Statistics in Clinical Trials

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visiting



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Contents

Preliminaries
0: Introduction
1: Background & Basic Concepts
2: Basic Trial analysis
3: Randomization
4: Size of the Trial
5: Multiplicity & Interim Analysis
6: Crossover Trials
7: Binary Response Data

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- Course web page

  http://nickfieller.staff.shef.ac.uk/tampere12/index.html

- Lecture notes and other course material

Purpose of Lectures

- There are 'complete' printed notes
  - These are not a textbook
    - some explanations are omitted
  - They are intended to allow you to concentrate on understanding & for me to cover some material very quickly
- Some lectures will be very close to the printed notes
  - This is **intended**
- Other lectures will fill in details & provide examples & **R** demos

- **Books**
  - **Campbell, M. J. (2001)** *Statistics at Square Two.* BMJ
  - **Matthews, J. N. S. (2000)** *An Introduction to Randomized Controlled Clinical Trials.* Arnold

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- **Objectives**
  - The objective of this course is to provide an introduction to some of the statistical methods and statistical issues that arise in medical experiments which involve, in particular, human patients. Such experiments are known collectively as ***clinical trials***.

- **New Techniques**, e.g.
  - Sample size calculations
  - McNemar's test
  - MantelHaenszel test
  - logistic regression
  - crossover trails
- **Issues in medical statistics**
  - ethics
  - design

- **Outline**
  - **Background**
    - historical development
    - placebo effect
    - blindness
    - phases of clinical trial

- **Outline (ctd)**
  - Basic trial analysis
    - parallel group
    - in series designs
    - factorial designs
    - sequential designs

- **Outline (ctd)**
  - Randomization
    - Objectives of randomization.
    - Simple
    - Restricted
    - Stratified

- **Outline (ctd)**
  - Size of trial
    - sample sizes needed to detect clinically relevant differences with specified power.
    - Implementation in **R**

- **Outline (ctd)**
  - Multiplicity and interim analyses
    - multiple significance testing
    - subgroup analysis
    - Bonferroni corrections.
  - Crossover trials
    - treatment, period and carryover effects

- **Outline (ctd)**
  - Binary responses
    - matched pairs and McNemar's test
    - logistic regression.

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- **Definition of clinical trial**
  - Any form of planned experiment which involves patients and is designed to elucidate the most appropriate treatment of future patients under a given medical condition

- **Notes**
  - Planned experiment
  - Inferential Procedure
    - want to use results on limited sample of patients to find out best treatment in the general population of patients who will require treatment in the future.

- **Historical Background**
  - 1537: Treatment of battle wounds:
  - 1741: Treatment of Scurvy
  - 1948: Streptomycin trial
  - **1954: Field Trial of Salk Polio Vaccine**
    - comparison between a randomized controlled doubleblind clinical trial and a nonrandomized open trial

- **Types of Trial**
  - Phase I trials: pharmacology & toxicity.
    - n=10 – 50
  - Phase II trials: safety & efficacy
    - n= 50 –100
  - **Phase III trials: treatment comparison**
    - **n= 100 – 1000**
  - Phase IV trials: Postmarketing surveillance
    - n= as many as possible

- Randomized Controlled Trials
  - Comparative
    - e.g. new *vs.*standard
  - Removes bias
    - Conscious or unconscious
  - Control group
    - As similar as possible to treated group

- **Placebo Effect**
  - **Blindness of trials**
    - Double blind
      Both patient & evaluator blind
    - Single blind
      either patient or evaluator blind

- **Ethical Considerations**
  - Treaty of Helsinki (1960+ammendments)
  - competition between individual and collective ethics
  - **unethical** to conduct research which is badly planned or executed.
    - Only compare treatment A with treatment B if we are genuinely unsure whether A or B is better

- **Local ethics committees**
  - Licence all clinical trials in their area
    - (hospital/city/region)
  - Informed Consent
  - unethical to perform a trial which has little prospect of reaching any conclusion
    - insufficient numbers
    - poor design

- **Publication Ethics**

  See BMJ Vol 323, p588, 15/09/01. (http://www.bmj.com)

  - **Concern** where authors have
    - not participated in design of study
    - had no access to raw data
    - little role in interpretation of data
    - not had control over publishing

- **Publication Bias**
  - Not all trials that take place are published
  - Only 20% of **all** cancer trials are published
    - http://theoncologist.alphamedpress.org/cgi/content/abstract/theoncologist.2008-0133v1

      (The Oncologist, 15 September 2008)
  - Only 6% of cancer trials run by *commercial industry* are published

- Contributors must now sign to declare:
  - full responsibility for conduct of study
  - had access to data
  - controlled decision to publish

- **Protocol**
  - written document
    - **all** details of trial conduct
- **Purpose**
  - motivation
  - aims

- **Design & conduct**
  - number of patients
    - and why
  - trial design & randomization
  - evaluation of response
    - baseline measure
    - principal response
    - subsidiary criteria

- techniques for analysis
  - Parametric or nonparametric
  - Adjustment for baseline imbalance
- **'informed consent' form**

- These details should be registered in registry of clinical trials http://clinicaltrials.gov/
  - In 2005, the International Committee of Medical Journal Editors announced they would only publish trials that had been registered
  - **BUT**
    - Mathieu, S. et al., 2009. Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials. *JAMA*, 302(9), 977-984.

