Randomized Trials

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Outline

• Background
• Goals of randomized trials
• Types of randomized trials
• Designing a randomized trial
• Other trial considerations
• Examples
• Summary
Randomized trial:
“A study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control.” (MedicineNet.com)

Observational study:
“A type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given).” (NCI/NIH)
Background

• Terminology:
  – Randomized controlled (or control) trial
    • Includes a control or placebo arm
  – Randomized controlled (or control) clinical trial
    • Includes control or placebo arm & focused on clinical research
  – Randomized clinical (comparative) trial
    • Includes standard of care as one arm which is usually not placebo

• Randomized trial
  – Applies to all types defined above...
Background

• First reported clinical trial:
  – To identify treatment for scurvy (1753, James Lind)
• Later randomized experiments appeared in psychology, education and agriculture
  – Fisher’s agriculture research popularized randomized experiments
• One of the early randomized controlled trial in medicine
  – “Streptomycin treatment of pulmonary tuberculosis” (1948, Hill et al)
  – Often noted b/c of used methods to conceal treatment assignment
Background

• Kefauver-Harris Amendments (1962) of Food, Drug, and Cosmetic Act
  – Response to thalidomide tragedy
  – Required disclosure of side effects in advertising
  – Required proof of effectiveness and safety of drugs before approval
    • Randomized trial was obvious choice for the FDA
• By 1970, FDA required randomized trial results with new applications
  – As of 2004, more than 150,000 randomized trials in the literature
Observational Studies

Observational Designs

- Case Series
- Cross-sectional
- Case-Control
- Cohort

Descriptive (no comparison group)

Analytic (comparison group)
Observational Study: Cross-Sectional Design

Compare the prevalence of disease in those exposed vs. unexposed

Population of Interest

Exposed and Outcome positive

Exposed and Outcome negative

Unexposed and Outcome positive

Unexposed and Outcome negative

Sample

Time present
Disadvantages of Cross-Sectional Design

• Not efficient for rare diseases
• Prevalent cases may not be representative of all cases
• Cannot calculate incidence rates or risk factors for developing disease
• Timing between exposure and disease is often unclear
• Timing of exposure is key for causal inference. Exposure must be known to precede outcome to be causal
Observational Study: Case-Control Design

Compare odds of exposure in cases relative to controls

Exposed

Unexposed

Past History

Exposed

Unexposed

Controls (no disease)

Cases (disease)

Source Population

Time

Past

Present
Disadvantages of Case-Control Design

- Temporal relationship of exposure & disease unclear in prevalent cases
- Relies on retrospective exposure data—may be limited and/or poor quality
- Sample of cases or controls may not be representative of population
  - Especially if hospital or clinic-based
Observational Study: Cohort Design

Determine risk of disease for exposed vs. unexposed

Population

- Disease present
- Disease free cohort

Exposed

- Disease Present
- Disease Absent

Unexposed

- Disease Present
- Disease Absent

not eligible

classify

classify

classify

sample

start

baseline

follow-up

Boston Children's Hospital
Until every child is well™
Disadvantages of Cohort Designs

• Potential for incidence estimates errors b/c loss to follow-up /drop outs
• Relatively long duration b/c need time to observe events
• Requires large disease-free group b/c waiting for disease to develop
  – not good for rare diseases
• Higher (highest) costs relative to other designs
Randomized Trial Schema

Only difference (theoretically) between the two groups is intervention
Note: due to large size #subjects required => multi-center
Goal of Randomized Trial

- Main difference from observational study is that investigator has direct control over the allocation of subjects to a study group
  - May include two or more groups, cross-over
  - Randomized unit may be individuals, households, communities, schools

- Advantage
  - Ability to demonstrate causality b/c apply intervention and then observe effect
Goal of Randomized Trial

• Designed to establish beneficial effects of intervention
  – Beneficial is important b/c some interventions will have side effects
    => ethically need to balance the benefit vs. harm
    => need to believe there is a potential for benefit

• When implementing an intervention that is different from standard of care need to inform the participants (i.e., informed consent)
Goal of Randomized Trial

- Wide range of interventions—few examples
  - Therapeutic agents
  - Prophylactic agents
  - Surgical procedures
  - Health service strategies
  - Educational program
  - Behavior intervention
Randomization

• Advantages:
  – Ensures groups are same for known and unknown factors
  – Eliminates selection bias by participants and researchers
  – Easier to blind/mask than observational studies

• Disadvantages:
  – Expensive in terms of time and money
  – Study is complex to explain to subjects
  – Volunteer biases- may not represent the wider population
Randomization

• Important steps:
  – Selecting randomization procedure
  – Deciding on whether need to conceal treatment (allocation concealment)

• Note: unequal assignment of subjects/groups to arms can be handled
Randomization Methods

• Common randomization methods
  – Blocked randomization (also called restricted randomization)
  – Stratified randomization
  – Minimization (example of adaptive randomization)
  – Cluster randomization

• Other randomization methods (rarely used)
  – Simple randomization
  – Matched pair design (special case of stratified randomization)
Randomization Methods

