Medical Statistics

MATH 38071

Notes

(Part I)

Course Contents

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

personalpages.manchester.ac.uk/staff/chris.roberts

Further Reading

Recommended Course Text

John N.S. Matthews ***An Introduction to Randomised Controlled Trials***. Taylor & Francis London (2^{nd} Ed. 2006 / 1^{st} 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 (4^{th} 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.

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?*

(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?*

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.

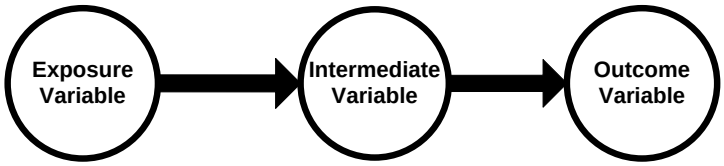
Bias is a major concern in medical research as it may occur in many different ways due to the complexity of clinical research.

<u>Types of Variable in Medical Studies</u>

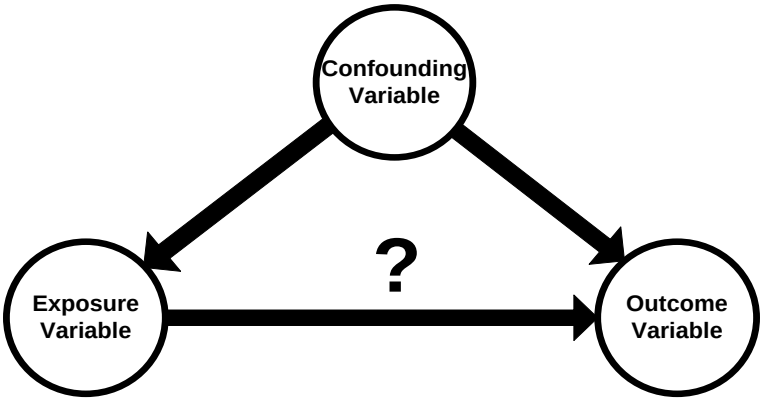
Outcome Variable: This is the *dependent variable* of interest in a medical study.

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?*

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?*

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 both 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.

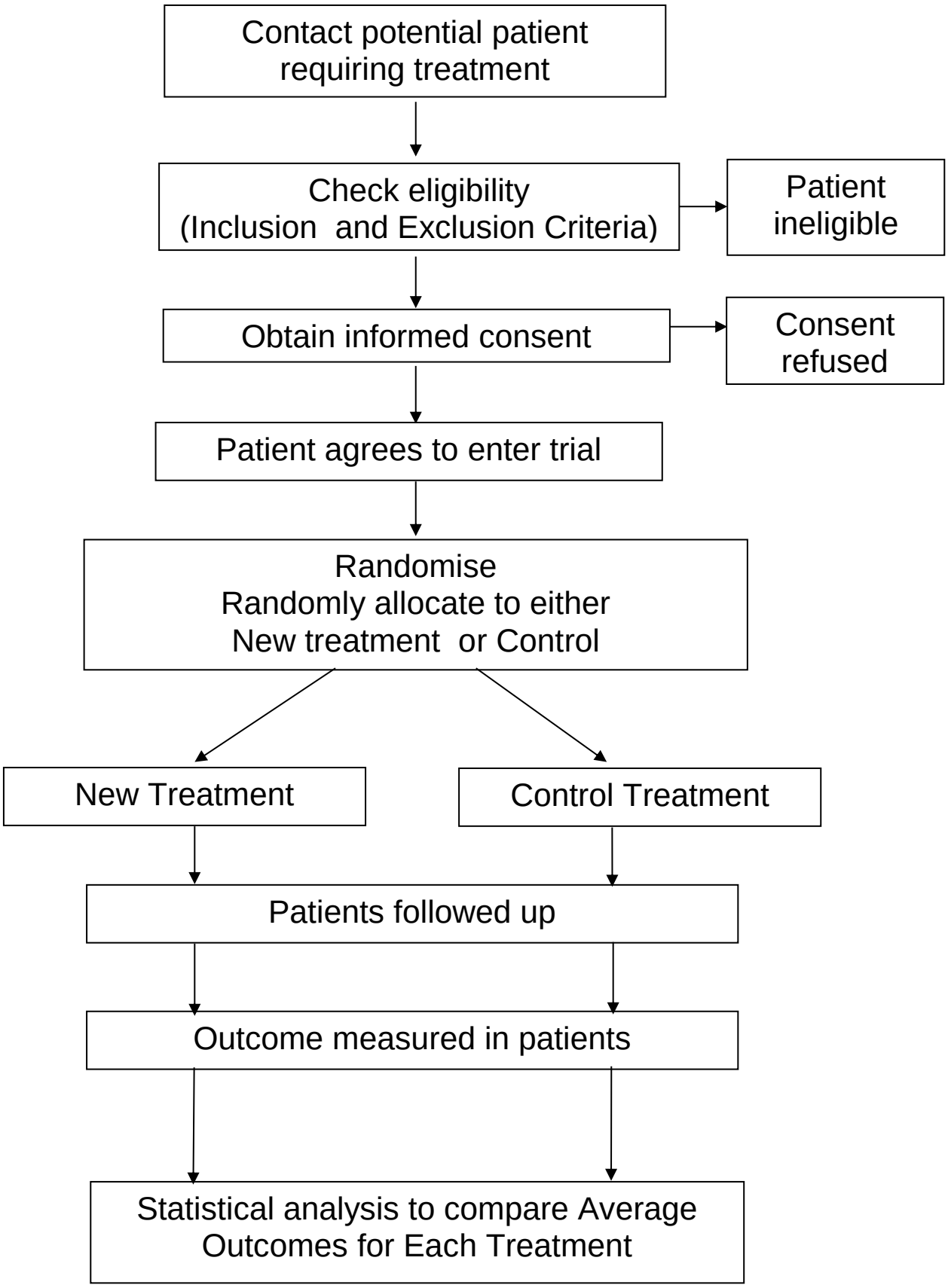
PERFORMANCE bias - Delivery of other aspects of treatment to each group may differ
Solution: Concealment after randomisation, Standardisation of additional treatments and other care procedures.

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 the 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.

2. Basic Analyses for Continuous Measures

2.1 Randomization and Causal Inference

One of the advantages of randomization is that it justifies causal inference from statistical analysis rather than just association. Consider a randomized controlled trial in which patients have been randomized to either a new treatment (*T*) or a control treatment (*C*). For the i^{th} patient an outcome measure, Y_i , has been determined. A patient has two *potential outcomes*, say $Y_i(T)$ and $Y_i(C)$. The ideal way to estimate the effect of treatment would be to give both treatments to each patient, and calculate the benefit of treatment as the difference between the two potential outcomes. The treatment effect for the i^{th} patient would therefore be $\tau_i = Y_i(T) - Y_i(C)$. The expected treatment effect is therefore,

$$\begin{aligned}\tau = E[\tau_i] &= E[Y_i(T) - Y_i(C)] \\ &= E[Y_i(T) - Y_i(C) | i \in T].\Pr[i \in T] + E[Y_i(T) - Y_i(C) | i \in C].\Pr[i \in C] \\ &= \left(E[Y_i(T) | i \in T].\Pr[i \in T] - E[Y_i(C) | i \in T].\Pr[i \in T]\right) \\ &\quad + \left(E[Y_i(T) | i \in C].\Pr[i \in C] - E[Y_i(C) | i \in C].\Pr[i \in C]\right)\end{aligned}$$

In most trials a patient can only receive one treatment. If a patient receives treatment *T*, the outcome $Y_i(C)$ cannot be observed. $Y_i(C)$ is called a *counter-factual* outcome for patients that treatment. Similarly, $Y_i(T)$ is the *counter-factual* outcome for patients receiving treatment *C*. Randomization allows us to assert: $E[Y_i(C) | i \in T] = E[Y_i(C) | i \in C]$ and $E[Y_i(T) | i \in C] = E[Y_i(T) | i \in T]$.

Define $\mu_T = E\left[Y_i(T) \middle| i \in T\right]$ and $\mu_C = E\left[Y_i(C) \middle| i \in C\right]$.

Hence

$$\tau = \left(\mu_T.\Pr[i \in T] + \mu_T.\Pr[i \in C]\right) - \left(\mu_C.\Pr[i \in T] + \mu_C.\Pr[i \in C]\right)$$
$$= \mu_T - \mu_C$$

The expected values, μ_T and μ_C, can be estimated by the sample means for each group, say $\overline{y}_T$ and $\overline{y}_C$. Hence, the expected treatment effect can be estimated by

$$\hat{\tau} = \overline{y}_T - \overline{y}_C \ .$$

If *Y is* a continuous normally distributed outcome measure, a statistical test of the null hypothesis $H_0 : \tau = 0$ can be carried out using a two independent samples t-test.

In observational studies there is no randomization. Other methods have to be used to allow one to assert that

$E\left[Y_i(T) \middle| i \in C\right] = E\left[Y_i(T) \middle| i \in T\right]$ and $E\left[Y_i(C) \middle| i \in T\right] = E\left[Y_i(C) \middle| i \in C\right]$

<u>Design methods</u>

Matching of cases with controls in case-control studies.

Stratification or matching exposed and unexposed subjects in cohort studies.

<u>Data analysis</u>

Using statistical modelling to adjust for confounding variables.

2.2 Glossary: Statistical Inference Terminology

Hypothesis test: A general term for the procedure of assessing whether "data" is consistent or otherwise with statements made about a "population".

Null Hypothesis: Represented by H_0 meaning "no effect", "no difference" or "no association" .

Alternative hypothesis: Represented by H_1 that usually postulates non-zero "effect", "difference" or "association".

Significance test: A statistical procedure that when applied to a set of observations results in a *p*-value relative to a null hypothesis.
A common misinterpretation of significant test is that failure to reject the null hypothesis justifies acceptance of the null hypothesis.

***p*-value:** Probability of obtaining a test statistic at least as extreme as the one that was actually observed, assuming that the null hypothesis is true.
A common misinterpretation of a p-value is to say it is the "probability of the null hypothesis".

Significance level (α) : The probability at which the null hypothesis (H_0) is rejected when the null hypothesis is actually true. Typical chosen to be 5%, 1%, or 0.1%. It is also referred to as the *test size*.

Critical value: This is the value of the test statistic corresponding to a given significance level.

Confidence interval: A range of values calculated from a sample of observations that are believed with a particular probability to contain the true population parameter value. A 95% confidence interval implies that if the process was repeated again and again 95% of intervals would contain the true value in the population.

2.3 The Two Samples t-test

If the outcome measure Y is normally distributed, a test statistic can be defined as $T = \dfrac{\bar{y}_T - \bar{y}_C}{\hat{SE}\left[\bar{y}_T - \bar{y}_C\right]}$ where

$\hat{SE}\left[\bar{y}_T - \bar{y}_C\right] = s.\lambda$, $\lambda = \sqrt{1/n_T + 1/n_C}$, $s = \sqrt{\dfrac{(n_T - 1)s_T^2 + (n_C - 1)s_C^2}{n_T + n_C - 2}}$ with s_T and s_C being the sample standard deviations for the two treatment groups.

A two-sided test of the null hypothesis $H_0 : \mu_T = \mu_C$ against the alternative hypothesis $H_1 : \mu_T \neq \mu_C$ compares $|T|$ with a critical value, $t_{\alpha/2}(\nu)$, where α is the significance level and $\nu = n_T + n_C - 2$ is the degrees of freedom. If $|T| > t_{\alpha/2}(\nu)$, the null hypothesis (H_0) is rejected.

$t_{\alpha/2}(\nu)$ is the percentage point of the central t-distribution with ν degrees of freedom such that upper tail probability $\Pr\left[t > t_\alpha(\nu)\right] = \alpha$.

