

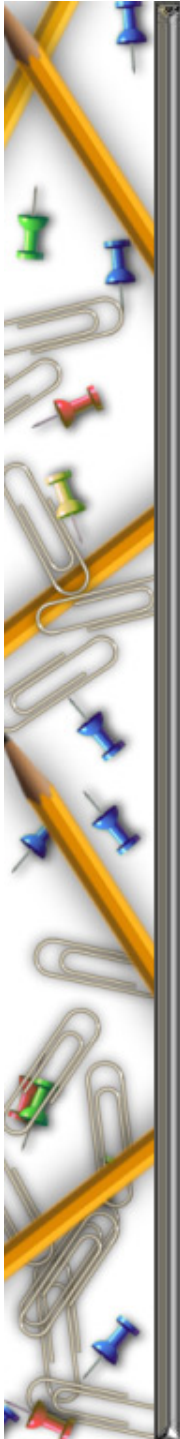


The Role of BIostatistics in Clinical Research

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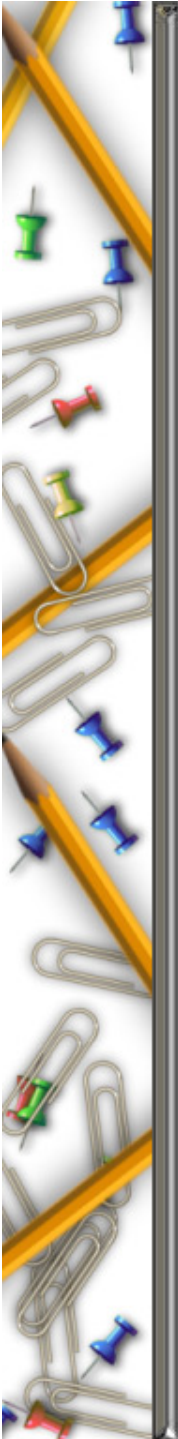
The Fundamentals of International
Clinical Research Workshop

DMID/ICSSC



How Many Biostatisticians do you need for your Study?

- No Biostatisticians are needed
- One Biostatistician
- Two Biostatisticians
- A Biostatistical center



Lead Study Biostatistician (LSB)
defends choices to questions raised
by stat reviewers (protocol or paper)

Responsibility = Credit/Blame



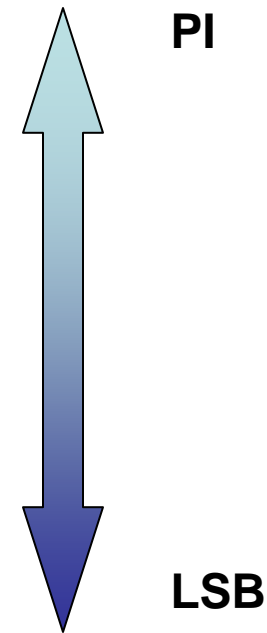
Biostatistician Role

- Protocol Development
- Data Management
- Study Implementation
- Study Monitoring
- Data Analysis
- Report/Manuscript Writing



Protocol Development

- Objectives
- Definition of Endpoints
- Study Design
- Sample size
- Analysis Plan



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Objectives

- Based on the objectives of the study:
 - Clear specification of the hypotheses to be tested (or parameters to be estimated)
 - Selection and definition of endpoints



Study Design

- Is the study design appropriate to provide the data needed to answer the objectives?
- Selection/recruitment of Participants:
 - Define procedures for minimizing selection bias. Sampling methods. Selection of Controls
 - If an RCT, define randomization procedures (sequence generation, and allocation concealment), blinding
- Design features:
 - Matching, blocking, stratification, length of follow up and frequency of contacts



Sample Size

- Justification in terms of power or precision for the primary endpoint
- Method used to calculate the sample size
 - Should be consistent with the primary method for data analysis, and appropriate for the study design
- Historical data to support the assumptions
- Justification in terms of feasibility



Analysis Plan Summary

- Provides the statistical methodology for the assessment of the primary objective(s):
 - Statistical Hypotheses and testing procedures
 - Primary Analysis Population
- Discusses statistical methods to be used in planned interim analyses. (Role of a DSMB)



Analysis Plan Summary

- Purposes:
 - Assuring objectives can be achieved
 - Justifying design and data collection



Protocol Review

- It is highly recommended that the LSB reviews the full protocol prior to final review/sign-off:
 - Clarity
 - Completeness
 - Consistency
 - Data quality issues
 - Feasibility



Protocol writing

- Objectives (input)
- Endpoints (input)
- Study Design (input)
- Randomization procedures (writes)
- Allocation concealment (input)
- Sample size (writes)
- Analysis plan (writes)

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Data Management

- CRF Development:
 - Content
 - Design
- Dataset specification:
 - Annotation of CRFs
 - Record Layout
- Validation:
 - Error checking specification
 - Test data

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Study Implementation

- Sampling Selection
- Implementation of Randomization procedures
 - Typically performed by an independent biostatistician with the instructions provided by the LSB
- Related Study Procedures



