatment strategy is what is relevant when faced with a new patient.
  - At time of initial treatment decision, it is unknown whether patient will adhere to treatment or whether other factors will intervene.
  - Analyses based on knowledge of future events are not very relevant to current decision.
Selected References

- Controlled Clin Trials 1988; Volume 9, issue 4 has a series of articles on randomization in clinical trials by John Lachin.

Acknowledgments:
Chris Coffey, Sylvan Green, Elizabeth Lazar
Data Collection, Reporting, and Quality Control

SCT Pre-Conference Workshop
Essentials of Randomized Clinical Trials

Laura Lovato
Senior Biostatistician
Wake Forest University School of Medicine

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Data Collection, Reporting, and Quality Control Issues

Part I: Data Collection and Quality Control
Introduction (GCP, QC, QA, SOP)
Steps in Data Collection
Primary sources of error
Standardization of procedures
Design of data collection forms
Types of data entry/management systems
Quality control methods

Part II: Basic Monitoring Reports
DSMB functions and membership
DSMB reporting
IRB reporting and annual review
Data Quality reports

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Definitions

- **GCP**: Good clinical Practice
- **SOP**: Standard Operating Procedure
- **QC**: all process controls and monitoring performed by local staff on a day-to-day basis to maintain data quality
- **QA**: involves independent review or auditing of key processes to uncover and remedy problems
- **GIGO**: Garbage In, Garbage Out: Inaccurate data are worse than no data at all
Definitions: Good Clinical Practice (GCP)

- Unified standard
- For design, conduct, analyses and reporting of clinical trials that involve human subjects
- To ensure that patients’ rights, safety and confidentiality are protected
- To promote scientific validity and data integrity

Introduction: Specific Principles of GCP Applicable to Data Collection

- Confidentiality of records should be protected
- All clinical trial data should be handled in a way to ensure accurate reporting, interpretation and verification
- An audit trail should be maintained for changes/corrections to forms and electronic data

http://www.fda.gov/oc/gcp/

What are the Primary Sources of Error in Data Collection Process?

"Oh look, a data trail to follow."
### Elements of Data Collection

1. Define Key Variables
2. Design of Case Report Forms
3. Standardization and Training
4. Data Acquisition
5. Data Recording / Data Management Systems
6. Study Closeout and Preparation for Analysis

### What are the Primary Sources of Error in Data Collection Process?

- **Missing data** – Not assessed, incomplete or irretrievable
- **Incorrect data** – more difficult to recognize
- **Excess variability** – can reduce the opportunity to detect real change

### Elements of Data Collection

#### #1 Define Key Variables
Define key variables

- Depend upon trial type and outcomes
- At baseline: characteristics of enrolled/non-enrolled participants related to major eligibility requirements
- Primary/Secondary outcome measures
- Variables that might confound/mediate/modify association
- Monitoring adherence to the protocol

Hint: Think

**Who, What, When, Where, How**

As you define your key variables, consider WHO, WHEN, WHERE, HOW these variables are to be collected

- Is the staff member doing the data collection blinded to treatment arm? If so, by what mechanism?
- In person, phone, web, etc?
- Time frame?
- If lab or ECG values: central reading center, scanning charts, asking subject?

Hint: Focus on key variables

Only important data should be collected

- As the volume of noncritical data increases, forms become burdensome and complicated leading to confusion
- Clinical care data often not needed as part of trial database
Elements of Data Collection
#2 Design of Case Report Forms

Design of Case Report Forms

• Purpose:
  • To collect complete and accurate data
  • To ensure standardization and consistency
  • In some cases, to reinforce the protocol

Design of Case Report Forms

• Clean, concise, consistent
• Well-organized with logical flow
• Few “write-in” or “text” answers
• No essay questions!
Design of Case Report Forms

• Selection of items to be collected
• Timing of visit schedule
• Ordering of Procedures

HINTS: Talk to someone at your institution/company that has done similar research
• Use the web – similar studies may have examples on the public side of their web sites

Forms Development

• Preparation of initial versions
• Review by investigators, statisticians, clinic staff, and data management staff
• Pilot-testing
• Debriefing and revamping

Pre-Testing Forms

• Mock visits/procedures conducted
• Simulation with practice participants
• Debriefing is essential to improve procedures
• Procedures/forms revised accordingly
Changes to Study Forms

- Often done early on to improve data collection
- Can be problematic when done repeatedly throughout the trial
  - Results in multiple versions of data sets
  - Can increase risk of errors (clinic, data entry, analysis)

Initial Version

Troponin results
1 At least 5x upper limit of normal
2 At least 2x upper limit of normal but less than 5x
3 Greater than upper limit of normal but less than 2x
4 Within normal limits