• Clustered randomization:
  – Allows us to randomize groups of subjects (hospitals, schools)
  – Controls for intervention “contamination” across subjects within the same cluster
  – Requires more complicated design and analysis
    • Randomization at cluster but ...
    • Outcomes observed on subjects
Types of Randomized Trial Hypotheses

Intervention vs. control hypothesis:

H1: Equivalence "same"

H2: Non-inferiority not "worse"

H3: Superiority "better"

Purpose determines statistical design.
Define "same", not "worse", "better"

Note: "better"=Clinically significant difference

\[ \delta = \text{Intervention Effect} - \text{Control Effect} \]
Types of Randomized Trial Designs

**Parallel design:**
- each group of participants is exposed to only one of the study interventions.

**Crossover design:**
- each of the participants is given all of the study interventions in successive periods.

**Factorial design:**
- when two or more experimental interventions are not only evaluated separately but also in combination and against a control.
Cluster randomized study: Pre-existing groups of subjects (e.g., schools, communities) are randomly selected to receive (or not receive) intervention

Designing a randomized trial

- **Objective** is to determine if the intervention:
  - “Works”
  - “Better” than current practice
- **Maximum benefit** and **minimize harm**
- **Control for errors**
  - False positive error ($\alpha$)
  - False negative error ($\beta$)
- **Note...** need to define “Works” and “Better”
Designing a randomized trial

• Define study population
  – Specific enough to draw inferences
  – Broad enough to accrue in reasonable time frame

• Define experimental methods
  – Treatment plan & scheduled assessments
  – If appropriate,
    • Reporting plan (eg. Adverse events)
    • Established criteria to evaluate outcomes (eg., toxicity-CTC criteria; response-response criteria, QOL scale)
## Designing a randomized trial

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>How much “better” (call this $\delta$) intervention should be compared to other group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention response (Yes/No) Binary outcome</td>
<td>Increase in response rates by $20%$</td>
</tr>
<tr>
<td>Pain score “Continuous” outcome</td>
<td>Reduction in pain score by $5$ points</td>
</tr>
<tr>
<td>Survival time Time to event outcome</td>
<td>Reduction in risk of failure by $30%$</td>
</tr>
</tbody>
</table>
Designing a randomized trial

- Specify the design parameters for primary comparison
  - power \((1 - \beta)\)
  - \(\alpha\)-level
  - test (1 or 2-sided)
- Based on power, \(\alpha\), test and \(\delta\), determine the required number of subjects
- Calculations influenced by fixed or sequential design and design type (eg., parallel, clustered)
Power vs. Sample Size

Power Curve

- **A**: Low return on investment
- **B**: Effective but inefficient use of resources
- **C**: Optimal use of resources

https://research.illinois.edu/regulatory-compliance-safety/rationale-numbers-animals
Designing a randomized trial

- Define ineligibility rate and anticipated accrual time
- Adjust for potential non-compliance and drop out
  - Important to plan for this at design stage
  - Difference in compliance and drop out rates between groups can bias the primary comparison
Designing a randomized trial

• Specify secondary and exploratory outcomes
  – Correlative endpoints (eg., genomic, immune, lab, QOL)
    • Number samples expect to be submitted and evaluated
    • Usually need to provide power calculations
  – Going to spend a lot of time and effort collecting the information
    • Make sure the resulting information will be “useful”!
Designing a randomized trial

• Well-defined protocol is key to successful randomized trial
  – Protocol contains complete specification for
    • Research plan
    • Treatment for individual subject
  – Most important quality control tool
• Be mindful of protocol deviations
  – Major deviations may affect validity of trial
  – Minor deviations usually do not
Other trial considerations

- Stratification
- Treatment Blinding
- Analysis Population - Intent to treat (ITT), Per Protocol (PP)
- Sequential Design (Interim Analysis)
- Data Safety and Monitoring Committee (DSMC)
- Reporting
Other trial considerations

Methodological elements used to strengthen the causal inference and study conduct:

• Stratification by baseline risk factors
  – Ensures that subjects with different outcome by baseline risk factors are equally represented in the two arms
  – Example: Primary outcome is time to death => Stratify by age b/c risk for dying increases with age
Other trial considerations

• Blinding to treatment assignment
  – Ensures that bias is not introduced from knowledge of treatment
  – Often used for subjective outcomes
  – Types:
    • Single blind=participant or investigator blinded
    • Double blind=both participant and investigator blinded
Other trial considerations

• Blinding to treatment assignment
  – Requires extra thought for implementation of the intervention
    • What additional procedures needed?
    • For therapeutic- have placebo pills/sham therapy?
  – Some cases impossible to implement
    • Treatments with known side effects
Other trial considerations

• Interim analysis (sequential designs)
  – Tool to protect the welfare of subjects
  – Allows for stopping of study if the intervention is
    • Unlikely to be “better” than “control” => futility
    • Likely to be “better” than “control” => efficacy
  – Issues considered at early stopping:
    ethics, precision, data quality, external study information
  – Lots of things to think about => talk to a statistician
Other trial considerations

