Strategies for Randomized Controlled Trials Data Analysis

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Introduction

- The strategy for data analysis depends on the study design
  - Method of randomization
    - Completely randomized
    - Paired-matched
    - Stratified
  - unit of randomization
    - Individually randomized
    - Cluster randomized
  - Multi-Centre

Intention to Treat Analysis

- Intention to Treat ITT
  - An ITT analysis is based on the initial treatment assignment and not on the treatment eventually received
  - Randomized controlled trials data analyzed by the ITT approach provide unbiased comparisons among the treatment groups
  - ITT analyses are done to avoid the effects of crossover and dropout, which may break the random assignment to the treatment groups
  - The principle of ITT has become widely accepted for the analysis of controlled clinical trials since 1960s

ITT and Per-Protocol Analysis

- ITT Issues
  - Poor treatment protocol adherence
  - Missing data
- Per-protocol analysis (Modified ITT)
  - is comparison of treatment groups that includes only those patients who completed the treatment originally allocated.
  - If done alone, this analysis leads to bias.
- Both ITT and per-protocol analysis are recommended

ITT and Per-Protocol Analysis

- Reasons subjects could be excluded from a trial
  - Non-eligibility
  - Non-compliance
  - Had other illnesses
  - Did not attend all visits
  - Moved out
  - Dropped out

ITT and Per-Protocol Analysis

- Construct a flow chart providing numbers of subjects
  - registered or eligible randomized
  - assigned to each group
  - withdrawn (lost to follow-up and other reasons)
  - by group
    - completing the trial (with outcome known)
    - not receiving / complying with treatment as allocated

Baseline characteristics by treatment groups

- Study groups should be compared at baseline for important demographic and clinical characteristics using descriptive statistics, not using tests of hypothesis
  - Calculate sample statistics (means and stds or medians and quartiles or frequency and percentages) by treatment group
  - Randomization is expected to produce similar baseline statistics (large sample size)
  - Compare baseline characteristics between treatment groups to identify potential confounders

Unadjusted Analysis

- Estimate the effect size, 95% confidence interval, and pvalue for the primary outcome measure
  - Binary (proportion difference); continuous (mean difference)
  - The statistical methods used to do analysis depends on the type of outcome measure
    - Two sample ttest of analysis of variance for continuous (normal) outcomes
    - Chi-squared test for categorical outcomes
    - Two sample Wilcoxon test or nonparametric analysis of variance for continuous (non-normal) outcomes

Adjusted Analysis

- Identify possible confounders
  - Variables with imbalance between groups
  - Variables related to outcome
    - examine association between different variables and the outcome
- Adjust for confounders
  - Include confounders in a multivariate regression model
  - Test for multi-collinearity of the regression model
  - Generally confounding in RCT is not as important as in observational studies

Adjusted Analysis

- For example if one of the two groups has older patients, then the observed difference (or lack of difference) could be attributed to the imbalance.
  - calculate "adjusted" measures of the association between treatment and outcome using appropriate statistical method.

Effect modifiers and stratified analyses

- Consider a multicentre study
  - Test for the homogeneity of treatment effect across centres
    - Including interaction of treatment by centre in the model
  - When there is homogeneity between centres, pool the effect over centres (adjust effect for centres)
- Effect Modifiers
  - Effect modification happens when a particular variable has separate, different exposure effects depending on another variable
    - A simple example of effect modification would be when a cancer treatment has different effects in men than in women.

Secondary Analysis

- Secondary Analysis
  - The primary analyses are pre-specified in the protocol
  - Some may be pre-specified, many are not
  - Secondary analyses are supplemental and of various sorts
  - analysis (or analyses) that are of secondary importance in a study
  - the Secondary analyses results range from being quite conclusive to being hypothesis generating

Sensitivity Analysis

- Sensitivity Analysis
  - a method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, models, values of unmeasured variables, or assumptions
- Why is sensitivity analysis necessary
  - The design and analysis of clinical trials often rely on assumptions that may have some effect, influence or impact on the conclusions if they are not met.
  - It is important to assess these effects through sensitivity analyses.
  - Consistency between the results of primary analysis and the results of sensitivity analysis may strengthen the conclusions or credibility of the findings.
  - However, it is important to note that the definition of consistency may depend in part on the area of investigation, the outcome of interest or even the implications of the findings or results.

Sensitivity Analysis

- How confident can I be about the results?
- Will the results change if I change the definition of the outcome (e.g., using different cut-off points)?
- Will the results change if I change the method of analysis?
- Will the results change if we take missing data into account?
  - Will the method of handling missing data lead to different conclusions?
- How much influence will minor protocol deviations have on the conclusions?
- How will ignoring the serial correlation of measurements within a patient impact the results?
- What if the data were assumed to have a non-Normal distribution or there were outliers?
- Will the results change if one looks at subgroups of patients?
- Will the results change if the full intervention is received (i.e. degree of compliance)?

Subgroup Analysis

- Analysis of the results of a study just in certain subgroups.
  - Subgroup analysis should be specified in advance, not seeing the data.
  - They should be included in the protocol.
  - Lack of power
  - Multiple testing
  - Opponents describe subgroup analyses as
    - “fishing expeditions” and
    - “data dredging exercises.
  - Advocates of subgroup analyses are alarmed by the risk of missing important differences in treatment effect, which could result in failure to detect important differences in heterogeneous populations