Study Monitoring

- Monitoring for Quality
 - The LSB should be kept informed of anything that affects the data
 - e.g., protocol violations, unintended unblinding, randomization errors, missing data, etc.)
- Monitoring for Safety/Efficacy:
 - Interim Analysis Reports
 - Use of an Independent Biostatistician
 - LSB still responsible for the content, analysis methodology, and data transfer coordination



Data Analysis

- Write a detailed analysis plan:
 - All hypothesis to be tested (or parameters to estimate)
 - Statistical Methods
 - Analysis populations
 - Interim analysis and adjustments to type I error
 - Hierarchy of analysis



Data Analysis

- Should be written prior to un-blinded review of the data or even prior to data collection:
 - Helps you prepare for report and manuscript writing
 - Helps in the validity and credibility of the results

Data Analysis

Fishing Expedition



Data Mining

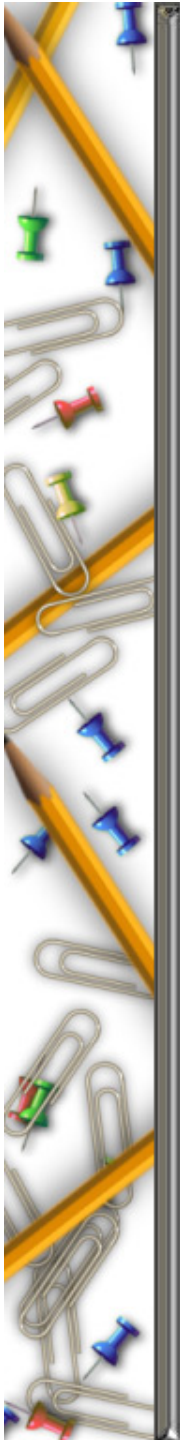
Data Dredging

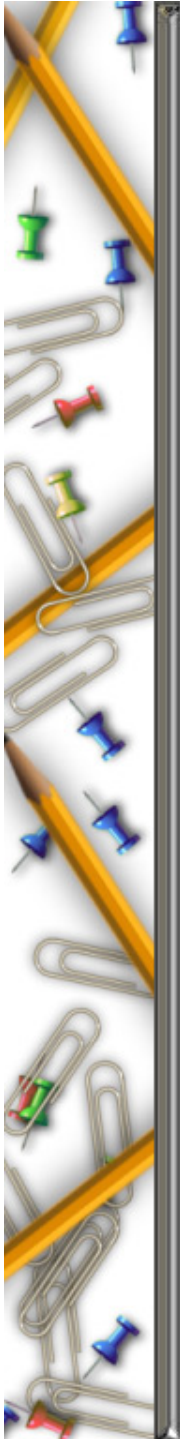
Data Torturing

Data Driven Analysis

Shotgun Approach

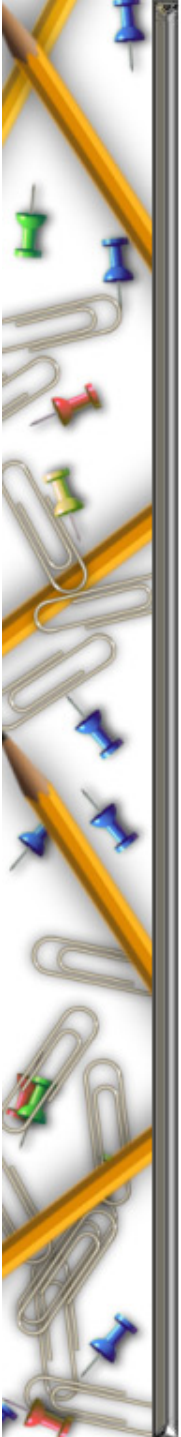
Exploratory Analysis





Report/Manuscript Writing

- Method Section:
 - Description of the data (design, endpoints)
 - Statistical Methodology
- Result Section:
 - Data presentation (tables, graphs, etc.)
- Discussion Section:
 - Appropriate interpretation of results
- Usually the third author in papers



How many biostatisticians does it take to change a light bulb?

- a) Only one, they're accustomed to menial work.
- b) Two, you have to plan for subject dropout in any clinical trial.
- c) Three, the probability of a biostatistician boring someone else to sleep is $2/3$.
- d) None, having the biostatistician's name appear on the protocol for changing the bulb will be enough.
- e) 1.5, the average of (a) to (d).
- f) It depends on the purpose for changing it and the design of the bulb.



How many Biostatisticians do you need for a Study?

- Lead Study Biostatistician
- Assistant Biostatistician
- Consultant Biostatistician
- Independent Biostatistician
- Verifying Biostatistician
- Supervising Biostatistician



Final Remarks

- The LSB should be involved in most aspects of a study
 - Plays a major role in protocol development, DM review, interim reporting, and data analysis
- The LSB ensures that ICH E9 guidelines on Statistical Principles are followed to:
 - Minimize Bias and Maximize Precision
- The LSB cares about data because s/he does the analysis, so s/he should be involved in any aspect/decision related to the data