Study Design and Statistical Analysis

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Outline

Designing Clinical Research Studies

Statistical Data Analysis

Designing Clinical Research Studies

- Study objective
- Target population
- Evidence to support the study
- Study design
- How big the study should be?
- What data to collect
- Follow-up?
- Data management, monitoring, quality control
- Data analysis plan
What is the Study Objective?
- Comparing two treatments in disease control?
- Identifying prognostic factors for disease development?
- Appropriate research questions that can be answered
- Translated into hypotheses (primary and secondary hypotheses)
- Primary hypothesis:
  - The most interested question
  - Capable of being adequately answered

What is the Target Population?
- Defined by the research questions (e.g., diabetes prevention)
- Ideal to study entire target population
- Valid if randomly select samples from the target
- Practically restricted to what’s available
- Impact generalization of the study results
- Minimize possible bias associated with sample selection

Example 1: TRIPOD Study (Diabetes, 2002)
- **Objective**: To test whether treatment of insulin resistance using TZD can delay or prevent type 2 diabetes
- **Population**: High-risk for diabetes (not diabetes yet) Hispanic women with prior GDM, at least 18 years old
Example 2: GDM cohort Study (Diabetes, 1999)

- **Objective:** To identify antepartum characteristics that predict the development of diabetes 11-26 months after index pregnancy in women diagnosed with GDM
- **Population:** Hispanic women with GDM who were not diabetic at postpartum visit

What Evidence to Support the Study

- PubMed, MEDLINE, etc., literature search and review
- Pilot study
- Clinical evidence/experience
- Meta analysis results

What Type of Study Design is Appropriate?

- **Clinical trials?**
- **Epidemiological study?**
- A clinical trial is an *experimental* study, require special consideration of ethics (DSMB)
- Epidemiological study is an *observational* study
Types of Clinical Study Design
- Clinical trials
  - Randomized controlled trial
  - Non-randomized controlled trial
  - Historical controls/database
  - Cross-over design
  - Factorial design
  - Single arm study: Phase I & II

Clinical Trial Phases
- Phase I:
  - Establish maximum dosage
- Phase II:
  - Look for preliminary evidence of efficacy and side effect
- Phase III:
  - Treatment is compared to control to demonstrate efficacy
- Phase IV:
  - Post marketing surveillance

Observational studies
- Case-control study
- Cross-sectional study
- Longitudinal cohort study
- Case series
- Case report
Types of Clinical Study Design (continued)

- Meta Analysis
  - A formal process with statistical methods to combine all the data from studies involving similar participants and similar objectives in a single analysis to reach a conclusion on the overall results

Clinical Trials Demonstrating Equivalency

- Designed to demonstrate equivalence of two treatments
- In difference trials, failure to reject the null (e.g., $p > 0.05$)
  - Does not mean the two are equal
  - Can only conclude that the evidence is inadequate to conclude they are unequal
- Need an equivalency trial to prove equivalency

Clinical Trials Demonstrating Equivalency

- A good standard treatment must exist
- A new one can be as effective as the standard but with
  - Less side effects
  - Less cost
  - Greater convenience
  - Higher quality of life
- Sample size is much larger than difference trial because a very small difference is compared
Randomization for Clinical Trials

- Reduce bias
- Achieve balance
- Quantify error attributable to chance (random)

Randomization Type

- Fixed allocation randomization
  - Simple randomization
  - Blocked randomization
  - Stratified randomization
- Adaptive randomization
  - Baseline adaptive randomization
  - Response adaptive randomization

Examples re-visit

- TRIPOD study: Randomized controlled clinical trial comparing two interventions (troglitazone vs. placebo)
- GDM cohort study: Epidemiological observational prospective cohort study to identify antepartum predictors for diabetes 11-26 months after pregnancy
How big the study should be?

- Key to the study power to detect the effect
- Small effect requires large sample size
- Power to detect the primary hypothesis should be \( \geq 80\% \)
- Pilot study does not require 80% power, mainly for preliminary data and feasibility

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How big the study should be?

- Estimated based on three parameters:
  - Type I error (false positive, 0.05)
  - Type II error (false negative, 0.20)
  - Effect size
- Effect size defined differently for different statistical methods
- Sample size is generally estimated by the primary hypothesis

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Design a Confirmative Phase III Trial

- Try to limit to one primary response variable
- Type I error increase if multiple responses, need to consider it in sample size estimation
- Hard to make conclusion if inconsistent results for multiple response variables
Examples re-visit

- TRIPOD study: The sample size was projected to provide power ≥ 80% to detect a ≥ 20% difference in cumulative diabetes incidence rates between treatment groups at a median follow-up of 42 month with a type I error of 0.05 (n=266)
- GDM cohort study: The sample size was estimated based on the relative risk 2-4 in developing diabetes comparing the highest to the lowest quartile of the baseline predictor variable

What Data to Collect?