Assumptions of the two-sample t-test

(i) Subjects are independent.

(ii) The variances of the two populations being compared are equal $\left(\sigma_T^2 = \sigma_C^2 = \sigma^2\right)$.

(iii) Data in each population are normally distributed.

One-sided and Two-sided Hypothesis Tests

A one-sided test restricts the alternative hypothesis to be either larger, that is $H_1 : \mu_T > \mu_C$ or smaller $H_1 : \mu_T < \mu_C$. For a two-sided test the alternative hypothesis is $H_1 : \mu_T \neq \mu_C$. A two-sided test is in essence two one-sided tests each with significance level $\alpha/2$. Based on rejection of the null with a two-sided test one can conclude that $\mu_T < \mu_C$ or $\mu_T > \mu_C$.

It is recommended that two-sided tests be used unless there is a strong a-priori reason to believe rejection in one direction is of absolutely no interest. In medical studies this is rarely the case, so two-sided tests are recommended and generally used. The decision to use a one-sided test in preference to a two-sided test should be made prior to analysing the data to prevent statistical analysis bias.

Confidence Intervals for the Difference of Means

If the outcome measure Y is normally distributed satisfying the assumptions for the t-test , a (1-α) confidence interval for the treatment effect τ is given by $\bar{y}_T - \bar{y}_C \pm t_{\alpha/2}(\nu)\hat{SE}\left[\bar{y}_T - \bar{y}_C\right]$ where

$\hat{SE}\left[\bar{y}_T - \bar{y}_C\right] = s\sqrt{1/n_T + 1/n_C}$ $s = \sqrt{\dfrac{(n_T - 1)s_T^2 + (n_C - 1)s_C^2}{n_T + n_C - 2}}$ and

$\nu = n_T + n_C - 2$.

Example 2.1: Ventilation Trial. *A trial of two ventilation methods during cardiac bypass surgery*. Seventeen patients undergoing cardiac bypass surgery were randomized to one of two ventilation schedules using 50% nitrous oxide 50% oxygen.

New For 24 hrs

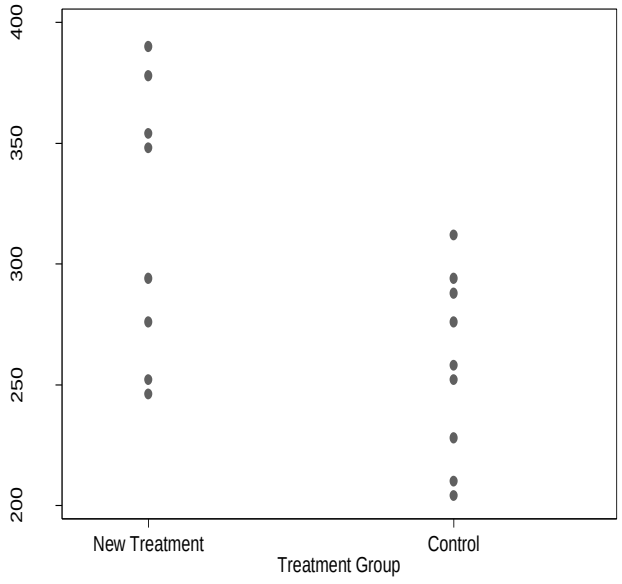
Control Only during operation

The outcome measure for the trial was red cell folate level at 24 hrs post-surgery.

Table 1.1 Red Cell Folate Level Data and Summary Statistics

Treatment Group	*New*	*Control*
Red Cell Folate Level (μg/l)	251 275 291 293 332 347 354 360	206 210 226 249 255 273 285 295 309
Mean	$\bar{y}_T = 312.9$	$\bar{y}_C = 256.4$
Standard deviation (s.d.)	$s_T = 40.7$	$s_C = 37.1$
Treatment group size	$n_T = 8$	$n_C = 9$

Figure 1.1 Dotplot of data



Ex 2.1 *Calculate the point estimate of the treatment effect of the New treatment compared to the Control treatment.*
Point estimate of the treatment effect is

$\hat{\tau} = \bar{y}_T - \bar{y}_C =$

Ex 2.2 *Using a two-sample t-test, test whether there is a significant treatment effect using a 5% two-sided significance level.*

(i) Calculate the pooled standard deviation

$$s = \sqrt{\frac{\left(n_T - 1\right)s_T^2 + \left(n_C - 1\right)s_C^2}{n_T + n_C - 2}} =$$

(ii) Calculate the standard error of the difference between means

$\hat{SE}\left[\bar{y}_T - \bar{y}_C\right] = s\sqrt{1/n_T + 1/n_C} =$

(iii) Calculate the test statistic

$$T = \frac{\bar{y}_T - \bar{y}_C}{\hat{SE}\left[\bar{y}_T - \bar{y}_C\right]} =$$

T is assumed to have a t-distribution with degrees of freedom $\nu = n_T + n_C - 2$. Hence $\nu =$.

Using Statistical Tables

A copy of the School of Mathematics Statistical Tables is available on the module page. These give the cumulative distribution for the t-distribution $t_{v,q}$ where q is the cumulative probability for q= *0.95,0.975, 0.99 and 0.995*. For a two-sided test of size α= 0.05, the critical values is the value of t that give a right tail probability equal to 0.025 ($\alpha/2$), which corresponds to $q=1-\alpha/2=0.975$ in the table. The critical value for a two-sided 0.05 size test is therefore

$$t_{15\,,\,0.975}=t_{0.025}(15)=2.1314.$$

The null hypothesis of no treatment effect would therefore be rejected at a 5% level, because $|T|>2.1314$. The test statistic T is also larger than $t_{15,0.995}=t_{0.005}(15)=2.9467$. Hence, the null hypothesis would also be rejected with a two-sided 1% significance level. The p-value is therefore less than 0.01. Using statistical software on can calculate the p-value for $T=2.995$ to be 0.009.

Ex 2.3 *Calculate the 95% confidence interval of the treatment effect*

A (1-α) confidence interval for the treatment effect τ is given by $\bar{y}_T-\bar{y}_C \pm t_{\alpha/2}(\nu)\hat{SE}[\bar{y}_T-\bar{y}_C]$ where $\hat{SE}[\bar{y}_T-\bar{y}_C]=s\sqrt{1/n_T+1/n_C}$

$\bar{y}_T-\bar{y}_C=$ $\quad$ $t_{0.025}(\nu)=$ $\quad$ $\hat{SE}[\bar{y}_T-\bar{y}_C]=$

The confidence interval is therefore

Figure 2.1 STATA Output for Two-Sample t-test and CI for

Ventilation Trial

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 Control |       9    256.4444    12.37393     37.1218    227.9101    284.9788
     New |       8     312.875    14.37935    40.67094    278.8732    346.8768
---------+--------------------------------------------------------------------
    diff |           -56.43056    18.86238               -96.63477   -16.22634
------------------------------------------------------------------------------
    diff = mean(Control) - mean(New)                                  t =  -2.9917

