Medical Statistics

MATH 38071

Notes

(Part I)

Course Contents

Notes, Exercises, Solutions and Past Papers with Solutions available at

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Further Reading

Recommended Course Text

John N.S. Matthews ***An Introduction to Randomised Controlled Trials***. Taylor & Francis London (2nd Ed. 2006 / 1st Ed. 2001)

An introductory text on clinical trials oriented towards mathematics and statistics students. Both editions in JRL are appropriate.

Background Reading

Books

Michael Campbell, David Machin, Stephen Walters ***Medical Statistics***. John Wiley London (4th Ed. 2010)

Introductory text oriented towards Medical Students. Provides overview of topics and covers a wider range than those considered in this course. Multiple copies available in JRL.

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1. Introduction Design, Bias & Ethical Considerations

Applications of Medical Statistics

- Medical research is a major field of application of statistical methods.
- Statisticians are involved with the design, conduct and analysis of medical research projects.

Examples of medical research in which statistical methods are applied include:

- Epidemiological Studies (Determining the cause of disease and ill health)
- Clinical Trials (Evaluation of the effectiveness of treatments)
- Laboratory Experimental Studies.
- Development of Diagnostic Methods
- Surveys of Patients and the Public

The problems raised by medical research data have led to important developments of statistical methodology.

Statistical Methods in Medical Research

Data Analysis

Design

- Choosing the study design.
- Determining the number of subjects that need to be included.
- Developing reliable and valid measures.

1.1 Types of Medical Research Study

Observational Studies in Epidemiology

(i) Case control studies.

Two sample of subjects are identified (i) Cases with the disease and (ii) Controls without. The level of exposure to the risk factor of interest is determined for each sample.

Example Doll & Hill (1954) carried out a case-control study to investigate whether smoking caused cancer. Patients admitted to hospital with lung-cancer were the cases. For each case, a control patients was selected of similar age and sex from patients admitted to the same hospital with a diagnosis other than cancer. Past smoking history was determined for each patient.

Table 1.1 Numbers of smokers and non-smokers among lung cancer patients and age-matched controls

	Status	Non-smokers		Total
		Number	(%)	Sample
Male	Lung Cancer	2	(0.3%)	649
	Controls	27	(4.2%)	649
Female	Lung Cancer	19	(31.7%)	60
	Controls	32	(53.3%)	60

Ex 1.1 *What are the limitations of this study and its design?*

Smoking status is determined retrospectively, which could be biased by recall..

(ii) Cohort studies.

A cohort of subjects is identified and the exposure to the risk factor measured. Subjects then followed up and outcome determined. The outcome is compared between those who are expose and non-exposed to the risk factor.

Example As part of the National Health and Nutrition Examination Survey in the USA (NHANES 1) , 7188 women age 25 to 75 were asked questions about alcohol consumption. After 10 years subjects were traced and cases of breast cancer identified. Breast cancer was 50% higher in drinkers than non-drinkers. The effect was still present after adjustment for obesity, smoking and menopausal status.

Ex 1.2 *What are the limitations of this design?*

Size and duration of study. Women were followed up for more than 10 year. A strength is that alcohol consumption was measured prior to determination of the outcome that is breast cancer.

Experimental studies

a) *Randomised controlled trials.*

b) Laboratory experiments.

Diagnostic and measurement studies

a) Testing the validity of diagnostic tests and outcome measures.

b) Testing the repeatability of a method of measurement.

c) Comparison of different measurement methods.

Systematic Reviews

a) *Meta-analysis based on summary statistics.*

b) Meta-analysis using individual patients data.

Some Terminology

Bias is a factor that tends to deviate the result of a study systematically away from its true value.

- Statistical: Related to properties of the estimator.
- Experimental: Due to the design of the study.

Bias is a major concern in medical research as it may occur in many different ways due to the complexity of clinical research.

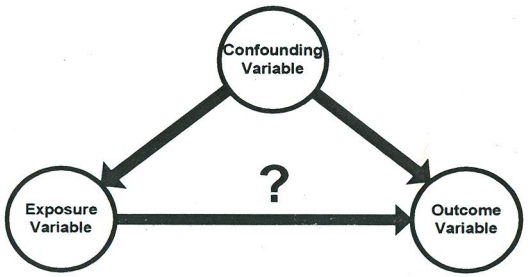
Types of Variable in Medical Studies

Outcome Variable: This is the *dependent variable* of interest in a medical study.

Exposure Variable: This could be a treatment or a risk factor for disease and is an *independent variable*.

Intermediate Variable: A variable on the causal pathway from exposure to outcome.

Confounding Variable: A variable that can cause or prevent the outcome of interest, independently of exposure, that is also associated with the factor under investigation.



Confounding variables may cause **bias**.