- Data Monitoring Committee/Data Safety and Monitoring Committee (DMC/DSMC)
  - Oversight committee
  - Ensure that the trial is safe and warrants continuation
  - Perform a qualitative review of adverse events
  - Evaluate study conduct
  - Provide recommendations on early stopping
  - Consider external research studies in their deliberations
Other trial considerations

- To improve trial reporting, an international group of scientists and editors published the Consolidated Standards of Reporting Trials (CONSORT) Statements – 1996, 2001, 2010
- Widely accepted/required by journals
- Extension of consort statement to cluster randomization trials (Campbell et al, BMJ, 2004)
Other trial considerations

• Registration of clinical trials is required on Clinicaltrials.gov.
Example 1: A Randomized Trial of Hyperglycemic Control in Pediatric Intensive Care

Patient population: children (36wks-13yrs) in ICUs after cardiac surgery or for other reasons
Two groups: tight control vs. standard treatment
Stratification factors: (brain injury, center, age, cardiac surgery, RACHS1/PIM2 score)
Randomization algorithm: minimization

Example 1: A Randomized Trial of Hyperglycemic Control in Pediatric Intensive Care

- **Primary endpoint:** the number of ventilator-free days (VFD) within the 30 days of randomization
- **Previous data in the same population:**
  - Mean VFD = 22.7-26.7 days depending on whether cardiac patients
  - Standard deviation = 7 days
- **Hypothesis:** Improvement in VFD by 2 days (i.e., clinically meaningful difference or “better”)
Example 1: A Randomized Trial of Hyperglycemic Control in Pediatric Intensive Care

• Design properties
  – Two sample t-test
  – Type I error of 1% (2-sided)
  – Power=90%
  – Required sample size =750 patients
  – Increased sample size further for non-compliance and to detect an interaction of treatment and whether cardiac subjects with 80% power

Example 2: Cognitive Behavioral Therapy & Medication Management Algorithm for Treatment of Depression among Youth Living with HIV in the United States

- Cluster randomized study (clinical research sites are the clusters)
- Primary endpoint: depression (measured by QIDS-SR) at 24 weeks
- Design properties
  - Hypothesis: Score improvement by 3-4 points (assume SD 3.75-5)
  - Two sample t-test
  - Type I error of 5% (2-sided); Power > 90%
  - 14 clusters; cluster size=10, intra-cluster correlation coefficient=0.02-0.05
  - N=140 individuals

IMPAACT 2002:
http://impaactnetwork.org/DocFiles/IMPAACT2002/IMPAACT%202002_V1_CM1_8MAR17.pdf
Example 3: RCHOP vs. CHOP +/- Maintenance therapy in patients with Diffuse Large B-cell Lymphoma (ECOG Study E4494)

- Primary objectives: Compare time to treatment failure (TTF) for
  - RCHOP vs. CHOP
  - MR vs. Observation

- Patient population:
  - Untreated DLBCL
  - Age >=60 years
  - ECOG PS 0-3

- Stratified factorial design with permuted blocks randomization

Example 3: RCHOP vs. CHOP DLBCL +/- Maintenance therapy (ECOG Study E4494)

- Design
  - Hypothesis: 33% reduction in induction TTF hazards for RCHOP relative to CHOP (superiority)
  - Two-sided log-rank test
  - Power = 82% ; alpha= 5%
  - N=630 subjects randomized x 4 years + 2 years of follow-up are required to observe 277 failures*
  - Expected that 380 subjects would continue to 2nd randomization
    - 80% power to detect 40% reduction in hazards (2-sided log-rank test, alpha=0.05)

* For time to event outcomes, power is based on the # events observed not the # subjects

Example 3: RCHOP vs. CHOP DLBCL +/- Maintenance therapy (ECOG Study E4494)

• Features
  – Primary analysis was ITT
  – Design required adjusting for competing risks of failure due to older population
  – Stratification factors:
    • Induction- international prognostic index (IPI)
    • Maintenance-IPI and induction response
  – Sequential design used with interim analysis planned at 50, 70 and 100% failures

Example 3: RCHOP vs. CHOP DLBCL +/- Maintenance therapy (ECOG Study E4494)

- Features
  - DMC monitored trial and released results early when the maintenance comparison crossed pre-specified boundary
  - Due to potential confounding by MR on RCHOP vs. CHOP comparison, two unplanned analyses performed:
    - A weighted analysis of R-CHOP vs CHOP with no MR (removes MR pts and doubles the weight of observation pts)
    - The four CR/PR groups: CHOP, CHOP + MR, R-CHOP, R-CHOP + MR
  - Trial was one included in FDA submission for rituximab approval

Example 3: RCHOP vs. CHOP DLBCL +/- Maintenance therapy (ECOG Study E4494)

Summary

• Randomized trial design requires careful thought like any experiment
• Analysis of well planned trial should be simple and easy to interpret
  – May still have complicating issues (E4494)
• Need to balance
  – Scientific objectives
  – Practical considerations
  – Ethical concerns
• Involve statistician at early stages
Questions