Issues to Consider in the Design of Randomized Controlled Trials

Jay Wilkinson, MD, MPH
Professor of Pediatrics & Epidemiology
Miller School of Medicine

Seminar Purpose

- To facilitate an interactive discussion between presenter and audience regarding issues relevant to the design of randomized controlled trials
- Please feel free to ask questions at any time during or after the presentation
- Presenter contact:

jwilkins@med.miami.edu

Learning Objectives

- The rationale for randomization
- The importance of statistical expertise in designing, monitoring, and interpreting the study
- Hypothesis classification
  - Superiority vs. non-inferiority vs. equivalence trials
- Controls

Learning Objectives

- Simple vs. adaptive vs. restricted randomization
- Blinding and allocation concealment
- DSMBs and stopping rules
- CONSORT
- Explanatory vs. intention to treat analysis

Randomized Controlled Trials (RCTs)

- Gold standard
- Difference from cohort (observational study)
- Limitations
  - Sample size and study power
- Meta-analysis

RCTs: Sources of Potential Bias

- Biases
  - Selection bias
  - Information/observer bias
    - **Loss to follow up- don't know patient outcome**
    - Patient subjective reports
    - Patient examinations/evaluations
    - Patient surveys- behavioral studies
    - Social desirability/please investigators

RCTs: Study Design Schematic

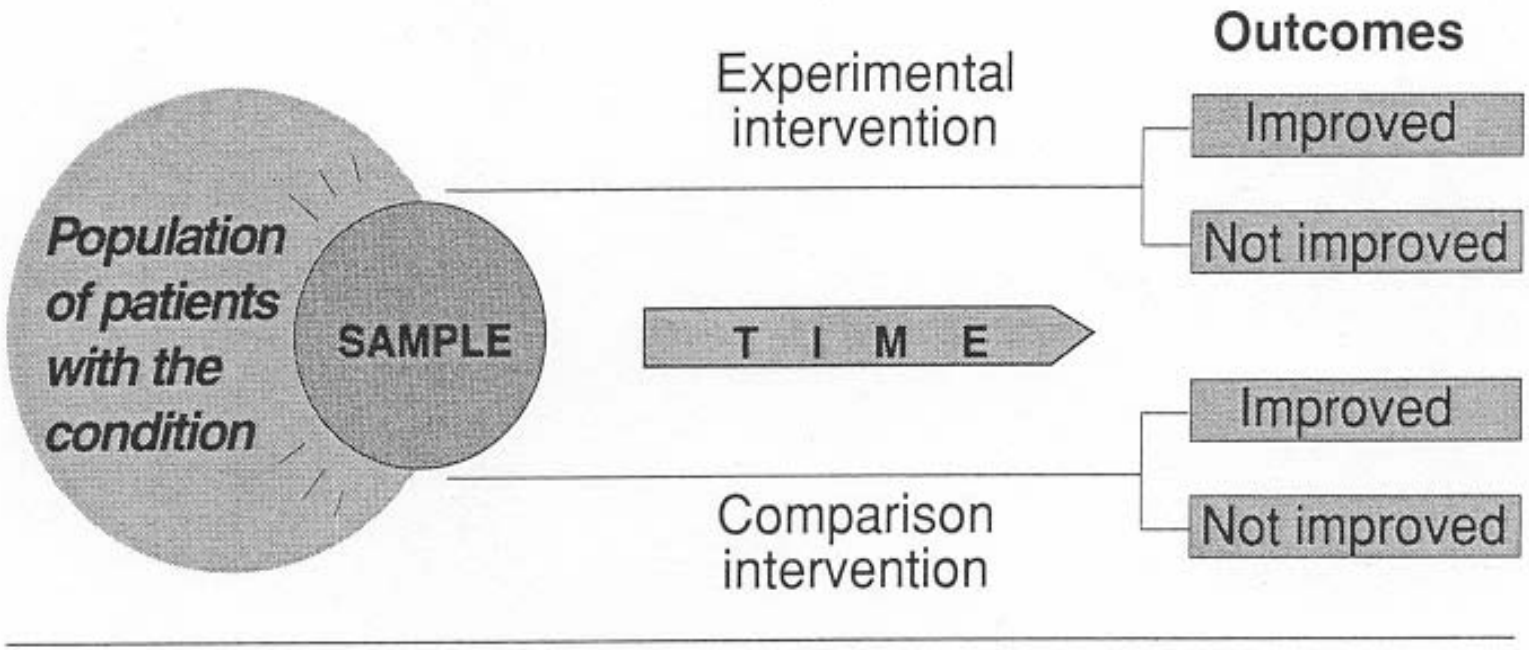

Figure 7.1. The structure of a clinical trial.