1.2 Clinical Trials Terminology

Treatment or **Intervention**: therapeutic drugs, prophylactics (preventative treatment), diagnostic tests (e.g. blood pressure), devices (e.g. replacement hip joint), procedures (e.g. surgery) or activities by the patient or therapist (e.g. physiotherapy).

Clinical Trial: A prospective study involving human subjects, designed to determine the potentially beneficial effect of therapies or preventative measures, where the investigator has control over who receives the treatment.

Prognostic Factor: A prognostic variable is a variable that influences outcome where the patient receives no treatment or the current standard treatment.

Ex 1.3 *Given an example of a prognostic factor in the treatment of Cancer?* Size, number or type of tumour

Type of Clinical Trial in Drug Development

Phase I

- to establish safe/tolerable levels of a new drug often using healthy volunteers.

Phase II

- to provide evidence of potential efficacy.
- to develop dosage regimes.

Phase III

- to compare efficacy and effectiveness with a control therapy.

The Importance of a Control Group

The simplest of clinical trial is a *case series* evaluation in which a group of patients who receive a new treatment are followed up and the outcome of treatment recorded.

The problem with case series evaluations of treatments is that it is impossible to know whether the observed outcome is

(i) the consequence of the treatment or

(ii) the natural course of the disease,

as some conditions can resolve without treatment. e.g. acute viral infections such as the common cold.

It is important therefore to have a control treatment against which a new treatment may be compared. In most circumstances the control should be the current standard treatment if there is one. The effect of a new treatment is then measured relative to the control.

Treatment Effect

In the controlled trials literature the term *treatment effect* means the relative effect of one treatment on the outcome compared to another.

Clinical Trials Protocol

Every well-designed clinical trial has a protocol. This documents the purpose and procedures of the trial including:

1. The trial objectives.
2. Description of treatments being compared.
3. The study population
    a. Inclusion criteria.
    b. Exclusion criteria.
4. Sample size assumptions and estimate
5. Procedure for enrolment of participants.
6. Method used to allocate treatment to participants.
7. Ascertainment of outcome
    a. Description and timing of assessments.
    b. Data collection method.
8. Data analysis
    a. Final analyses.
    b. Interim analyses
9. Trial termination policy.

Published reports of clinical trial should present all this information in detail.

An Early Controlled Clinical Trial - Treatment of Scurvy

(James Lind 1753 -www.jameslindlibrary.org)

"On 20 May 1747, I took 12 patients in the scurvy on board the 'Salisbury'. The cases were as similar as I could have them. They all … had … putrid gums, the spots and lassitude …

"They laid together … and had one diet common to all … two cider, two others Elixir Vitril [H_2SO_4], two vinegar , two sea water, two oranges and lemons , the two remaining Nutmeg."

"One of the two receiving oranges and lemons recovered quickly and was fit for duty after 6 days. The second was the best recovered of the rest and assigned the role of nurse to the remaining 10 patients."

Ex1.4 *What are the limitations of this study?*

- sample size
- no statistical inference!
- method of allocation of treatment to patients. Lind could have given his favoured treatment to patients with the best prognosis
- method of determining outcome is unclear.

1.3 Bias in Controlled Trials

When interpreting the results of a controlled trial one needs to consider potential sources of bias.

SAMPLING bias - Unrepresentative nature of study sample. Patient included may not be typical of the usual clinical population.

ALLOCATION bias – The prognosis of patients receiving each treatment may differ.

PERFORMANCE bias - Delivery of other aspects of treatment to each treatment group may differ e.g. In a clinical trial comparing surgical procedures the post-operative care could differ between treatments.

FOLLOWUP bias -Type and number of patients lost to follow-up may differ between treatment groups.

ASSESSMENT bias – The researcher may record the outcome more or less favourably for one treatment group than another due to their prejudice.

STATISTICAL ANALYSIS bias – carry out multiple inferential analyses before choosing the one most favourable to the desired conclusion.

Methods for Preventing Bias

Concealment is considered to be the most effective way of preventing bias. It refers to the practice of withholding details of the allocated treatment from the participants in a trial (patients, care providers, researchers or statistician).

Randomisation , that is the process of randomly choosing the treatment a patient receives, is also important.

Bias Due to Lack of Concealment Prior to Treatment Allocation

Knowledge of the next treatment allocation may influence

(i) Patient's willingness to participate.

(ii) Clinician's determination to recruit a particular patient into trial leading to sampling and allocation bias.

These may both vary due to the characteristic or prognosis of the patient. It is important therefore that the next treatment allocation is concealed from both the patient and clinician prior to the decision to join the trial being made.

After a patient has been allocated treatment it may be possible to continue to conceal the allocation from both the patient and the clinician.

Bias Due to Lack of Concealment after Treatment Allocation

Patients

- Default from treatment.
- Seek alternative treatments.
- Modify health related behaviour such as diet or lifestyle.