- Defined by research questions
- Should collect at least all the measurements needed to test each of the hypotheses, including prognostic and confounder measures
- Can include other measures if minimal impact to the study (for future hypothesis exploration)
- All measurements should be assessed unbiased (blinding data assessor and subjects if needed)

Surrogate Measures

- What is a surrogate measure?
  - Substitute measure to the clinical outcome
- When do we use it?
  - For rare event (sample size)
  - For difficult to measure clinical outcome
  - A good surrogate exist
  - Prefer a continuous measure
**Surrogate Measures**

What is a good surrogate measure?
- Pathway to clinical event
- Changes is highly correlated with real clinical outcome of interest
- Can be assessed with little error
- Acceptable by scientific and medical communities
- Acceptable by subjects
- Cost-effective
- Example: IMT, CD4, PSA

**Follow-up?**

- Needed for clinical trials
- Needed for observational prospective longitudinal studies
- May schedule intermediate visits to capture changes (more information)
- Need to monitor
  - Attrition rate
  - Missing visits
  - Protocol compliance (clinical trials)
  - Adverse event (clinical trials)

**Data Analysis Plan**

- Needs to be considered during planning stage
- Defines the sample size estimation
- Collaborate with biostatistician to define the correct approach
I. Study Design & Analysis Variables

- Study design
  - Know the study design and how data are collected
  - Are observations independent, paired or repeated?
  - For non-independent observations, data correlation needs to be adjusted (e.g., multiple observation per subject, family members)

- Analysis Variables
  - Are the variables continuous, categorical or discrete?
**Variables Types**

- Continuous variables: can be measured as precisely as instrumentation permits (e.g., age, BMI, glucose)
- Discrete variables: countable (e.g., treatment group, diabetes, contraceptive methods)
- Continuous variables can be “discretized” (e.g., age < 50 vs ≥ 50, for clinical interpretation)
- Discrete measures can be made continuous (e.g., scores ranked from 1 to 10)

**II. Analysis Questions**

- Translate the research questions into statistical hypothesis (null vs. alternative)
- What are the dependent variables, independent variables, adjustment variables?
- 1 or 2-sided test? What type I error?

**Null vs. Alternative**

- Null hypothesis: hypothesis that not of interest
  - For difference trial: no difference, no effect, no change, etc
  - For equivalency trial: has difference
- Alternative hypothesis: hypothesis of interest
  - For difference trial: has effect, change, etc
  - For equivalency trial: no difference
Dependent vs. Independent Variables

- Dependent variables: outcomes, endpoints, response (e.g., diabetes development)
- Independent variables: treatment, groups, risk factor, casual variables
- Adjusted variables: confounders, variables which could bias the estimate of the relationship between the dependent and independent variables

1 or 2-sided Test & Type I error

- 1-sided test: tested parameter under alternative hypothesis is either greater than or less than what under the null, but not both (1 direction only)
- 2-sided test: tested parameter under alternative hypothesis can be greater than or less than what under the null (both directions)
- Type I error: probability of rejecting the null when null is true (false positive rate), defines the significance cut point (commonly used 0.05)

III. What statistical tests to use?

- Dependent variable is dichotomous
- Dependent variable is continuous
- Dependent variable is time to event
### III. What statistical tests to use?

- **Dependent variable is dichotomous (e.g., diabetes status)**
  - **Independent variable is dichotomous (e.g., tx group):**
    - Chi-square, Fisher’s exact, McNemar’s test
  - **Independent variable is discrete > 2 categories:**
    - Chi-square, Fisher’s exact, McNemar’s test

All nonparametric

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### III. What statistical tests to use?

- **Dependent variable is dichotomous (e.g., diabetes status)**
  - **Independent variable is continuous (e.g., age):**
    - Logistic regression
  - **Covariate adjustment:**
    - Logistic regression

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### III. What statistical tests to use?

- **Dependent variable is continuous (e.g., glucose, HbA1c)**
  - **Independent variable is dichotomous (e.g., tx group):**
    - T-test, Wilcoxon test
  - **Independent variable is discrete with > 2 categories:**
    - ANOVA, Kruskal-Wallis

Assumption for t-test, ANOVA: normal distribution
III. What statistical tests to use?

