UNIVERSITY OF LONDON

GOLDSMITHS COLLEGE

B. Sc. Examination 2002

STATISTICS

ST53011A (ST319) Medical Statistics

Duration: 2 hours 15 minutes

Date and time:

Answer any FOUR questions.

Full marks can be obtained for complete answers to FOUR questions.

WHITE, YEATS & SKIPWORTH: Tables for Statisticians to be provided.

Electronic calculators may be used. The make and model should be specified on the script. The calculator must not be programmed prior to the examination. Calculators which display graphics, text or algebraic equations are not allowed.

NOTE: Full details of all calculations are to be shown; pre-programmed statistical tests and procedures on a calculator, apart from mean and standard deviation, must not be used.

Question 1 (a) Explain what is meant by Phase I, Phase II, Phase III and Phase IV clinical trials. [12]

(b) Why is randomisation used in Phase III trials rather than a systematic assignment? [5]

(c) Explain how to produce a randomisation list using the biased coin method. Why is this method used? [4]

(d) Explain how to produce a randomisation list using random permuted blocks. In what circumstances can this method be used? [4]

Question 2 (a) Discuss the factors to be considered in planning interim analyses of the results of a clinical trial. [12]

(b) Describe how a *sequential design for paired preferences* (such as the trial on reactions to antivenom for snake bites we studied) is carried out. Why are such designs not used more widely? [7]

(i) Explain the difference between an Open sequential plan and a Restricted sequential plan for such a design. (Suitable diagrams may help your explanation). [3]

(ii) What is the advantage and disadvantage of an Open sequential plan? [3]

Question 3 A study is to be carried out to compare a new diet for obese patients. The primary outcome measure is the reduction in weight after one year. From previous trials it is known that the standard deviation of the reduction is likely to be about 4kg and the reduction will be approximately normally distributed. The investigators agree that if the new diet reduces weight 2kg more than the standard diet it would be of clinical importance. A one-sided test of the null hypothesis that there is no difference in the mean reduction for the two diets will be carried out.

(a) What are meant by Type I and Type II errors? [4]

(b) What is meant by the significance level of the test? [2]

(c) What is meant by the power of the test? [3]

(d) For a test with significance level α and power $1-\beta$ show that the number of patients, n, required for each treatment is

$$n = 8[\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$$

where Φ is the cumulative distribution function of a standard normal random variable. [8]

(e) Hence find the number of patients required for a significance level of 0.05 and power 0.90. [4]

(f) If the investigators can only include a total of 100 patients in their study what will be the power of the test if the significance level remains at 0.05? [4]

Question 4 (a) Explain the difference between *parametric* and *non-parametric* approaches to survival analysis. [3]

(b) Suppose T is the survival time of patients with density function $f(t)$ and distribution function $F(t)$. Define the *hazard function* and the *survival function.* [4]

(c) Suppose for n patients we observe the survival time t_i and a censoring indicator w_i which equals 1 if the time is uncensored and 0 if the time is censored. Show that the likelihood can be written in terms of the hazard function and the survival function. [3]

(d) The following table shows the survival times in months of 20 patients following a heart attack. A $*$ indicates a censored observation.

2	3	5*	6	6	7	8	9*	10	10
11	12	14	14	15	24*	24*	24*	24*	24*

(i) If the survival times follow an exponential distribution with mean λ^{-1} find the maximum likelihood estimate of λ. [4]

(ii) Hence estimate the survival function and sketch it on a graph. [3]

(iii) Estimate the Kaplan-Meier survival curve and plot it on the same graph. [6]

(iv) Comment on the use of the exponential distribution as a model for survival times. [2]

Question 5 (a) What is the difference between a *parallel group design* and a *cross-over design* in a clinical trial to compare two treatments? [2]

(b) In a trial of a new drug for the treatment of asthma, each of 10 patients was given the drug for a period of 14 days and a placebo for a separate period of 14 days, the order of administration being chosen randomly for each patient. The table shows the maximum percentage fall in FEV1 on the drug and placebo after six minutes on an exercise treadmill following treatment.

Group A (drug/placebo)			Group B (placebo/drug)		
Patient	Period 1	Period 2	Patient	Period 1	Period 2
2	18.70	8.47	1	20.00	8.47
3	48.89	20.45	4	22.98	0.12
6	2.99	20.29	5	26.47	10.53
7	17.07	23.30	8	24.84	7.28
9	16.05	36.10	10	20.66	10.94

Stating any assumptions you make, test for (i) a period effect, (ii) a treatment $\times$ period interaction, (iii) a treatment effect, and report on your conclusions. [19]

(c) Comment on the ethics of this trial. [4]

Question 6 (a) Briefly explain the difference between a *relative risk* and an *odds ratio*. Give an example of when each measure is appropriate. [4]

(b) Wald et al (BMJ 293, 1217-1222) review the results of four studies of women in the USA examining the relationship of passive smoking to lung cancer. The data are shown in the table below.

	Lung cancer cases		Controls		
Study	Exposed	Unexposed	Exposed	Unexposed	Total
1	14	8	61	72	155
2	33	8	164	32	237
3	13	11	15	10	49
4	91	43	254	148	536

(i) Calculate the odds ratios of lung cancer associated with passive smoking exposure for each of the four studies separately. [4]

(ii) Calculate a 95% confidence interval for the odds ratio for the study showing the highest odds of having lung cancer associated with passive smoking exposure. [4]

(iii) Use the Mantel-Haenszel procedure to find an estimate and 95% confidence interval for the common odds ratio of lung cancer for passive smokers compared to those who are unexposed. [10]

(iv) What factors need to be borne in mind when drawing inferences from these results? [3]