Ho: diff = 0                                     degrees of freedom =       15

   Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0046         Pr(|T| > |t|) = 0.0091          Pr(T > t) = 0.9954
```

Ex 2.4 *Briefly comment on the results of the ventilation trial.*

"For patients receiving bypass surgery there was evidence that ventilation for 24 hrs significantly increased post-operative red folate levels by ____ μgl (95% c.i. _____to _____ μgl, p<_____) compared to ventilations restricted to the duration of the operation."

2.4 Assumptions of the two sample t-test and confidence interval

The two-sample t-test makes three assumptions:

I. Subjects are independent.

Independence relates to the design - are patients' outcomes independent or could patients be interacting in some way? In most but not all trials this is plausible.

II. The variance of the two populations being compared are equal $\left(\sigma_T^2 = \sigma_C^2 = \sigma^2\right)$.

It is sometimes suggested that one should carry out a test comparing variances $\left(H_0 : \sigma_T^2 = \sigma_C^2\right)$, such as Levene's test for equality of variances, to choose between using the t-test or tests such as the Satterthwaite or Welch test that do not assume $\sigma_T^2 = \sigma_C^2$. Unfortunately, this procedure has problems. First, the adverse effect of unequal variance on the results of a t-test is greatest when sample size is small, but in this circumstance the Levene's test will have low power to reject $H_0 : \sigma_T^2 = \sigma_C^2$. Secondly, this is a misuse of statistical test, as one cannot use a test to establish the null hypothesis $\left(H_0 : \sigma_T^2 = \sigma_C^2\right)$ only the alternative $\left(H_1 : \sigma_T^2 \neq \sigma_C^2\right)$.

III. Data in each population are normally distributed.

Sometimes tests of normality, such as the Kolmogorov-Smirnov test, are suggested to check the distributional assumptions. These have the same problem as the Levene's test as the assumptions of normality is most critical where sample size is small. A better alternative is to check the distributional assumption graphically. Alternatively one might consider external evidence from other studies using the same measure in similar subjects perhaps with a much larger sample size.

Where equality of variance is not plausible the Satterthwaite test or the Welch test can be used in place of a two-sample t-test.

Where data are non-normal data can be transformed to be closer to normally distributed, by taking the log, square-root, or reciprocal of the measure so that a t-test can be used. Note that inference now relates to the transformed values. For example if a log transformation is used inference now relates to the ratio of geometric means. Alternatively a non-parametric methods that make no distributional assumptions can be used such as the Fisher-Pitman permutation test or the Mann Whitney U-test can be used.

To simplify calculations equality of variance and normality can be assumed in all exercises and exam questions. It is important therefore only to be aware of the assumptions and the alternatives.

3. Analyses of Binary Outcome Measures

3.1 Treatment Effect for Binary Outcome Measures

Suppose the outcome measure Y_i is binary, examples of which might include death, survival, recurrence or remission from disease, sometimes referred to by the neutral term "event". One summary of outcome is the proportion of patients that had the event in each treatment group, which estimates the probability of events in each treatment, say π_T and π_C, or population rates. An alternative parameter is the odds of the event, which is the probability of the event divided by the probability of the complimentary event.

Table 3.1 Notation for a Trial with a Binary Outcome

Frequency Dist.	Treatment	Control
Yes	r_T	r_C
No	$n_T - r_T$	$n_C - r_C$
Total	n_T	n_C
Probability of Event (Population proportion)	π_T	π_C
Sample proportion	$p_T = \frac{r_T}{n_T}$	$p_C = \frac{r_C}{n_C}$
Odds of Event Population Odds	$\frac{\pi_T}{(1-\pi_T)}$	$\frac{\pi_C}{(1-\pi_C)}$
Sample Odds	$q_T = \frac{r_T}{n_T - r_T}$	$q_C = \frac{r_C}{n_C - r_C}$

The effect of treatment can be measured in three ways

Rate or Risk Difference, $RD = \pi_T - \pi_C$,

Rate Ratio, $RR = \dfrac{\pi_T}{\pi_C}$

Odd Ratio, $OR = \dfrac{\dfrac{\pi_T}{(1-\pi_T)}}{\dfrac{\pi_C}{(1-\pi_C)}} = \dfrac{\pi_T(1-\pi_C)}{(1-\pi_T)\pi_C}$

3.2 Inference for the Rate Difference

The rate difference (*RD*) is estimated by $\hat{RD} = p_T - p_C$ where

$p_T = \dfrac{r_T}{n_T}$ and $p_C = \dfrac{r_C}{n_C}$. The numbers of successes r_T and r_C have distributions $Bin[n_T, \pi_T]$ and $Bin[n_C, \pi_C]$. From properties of the binomial distribution the variance of r_T equals $n_T.\pi_T(1-\pi_T)$.

Hence the proportion $p_T = \dfrac{r_T}{n_T}$ is given by

$Var[p_T] = \dfrac{Var[r_T]}{n_T{}^2} = \dfrac{\pi_T(1-\pi_T)}{n_T}$ and similarly for $Var[p_C]$.

Since treatment groups are independent, it follows that

$$Var[RD] = Var[p_T - p_C] = Var[p_T] + Var[p_C] = \frac{\pi_T(1-\pi_T)}{n_T} + \frac{\pi_C(1-\pi_C)}{n_C}$$

.

This can be estimated by substituting p_T and p_C for π_T and π_C.

Hence,

$$\hat{SE}[\hat{RD}] = \hat{SE}[p_T - p_C] = \sqrt{\frac{p_T(1-p_T)}{n_T} + \frac{p_C(1-p_C)}{n_C}}\,.$$

This is used for confidence interval construction.

Under the null hypothesis $H_0 : RD = 0$, $\pi_T = \pi_C = \pi$ say. The pooled proportion π can be estimated by $p = \frac{r_T + r_C}{n_T + n_C} = \frac{n_T p_T + n_C p_C}{n_T + n_C}$ with $E[p] = \frac{n_T \pi_T + n_C \pi_C}{n_T + n_C}$.

Hence, the null standard error can be defined as

$$\hat{SE}_{null}\left[\hat{RD}\right] = \sqrt{\frac{p(1-p)}{n_T} + \frac{p(1-p)}{n_C}} = \sqrt{p(1-p)\left(\frac{1}{n_T} + \frac{1}{n_C}\right)}.$$

This is used for statistical inference on $H_0 : RD = 0$.

Two-Sample z-test of Proportions

A test of $H_0 : RD = 0$ vs $H_1 : RD \neq 0$ can be constructed as

$$Z_{RD} = \frac{\hat{RD}}{\hat{SE}_{null}\left[\hat{RD}\right]} = \frac{p_T - p_C}{\hat{SE}_{null}\left[p_T - p_C\right]}.$$

Under assumptions given below Z_{RD} is approximates a standardised normal distribution, $N[0,1]$. This is the two sample z-test for proportions corresponding to the two-sample t-test for means.

Two-Sample z-test of Proportions

$$Z_{RD} = \frac{p_T - p_C}{\hat{SE}_{null}\left[p_T - p_C\right]} \text{ and } \hat{SE}_{null}\left[p_T - p_C\right] = \sqrt{p(1-p)\left(\frac{1}{n_T} + \frac{1}{n_C}\right)}$$

where $p = \frac{r_T + r_C}{n_T + n_C}$.

For an α-size two-sided test of $H_0 : RD = 0$ vs $H_1 : RD \neq 0$ compare Z_{RD} against critical values defined by $\pm z_{\alpha/2}$. Alternatively, the p-values for the two-sided test is given by $2\left(1 - \Phi\left(\left|Z_{RD}\right|\right)\right)$ where Φ is the cumulative density of the standardized normal distribution.

Confidence Interval

A (1-α) confidence interval for $RD = \pi_T - \pi_C$ is given by

$$p_T - p_C \pm z_{\alpha/2}\hat{SE}\left[p_T - p_C\right]$$

where $\hat{SE}\left[p_T - p_C\right] = \sqrt{\frac{p_T(1-p_T)}{n_T} + \frac{p_C(1-p_C)}{n_C}}$

Assumptions

(i) subjects are independent and

(ii) $n_T\, p$, $n_C\, p$, n_T (1-p), n_C (1-p) are all greater than 5.

There are improved formulae for the z-test and confidence interval that include a *continuity correction* to improve the normal approximation of the binomial distribution, but these methods are not considered any further in this module.

Example 3.1. The Propranolol Trial

91 patients admitted with myocardial infarction were randomly allocated to propranolol or placebo. The table below records survival status of propranolol treated patients and control patients 28 days after admission

Status 28 days after admission	*Propranolol*	*Placebo*
Alive	38	29
Died	7	17
Total	45	46

Ex 3.1 *For the Propranolol Trial data calculates the point estimate of the difference in survival rate*

For the Propranolol group the rate =

For the Placebo group the rate =

Therefore RD=

Ex 3.2 *Check the assumptions of z-test of proportions*

The assumptions of the z-test of proportions are that $n_T\,p$, $n_C\,p$, n_T (1-p), n_C (1-p) are all greater than 5.

$$p = \frac{r_T + r_C}{n_T + n_C} =$$

Hence $n_T\,p$, $n_C\,p$, n_T (1-p), n_C (1-p) are

Ex 3.3 *Compare the survival rate for the two treatments using a z-test of proportions.*

From above *p*=0.736. , $p_T - p_C = \frac{r_T}{n_T} - \frac{r_C}{n_C} =$

$$\hat{SE}_{null}\left[p_T - p_C\right] = \sqrt{p(1-p)\left(\frac{1}{n_T} + \frac{1}{n_C}\right)} =$$

$$Z_{RD} = \frac{p_T - p_C}{\hat{SE}_{null}\left[p_T - p_C\right]} =$$

From table of the normal distribution the critical values of a two-sided 5% level test are ± 1.960

$$p - value = 2\left(1 - \Phi\left(|Z|\right)\right) =$$

Note that it does not matter whether the z-test is compute based on the proportion who have died or the proportion still alive.

Normal Distribution and Normal Statistical Tables

Suppose Φ is the cumulative distribution function of a standardized normal distribution $N[0,1]$. In this module the percentage point z_α of a random variable Z with distribution $N[0,1]$ is the value such that $P[Z > z_\alpha] = 1 - \Phi(z_\alpha) = \alpha$.

Tables provided by the Mathematic department define a percentage point the percentage point z_q to be the value such that $P[Z < z_q] = \Phi(z_q) = q$.

Table 3.2 Summary of Important Percentage Points of the Standardized Normal Distribution

α	q	z
0.2	0.8	0.8416
0.1	0.9	1.2816
0.05	0.95	1.6449
0.025	0.975	1.9600
0.01	0.99	2.3263
0.005	0.995	2.5758

Calculation of 95%-Confidence interval for difference of proportions

Ex 3.4 *For the Propranolol Trial calculate a 95% confidence interval of the difference in survival rate for the two treatments.*

$$\hat{SE}\left[p_T - p_C\right] = \sqrt{\frac{p_T\left(1-p_T\right)}{n_T} + \frac{p_C\left(1-p_C\right)}{n_C}} =$$

From tables $z_{0.025} =$

(1-α) confidence interval calculated from $p_T - p_C \pm z_{\alpha/2}\hat{SE}\left[p_T - p_C\right]$

Ex 3.5 *Briefly comment on the effect of propranolol treatment on survival.*

" There was evidence that for patients admitted with myocardial infarction those treated with propranolol had an improved survival at 28 days post admission ( ) as compared to untreated patients ( ) with a difference of (95% c.i. to p-value =)."

Note. In the critical appraisal paper they write *p* to represent th p-value

Figure 3.1 STATA Output for z-test of proportions for the Propranolol Trial Data based on numbers of death before 28 days

```
Two-sample test of proportion                Placebo: Number of obs =       46
                                          Propranolol: Number of obs =       45
------------------------------------------------------------------------------
    Variable |       Mean   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     Placebo |   .3695652   .0711683                      .2300779    .5090526
 Propranolol |   .1555556   .0540284                      .0496619    .2614493
-------------+----------------------------------------------------------------
        diff |   .2140097   .0893532                      .0388806    .3891387
             |  under Ho:   .0923926     2.32   0.021
------------------------------------------------------------------------------