- Dependent variable is continuous (e.g., glucose, HbA1c)
  - Independent variable is continuous (e.g., age):
    - Correlation, linear regression
  - Covariate adjustment:
    - General linear regression
    - Assumption: normal distribution

- Dependent variable is time to event (e.g., time to development of diabetes)
  - Independent variable is dichotomous (e.g., group):
    - Logrank test
  - Independent variable is categorical (>2):
    - Logrank test
    - Log-rank test is nonparametric

- Dependent variable is time to event (e.g., time to development of diabetes)
  - Independent variable is continuous (e.g., age):
    - Cox regression
  - Covariate adjustment:
    - Cox regression
    - Cox regression is semi-parametric, assumption is proportional hazard
III. What statistical tests to use?

- Analysis approach for repeated measures (e.g., glucose change over time)
- Fixed effect (no variation in parameters between individuals):
  - Generalized estimating equation (GEE)
- Random effect (has variation in parameters between individuals):
  - Mixed-effect model
  - Assumption: normal distribution for continuous

Examples Re-visit

- TRIPOD study:
  - Dependent variable: time to development of diabetes
  - Independent variable: treatment group
  - Adjusted covariates: baseline unbalanced variables and on-trial characteristics
  - Analysis approach: logrank test & Cox regression

TRIPOD: Diabetes Rate

<table>
<thead>
<tr>
<th>Months on Study</th>
<th>Cumulative Probability of Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>10%</td>
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<tr>
<td>20</td>
<td>20%</td>
</tr>
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<td>30</td>
<td>30%</td>
</tr>
<tr>
<td>40</td>
<td>40%</td>
</tr>
<tr>
<td>50</td>
<td>50%</td>
</tr>
<tr>
<td>60</td>
<td>60%</td>
</tr>
</tbody>
</table>

Placebo

Troglitazone

RR=0.45 (p<0.009)

Buchanan et al: Diabetes, 2002
Examples Re-visit

GDM cohort study:
- Dependent variable: Diabetes status 11-26 months after index pregnancy
- Independent variable: Antepartum characteristics
- Adjusted covariates: Variables in the final model were adjusted for each other to assess independent prediction
- Analysis approach: logistic regression

GDM cohort result:

<table>
<thead>
<tr>
<th>Final Model</th>
<th>P value</th>
<th>Adjusted OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-h glucose, diagnostic OGTT</td>
<td>0.003</td>
<td>15.2</td>
</tr>
<tr>
<td>β-cell compensation index</td>
<td>0.009</td>
<td>0.09</td>
</tr>
<tr>
<td>Basal glucose production rate</td>
<td>0.04</td>
<td>5.3</td>
</tr>
</tbody>
</table>

*Highest vs. lowest tertile

Issues in Data Analysis

- Dropouts, non-compliance
- Intent-to-treat vs. response-to-treat analysis
- Missing data
  - MCAR, MAR, non-ignorable
  - Hard to test missing data mechanism
  - Perform sensitivity analyses
- Interaction - Subgroup analysis
- Multiple comparison issue
Multiple Comparison
- Repeatedly testing using the same data will increase chance finding – increase type I error
- In decreasing order of conservativeness:
  - Bonferroni multiple comparison procedure
  - Scheffe S test
  - Tukey HSD (honestly significant difference) test
- Fisher’s LSD test (least significant difference):
  - Did not provide appropriate type I error protection

Final Recommendation for Conducting Clinical Research
- Inclusion of the biostatistician from study design through manuscript preparation
- Good communication & collaboration between clinical investigators and biostatistician is essential
- Biostatistician should make effort to understand the disease under investigation
- Clinical investigator should also make effort to understand the biostatistics

Course Offerings in Preventive Medicine
- PM510: Introduction to Biostatistics (Fall, Spring and Summer)
- PM512: Introduction to Epidemiology (Fall and Spring)
- PM523: Clinical Trials (Spring)
- PM599: Biomedical Informatics (Summer)
- Information: Mary Trujillo: 323 442-1810
MS in Clinical and Biomedical Investigations

- Provide training to medical students, fellows, faculty and health professionals to appropriately conduct medical and translational research
- One-year of didactic course work
- One year of mentor-supervised research leading to grant proposals or peer-review paper(s)

Research tracks depend on research interests of applicant:
- Patient-oriented translational research
- Community-based intervention trials
- Design, conduct and analysis of clinical trials
- Epidemiology and disease etiology
- Molecular biology
- Cell biology
- Others

Patient-oriented translational research