New Version

Troponin results
1 At least 5x upper limit of normal
2 At least 3x upper limit of normal but less than 5x
3 At least 2x upper limit of normal but less than 3x
4 Greater than upper limit of normal but less than 2x
5 Within normal limits
Changes to Study Forms

Initial Version

Time to Bed: __p.m.
Time Arise: __a.m.
Hours of Sleep: ____ hours

New Version

Time to Bed: (24 hour clock)
Time Arise: (24 hour clock)
Hours of Sleep: ____ hours

Elements of Data Collection

#3 Standardization and Training
Standardization & Training

Manual of Procedures
(prior to and during the study)
• Standardized procedures
• Clearly written, detailed instructions
• Timely updates and clarifications
• Accessibility is essential

Training and Certification
• Central, regional, or local (webinar)
• “Train the trainer” model
• Use Audio-visuals
• Certification/recertification to maintain skills
Site Visits

Quality assurance visit of a clinical trial unit (e.g., clinical centers, coordinating center, central lab, etc.) by a team of experts to observe operations and assess performance.

Elements of Data Collection

#4 Data Acquisition

Data Acquisition

- Self-administered
  - Web site
  - Mobile device
  - Paper Form
    - at home
    - in clinic
- Staff administered
  - Who is collecting assessment data?
  - Expertise
  - Are they Blinded vs. Unblinded to treatment assignment?
Avoid assessment bias by requiring assessors to be blinded to treatment assignment

Elements of Data Collection
#5 Data Recording and Data Management Systems
Data Recording

- Traditionally, refers to transcribing information onto case report forms (paper -> database)
- Trend toward direct computer entry with no prior hard copy, with no source document
  (e.g., iPad, accelerometers, pedometers, social networks, text messages, smart phones, video game consoles, IRV)
- Both approaches depend on well-designed forms/data entry screens

Data Recording

- Direct computer entry:
  - No source document
  - Security Risks
    - Devices could be stolen
    - Not password protected
    - Cash
    - Used in more public settings
  - Who pays for device?
  - Who is actually recording/receiving the information?

Data Recording: acceptable direct data transmissions

- Aggregate data
- Coded answers that do not describe (or contain metadata that describes) health information
- Health information by itself without any of the 18 identifiers
  - Behavioral data
    - Food diaries, exercise logs, your 'MII' in Wii
  - Transmitted raw data without describing meta data
    - Ex. 5.5 is not PHI but HbA1c=5.5 is*
  - Outward bound messages (e.g., exercise reminders)

Thanks to Scott Rushing for this slide
Data Management

Design of data management system
- Data entry/editing capability
- Desirable features:
  - Ease of screen set up and use
  - Range, field type, skip pattern checks
  - Query system
  - Ability to accommodate double data entry
  - Word processing or spreadsheet software not advocated

Data Management

Design of data management system
- Web-based systems also have administrative functions
  - Communications hub,
  - Information/Resource Center,
  - Coordination of publications process,
  - Management of Adjudication System

Data Entry
Types of traditional data entry systems
- Local
  - Data keyed onsite by clinic personnel
  - Potential for quick resolution of data omissions, errors, and inconsistencies
- Central
  - Forms mailed/faxed to sponsor or data coordinating center
  - Data entered by experienced keyers
  - Forms stored centrally.
Data Entry
Web-based data entry systems

- Provides flexibility
  - Data entry can be local or mix local/central
  - No specific hardware requirements
  - No specific software requirements for internet browser
- Secure link provided
- Data from multiple sources are consolidated on a central server

Data Entry
Web-based data entry systems

- Security features/protection of human subjects’ rights (privacy and confidentiality)
- Controlled Access
- Identification and authentication
  - Requires valid user id and password
  - Password expire every 90 days
  - Specific access rights based on study function

Data Entry
Web-based data entry systems

- Audit trail
- Each and every access into the system is documented
- Every page that is accessed is documented
- All versions of any record entered are kept and date/time stamped (with user id)
Data Entry
Web-based data entry systems

- Virus protection/scanning strategies to monitor and eliminate security threats
- Database server behind firewall
- Disaster recovery plan
- Regular backup for all data
Recruitment and Adherence

Chapter 1 - Introduction
Chapter 2 - Recruitment - A. Media Info
Chapter 2 - Recruitment - B. Community Resource
Chapter 2 - Recruitment - C. Med Pro & Institute
Chapter 2 - Recruitment - D. Ticks
Chapter 3 - Randomization - Tools & Materials
Chapter 4 - Maintenance - A. Clinic and Participant Tools
Chapter 4 - Maintenance - B. Follow-up Maintenance
Chapter 4 - Maintenance and Motivational Tools for Staff & Participants
Chapter 5 - Incentive Cards
Chapter 5 - Greeting Cards English
Chapter 5 - Greeting Cards French
Chapter 5 - Greeting Cards Spanish
Chapter 5 - Images
Chapter 5 - Sympathy Cards

Web site as a communication hub

Adherence A Short Course 12-02.doc
Participant Retention Letter 4-17-03.doc
Participant Retention Letter 603 Adherence.doc
Participant Retention Letter Cert For Missed Visits.doc
Participant Retention Letter Restart.doc
Red Flag Adherence Worksheet.doc
Visit reminder examples.doc
Search Tips Computer Search.doc
Search Tips Internet Resources
For Finding Lost ACCORD Participants.doc
Study Status Form V3 2.pdf
Study Status Form O by O v3 2.pdf
Special notes on study closeout

- Continuous monitoring throughout the trial reduces the clean-up job at the end of the study

- Letter to participants (treatment assignment?)