     diff = prop(Placebo) - prop(Propranolol)                  z =   2.3163
                                   Ho: diff = 0
      Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(Z < z) = 0.9897         Pr(|Z| < |z|) = 0.0205          Pr(Z > z) = 0.0103
```

Numbers Need to Treat

Numbers need to treat (NNT) is defined as the average of the number of patients that need to be treated to prevent one additional bad outcome. This measure is popular with doctors as it gives them a measure of the population level benefit of any treatment.

NNT is simply the reciprocal of the rate difference RD, that

$$NNT = \frac{1}{RD}.$$

A confidence interval of NTT can be found by taking the reciprocal of the confidence limits of *RD*. Note that the confidence interval becomes nonsensical if the confidence interval of RD includes zero.

Ex 3.6 Calculate the point estimate and 95% confidence interval of NNT for propranolol .

3.3 Inference Based on the Odd Ratio

The odd ratio $OR = \dfrac{\pi_T(1-\pi_C)}{(1-\pi_T)\pi_C}$ can be estimated by $\hat{OR} = \dfrac{p_T/(1-p_T)}{p_C/(1-p_C)}$.

Since $p_T = \dfrac{r_T}{n_T}$ and $p_C = \dfrac{r_C}{n_C}$, $\hat{OR} = \dfrac{r_T(n_C - r_C)}{(n_T - r_T)r_C}$.

Example cont. Propranolol Trial

Status 28 days after admission	***Propranolol***	***Placebo***
Alive	38	29
Died	7	17
Total	45	46
Proportion surviving	84% (38/45)	63% (29/46)

Ex 3.7 Calculate the odds ratio of survival until 28 days for propranolol treatment as compared to placebo

$$\hat{OR} = \frac{r_T(n_C - r_C)}{(n_T - r_T)r_C} =$$

The odds ratio takes values in the range $(0,\infty)$. An odds ratio equal to 1 implies no effect. If the odds ratio is greater than 1, it implies increased odds and below 1 implies reduced odds. The odd ratio for an event (say death) is the reciprocal of the odd ratio for the complimentary event (say survival).

Confidence Intervals for Odds Ratios

The sampling distribution of odds ratio (OR) is poorly approximated by the normal distribution. Instead, confidence intervals for the $\log_e[OR]$ are calculated and then exponents (anti-logs) taken to get the confidence interval of the odds ratio. This means that the resulting confidence interval is not symmetric about the point estimate.

With the notation above $SE\left[\log_e\left[\hat{OR}\right]\right] = \sqrt{\frac{1}{r_T} + \frac{1}{n_T - r_T} + \frac{1}{r_C} + \frac{1}{n_C - r_C}}$

This can be derived as follows:

$$Var\left[\log_e\left[\hat{OR}\right]\right] = Var\left[\log_e\left[\frac{p_T(1-p_C)}{(1-p_T)p_C}\right]\right]$$

$$= Var\left[\log_e\left[\frac{p_T}{(1-p_T)}\right] - \log_e\left[\frac{p_C}{(1-p_C)}\right]\right]$$

$$= Var\left[\log_e\left[\frac{p_T}{1-p_T}\right]\right] + Var\left[\log_e\left[\frac{p_C}{1-p_C}\right]\right] \text{(*)}$$

because treatment groups are independent. Approximate standard errors can be calculated using the *Delta Method*, which is based on a Taylor Series approximation. This states that

$$Var\left[f(x)\right] \cong f'(x)^2_{x=E[x]} Var[x].$$

Considering $f(p_T) = \log_e\left[\frac{p_T}{1-p_T}\right]$,

Hence $f'(p_T) = \frac{1}{p_T} + \frac{1}{1-p_T} = \frac{1}{p_T(1-p_T)}$

Since $E[p]=\pi$ and $Var[p_T]=\dfrac{\pi_T(1-\pi_T)}{n_T}$,

it follows that

$$Var\left[\log_e\left[\frac{p_T}{1-p_T}\right]\right]=\left(\frac{1}{\pi_T(1-\pi_T)}\right)^2\frac{\pi_T(1-\pi_T)}{n_T}=\left(\frac{1}{n_T\pi_T(1-\pi_T)}\right).$$

Similarly,

$$Var\left[\log_e\left[\frac{p_C}{1-p_C}\right]\right]=\left(\frac{1}{n_C\pi_C(1-\pi_C)}\right).$$

Substitution in the equation (*) above give

$$Var\left[\log_e\left[\hat{OR}\right]\right]=\frac{1}{n_T\pi_T(1-\pi_T)}+\frac{1}{n_C\pi_C(1-\pi_C)}$$

$$=\frac{1}{n_T\pi_T}+\frac{1}{n_T(1-\pi_T)}+\frac{1}{n_C\pi_C}+\frac{1}{n_C(1-\pi_C)}.$$

The standard error can be obtained by substitution of p_T and p_C for π_T and π_C.

Hence $SE\left[\log_e\left[\hat{OR}\right]\right]=\sqrt{\dfrac{1}{n_Tp_T}+\dfrac{1}{n_T(1-p_T)}+\dfrac{1}{n_Cp_C}+\dfrac{1}{n_C(1-p_C)}}$

$=\sqrt{\dfrac{1}{r_T}+\dfrac{1}{n_T-r_T}+\dfrac{1}{r_C}+\dfrac{1}{n_C-r_C}}$ as required ■

Using this result the (1-α) confidence interval of $\log_e[OR]$ is

$$\log_e\left[\frac{r_T(n_C-r_C)}{(n_T-r_T)r_C}\right]\pm z_{\alpha/2}\sqrt{\frac{1}{r_T}+\frac{1}{n_T-r_T}+\frac{1}{r_C}+\frac{1}{n_C-r_C}}$$

Confidence intervals for the odds ratio are obtained by taking the exponents.

Ex 3.8 *For the data from the Propranolol trial calculate the 95% confidence interval for the odd of survival at 28 days for propranolol as compared to placebo.*

$\log_e\left[\hat{OR}\right] =$

$$\hat{SE}\left[\log_e\left[\hat{OR}\right]\right] = \sqrt{\frac{1}{r_T} + \frac{1}{n_T - r_T} + \frac{1}{r_C} + \frac{1}{n_C - r_C}} =$$

95% Confidence intervals of $\log_e\left[\hat{OR}\right]$ are given by

$\pm 1.96 \times$, that is

Taking exponentials 95% Confidence interval of $\hat{OR}$ is (,)

Hypotheses Test for the Odds Ratio

A test of the null hypothesis H_o:OR=1 could be based on the statistic $Z_{lor} = \dfrac{\log_e\left[\hat{OR}\right]}{\hat{SE}\left[\log_e\left[\hat{OR}\right]\right]}$ i.e. test $H_0 : \log_e\left[\hat{OR}\right] = 0$. In practice one does not do this as the test of the null H_o: OR=1 is equivalent to the test based on the rate difference, H_o: RD=0, which is preferable as it does not depend an approximate standard error determined using the delta method. The p-value for the z-test of proportions calculated above is therefore used for hypothesis tests of the odds ratio in preference to the statistic Z_{lor}.

Ex 3.9 Summarize the results of the propranolol trial based on Odds Ratios analysis.

" There was evidence that propranolol increased the odds of survival compared to placebo (OR= 3.18, 95% c.i. 1.17 to 8.67, p=0.022)."

Interpretation of the Odds Ratio

Many people find odds ratios difficult to interpret, but the odds ratio is an important measure of effect in medical statistics. One reason for this is that the odds ratio can be estimated by logistic regression, which enables estimation of the odds ratio adjusted for other variables. This is very important for observational studies as it enables adjustment of effects for confounding variables. What is more the odds ratio is essential for case control studies as it is not possible to estimate either the risk difference or the risk ratio of the outcome due to the way in which subjects have been selected.

3.4 Analyses Based on the Rate Ratio

The rate ratio $RR = \frac{\pi_T}{\pi_C}$ can be estimated by $\hat{RR} = \frac{p_T}{p_C}$

Confidence intervals for the rate ratio, also called the risk ratio, can be constructed in a similar way to the odds ratio. As with the odds ratio the hypotheses test for the rate ratio is equivalent to that for the rate difference (*RD*) and so the z-test for proportions is still used to test hypotheses.

4. Sample Size And Power In Parallel Group Clinical Trials

4.1 Sample size and power

Sample calculation is important for two reasons

- If too few patients are recruited, the trial may lack statistical power, so the study is likely to fail to answer the question it is attempting to address.
- If more patients than the minimum required to answer the question are recruited, some patients may be exposed to an inferior treatment unnecessarily.

As patient recruitment is often difficult, the first reason is generally more important than the second.

Two approaches to sample size in clinical trials

(i) Predetermined trial size

The number of patients to be recruited is fixed before the trial starts.

(ii) Trial size determined by outcome

Statistical analyses, called *interim analyses*, are carried out intermittently as the trial progresses. The trial is stopped if benefit or harm is demonstrated. Whilst this type of trial design is attractive, outcome needs to be determined shortly after recruitment so the interim analysis can be completed. Statistical analysis is also much more complex as it needs to account for multiple statistical testing.

Predetermine sample size is much more often used as they are easier to organise and run. To maintain an overall significance level of α, called the family wise error rate, the test size for each

test is made smaller, but this is complex as sequential statistical tests are not independent. This is a hybrid called a *group sequential trial design* that has a maximum sample size but also has interim analyses to allow early termination.

4.2 Statistical Power

Consider a trial comparing a new treatment group (*T*) to a control group (*C*). Suppose τ is the treatment effect. To test for a treatment effect ($\tau \neq 0$) the two-sided hypothesis are:

Null hypothesis H_0: $\tau = 0$

Alternate hypothesis H_1: $\tau \neq 0$

If H_0 is rejected, when H_0 is true, a *Type I* or *false positive* error has occurred.

Pr [T*ype I error*] = Pr [Reject H_0 | H_0] = α,

which is the significance level.

If instead H_0 not rejected, when H_0 is false, a *Type II* or false negative error has occurred. Define β as the probability of a *Type II* error. This depends on the significance level α and the magnitude of the effect that we wish to detect.

Pr [*Type II error*] = Pr [*Not reject* H_0 | H_1] = $\beta(\alpha, \tau)$

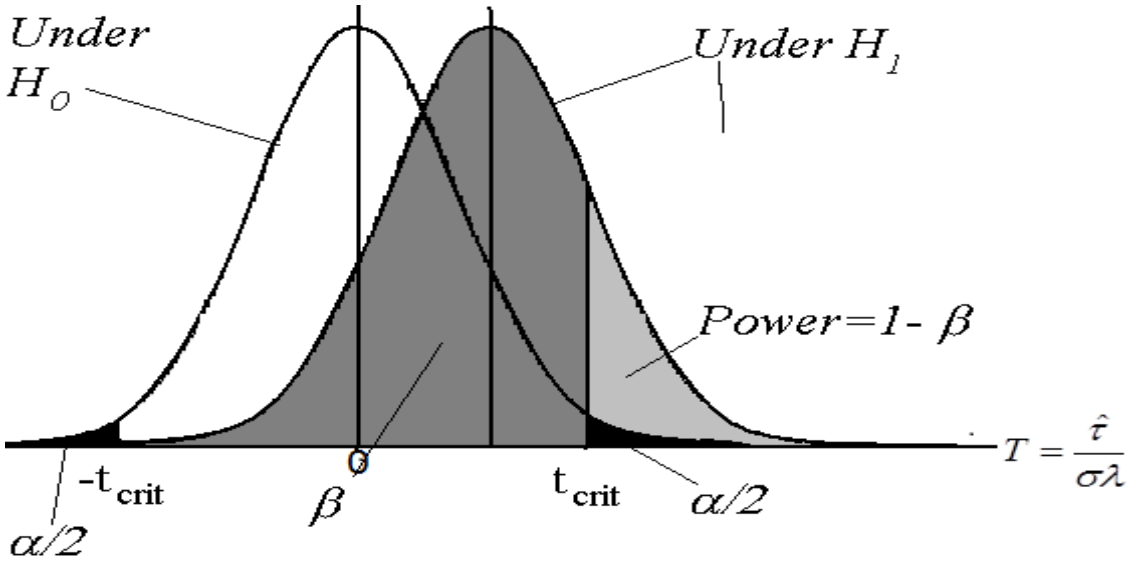
Statistical Power is the probability that a test will detect a difference τ with a significance level α. *Power* =1 - $\beta(\alpha, \tau)$

Calculation of Power

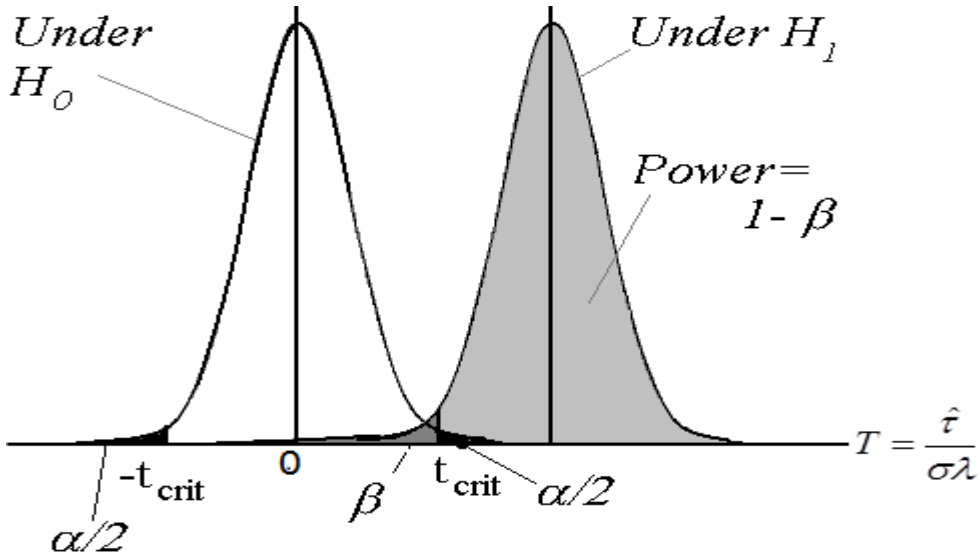
As previously defined the test statistic of a two sample t-test is $T = \dfrac{\hat{\tau}}{\sigma\lambda}$ where $\lambda = \sqrt{1/n_T + 1/n_C}$.

Fig 4.1 Illustration of power calculation for a normally distributed outcome for a two-sided two-sample t-test.

(i) Smaller Sample Size – Low Power



(ii) Larger Sample Size - Increased Power



Under H_1 the test statistic $T = \frac{\hat{\tau}}{\sigma\lambda}$ has the non-central t-distribution.

If F is the cumulative distribution of the non-central t-distribution with $n_T + n_C - 2$ degrees of freedom and non-centrality parameter $\frac{\hat{\tau}}{\sigma\lambda}$, then

$$Power = 1 - \beta(\alpha, \tau) = \left(1 - F\left(t_{\alpha/2}(n_T + n_C - 2) - \frac{\tau}{\sigma\lambda}\right)\right) + F\left(-t_{\alpha/2}(n_T + n_C - 2) - \frac{\tau}{\sigma\lambda}\right)$$

4.3 Sample Size Calculation for Continuous Outcome Measures

Because the central and non-central t-distributions have degrees of freedom determined by sample size there is not a closed form formula for sample size based on this distribution. Instead, we shall use the normal distribution as an approximation for the central and non-central t-distributions to get an approximate formula.

For a normally distributed outcome variable the approximate number of subjects required in each of two equal sized groups to have power 1-β to detect a treatment effect τ using a two group t-test with an α two-sided significance level is

$$n = \frac{2\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_{\beta}\right)^2,$$

where σ is the within group standard deviation.

Assuming n is sufficiently large such that a normal approximation to the central and non-central t-distribution is adequate, the test

statistic *T* has the standard normal distribution $N[0,1]$ under H_o and $N\left[\frac{\tau}{\sigma\lambda},1\right]$ under H_1. Therefore

$$Power = 1-\beta = \left(1-\Phi\left(z_{\alpha/2}-\frac{\tau}{\sigma\lambda}\right)\right)+\Phi\left(-z_{\alpha/2}-\frac{\tau}{\sigma\lambda}\right) \quad \textbf{[1]}$$

where $\lambda = \sqrt{1/n_T + 1/n_C}$ and Φ is the cumulative distribution for $N[0,1]$. The second term on the RHS of equation **[1]** is negligible, therefore

$$Power = 1-\beta \cong 1-\Phi\left(z_{\alpha/2}-\frac{\tau}{\sigma\lambda}\right) .$$

Hence

$$\beta \cong \Phi\left(z_{\alpha/2}-\frac{\tau}{\sigma\lambda}\right).$$

Since $\Phi^{-1}(\beta) = -z_\beta$, it follows that $-z_\beta = z_{\alpha/2}-\frac{\tau}{\sigma\lambda}$

giving $\frac{\tau}{\sigma\lambda} = z_{\alpha/2}+z_\beta$. **[2]**

If equal sized groups are assumed $(n_T = n_C = n)$, then $\lambda = \sqrt{2/n}$.