- Mathieu, S. et al., 2009. Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials. *JAMA*, 302(9), 977-984.
- 323 trials in 10 leading journals
- Less than half were registered with primary outcome stated
  - » (89 not registered at all)
- A third of properly registered trials switched primary outcome in publication
- In most of these registered outcome showed no positive result but published primary did
- See Ben Goldacre, Guardian, 03/10/09
- Links on course web page (and to registry of clinical trials)

Evidence Based Medicine

- EBM
  - Objective is to consider critically all evidence that a treatment is effective
    - can never ***prove*** effectiveness or otherwise
    - formal hypothesis test can only assess *strength of evidence*
    - statistical test can only add to overall evidence
  - Randomized controlled trials are often regarded as the 'gold standard'
    - However RCTs often criticised, e.g. AIDS
    - Sometimes inappropriate, even for 'intervention studies'

- British Medical Journal
  - Smith & Pell (2003), **327**, 1459 – 1461
    - *Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials*

- **Results**
  - Our search strategy did not find any randomised controlled trials of the parachute.
- **Meta-analysis**
  - Our statistical approach was to assess outcomes in parachute and control groups by **odds ratios** and quantified the precision of estimates **by 95% confidence intervals**. We chose **the Mantel-Haenszel test** to assess heterogeneity, and **sensitivity and subgroup analyses and fixed effects weighted regression** techniques to explore causes of heterogeneity. We selected a **funnel plot** to assess publication bias visually **and Egger's and Begg's tests** to test it quantitatively. **Stata** software, version 7.0, was the tool for all statistical analyses.

- **Discussion**
  - **Evidence based pride & observational prejudice**
    - It is a truth universally acknowledged that a medical intervention justified by observational data must be in want of verification through a randomised controlled trial
    - We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Evidence Based Medicine

- Although RCTs are generally the best for evaluating interventions they are not the only way
  - How do we evaluate quality of other types of evidence (especially observational studies)?
- Bradford-Hill Criteria
  - Sir Austen Bradford-Hill, FRS: statistical epidemiologist, co-author of first smoking & lung cancer study

- Bradford-Hill Criteria
  - help to assess cause or influence
    e.g. of medication or environmental factor
    - Temporality
    - Consistency
    - Coherence
    - Strength of association
    - Biological gradient
    - Specificity
    - Plausibility
    - Freedom from bias
    - Analogies

- **Summary & Conclusions**
  - Clinical trials are ***planned*** experiments from which wider ***inferences*** are to be drawn involving human subjects
  - Randomized controlled trials are the only effective type of clinical trial
    - they conform to the Bradford-Hill criteria
  - Bradford-Hill criteria provides method of validating conclusions from other types of study when RCTs are inappropriate

- **Summary & Conclusions** (ctd)
  - 4 phases of Clinical Trials
    - Phase III is comparative
  - Blind trials (double or single)
    - preferable to reduce bias
  - Placebo effects assessed by controls
  - Ethics are statisticians' responsibility

My work in medical statistics

- **Consulting**
  - Analysis of stage 3 clinical trials for pharmaceutical companies (with SSU)
    - One **complete** trial lasting ~5 years (on alpha-beta blockers for hypertension)
    - Complete:- design, sample size, data entry, management & auditing, analysis,
  - Advice on design & analysis at statistical clinics
  - Advice on sample size calculations
    - Most common problem everybody encounters
- **Research**

My work in medical statistics

- **Research**
  - Analysis of restricted randomization trials *(with Elsa Valdez-Marquez)*
    - (see '**minimization**' methods later)
    - Efficient designs for small trials (~50) with subject with several prognostic factors
  - Non-inferiority trials *(with Nor Afzalina Azmee)*
    - Trials to test whether a new drug is 'no worse' than a standard drug (& better than a placebo)
  - Biomarkers

My work in medical statistics

- **Research**
  - Biomarkers *(with Lu Zu, Quintiles, AstraZeneca)*
    - 'Personalised medicine'
      - Treatment given to those most likely to benefit
    - "Characteristic that is measured & evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"
      - » ***Biomarkers Definitions Working Group 2001***
- Other work in ScHARR MSG:
  - Sample size calculations, biomarkers, quality of life measures, etc etc