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Study Designs, Objectives, and Hypotheses

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Section A

Variations in Study Designs
Many Designs Available

- Parallel
- Cross-over
- Factorial
- Cluster
- Others
Categories of Trials

- Phases
- Control groups
- Chronic vs. short-term treatment
- Single vs. multiple centers
- Exploratory vs. confirmatory
Study Designs

- Focus on trials intended to provide primary evidence of safety and efficacy ("pivotal" trials)
- Regulations permit substantial flexibility ("adequate and well-controlled trials")
Selecting a Study Design

- What are the objectives?
- What are the expectations?
  - Major advance
  - Modest advance
  - Reduction in side effects
- What are the practicalities?
  - Available population
  - Relevant population
  - Potential impact on medical practice
  - Ability to blind/mask
Parallel Groups

- Multiple concurrent experimental arms
  - Different treatments
  - Different doses
- Control arm(s)
  - Placebo, active control
- Balance/imbalanced randomization
Parallel Design

- Classical clinical trial approach
- Two study groups
- Randomized assignment

Factorial Designs

- Evaluates multiple factors simultaneously
- 2 X 2 most practical, but little used
- Sometimes a combination cannot be given (incomplete factorial)

## ISIS-3 Design

<table>
<thead>
<tr>
<th>Anti-thrombotic agent</th>
<th>Fibrinolytic agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>SK</td>
</tr>
<tr>
<td>Aspirin and heparin</td>
<td>tPA</td>
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<tr>
<td></td>
<td>APSAC</td>
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</tbody>
</table>

Factorial Design

- Evaluates two interventions simultaneously
- Four possible treatment combinations
- Efficient approach in some circumstances
- Potentially more informative approach
- Increases proportion getting active treatment
- Major concern: interaction of interventions
Problems with Factorial Design

- Patients must be willing and able to take any of the treatment combinations
- Optimal dose modification strategy for toxicity may be hard to determine
- May require burdensome administration scheme if blinded
- Interaction complicates interpretation of treatment effects
Bottom Line on Interaction

- You can’t rely on detecting modest interactions if studies are powered for main effects
- Interaction is important to study if agents are likely to be used together
Crossover Designs

Randomization

Treatment A

Evaluation of Outcomes

Treatment B

Evaluation of Outcomes

Treatment A

Treatment B

Advantages of Cross-Over Designs

- Address question of major interest
  - Will this patient do better on drug A or drug B?
- Removes “patient effect” thereby reducing variability and increasing precision of estimation
- Opportunity to receive both treatments (or be assured of receiving active treatment at some point) is attractive to patients
- Under assumption of no carryover effect, design provides more information than simple parallel design
Disadvantages of Cross-Over Designs

- Assumption of no carryover effects is difficult to test
- May be difficult to determine appropriate length of washout period so as to avoid carryover effects
- There may be “period” effects in addition to carryover effects
  - Progression of disease
  - Dropouts
Cluster Design

- Groups or clusters randomly assigned, not individuals
  - Examples: villages, classrooms, platoons

Study Designs

- Treatment allocation method
- Blinding of assigned treatment
- Choice of control group
  - ICH E10
In the Next Lecture Section We’ll Look at . . .

- Objectives and hypotheses
  - How to meet objectives
  - Hierarchy of strength of evidence
  - Phases of trials
Section B

Objectives and Hypotheses
In the Beginning

- Begin with a clear statement of the major scientific questions posed by the study, usually conveyed in quantitative terms
Objectives by Phase

- **Phase I**
  - Determine optimal or tolerable dose
  - Describe adverse event or PK profile
  - Establish feasibility of treatment approach

- **Phase II**
  - Estimation of activity
  - Comparison of doses or schedules
  - Estimation of factors for Phase III

- **Phase III**
  - Demonstrate superiority or non-inferiority
  - Estimate rates of adverse events

- **Phase IV**
  - Address remaining outstanding issues
Examples

- To select the optimal dose that satisfies specific criteria
- To demonstrate that the two year mortality rate on treatment A is less than on treatment B
The Objective Is to . . .

- Classify
- Order
- Estimate differences
- Estimate rates
Cohesive Driving Force

- All other properties of the trial, the study population, the primary endpoint, the sample size, the primary analysis, flow from the study objective
Study Hypotheses

- The study objective corresponds to the primary hypothesis of the study, e.g., the null hypothesis, $H_0$
  - The two year mortality rate on treatment A equals the two year mortality rate on treatment B
In the Next Lecture We’ll Look at . . .

- Study populations
  - Who should we recruit?
  - Who do we actually recruit?
  - Eligibility criteria
  - To whom do the results apply?