Treating health professionals

- Change expectation of treatment which might affect the patient's response.
- Influence choice of secondary treatments.

Outcome Assessor

- Outcome assessor's awareness of the patient's treatment may influence the measured outcome.
- Knowledge of treatment may influence the patient's self-assessment of outcome.

Double Blind Clinical Trial Neither the patient nor the treating/assessing clinician knows which treatment a patient is receiving. This should reduce bias in performance of other aspects of treatment, follow-up and assessment of outcome.

Single Blind Clinical Trial Treatment allocation is concealed from the patient but not the clinician.

An Open / Unconcealed Clinical Trial

Patients and treating health professional both know which treatment the patient is receiving.

Placebo Treatments

A *placebo* drug is an inactive substance designed to appear exactly like a comparison treatment, but devoid of the active component.

- A placebo should match the active treatment in appearance, labelling and taste. The appearance of drug and placebo should be tested before the trial to make sure patients cannot identify the placebo.

- The term placebo may also be used to describe a treatment that has been shown to have no or minimal effect, which is to be used as a control treatment. For example a patient information leaflet has been shown to have no effect on outcome for some conditions so it may be considered to be a placebo (although it may differ in appearance from the active treatment).

- Use of placebo treatment will be unethical if an established active treatment exists that is known to be effective. In such cases an active control group, such as best standard treatment, should be used in place of a placebo.

Ex 1.5 Given an examples of a treatments that could/ could not be tested in a double blind trial.

Drug treatment can be tested in a double blind trial, although sometimes this is not possible due to the requirement to modify dose.

Most surgical treatment cannot be tested in a double blind trial.

Problems of Implementing Concealment

- The patient may guess which of the drug treatments being tested they are receiving from taste.
- The patient, clinician or researcher may guess from appearance or side effects.
  Example: Trial of Aspirin for Myocardial Infarction Prevention
  380 trial participants asked which drug they received.
  50% correct, 25 % incorrect, 25% refused or selected a drug not being tested.

  Example: Staining of teeth in trials of fluoride toothpastes.

- The drugs may have different dosage or frequency or delivery systems.
  Example: In the treatment of asthma different drugs may have different frequencies. It may therefore be necessary to include placebo drugs to give each treatment the same dosage regime.

Matching active drug and placebo may be difficult and costly. Double-blind trials can become much more complex for chronic diseases where the patients are on long-term medication that might require adjustment of dosage. Procedures also need to be in place should a patient lose their tablets. This complexity may make it impossible for trials of some drug to be double blind.

1.4 The Importance of Randomisation

- It enables **concealment of allocation** from participants prior to randomisation thereby preventing allocation bias.
- It creates treatment groups with similar distribution of patient characteristics (both recorded and unrecorded) thereby supporting causal inference.
- It provides a logical basis for **statistical inference**.

Note that *Randomisation* is not the same as *Random Sampling* .

Problems of Randomisation

- Lack of equipoise. May be unethical if there is already evidence that one treatment is better or that patients may incur harm due to one treatment.
- Sampling bias. Patients that agree to participate in a randomised trial may be atypical, for example the elderly and frail are known to be less likely to participate.

Even with randomisation it is still possible for allocation bias to occur due to the play of chance leading to differences in treatment groups. This is called **chance bias**.

Summary: Biases in Controlled Clinical Trials

SAMPLING bias - Unrepresentative nature of study sample.
Solution: Modify patient recruitment – change inclusion and exclusion criteria.

ALLOCATION bias - Prognosis of patients receiving each treatment may differ.
Solution: Randomisation + making sure it is carried out correctly.