- Lost-to-Follow-up (National Death Index, web-based searches, paid search firm)

Special notes on study closeout

- “Freezing” data at various points of cleanliness

- Data dictionaries created

- Responsibilities to sponsor (i.e., public use datasets, storing study materials)
Data Preparation for analysis

• Cleaning/editing
• Inconsistencies
• Omissions/discrepancies
• Merging records
• Documenting analysis files
  • Definition of variables/cut points
  • Validation of calculated variables
  • Verification of statistical outliers/distribution of data

Part II. Basic Monitoring and QC Reports

DSMB functions and membership
DSMB reporting
IRB reporting and annual review
Data Quality reports

Data Monitoring Reports

Examples of the following:
• Recruitment
• Baseline and Follow-up data quality (includes lab, ecg, drug distribution, etc.)
• Adherence to protocol (clinicians and participants)
• Lost to follow-up, Refusals
Recruitment Monitoring Example

Randomize

5000 6000 7000 8000 9000 10000

Site Active

40 50 60 70

ACTUAL GOAL

Number of Sites

0 10 20 30 40 50 60

Recruitment Monitoring Example

0 10 20 30 40 50 60

Weeks

Number Enrolled

0 1000 2000 3000 4000 5000

Monitoring Baseline Assessments

Are the study groups comparable at the time of randomization?

• Risk or prognostic factors, important demographic characteristics, medical history

• Randomization on average produces balance between groups – no guarantee!
Monitoring Baseline Assessments

Easiest way: compare each variable by treatment assignment using means, medians, ranges

Note that the groups will never be identical: 5% of the comparisons will show differences at the 0.05 significance level

Monitoring Follow-up assessments

1. Number of Visits completed as planned: %

2. Completeness of data: missing forms, missing data on forms

3. Quality of data received: data queries on each field (at data entry and/or retrospective data queries)
Monitoring Adherence

- Come at adherence from many different angles:
  - Participant adherence
  - Clinical site staff adherence to the protocol
- Long-term trials, look at changes over time
- Separate by calendar time, clinic visit, by clinic if a multi-center trial
- Tables and/or graphs
### Monitoring Adherence

<table>
<thead>
<tr>
<th>ID #</th>
<th>Trial Status</th>
<th>Date of Last Form</th>
<th>Days</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ppt1</td>
<td>Non-adherent</td>
<td>15JAN2008</td>
<td>216</td>
<td>10/20/2007 by Jill Jones (CCN): Elevated CK &gt; 5X ULN on 2 occasions. Does patient have symptoms? 12/08/2007 by Joe Smith (CS): Will reassess for symptoms of myositis at next visit. 01/15/2008 by Joe Smith (CS): Yes-pt has symptoms. 04/17/2008 by Jill Jones (CCN): Looks like both blinded lipid med and statin were stopped. Last LDL is &gt; 120. Consider checking CK next visit off all lipid meds (looks like he may have some CK elevation even off of lipid meds); then rechallenge with low dose blinded lipid med. 04/28/2008 by Joe Smith (CS): participant rechallenged on low-dose blinded meds, will check in 6-8 weeks. Enter a comment</td>
</tr>
<tr>
<td>Ppt2</td>
<td>LTF</td>
<td>12DEC2008</td>
<td>69</td>
<td>01/09/2009 by Joe Smith (CS): This patient has moved to Papua New Guinea for his work and couldn’t come for his interval visit in December. Not forwarding address. 01/12/2009 by Jill Jones (CCN): per our phone conversation, try alternate contacts to see if you can get phone contact info for an events assessment at minimum. Enter a comment</td>
</tr>
</tbody>
</table>

### Monitoring Lost to Follow-up, Refused

- Separate groups: Lost to Follow-up versus Participant refusals (withdrawn consent)
- Investigators will want to know why participants are lost (e.g., moved out of range) and refused (e.g., withdrawn consent due to problems with protocol)
- Anticipate participants prone to becoming lost: monitor missed visit patterns and what happened to them
- Second tier: participants not officially LOST or REFUSED, but are no longer coming to the clinic or taking study medications

### Data Safety Monitoring Board (DSMB)

Institutional Review Board (IRB) Reporting
Data and Safety Monitoring Boards (DSMBs) are often given the responsibility of monitoring the accumulating data.