Substitution into **[2]** gives $\frac{\tau}{\sigma}\sqrt{\frac{n}{2}} = z_{\alpha/2}+z_\beta$.

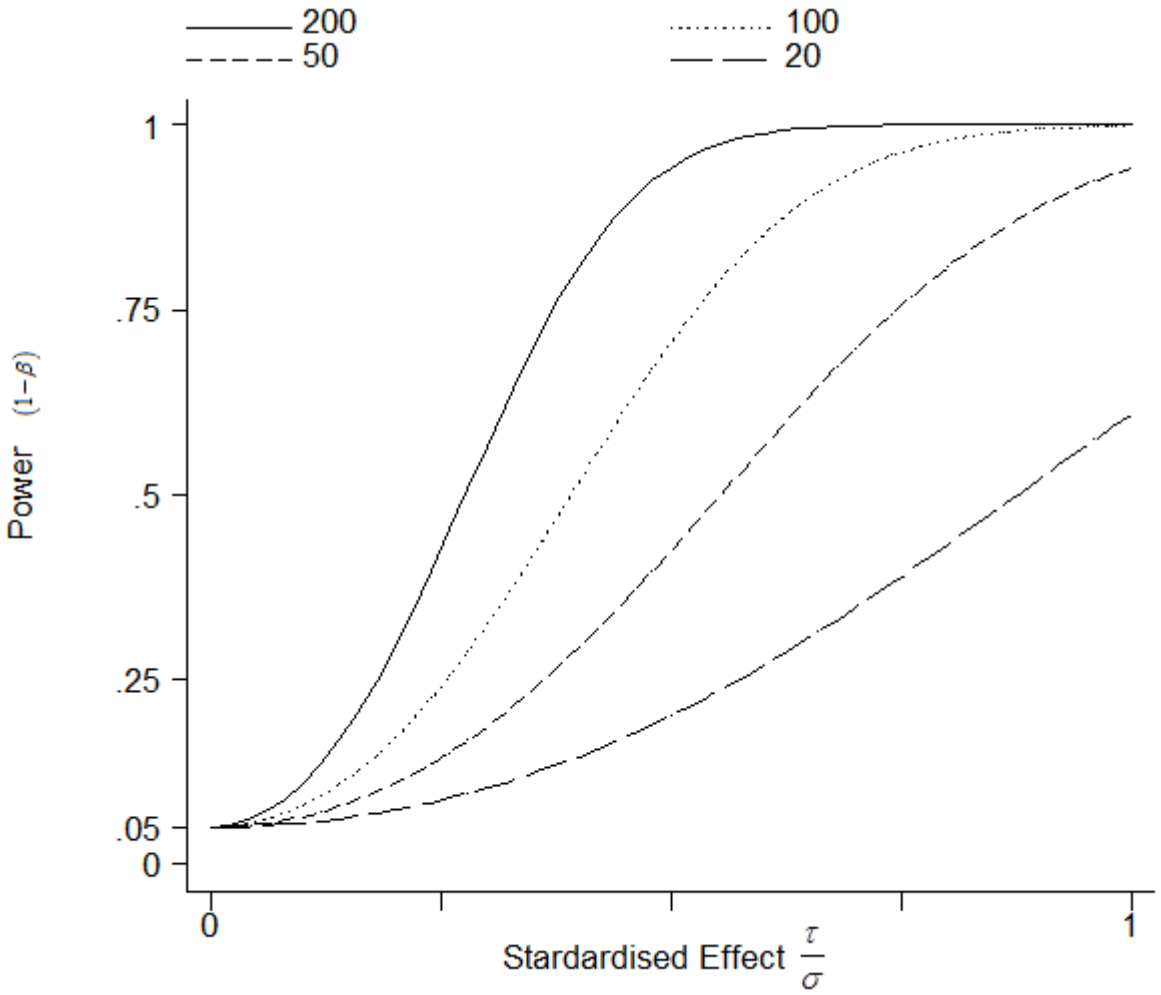
Rearrangement gives $n = \frac{2\sigma^2}{\tau^2}\left(z_{\alpha/2}+z_\beta\right)^2$ as required■

Power

From the above derivation the power of a trial with two groups of size n_T and n_C to detect an treatment effect of magnitude τ using a two group t-test with an α two-sided significance level is

$1-\Phi\left(z_{\alpha/2}-\frac{\tau}{\sigma\lambda}\right)$ where Φ is the cumulative distribution function of $N[0,1]$ and $\lambda=\sqrt{1/n_T+1/n_C}$.

Figure 4.2 Plot of Power (1 - β) against standardised effect define as τ/σ for various total sample sizes for a two sample t-test assuming a 5% two-sided significance level and equal size groups.



Ex 4.1 A clinical trial is planned to compare cognitive behavioural therapy (CBT) and a drug therapy for the treatment of depression. The primary outcome measure is the HoNOS scale, which is a measure of impairment due to psychological distress. From published data the *within group standard deviation* of HoNOS is estimated to be 5.7 units.

(i) Calculate the sample size required for each treatment to detect a treatment effect of 2 units on the HoNOS scale with 80% power and a two group t-test with a 0.05 two-sided significance level.

$\tau =$ $\sigma =$

$\alpha =$ $\beta =$

$z_{\alpha/2} =$ $z_{\beta} =$

Using the formula, $n = \frac{2\sigma^2}{\tau_S^2}\left(z_{\alpha/2} + z_{\beta}\right)^2$

Sample size per group =

Software assuming t-distribution give sample size per group= 129

(ii) Assuming the same significance level, what power would the study have with only 50 patients into each treatment?

$$Power = 1 - \Phi\left(z_{\alpha/2} - \frac{\tau}{\sigma\lambda}\right) =$$

Note Power determine using statistical software that assumes a t-distribution rather than a normal approximation equals to 0.41.

The Effect of Unequal Randomisation on Sample Size

Suppose the allocation ratio between treatment groups is 1:*k*. i.e. for every patient allocated to one group on average *k* are allocated to the other. For a continuous outcome, it can be shown that the total sample size to give the same power is increased by

$$\frac{(k-1)^2}{4.k} N$$

where *N* is the sample size assuming equal allocation. Derivation of this formula is set as an exercise.

Table 4.1 Increase in total sample size required to maintain power when allocation is unequal

Allocation Ratio	***k***	Percentage Increase in sample size $\frac{(k-1)^2}{4.k}$
3:2	1.5	4.2%
2:1	2	12.5%
3:1	3	33.3%
4:1	4	56.3%

From table 4.1 it can be seen that as the allocation ratio increases the sample size to achieve the same power increases, but the effect is not great until the allocation ratio exceeds 2:1.

Practical Considerations when Calculating Sample size

- To estimate sample size we need to choose a value of τ. One might take τ to be the minimum difference that is thought to be clinically important, which is called the *minimum clinically important difference* (MCID). Alternatively, one may have an idea of the size of the treatment effect τ and choose that instead.

- An estimate of σ is needed to complete the calculation. This is often obtained from previous trials using the same outcome in a similar population.

- Power (1-β) = 0.8 or 0.9 and a significance level of 5% are generally used.

- The above formula is for a two-side significance test. The sample size formula for a one-sided test is obtained by replacing $\alpha/2$ by α in the formulae derived.

- Where a trial compares several outcomes, it is usual to specify one measure as the **primary outcome measure** for which sample size is then determined.

4.4 Sample Size Calculation for Binary Outcome Measures

For a binary outcome measure the approximate number of subjects required in each of two equal sized groups to have power (1-β) to detect a treatment effect $\tau = \pi_T - \pi_C$ using a two sample z-test of proportions with a two-sided significance level α is

$$n = \frac{\left(z_{\alpha/2}\sqrt{2\pi\left(1-\pi\right)} + z_{\beta}\sqrt{\pi_T\left(1-\pi_T\right)+\pi_C\left(1-\pi_C\right)}\right)^2}{\tau^2}$$

were $\pi = \frac{\pi_T + \pi_C}{2}$.

Suppose p_T and p_C are the observed proportion of successes in each group. The test statistic for the two-tailed z-test of proportions test is $T = \frac{\left|p_T - p_C\right|}{\sqrt{\left(p\left(1-p\right)\right).\lambda}}$ with $\lambda = \sqrt{1/n_T + 1/n_C}$ and $p = \frac{r_T + r_C}{n_T + n_C}$.

The distribution of T is approximately $N\left[0, \pi\left(1-\pi\right)\left(\frac{1}{n_T}+\frac{1}{n_C}\right)\right]$ under the null hypothesis, with critical values $z_{\alpha/2}$ and $-z_{\alpha/2}$ for an α level two-sided test with $\pi = \frac{\pi_T n_T + \pi_C n_C}{n_T + n_C}$.

Suppose $\tau = \pi_T - \pi_C$ is the effect under the alternative hypothesis. Without loss of generality assume that $\tau > 0$. The power $1-\beta$ equals

$$\Pr\left[\, p_T - p_C < -z_{\alpha/2}\lambda\sqrt{\pi\left(1-\pi\right)}\,\right] + \Pr\left[\, p_T - p_C > z_{\alpha/2}\lambda\sqrt{\pi\left(1-\pi\right)}\,\right].$$

The distribution of $p_T - p_c$ under the alternative hypothesis is $N\left[\tau, \frac{\pi_T(1-\pi_T)}{n_T} + \frac{\pi_C(1-\pi_C)}{n_C}\right]$.

Since $\tau > 0$, $\Pr\left[p_T - p_C < -z_{\alpha/2}\lambda\sqrt{\pi(1-\pi)}\right]$ will be negligible.

Therefore

$$1-\beta = 1-\Phi\left(\frac{z_{\alpha/2}.\lambda.\sqrt{(\pi(1-\pi))} - \tau}{\sqrt{\frac{\pi_T(1-\pi_T)}{n_T} + \frac{\pi_C(1-\pi_C)}{n_C}}}\right)$$ where Φ is the cumulative density function of $N[0,1]$. Since $\Phi^{-1}(\beta) = -z_\beta$, it follows that

$$-z_\beta = \frac{z_{\alpha/2}.\lambda.\sqrt{(\pi(1-\pi))} - \tau}{\sqrt{\frac{\pi_T(1-\pi_T)}{n_T} + \frac{\pi_C(1-\pi_C)}{n_C}}}.$$

Assuming equal size groups $(n_T = n_C = n)$, then $\lambda = \sqrt{2/n}$.

Rearrangement gives

$$-z_\beta \frac{\sqrt{\pi_T(1-\pi_T) + \pi_C(1-\pi_C)}}{\sqrt{n}} = z_{\alpha/2}\frac{\sqrt{2\pi(1-\pi)}}{\sqrt{n}} - \tau$$

Further rearrangement gives

$$\sqrt{n} = \frac{z_{\alpha/2}\sqrt{2\pi(1-\pi)} + z_\beta\sqrt{\pi_T(1-\pi_T) + \pi_C(1-\pi_C)}}{\tau}$$

so that

$$n = \frac{\left(z_{\alpha/2}\sqrt{2\pi(1-\pi)} + z_\beta\sqrt{\pi_T(1-\pi_T) + \pi_C(1-\pi_C)}\right)^2}{\tau^2}$$

giving the required result ■

This formula assumes a normal approximation to the binomial i.e. $n.\pi \geq 5, n(1-\pi) \geq 5$. It may be inaccurate if π_T or π_C, close to either 0 or 1.

The power of a trial with two groups of size n_T or n_C to detect a treatment effect $\tau(=\pi_T - \pi_C)$ using a two sample z-test of proportions with an α size two-sided significance level is

$$1-\Phi\left(\frac{z_{\alpha/2}\lambda\sqrt{\left(\pi(1-\pi)\right)}-\tau_S}{\sqrt{\frac{\pi_T(1-\pi_T)}{n_T}+\frac{\pi_C(1-\pi_C)}{n_C}}}\right)$$

where Φ is the cumulative distribution function $N[0,1]$ and

$\lambda = \sqrt{1/n_T + 1/n_C}$ and $\pi = \frac{\pi_T n_T + \pi_C n_C}{n_T + n_C}$.

Ex 4.2 In a placebo controlled clinical trial the placebo response is 0.3 and we expect the response in the drug group to be 0.5. How many subjects are required in each group so that we have an 90% power at a 5% significance level?

π_T = π_C = τ =

π =

$\sqrt{2\pi(1-\pi)}$ =

$\sqrt{\pi_T(1-\pi_T)+\pi_C(1-\pi_C)}$ =

From statistical table $z_{\alpha/2}$ = z_β =

$$n = \frac{\left(z_{\alpha/2}\sqrt{2\pi(1-\pi)} + z_\beta\sqrt{\pi_T(1-\pi_T)+\pi_C(1-\pi_C)}\right)^2}{\tau^2}$$

=

4.5 Other Considerations Affecting Trial Size

In many trials it is not possible to follow-up every patient to obtain outcome data. This can be due to many factors such as length of follow-up, commitment of patients, or severity of the condition. In these situations sample size calculation needs to take account of the potential loss of patients to follow-up. Similarly, patient recruitment into a trial may only be a small fraction of the percentage of patients that are potentially eligible.

Ex4.3 The total sample size of patients for a trial has been estimated to be 248 to achieve the required power.

(i) It is thought that outcome data may not be obtained for 15% of patients randomised. How many patients need to be randomised?

(ii) It is thought that only 20% of patients screened for the trial will be eligible and agree to join the trial. How many patients need to be screened?

5. Methods of Treatment Allocation in Randomised Controlled Trials

In most clinical trials patients join when they require treatment, they will then need to be randomised before they can start a trial treatment. Recruitment may therefore take place over many months or years. Because of this random sampling can rarely be used to select patients for a particular treatment as one cannot define a sampling frame. Instead they are randomly allocated a treatment. The four most commonly used methods of random allocation are:

- Simple Randomisation.
- Block Randomisation also called Randomised Permuted Blocks.
- Stratified Randomisation.
- Minimization.

5.1 Simple Randomisation

This is equivalent to tossing a coin as the probability of receiving each treatment is kept constant throughout the trial. It is usually carried out using a pseudo-random number generator, which is then used to create a randomisation list. All the treatment allocations on the list are then used in sequence as patients are recruited.

Imbalance with Simple Randomisation

If simple randomisation is used, the numbers of subjects in each treatment group is a random variable and so resulting groups may not be of equal size. The probability of different degrees of imbalance can be estimated using the binomial distribution. For a trial with two treatment groups and an equal allocation ratio and total size N, the number allocated to each treatment is B[N,0.5].

Table 5.1 Probability of imbalance for difference trial sizes when using simple randomisation

Total Number of Patients	Percentage difference in numbers ≥			
	100%	50%	30%	20%
	Ratio of larger to small sample sizes≥			
	2:1	3:2	4:3	6:5
20	12%	50%	50%	82%
50	2%	20%	32%	48%
100	0%	6%	19%	37%
200	0%	1%	6%	18%
500	0%	0%	0%	4%
1000	0%	0%	0%	0%

In table 5.1 we see simple randomisation gives equal sized groups that in the long run, but may be quite unequal for small sample sizes.

Effect of Unequal Sample Size on Power

Suppose the total sample size estimated assuming equal size groups is *N* for a power $(1-\beta)$. Suppose that there is imbalance in treatment group sizes due to randomisation with $\frac{n_T}{n_C} = k$. It can be shown that power for a given value of k is

$$1-\Phi\left(z_{\alpha/2} - \left(\frac{2\sqrt{k}}{k+1} \right)\left(z_{\alpha/2} + z_{\beta} \right) \right).$$

for a normally distributed outcome measure. Derivation of this result is set as an exercise.

Table 5.2 Loss of power relative to 1:1 for different levels of imbalance

Ratio of group sizes	k or 1/k	Power
6:5	1.2	0.797
4:3	1.33	0.792
3:2	1.5	0.784
2:1	2	0.752

For a given total sample size the power is reduced as the imbalance increases.

Summary: Simple Randomisation

Advantages

- Simple and not predictable.
- Similar treatment group sizes in large trials.

Disadvantages

- Imbalance in treatment groups sizes leads to some loss of power in small trials.
- Does not balance treatment groups for prognostic factors other than by chance. There is the possibility of chance bias due to more people with a particularly poor or good prognosis ending up in one or other treatment group.

The alternative to simple randomisation is an *adaptive randomisation* in which the probability of being allocated to a particular treatment varies from patient to patient. It can depend on the numbers previously allocated to each treatment or the characteristics of patients previously recruited.

5.2 Blocks Randomisation