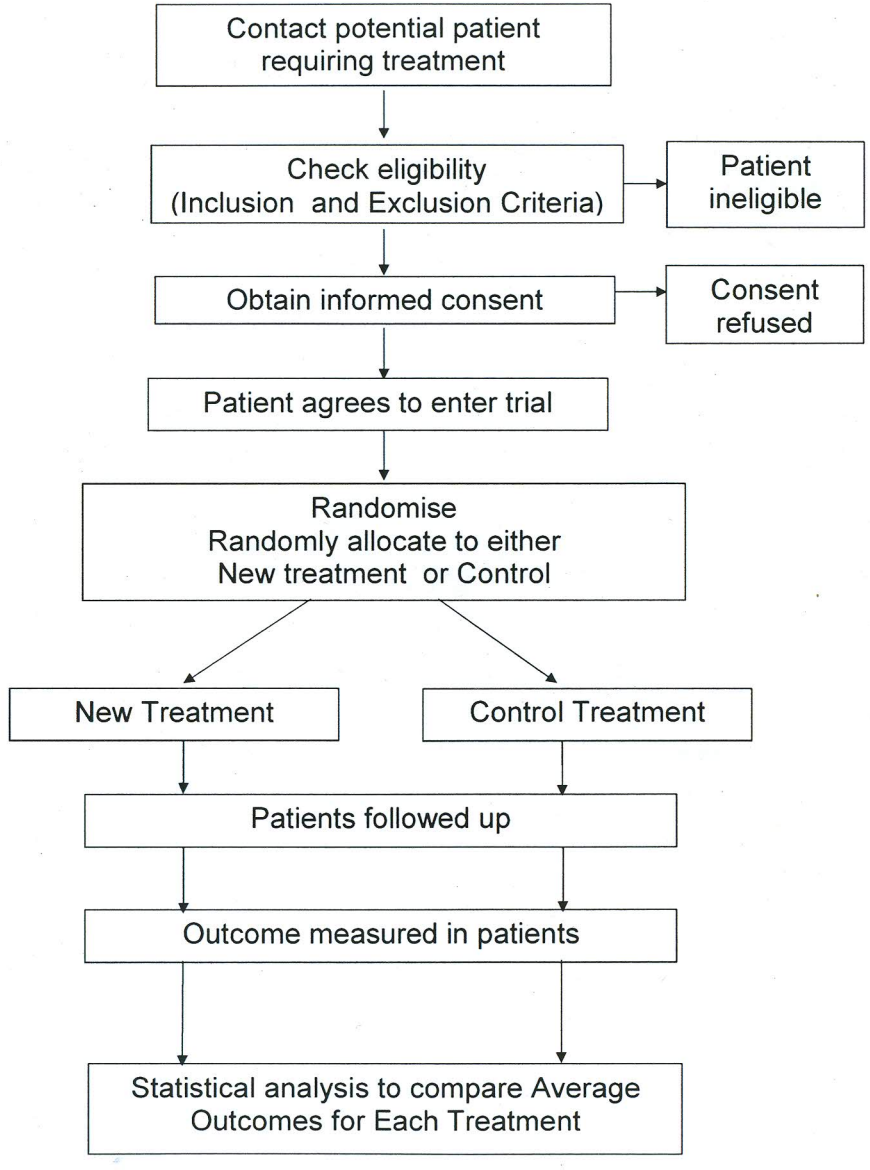
PERFORMANCE bias - Delivery of other aspects of treatment to each group may differ
Solution: Concealment after randomisation, Standardisation of additional treatments and other care procedures.

FOLLOWUP bias -Type and number of patients lost to follow-up may differ between treatment groups.
Solution: Rigorous follow-up of all patients in both treatment groups.

ASSESSMENT or **MEASUREMENT** bias – The researcher may record the outcome more or less favourably for one group.
Solutions: Conceal treatment allocation from outcome assessor.

ANALYSIS bias –Different statistical analyses may give different results.
Solutions: Use of a predefined statistical analysis plan, Statistical analysis carried out with the treatment allocation anonymized.

Figure 1.1 Schematic Diagram of a Randomised Controlled Trial



1.5 Ethical Issues Related to Randomised Trials

Ethical dilemmas

- Is it ethical to withhold a new treatment that is thought to be better?
- Is routine practice based on inadequately tested treatments with no proven efficacy ethical?
- How much should the patient be told about the two treatments being compared?

Ethical Principles

- Patients must never be given a treatment that is known to be inferior. Treatments should be in equipoise, that is there needs to be uncertainty regarding which treatment is better.
- Prior to recruitment patients must be fully informed about possible adverse reactions and side-effects they may experience.
- Once informed, they, or their representative in the case of non-competent patients, must give consent, preferably in writing.
- Withholding consent must not compromise the patient's future treatment.
- Patients who have entered a trial must be able to withdraw at any time.

Mechanism to protection the interest of the patients

- Ethics committee approval of research proposals.
- Individual Informed consent by the patient.
- A data monitoring and ethical committee to monitor progress of trial.

1.6 Some Important Randomised Controlled Trials

Streptomycin in the treatment of pulmonary tuberculosis (UK Medical Research Council, 1948)

- Streptomycin and bed rest vs. bed rest alone.

Important features:

- Randomisation using sealed envelopes.
- Blinded, replicated and standardised assessment of x-rays.
- Significantly better survival and radiological outcome in the streptomycin group.

Antihistaminic drugs for the treatment of the common cold (UK Medical Research Council, 1950) - Sample size of 1550 cases.

Important features:

- Use of a placebo to make the trial double blind.
- Important as patients asked to evaluate their own outcome.

The end result showed no difference (40% antihistamine, 39% placebo)

Salk Polio Vaccine Trial (USA 1954)

- Observational study - school grade 2 pupils vaccinated and compared with unvaccinated grade 1 and 3.
- Randomised controlled double blind trial – 400,000 children.

Important features:

- Large population based trial of preventative intervention.
- Demonstrated bias of non-randomised studies.
- Used a saline as a placebo vaccine.