

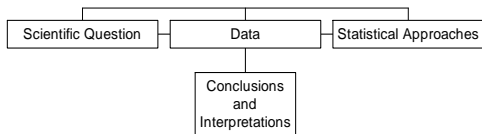
Biostatistics and Design in Clinical Research

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Outline

- Role of Biostatistician
- Study Design
- Analysis Plan
- Power Analysis
- Study section reviewers perspective
- Grant Writing Examples

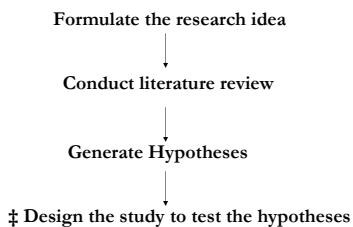
Statistical Collaboration



What is a Biostatistician and how does he/she differ from a statistician?

- Understands study designs (Epidemiology)
- Knows enough basic biology to be dangerous (biologist)
- Advanced training in statistical methods and there application (statistician)
- Not as strong in theoretical statistics as a mathematical statistician

When should you get help from a biostatistician?



‡ Good time to seek help

How not to interact with a Biostatistician

- Don't design the study yourself then expect a biostatistician to bail you out with the analysis
 - Example of VA study
- Don't write the entire grant then show up on Thursday asking for help when it needs to be submitted on Friday
 - My lessons learned
- Don't ask them to read several papers on background material
 - Starting off on the "wrong foot"

Study Design

Selecting the “Best” study design

- Factors that must be considered when exploring options for study design
 - Resources (\$) (Ideal study design may be cost prohibitive)
 - Population available
 - Time for completion
 - Patient burden

Types of Research Designs

- Experimental – randomization (clinical trials)
- Quasi-experimental – assignment to groups is not random (natural experiment)
- Observational – investigator does not manipulate/have control over the situation

Experimental Design Key Concepts

- P - Prospective?
- C - Placebo controlled?
- R - Randomized?
- D - Double-blind?
- L - Longitudinal?
- S - Subjects?
- M - Primary dependent measure?

Sample Design Paragraph

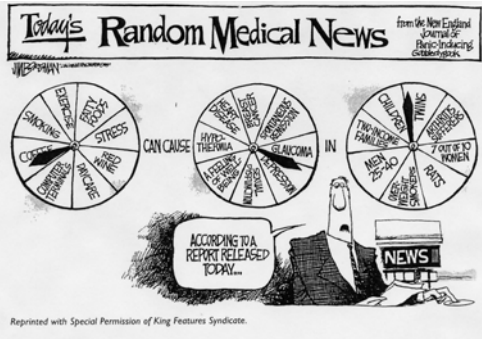
- This prospective (**P**), randomized (**R**), controlled trial will assess the efficacy of Treatment X as compared to Usual Care (**C**). Although the pediatrician will not be blind, patients (**S**), evaluators, and data collectors will be blinded to the level of intervention (**D**). Evaluations of functional status (**M**) will be made immediately prior to, 3 days after, and 180 days after treatment (**L**).

Study Design

What is the source of patients or experimental units?

- Who/What will be studied and why
- Any limitations on the source
- Any specific exclusions

Once a study or experiment is concluded how does one assess if the treatment or intervention was affective?



Analysis Plan

Outline of Analysis Plan

- Research Question 1
 - Type of data collected
 - Type of comparison
 - Statistical approach
 - Primary method of analysis for Q1
 - Additional exploration
- Research Question 2 ...

Algorithm for Choosing a Statistic

	Nominal (e.g. ethnicity)	Ordinal (e.g. no, moderate, severe)	Continuous (e.g. BP, HT, CO)
Correlation of Variables	Chi square test & Contingency Coefficient	Spearman Correlation	Pearson Correlation & Regression
Comparison of Groups (G)	Chi square test	Kruskal-Wallis ANOVA	Between Groups ANOVA
Comparison over time (T)	McNemar's chi square	Friedman ANOVA	Repeated Measures ANOVA
Comparison of G & T			Mixed Linear Models

Power Analysis

STATISTICAL POWER

Statistical power is the likelihood that a particular study will be able to detect and effect or difference given a true difference really exists. Commonly used values for power are 80% and 90%.

Note: Studies with power less than 80% are very unlikely to get funded.

Power Analysis

- Choose method of analysis
- Choose effect size
- ✓ Personal experience
- ✓ Pilot study
- ✓ Clinical norms
- ✓ Published research
- Choose alpha level ($\alpha=0.05$)
- Choose power level (80-90%)
- Compute sample size

Do I need sample size estimation or power calculation?