Block Randomisation, also referred to as *Randomised Permuted Blocks,* aims to keep treatment group sizes in a particular ratio, which is usually 1:1. Blocks of treatment allocations are created with each block containing the treatments in the required ratio. Blocks are then randomly selected to construct a randomisation list. All the treatment allocations on the list are then used in sequence as patients are recruited.

Procedure for Block Randomisation

1. Suppose the number of treatments being compared is *N*. Choose a block length L (>N). With equal allocations this must be an integer multiple of the number of treatments being compared, say *N*.
2. All sequences of treatment allocations for the chosen block size are then enumerated. For a block size *L* with *N* treatments, the number of unique blocks is $P = \frac{L!}{(M!)^N}$ where M=L/N assuning equal allocation ratio.
3. Select a sequence of numbers between 1 and *P* at random from random number tables or equivalent.
4. Assemble a randomisation list by selecting the blocks according to the sequence of random numbers.
5. Patients are then allocated in turn according to the list.

Ex5.1 *Assuming equal allocation is required, create a randomisation list of 20 patients for a trial with two treatments using block randomisation with a block size of four and the random number sequence 1, 6, 3, 1, 4.*

L= and N = gives $P =$ unique blocks .

Using the labels A and B for the two treatment the unique blocks are

The blocks can then be chosen using the random number sequence and added to the table create the randomisation list.

Table 5.3 Randomisation list constructed using block randomisation

Patient Num	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Block																				
Treat.																				

Summary: Block Randomisation

Advantages compared to Simple Randomisation

- Reduces imbalance in group sizes. For two groups with block length L and allocation ratio of (1:1) the maximum imbalance during the trial is L/2 and group sizes are balanced at the end of each block.
- Prevents bias due to secular (time) trends in prognosis of patient recruited as similar proportions of each treatment are allocated in each time period of the trial.

Disadvantages

- More complicate than simple randomisation.
- With a small block length it may be possible to predict the next allocation. For this reason a block size of 2 is never used. One way to reduce predictability is to use a random mixture of block of different sizes. e.g. for two treatments use blocks of sizes 4, 6 and 8.

5.3 Allocation and Prognostic Factors

Block randomisation only balances the design with respect to size. As with simple randomisation, it does not balance treatment groups for prognostic factors. By chance, the composition of the two groups may differ. For example, suppose a small proportion of eligible patients have a particularly poor or good prognosis. From the table 5.1 it can be seen that these could be unequally distributed between treatment arms, causing chance bias.

Since it is desirable to have treatment groups that have a similar composition in terms of important prognostic factors, it makes sense to vary the allocation probability to achieve this. Two methods that allow this are *Stratified Randomisation* and *Minimization*. Nevertheless block randomisation is still relevant, as it is required for stratified randomisation.

Stratified Randomisation

A small number of prognostic factors can be balanced using this form of randomisation by using different block randomisations for groups or strata of patients. Before the trial begins strata need to be defined either by a categorical variable such as gender or by dividing a continuous variable such as age into bands.

Procedure for Stratified Randomisation

1. Select a categorical variable that defines the strata e.g. age banding (-64, 65-74,75+)
2. Construct separate randomisation list for each strata using block randomisation.

Stratification may be extended to two or more factors but the number of block randomisation lists required rapidly becomes large. For example 3 factors each with just 2 levels would requires $2^3 = 8$ separate lists. As well as the added complexity, with many lists there may be many incomplete blocks to be left at the end of the trial that could cause imbalance unless the trial is large.

Note that if simple randomisation is used to prepare the list for each strata in place of block randomisation, the benefit of stratified randomisation is lost, as this will be no different to simple randomisation.

Summary Stratified Randomisation

Advantages

- Balances groups on prognostic factors used to stratify.

Disadvantages

- More complex to organize and administer, which could lead to mistakes.
- Only feasible with a small number of strata / prognostic factors.

Minimisation

To carry out minimization one begins by selecting the factors we wish to control. These need to be categorical variable or converted into such by banding.

There are two type of minimization, *deterministic* and *stochastic*, the difference between which is explained below.

Procedure for Minimisation

1. For each levels of each factor being controlled, a running total is kept for the numbers of parents assigned to each treatment.
2. When a new patient is recruited, the totals for that patient's characteristic are added together for each treatment group. The patient is then assigned to
   (i) the treatment group with smaller total.
   (deterministic minimization)

   or

   (ii) probabilistically using a larger probability (say 0.6 or 0.7) for the treatment group with the smaller total.
   (stochastic minimization)
3. After each patient is entered into the trial, the relevant totals for each factor are updated based on the treatment allocation that took place, ready for the next patient.

4. If totals are equal, simple randomisation is used. Hence, the first patient is allocated using simple randomisation as all totals are zero at the start of the trial.

Ex 5.2 *The table below summarizes the minimization totals after 50 patients have been recruited into a trial with two minimization factors Sex and Hospital. Fill in the characteristics of the 51st and 52nd patients. Using these characteristics apply deterministic minimization to allocation the 51st and 52nd patients showing the up-dated minimization totals and the treatment allocation for each patient*

Factor	Sex				Hospital								Treatment
Level	Male		Fem.		I		II		III		Total		Allocated
Treat	A	B	A	B	A	B	A	B	A	B	A	B	
Patient No													
50	16	14	10	10	13	12	9	6	4	6	26	24	A
51													
52													

Characteristics of Patient 51: Sex = Hospital =

Treatment	Sex	Hospital	Total
A			
B			

Characteristics of Patient 52: Sex = Hospital =

Treatment	Sex	Hospital	Total
A			
B			

We have used deterministic minimisation in this example for illustrative purposes, but deterministic minimization can be predictable based on knowledge of previous allocations. Stochastic minimisation is recommended but this is complicate without specialist software.

Summary: Minimization

Advantages

- Balance can be achieved on a larger set of prognostic factors than for stratified randomisation.

Disadvantages

- Complicated as randomisation list cannot be prepared in advance but depend on the characteristics of patients as they are recruited to the trial. It is tedious to do without specialist software.

Comparison of Stratified Randomisation and Minimization

Stratified randomisation maintains balance on all combinations of factors. If a study is stratified on say gender and severity (mild, severe), balance between treatments would be maintained on each four combinations (male & mild), (male & severe), (female & mild) and (female & severe).

Minimisation maintains balance between treatments for each level of a factor but not on combinations of factors.

6. Statistical Analysis Using Baseline Measurements

6.1 Baseline Data in Clinical Trials

In most clinical trials data is collected on the characteristics of patients in addition to the outcome measures. As well as recording demographic data such as age and sex, information will be collected regarding the clinical status of the patient at the time of entry into the trial, which could include values of the trial outcome measures at entry into the trial. For example in a trial comparing treatments for osteoarthritis of the knee, one might record information regarding pain, physical impairment or psychological distress, on entry into the trial . Such data may be required to confirm that patients satisfy the inclusion criteria for the trial. It is also used to describe the characteristic of patients entering the trial. Standard practices would be to present a table summarizing the characteristics for each treatment group.

Data collected prior to randomisation are called *baseline* data. This data can also be used in the estimation and testing hypotheses regarding the treatment effect. As we shall see, for just one outcome measure, there are several ways in which this can be done. If these are all carried out and the investigator allowed to choose on the basis of the results, it is likely that the most favourable will be presented. Alternatively, all could will be presented, which could be a problem, if they give conflicting results. Either way, this could distort the published report and would be a source of *statistical analysis* bias. To prevent this the choice of

analysis should not be based on the results of the analyses of the trial, but need to be documented in advance in a statistical analysis plan. To do this we require criteria to make the decision in advance as to which method of analysis should be used .

Ex 6.1 The FAP Trial Data

FAP is a genetic defect that predisposes those affected to develop large numbers of polyps in the colon that are prone to become malignant. In this trial patients with FAP were randomly allocated to receive a drug therapy (sulindac) or a placebo.

Patient ID	Treatment Group	Polyp Size	
		Baseline (X)	12 Months (Y)
1	sulindac	5.0	1.0
2	placebo	3.4	2.1
3	sulindac	3.0	1.2
4	placebo	4.2	4.1
5	sulindac	2.2	3.3
6	placebo	2.0	3.0
7	placebo	4.2	2.5
8	placebo	4.8	4.4
9	sulindac	5.5	3.5
10	sulindac	1.7	0.8
11	placebo	2.5	3.0
12	placebo	2.3	2.7
13	placebo	2.4	2.7
14	sulindac	3.0	4.2
15	placebo	4.0	2.9
16	placebo	3.2	3.7
17	sulindac	3.0	1.1
18	sulindac	4.0	0.4
19	sulindac	2.8	1.0

Piantadosi S. Clinical Trials: A methodological Perspective p302 , Wiley 1997

6.2 Possible Treatment Effect Estimators

(i) Unadjusted

Suppose the random variable Y_i represents the continuous outcome for the i^{th} patient in either the new treatment group (T) or the control group (C), and suppose

$$Y_i = \mu_U + \varepsilon_i \qquad \text{for } i \in C$$

$$Y_i = \mu_U + \tau_U + \varepsilon_i \qquad \text{for } i \in T$$

with ε a random variable with $E\left[\varepsilon_i \mid_{i \in T}\right] = E\left[\varepsilon_i \mid_{i \in C}\right] = 0$.

$$\tau_U = E\left[Y_i \mid_{i \in T}\right] - E\left[Y_i \mid_{i \in C}\right] ,$$

which can be estimated by

$$\hat{\tau}_U = \bar{Y}_T - \bar{Y}_C$$

(ii) Changes Scores

Suppose X_i is the value of outcome measure Y_i recorded at baseline. Medical researchers sometimes calculate the change from baseline, $C_i = Y_i - X_i$, which is call the *change score*.

Treatments are compared using C_i instead of Y_i .

$$C_i = Y_i - X_i = \mu_C + \varepsilon_i' \qquad \text{for } i \in C$$

$$C_i = Y_i - X_i = \mu_C + \tau_C + \varepsilon_i' \qquad \text{for } i \in T$$

with ε' a random variable with $E\left[\varepsilon_i' \mid_{i \in T}\right] = E\left[\varepsilon_i' \mid_{i \in C}\right] = 0$.

$$\tau_C = E\left[C_i \mid_{i \in T}\right] - E\left[C_i \mid_{i \in C}\right],$$

which can be estimated by

$$\hat{\tau}_C = \bar{C}_T - \bar{C}_C = \left(\bar{Y}_T - \bar{X}_T\right) - \left(\bar{Y}_C - \bar{X}_C\right)$$

where $\bar{C}_T$ and $\bar{C}_C$ are the sample means of the change score for each group.

For both these methods of analysis statistical inference can be based on the two-sample t-test and the associated confidence interval.

Figure 6.1 STATA Output for FAP trial

(i) Unadjusted Analysis