The DSMB is responsible for assuring that study participants are not exposed to unnecessary or unreasonable risks.

The DSMB is also responsible for assuring that the study is being conducted according to high scientific and ethical standards.

Why have DSMBs?

- **Protect safety of trial participants**
  - Investigators are in a natural conflict of interest
    - Vested in the study
    - They, and their staff, are paid by the study
  - Having the DSMB externally review efficacy and safety data protects:
    - The credibility of the study
    - The validity of study results

**Principle 1 - Responsibilities.** The primary responsibilities of a DSMB are to safeguard the interests of study patients and to preserve the integrity and credibility of the trial.

**Principle 2 – Composition.** The DSMB should have multidisciplinary representation, including topic experts from relevant medical specialties and biostatisticians.
**DSMB Reporting**

**Principle 3 - Conflicts.** Individuals with important conflicts of interest (financial, intellectual, professional, or regulatory) should not serve on a DSMB.

**Principle 4 – Confidentiality Issues.** Trial integrity requires DSMB members not to discuss details of meetings elsewhere.

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**DSMB Reporting**

Frequency of DSMB meetings depends on disease topic and specific intervention – most meet 1-4 times per year.

Early in the trial, DSMB review will focus more on safety, quality of conduct, and trial integrity rather than on efficacy evaluation.

Single-study DSMBs
Multi-study DSMBs
  - Cancer Cooperative Groups
  - HIV trial networks

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**DSMB Reporting**

Later meetings may include formal efficacy or futility analyses.

Ethical principles mandate that clinical trials begin with uncertainty as to which treatment is better.

This uncertainty should be maintained during study.

If interim data become sufficiently compelling, ethics would demand that the trial stop and the results made public.
Hence, interim monitoring of safety and efficacy data has become an integral part of modern clinical trials. Any efficacy or safety data analyzed by treatment arm will be discussed only in a closed session. Only the DSMB members and study statistician will attend the closed session. It is critical not to reveal information presented in closed session to the study investigators, except as explicitly authorized by the DSMB.

A typical agenda for a DSMB meeting:

- Closed executive session
  - Review of agenda, additions to agenda
- Open session with investigators
  - Review current status and conduct of study
  - Accrual update
- Closed session with unblinded investigators
  - Review safety data
  - Review interim analysis (if appropriate)
- Closed executive session
- Open session with investigators
  - Discussion/Recommendations

At the conclusion of each meeting, the DSMB makes a recommendation to the sponsor:

- Study should continue without modification
- Study should continue with the following modifications
- Study should be stopped for safety/efficacy/futility

DSMB will also summarize any areas of concern regarding performance and safety. Soon thereafter, the DSMB chair will provide a written summary of the board’s recommendations.
**DSMB Reporting**

Early termination of a trial should be considered if:

- Interim data indicate intervention is harmful
- Interim data demonstrate a clear benefit
- Significant difference by end of study is probable
- No significant difference by end of study probable
- Severe logistical or data quality problems exist

The DSMB may recommend that the study protocol be terminated, temporarily suspended, or amended.

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**INTERIM MONITORING**

The study protocol should include a section describing proposed plan for interim data monitoring.

This plan should detail:

- What data will be monitored?
- The timing of all interim analyses?
- The frequency of data reviews.
- Criteria that will guide early termination

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**INTERIM MONITORING**

The decision to stop a trial early is complex, requiring a combination of statistical and clinical judgment.

Stopping a trial too late means needlessly delaying some participants from receiving the better treatment.

Stopping a trial to early may fail to persuade others to change practice.

Statistical methods have been developed for interim monitoring of clinical trials to minimize the role of subjective judgment.
Data Safety Monitoring Boards

WHI experience:


Institutional Review Boards

From the Dept of Health & Human Services:
http://www.hhs.gov/ohrp/

From the Wake Forest IRB:
http://www1.wfubmc.edu/OR/IRB/Policy+Guidelines+and+Regulation.htm

From the FDA:
http://www.fda.gov/ohrui/irb/faqs.htm#IRB0rg
Under FDA regulations, an Institutional Review Board is a group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research.

IRB Statistical Reports
- Basic study progress reports
- Recruitment and Monitoring reports
- Safety reports
- Data and Safety Monitoring Board letters / recommendation to continue study
Summary: what have we learned?

- Part I: Data Collection and Quality Control
  - Introduction (GCP, QC, QA, SOP)
  - Steps in Data Collection
  - Primary sources of error
  - Standardization of procedures
  - Design of data collection forms
  - Types of data entry/management systems
  - Quality control methods
- Part II: Basic Monitoring Reports
  - DSMB functions and membership
  - DSMB reporting
  - IRB reporting and annual review
  - Data Quality reports