Tutorial 1 - Clinical Trials

Problem 1

In an open (unblinded) trial of the beta-blocker alprenolol given to patients after myocardial infarction, randomization to alprenolol or the standard treatment was carried out at the time of admission to hospital.

The start of the medication was two weeks after admission to hospital, by which time 60% of the original 393 patients had been withdrawn from the trial. The main reasons for withdrawal were death, non-confirmation of myocardial infarction or contraindication for the beta-blocker (contraindication means that there is a clinical reason why the patient should not be given a beta blocker: e.g. it may be incompatible with other treatments the patient is receiving, or the patient may also be suffering from another illness which might make the beta blocker harmful rather than potentially beneficial). Of the 162 patients actually treated, 69 received alprenolol and 93 received the control treatment.

(a) Why might the numbers of withdrawals have been different in the two groups?

(b) Is a hypothesis test to compare the proportions withdrawn in the two groups of any value?

(c) How could this problem have been avoided?

Problem 2

What do you understand by the terms *double blind*, *single blind* and *blinded evaluation*? Why are these incorporated in the design of randomised, controlled trials?

Problem 3

For each of the following situations, is it feasible to conduct a double-blind clinical trial? If so, briefly describe how you might implement the blinding.

(a) Comparison of cream (applied directly to skin) and tablets (to be swallowed) in the treatment of eczema.

(b) Comparison of surgical treatment and radiotherapy for breast cancer.

(c) Comparison of two different dosage regimes for the same antibiotic for treating urinary infections: 100mg once a day after breakfast compared with 25mg four times a day after meals.

Problem 4

It is generally accepted that clinical trials in which historical controls are used for comparison tend to overestimate the true effect of a new treatment. Define *historical controls*, explain why they tend to overestimate the true effect of new treatments, and suggest how the trial design should be modified to avoid this problem.

Problem 5

In the protocol for a clinical trial to compare two treatments for high blood pressure, the following paragraph appeared:
To demonstrate a difference in blood pressure reduction between the treatments of 5 mmHg or more, with a significance level of 5% and a power of 80%, 40 patients completing the study per group are required. This is based on a standard deviation of 8 mmHg in blood pressure reduction calculated from previous studies.

(a) Explain clearly the reason for inclusion of this paragraph in the protocol.

(b) Using the formula in the lecture notes verify the calculation in the above paragraph and show how the required sample size will vary in each of the following circumstances:

(i) a difference in blood pressure reduction of 2 mmHg or more is thought to be of clinical relevance.

(ii) the study is required to have 95%, rather than 80% power to detect a difference of 5 mmHg or more.

(c) Suppose that the trial organisers had difficulty recruiting patients to the study, and that only 25 patients per group were obtained. What power does the study have to detect a difference in mean reductions of 5 mmHg at the 5% significance level?

Problem 6

A clinical trial is planned to compare a new treatment with a standard treatment in patients who have suffered a heart attack. The principal outcome measure is mortality within 6 months.

(a) If mortality on the standard treatment is 8% and it is hoped that the new treatment will reduce this to 5%, use the formula in the lecture notes to estimate the number of patients required in each group to give 90% power to detect a difference of this size at the 5% significance level.
(b) Suppose now that the organizers plan to carry out 5 interim analyses of the data (i.e. after 20%, 40%, 60%, 80%, 100% of patients have completed the trial). Determine an appropriate p-value for each of these interim analyses, using Pocock's method. Note, no calculation is needed to answer this question.
(c) What effect will this use of interim analyses have on the expected duration of the trial, in comparison to carrying out a single analysis at the end of the trial?
(d) Explain the main drawback to using Pocock's method in practice and describe how this is overcome by the Haybrittle-Peto and O'Brien-Fleming methods.

Problem 7

A randomized, double blind trial was carried out to compare low and high doses of a new antidepressant with amitriptyline (an established treatment for depression at the time of the study). Fifty patients entered the trial, but 15 had to withdraw due to possible side effects from treatment. The results are shown in the table below.

Table 1: Clinical assessment of treatment effect in an anti-depressant trial.

	Low dose	**High dose**	**Amitriptyline**
Very effective	2	8	6
Effective	4	2	8
Ineffective	3	2	0
Total assessed	9	12	14
Withdrawn patients	6	8	1
Total randomized	15	20	15

(a) If withdrawals are ignored, which treatment subjectively appears to be most effective?

(b) If withdrawals are now counted as treatment failures (i.e. as *ineffective*) in an *intention to treat* analysis, which treatment subjectively appears to be best?

(c) Which of these two approaches do you think is more reasonable?

Problem 8

The following table was presented in a report of a meta-analysis of six trials of a treatment for chronic renal disease.

Table 2: Individual and overall odds ratios in six randomised trials of protein restriction in chronic renal disease.

Study	**Odds ratio (treatment/control)**	**95% Confidence Interval**
1	0.46	0.19 to 1.13
2	0.29	0.04 to 2.11
3	0.61	0.34 to 1.09
4	0.37	0.12 to 1.17
5	0.28	0.08 to 0.95
6	1.09	0.40 to 3.02
All studies	**0.54**	**0.37 to 0.79**

(a) Define *meta-analysis* and interpret the results in the table for *all studies*.
(b) What reservations would you attach to your interpretation?