```
Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
Sulindac |       9    1.833333    .4711098    1.413329    .7469522    2.919714
 Placebo |      10    3.110000    .2306753    .7294595    2.588176    3.631824
---------+--------------------------------------------------------------------
    diff |           -1.276667    .5245527                .130485    2.422848
------------------------------------------------------------------------------
    diff = mean(Sulindac)- mean(Placebo)                          t =  -2.4338
Ho: diff = 0                     Satterthwaite's degrees of freedom =  11.6981

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0160         Pr(|T| > |t|) = 0.0320          Pr(T > t) =0.9840
```

(ii) Change Score Analysis

```
Two-sample t test with unequal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
Sulindac |       9   -1.522222    .5969314    1.790794   -2.898749   -.1456959
 Placebo |      10   -.1900000    .2857544    .9036346   -.8364213    .4564213
---------+--------------------------------------------------------------------
    diff |            -1.332222    .6618026               -.1160118    2.780456
------------------------------------------------------------------------------
    diff = mean(Sulindac)- mean(Placebo)                          t =  -2.0130
Ho: diff = 0                     Satterthwaite's degrees of freedom =  11.5476

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0340         Pr(|T| > |t|) = 0.0680          Pr(T > t) =0.9660
```

Note: Adjusted degrees of freedom have been used in both analyses. This method, called the Satterthwaite test and mention in 2.2, adjusts inference for variance of the two arms being unequal.

(iii) Analysis Adjusted by Baseline Variables

Suppose that X is a baseline variable. Suppose for some values θ we define an adjusted treatment effect as

$$A_i = Y_i - \theta X_i = \mu_A + \varepsilon_i'' \qquad \text{for } i \in C$$

$$A_i = Y_i - \theta X_i = \mu_A + \tau(\theta) + \varepsilon_i'' \qquad \text{for } i \in T$$

with ε_i'' a random variable with $E\left[\varepsilon_i'' \mid i \in T\right] = E\left[\varepsilon_i'' \mid i \in C\right] = 0$.

Taking expectations,

$$\tau(\theta) = E\left[Y_i - \theta X_i \mid i \in T\right] - E\left[Y_i - \theta X_i \mid i \in C\right],$$

which can be estimated by

$$\hat{\tau}(\theta) = \bar{A}_T - \bar{A}_C = \left(\bar{Y}_T - \theta \bar{X}_T\right) - \left(\bar{Y}_C - \theta \bar{X}_C\right)$$

- For simplicity it will be assumed that X is a single variable, but it could be a vector of covariates.

- Baseline variables can be binary or continuous. If X is a binary variable, it is generally convenient to code it with 0 and 1. A variable coded in this way is sometimes called an *indicator* or *dummy* variable.

6.3 Comparison of Adjusted and Unadjusted Analyses

In a randomised controlled trial $E\left[\hat{\tau}(\theta)\right]=\tau(\theta)$ is independent of θ. Hence the expected values of unadjusted, change and an adjusted estimate of the treatment effect are all equal, that is

$$E\left[\hat{\tau}_U\right]=E\left[\hat{\tau}_C\right]=E\left[\hat{\tau}(\theta)\right]$$

Proof

Considering $\hat{\tau}(\theta)=\left(\bar{Y}_T-\theta\bar{X}_T\right)-\left(\bar{Y}_C-\theta\bar{X}_C\right)$.

$$E\left[\hat{\tau}(\theta)\right]=E\left[\bar{Y}_T\right]-E\left[\bar{Y}_C\right]-\theta\left(E\left[\bar{X}_T\right]-E\left[\bar{X}_C\right]\right).$$

Randomisation means that $E\left[\bar{X}_T\right]=E\left[\bar{X}_C\right]$.

Therefore $E\left[\hat{\tau}(\theta)\right]=E\left[\bar{Y}_T\right]-E\left[\bar{Y}_C\right]$, which is independent of θ.

Values of θ equal to 0 and 1 correspond to the treatment effect in an unadjusted $\left(\hat{\tau}_U\right)$, and change $\left(\hat{\tau}_C\right)$ giving the required result ■

Suppose $\sigma_X^2, \sigma_Y^2, \sigma_{XY}$ are the variances and covariance of X and Y with $\lambda = \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}$. The treatment effect $\hat{\tau}_A$ has a minimum variance when $\theta = \beta$ equal to $Var\left[\hat{\tau}(\beta)\right] = \lambda^2 \sigma_Y^2 \left(1 - \rho^2\right)$ where β is the regression coefficient of *Y* on *X* and ρ is the correlation between *X* and *Y* conditional on treatment group.

Proof

Again consider $\hat{\tau}(\theta) = \left(\bar{Y}_T - \theta \bar{X}_T\right) - \left(\bar{Y}_C - \theta \bar{X}_C\right)$

$$Var\left[\hat{\tau}(\theta)\right] = Var\left[\bar{Y}_T - \bar{Y}_C - \theta\left(\bar{X}_T - \bar{X}_C\right)\right]$$

$$= Var\left[\bar{Y}_T - \bar{Y}_C\right] + Var\left[\theta\left(\bar{X}_T - \bar{X}_C\right)\right] - 2Cov\left[\bar{Y}_T - \bar{Y}_C, \theta\left(\bar{X}_T - \bar{X}_C\right)\right]$$

$$= Var\left[\bar{Y}_T - \bar{Y}_C\right] + \theta^2 . Var\left[\bar{X}_T - \bar{X}_C\right] - 2\theta . Cov\left[\bar{Y}_T - \bar{Y}_C, \bar{X}_T - \bar{X}_C\right] \quad \textbf{[1]}$$

Considering the first term

$$Var\left[\bar{Y}_T - \bar{Y}_C\right] = Var\left[\bar{Y}_T\right] + Var\left[\bar{Y}_C\right] - 2Cov\left[\bar{Y}_T, \bar{Y}_C\right] .$$

Since treatment groups are independent, $Cov\left[\bar{Y}_T, \bar{Y}_C\right] = 0$.

Therefore $Var\left[\bar{Y}_T - \bar{Y}_C\right] = Var\left[\bar{Y}_T\right] + Var\left[\bar{Y}_C\right]$.

Since observations are independent, $Var\left[\bar{Y}_T\right] = \frac{\sigma_Y^2}{n_T}$ and

$Var\left[\bar{Y}_C\right] = \frac{\sigma_Y^2}{n_C}$.

Therefore $Var\left[\bar{Y}_T - \bar{Y}_C\right] = \lambda^2 \sigma_Y^2$ where $\lambda = \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}$.

Similarly $Var\left[\bar{X}_T - \bar{X}_C\right] = \lambda^2\sigma_X^2$ and $Cov\left[\bar{Y}_T - \bar{Y}_C, \bar{X}_T - \bar{X}_C\right] = \lambda^2\sigma_{XY}$.

Substitution into **[1]** gives $Var\left[\hat{\tau}(\theta)\right] = \lambda^2\left(\sigma_y^2 + \theta^2\sigma_X^2 - 2\theta\sigma_{XY}\right)$ **[2]**

A minima can be found by differentiation with respect to θ.

$$\frac{\partial}{\partial\theta}Var\left[\hat{\tau}(\theta)\right] = \lambda^2\left(2\theta\sigma_X^2 - 2\sigma_{XY}\right).$$

This equals zero when $\theta = \sigma_{XY}/\sigma_X^2$, which is the coefficient for regression of *Y* on *X* within each treatment group.

The second derivative $\frac{\partial^2}{\partial\theta^2}Var\left[\hat{\tau}(\theta)\right] = 2\lambda^2\sigma_X^2$.

As this is positive, it follows that this is a minimum. The treatment effect estimate with minimum variance is therefore

$$Var\left[\hat{\tau}(\beta)\right] = \lambda^2\left(\sigma_Y^2 + \beta^2\sigma_X^2 - 2\beta\sigma_{XY}\right) = \lambda^2\sigma_Y^2\left(1 - \frac{\sigma_{XY}^2}{\sigma_X^2\sigma_Y^2}\right)$$

Since $\sigma_{XY}/\sqrt{\sigma_X^2\sigma_y^2} = \rho$, $Var\left[\hat{\tau}(\beta)\right] = \lambda^2\sigma_Y^2\left(1-\rho^2\right)$ as required ■

Estimation of β and $\tau(\beta)$

The treatment effect $\tau(\beta)$ can be estimated by fitting a linear model, which is a generalization of linear regression. The general form of a linear model with *k* covariates is

$$Y_i = \mu + \beta_1 X_{1i} + ... + \beta_k X_{ki} + \varepsilon_i .$$

where the *X*'s are the *k* covariates and the β's the corresponding *k* coefficients. The random variable ε_i is usually assumed to be $N\left[0, \sigma^2_{\varepsilon''}\right]$. If one of the *X*'s is an indicator variable, the coefficient β is the difference in the mean value of *Y* for *X* =1 as compared to *X*=0 , adjusted for other *X*'s.

When considering the analysis of data from a randomised trial it is notational clearer to separate the matrix of covariates into an indicator variable I_i equal to 1 for treatment *T* and 0 for the control *C,* and a matrix *X* of other covariates. The model is then written as

$$Y_i = \mu_A + \tau I_i + \beta X_i + \varepsilon_i$$

and the treatment effect is the coefficient of the indicator variable I_i. Statistical inference is simply the test of whether the coefficient of the indicator variable I_i differs from zero, that is $H_0 : \tau = 0 vs$ $H_1 : \tau \neq 0.$ The matrix of coefficients, β, for other variable is generally of less interest and often not given in published reports of trials.

Fig 6.2 STATA Output for FAP trial

Linear Model Analysis Adjusting for Baseline Polyp Size