- Sample Size Estimation
 - Sample size can be estimated for a fixed power level
- Statistical Power
 - Other factors dictate sample size (fixed)
- “Two sides of the same coin”

Writing statistical methods and power estimation sections for your grant

What are study section reviewers looking for?

- Are methods described adequately and in unambiguous terms?
 - Assume at least one biostatistician will be on the study section
- Is selected analysis appropriate for the data type and study design?
 - Get a biostatistician to review your plan

- What are the assumptions of the selected methods and will they be met?
 - Every methods has assumptions – know what they are
 - Outline plan if they are not met – transformation/different method

What are reviewers looking for in power estimation section?

- Does the power calculation match the analytical plan?
- Is enough information provided to allow check on calculations
 - Make sure there is
- Do they provide power calculations for each AIM they are proposing to test?

EXAMPLE cont.

Typical statement for a grant regarding statistical power to compare means values between to groups:

A sample size of 127 in each group will have 80% power to detect a difference in means of 20 (the difference between a Group 1 mean of 190 and a Group 2 mean of 170) assuming that the common standard deviation is 50 using a two group t-test with a 0.05 two-sided significance level.

- Is there sufficient evidence to support values used in power calculations?
 - Pilot data
 - Published results
 - Clinical norms or expectations

Terminology

- Need to use statistical terminology
 - Not for the lay person
- Make sure you understand the terms being used and that they are being used appropriately
 - Have a biostatistician review it

Level of Detail

- Enough information to reassure reviewer that you understand the selected method
- Do not include descriptions of commonly used methods (e.g. mean, t test)
- If you have complex statistical methods use an appendix and summarize for text

Format for statistical methods and power calculations

- One section for both
 - Advantage – can be written in a more general form with references to appropriate AIMS – may use less space
 - Disadvantage – difficult to provide adequate details in terms of exactly which variable will be used where – can be more confusing in its presentation

- Include statistical method and power calculation in description of methods for each AIM
 - Advantage – makes it real clear which statistical method(s) relates to each AIM – insures power calculations are provided for each AIM – easy for reviewer to see they match
 - Disadvantage – may take up more space (but added clarity makes it worth it)

Example:

AIM1 – To show that diet X plus nutritional education Y in combination are most effective means to achieve weight reduction

AIM2 – That the above combined factors are more effective in females than males

Study Design – randomized prospective interventional trial

ARM1 – control (N1=100)

ARM2 – Diet only (N2=100)

ARM3 – Diet and Education (N3=100)

STATISTICAL METHODS #1

Data will be collected during each clinical visit and will be double entered into an Access database for quality control. Comparisons between study groups will be made using SAS 10.0. Calculations show that we will have greater than 80% statistical power.

STATISTICAL METHODS #2

Data will be collected during each clinical visit and will be double entered into an Access database for quality control. Comparisons between study groups will be made using Oneway ANOVA, all statistical tests will be conducted at the $\alpha=0.05$ level. Calculations show that we will have greater than 80% statistical power to detect a mean difference.

Statistical Methods #3

The change in weight will be computed for each individual as the difference between their baseline and final weights. Comparisons of mean weight changes between study groups will be made using Oneway ANOVA, all statistical tests will be conducted at the $\alpha=0.05$ level. Assuming a mean difference of 30 lbs between each of the groups and standard deviation of 10 lbs, we will have greater than 80% statistical power to detect a difference this large or greater.

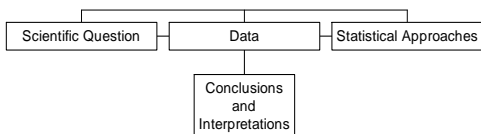
Statistical Methods #4

(Add to Statistical Methods #3)

Oneway ANOVA assumes that the data are normally distributed. Normality of the data will be tested using normal probability plots and histograms. Transformation will be used if necessary to insure the weight change data are normally distributed.

Mean weight change estimates and standard deviations used for power calculations were obtained in a pilot study N=10 subject per ARM.

Statistical Collaboration



What I hope that an investigator brings to our first meeting

- Basic description of background and motivation for the study
 - Don't go over-board – keep it as simple as possible
- 1-3 hypothesis of interest
- Related endpoints or output variable for each hypothesis
- Factors that may need to be adjusted for (confounding or effect modifying)

An Equation to Remember

Good Science + Bad Analytical Plan = No Funding



*“If you ask me a question
I don’t know,
I’m not going to answer”*



Yogi Berra

Questions???

THANK YOU!