Statistical Expertise

- Before starting the RCT design
  - Have statistical and/or epidemiological partner
  - Will decide optimal sample size to maximize study power
  - Will decide optimal randomization scheme
  - Will decide optimal allocation ratio
  - Will allow for establishment of stopping rules
  - Will design the optimal analytic plan
  - Ensure compliance with CONSORT

RCTs: Hypothesis Classification

- Superiority
  - Experimental condition is superior to the control
- Active control trials
  - Non-inferiority
  - Equivalence
  - Require larger sample sizes

Active Control Trials

- The term active-control trial refers to all studies in which the control treatment is an active one.
  - If the intent is to show that the differences between control and study treatments are not large in either direction the study is called an equivalence trial.
  - If the intent of a study is to demonstrate that the study treatment is not substantially worse than than the control treatment the study is called a non-inferiority trial.
- Both types of trials seek to reject the possibility that differences in treatment effects equal or exceed a preset limit or margin.

Control Groups

- Placebo
- Active treatment controls
- Attention controls
- No treatment

RCTs: Randomization

- Clinical Trials- Design
  - **Randomization:**
    - Most effective means of of accounting for potential confounders
    - Treatment groups should be equivalent at baseline if randomization successful
    - Also controls for selection bias

RCTs: Randomization Approaches

- Simple Randomization
  - Most often used
  - All subjects have equal probability of assignment to any treatment condition
  - May lead to imbalance in condition assignments
- Adaptive
  - Covariate adaptive
    - Stratified (blocked) vs. minimization
  - Response adaptive (“play the winner”)
    - Treatment success increases allocation to treatment

RCTs: Randomization Approaches

- Restricted randomization
  - Permuted block randomization
  - Adaptive biased-coin (urn) randomization

RCTs: Permuted Block Randomization

- 2 treatments (A or B); block size= 4
  - 6 permutations
  - Randomly select permutations
  - {AABB, ABAB, BAAB, BABA, BBAA, ABBA}

- Vary block sizes and blind system to avoid selection bias

RCTs: Permuted Block Randomization

- To ensure balance between treatment groups, participants are allocated in blocks
- Each block has equal numbers of treatment (A) and control (B)
- Order of treatments randomly permuted (rearranged) so that all possible permutations are created
- BLOCK SIZE 4: 6 possible permutations
- BLOCK SIZE 6: 8 possible permutations

RCTs: Use of Blinding

- Clinical Trials- Design
  - Blinding (Masking): effective at controlling many forms of potential bias
    - Single vs. double blinding*
    - Decrease observation and reporting bias
    - Classification, outcome ascertainment
    - Subject reporting
  - Allocation Concealment

Data Safety Monitoring Board

- Appointed to periodically examine results to ensure ethical treatment of participants
- Stopping Rules
  - Statistical boundaries
    - If H_0 is upheld- continue trial
    - If H_0 is not upheld- consider discontinuing trial
- Final decision regarding trial progress is made by the DSMB informed by the interim analyses

RCTs: Stopping Rules

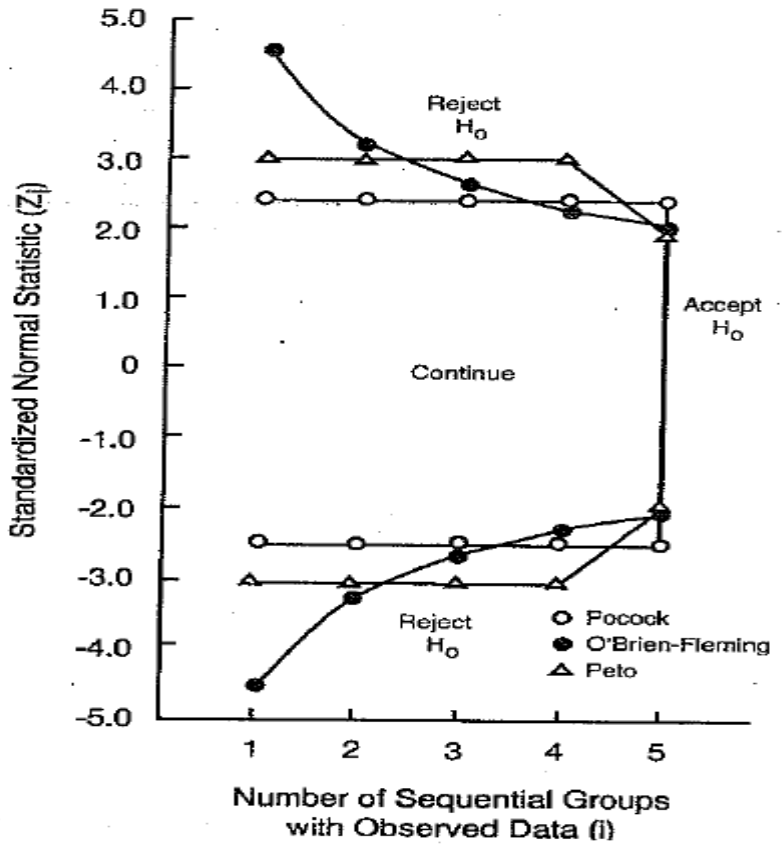

Fig. 15-4 Three group sequential stopping boundaries for the standardized normal statistic (Z_i) for up to five sequential groups with two-sided significance level of 0.05.