```
      Source |       SS       df       MS              Number of obs =      19
-------------+------------------------------           F(  2,    16) =    3.48
       Model |  8.63531123     2  4.31765562           Prob > F      =  0.0556
    Residual |  19.8541618    16  1.24088511           R-squared     =  0.3031
-------------+------------------------------           Adj R-squared =  0.2160
       Total |  28.4894731    18   1.5827485           Root MSE      =   1.114

------------------------------------------------------------------------------
      size12 |      Coef.   Std. Err.      T    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       size0 |   .2087081    .243071     0.86   0.403    -.3065794    .7239956
   treatment |  -1.288262   .5120029    -2.52   0.023    -2.373659   -.2028639
       _cons |   2.421263   .8760753     2.76   0.014     .5640666    4.27846
-------------+----------------------------------------------------------------
```

Table 6.2 summarizes the treatment effect and inference for all three analyses. The null hypothesis of no treatment effect would not have been rejected at a 5% level if the change score analysis had been carried out.

Table 6.2 Summary of treatment effect estimates for the FAP trial

	Treatment Effect	*SE*	*95% C.I Lower*	*Upper*	*p-value*
Unadjusted $\hat{\tau}_U$	-1.28	0.52	-2.42	-0.13	0.032
Change $\hat{\tau}_C$	-1.33	0.66	-2.78	0.12	0.068
Linear Model $\hat{\tau}(\beta)$	-1.29	0.51	-2.37	-0.20	0.023

Comparison of standard errors of Unadjusted, Change Score and Linear Model Analyses

From above $Var\left[\hat{\tau}(\beta)\right] = \lambda^2\sigma_Y^2\left(1-\rho^2\right)$, which is a quadratic in ρ.

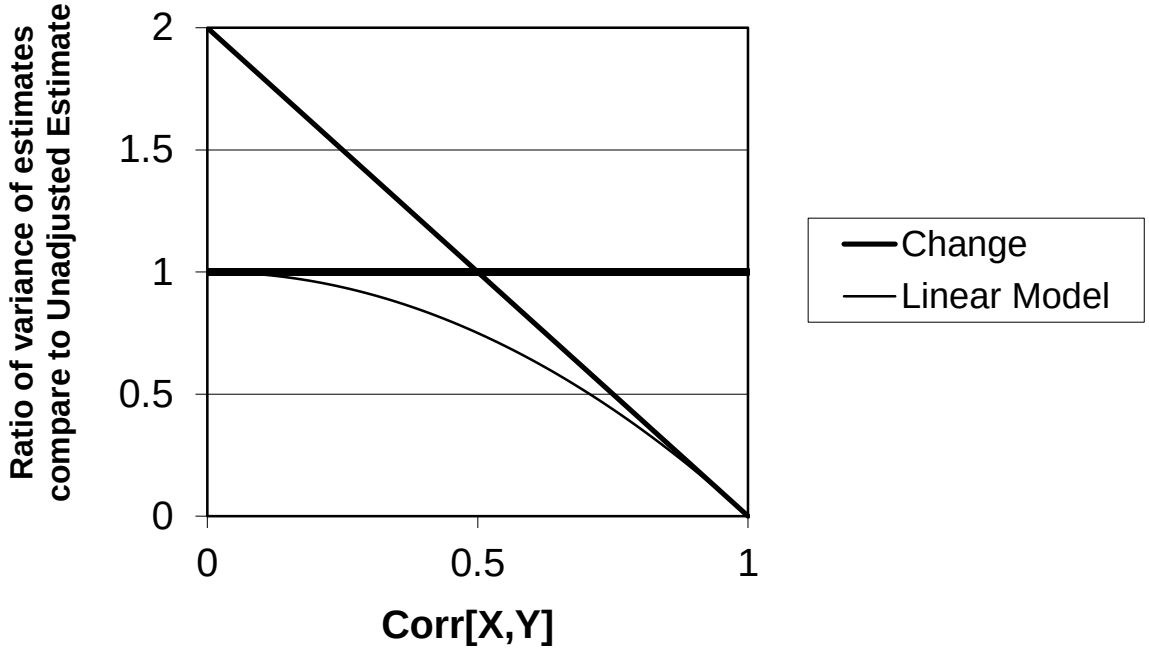
From [2] $Var\left[\hat{\tau}_C\right] = \lambda^2\left(\sigma_Y^2+\sigma_X^2-2\sigma_{XY}\right) = \lambda^2\left(\sigma_Y^2+\sigma_X^2-2\sigma_Y\sigma_X\rho\right)$, which is a linear function of ρ .

Assuming $\sigma_X^2 = \sigma_Y^2$, $Var\left[\hat{\tau}_C\right] = 2\lambda^2\sigma_Y^2(1-\rho)$.

The unadjusted standard error is simply $Var\left[\hat{\tau}_U\right] = \lambda^2\sigma_Y^2$

Hence $\dfrac{Var\left[\hat{\tau}(\beta)\right]}{Var\left[\hat{\tau}_U\right]} = 1-\rho^2$ and $\dfrac{Var\left[\hat{\tau}_C\right]}{Var\left[\hat{\tau}_U\right]} = 2(1-\rho)$.

Figure 6.3 comparison of Change Score and Linear models with the unadjusted analysis assuming $\sigma_X^2 = \sigma_Y^2$.



Summary Analyses using Baseline Data

All three estimates of the treatment effect defined in (6.2) are unbiased, but an estimate of the treatment effect based on a linear model has smaller expected variance, where baseline covariates correlate with the outcome measure and it does not matter whether this correlation is positive or negative.

Reducing the variance of the treatment effect estimate is important as this increases the precision of the estimate, thereby giving greater power for a given sample size. As a consequence, if a baseline variable is thought to predict outcome, an analysis adjusting for this variable is recommended. Where an outcome measure is recorded at baseline, then it is usually a strong predictor of outcome, and the variable should be used as a covariate.

To prevent the analysis bias, a single set of baseline covariates should be selected prior to starting analysis. This should be recorded in the statistical analysis plan of the trial. This choice will therefore need to be based on prior knowledge or reasoning as to what variables are likely to predict outcome irrespective of which treatment is received.

6.4 A Flawed Analysis using *Within Group Change from Baseline*

A statistical analysis sometime seen in the medical literature is to carry out a separate paired t-test on each treatment groups. Treatments are then compared by using the results of the separate statistical tests. If improvement in one group is statistically significant but not the other, it is concluded that one treatment is more effective than the other. This analysis is illustrated below with the FAP data

Figure 6.4 STATA Output for paired t-test analysis of each treatment

Results for: polyp.mtw (treat = 0)

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
  size12 |      10        3.11    .2306753    .7294595    2.588176    3.631824
   size0 |      10         3.3    .3076795     .972968    2.603981    3.996019
---------+--------------------------------------------------------------------
    diff |      10        -.19    .2857544    .9036346   -.8364213    .4564213
------------------------------------------------------------------------------
     mean(diff) = mean(size12 - size0)                             t =  -0.6649
 Ho: mean(diff) = 0                              degrees of freedom =        9

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.2614         Pr(|T| > |t|) = 0.5228          Pr(T > t) = 0.7386
```

Results for: polyp.mtw (treat = 1)

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
  size12 |       9    1.833333    .4711098    1.413329    .7469522    2.919714
   size0 |       9    3.355556    .4163703    1.249111    2.395404    4.315707
---------+--------------------------------------------------------------------
    diff |       9   -1.522222    .5969314    1.790794   -2.898749   -.1456959
------------------------------------------------------------------------------
     mean(diff) = mean(size12 - size0)                             t =  -2.5501
 Ho: mean(diff) = 0                              degrees of freedom =        8

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0171         Pr(|T| > |t|) = 0.0342          Pr(T > t) = 0.9829
```

Why the Analysis using Within-Group Changes is Flawed

The main reason why this method is flawed is because the two p-values relate to two separate hypotheses test and so do not directly test the benefit of one treatment as compared to the other, that is they do not compare the two potential outcomes.

Use of this type of analysis also suggests other misunderstandings.

- Failure to reject the null hypothesis, for a treatment does not imply that there is no change. The absolute change within each treatment groups could be the same but unequal variances may affect the probability of rejecting the null hypothesis for one treatment and not another.

- Tests of within group change are often statistically significant, but change within a treatment group may not be due to treatment. It may occur because the condition naturally resolves. They may tell us more about the natural history of the condition than the benefit of receiving treatment one treatment as compared to another.

Unfortunately, clinical researchers often carry out this type of analysis, when the statistical analysis directly comparing the two treatments is not statistically significant. This is done in the desperate search for a statistically significant result to report.