Trial Design Module Part 2: Key Concepts

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Agenda

- Endpoints
- Randomization
- Masking/blinding
- Control Group
- Trial Designs

Endpoints

- Primary
- Secondary
- Direct
- Surrogate
- Symptom assessment
  - FDA Guidance: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*

Examples of Surrogates

Surrogate	Condition/Disease
arterial blood pressure	CVA, MI, heart failure
Cholesterol and triglyceride levels	atherosclerotic disease
Increased IOP	Loss of Vision
Blood sugar	Survival/complications of DM
Disease-free survival; time to progression; progression free survival	Cancer survival

Randomization…

- Compare outcomes of trial group and control group following an intervention
  - Single arm
  - Two or more arms
- Controlled, randomized, double-blind trials are the “Gold Standard” in clinical research
- Simple or Complex using software programs

…Randomization

Advantages

- Difference is *because* of the intervention
- Minimizes investigator bias
- Allows stratification within treatment groups

Disadvantages

- Results not always generalizable
- Recruitment
- Acceptability of Randomization Process
- Administrative Complexity

Types of Randomization

- Simple
  - Treatment A or Treatment B
- Block
  - AABB, ABAB, BABA, ABBA, BBAA, BAAB
- Stratification

Stratification

- Partitioning subjects by factor other than the treatment
- Examples of stratification factors include:
  - Demography: gender, age
  - Disease severity, risk factors
  - Prior treatments
  - Concomitant illness

Another Alternative: Post-stratification

- Stratification done after randomization
  - Easier and less costly to implement
  - Often *nearly* as efficient
  - May be less convincing
  - Cannot correct for cases of extreme imbalance or confounding of covariates

Masking/Blinding

- Minimize potential investigator and subject bias
- Most useful when there is a *subjective* component to treatment or evaluation
- Assures that subjects are similar with regard to post-treatment variables that could affect outcomes
- 3 types:
  - Single
  - Double
  - Triple

Control Group

- Group of research participants who ***do not*** receive the experimental treatment
- Purpose: to distinguish treatment outcomes from other outcomes
- Considerations for control group selection:
  - Available standard therapies
  - Goals of Controlled Clinical Trials
  - Significance of Control Group
  - Ethical considerations
  - Types of Control Groups

Types of Controls

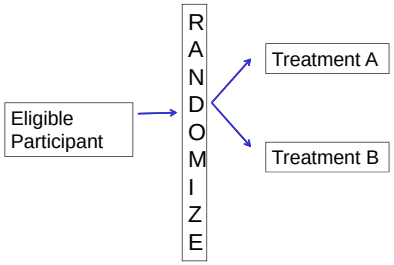
- Concurrent Controls
  - Placebo control
  - No treatment control
  - Dose-response control
  - Active Control
- External control
  - Historical control
  - Same time period another setting
- Multiple control groups

Taken from: ICH HARMONISED TRIPARTITE GUIDELINE:CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS, E10

Intent-to-treat

- Compares participants in the groups they were originally randomized to whether they completed intervention or not

Parallel Design…



…Parallel Design

Low dose vs. higher dose

Randomization (n=50)

25 — 25

New Agent/ Intervention Low Dose

New Agent/ Intervention Higher Dose

Placebo (Inactive) vs agent

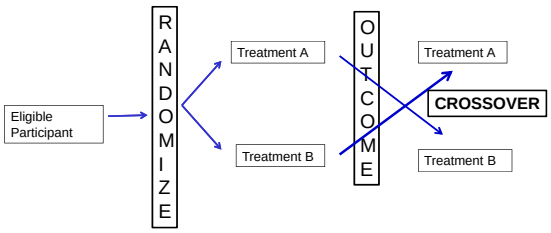
Randomization (n=50)

25 — 25

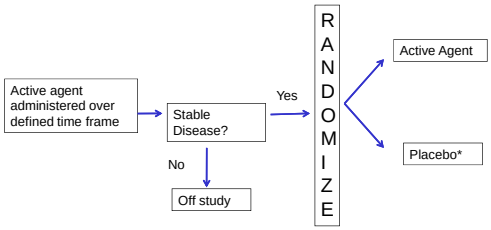
New agent alone or + placebo

New agent + standard of care

Crossover Design



Randomized Discontinuation Design

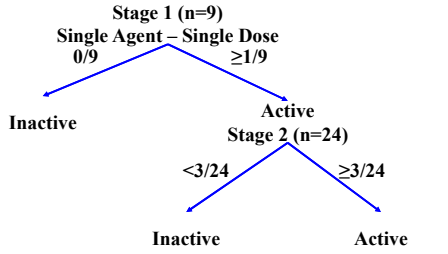


* Patients with progressive disease on placebo can switch back to active agent.

Adaptive Design

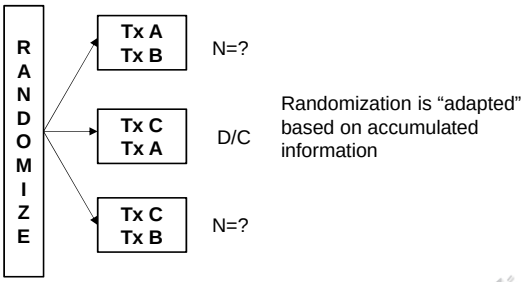
- Use of accumulated data to decide how to modify aspects of the ongoing study without effecting validity and integrity of trial
- FDA Draft Guidance Document 2010
  - *Adaptive Design Clinical Trials for Drugs and Biologics*
  - Prospectively planned modification of one or more aspects of the study design and hypotheses based on analysis of data

Standard 2 Stage Design



Two-stage design with early stopping rule for efficacy or futility

Adaptive Designs



Randomization is "adapted" based on accumulated information