CONSORT: Consolidating Standards of Reporting Trials

www.consort-statement.org

- CONSORT Statement
  - An evidence-based, minimum set of recommendations for reporting RCTs
  - It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation
  - A 25-item checklist and a flow diagram
    - The checklist items focus on reporting how the trial was designed, analyzed, and interpreted
    - The flow diagram displays the progress of all participants through the trial

RCTs: Interpretation

- Study question is effect of offering therapy, not necessarily actually complying with it
  - "**Intention to treat**"
- **Efficacy:** Does the treatment work under ideal conditions?
- **Effectiveness:** Does the treatment work, and is it feasible, in everyday practice?

RCTs: Analysis Approach

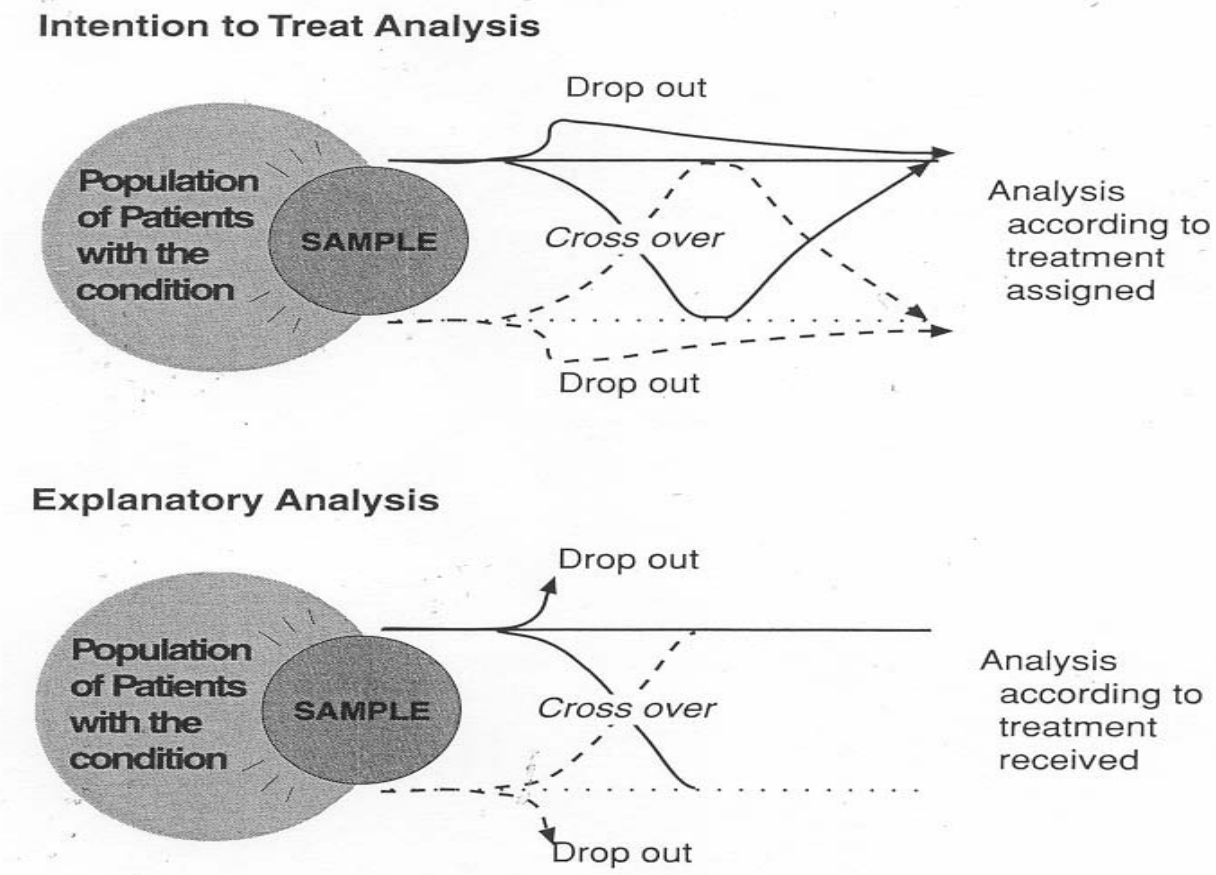

Figure 7.6. Intention to treat and explanatory trials.

THANK YOU

ANY QUESTIONS?