The University Of Sheffield.

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Neaves Tables
Graph Paper

SCHOOL OF MATHEMATICS AND STATISTICS MAS6012

Session 2011–2012 **3 Hours**

Medical Statistics, Sampling, Design

RESTRICTED OPEN BOOK EXAMINATION.
Candidates may bring to the examination lecture notes and associated lecture material (but no textbooks) plus a calculator that conforms to University regulations.
*All answers will be marked but credit will be given for only the best **FIVE** answers.*
All questions carry equal marks. Total marks 100.

Registration number from U-Card (9 digits) – to be completed by student

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1 In a clinical trial to assess the effectiveness of a homeopathic remedy in relieving migraines, a practitioner regards an increase in symptom-free periods of 3 weeks, when compared with that achieved by a placebo, as clinically significant. She assesses the standard deviation of symptom free periods to be five weeks.

(a) She intends to use a two-sample t-test with 5% significance level with 80% power. Previous similar trials suggest that an average of 15% of subjects recruited will fail to meet the inclusion criteria, how many subjects should she recruit for the study if she makes due allowance for an average exclusion rate?

(6 marks)

(b) What power will her test have if the actual exclusion rate is 20%?

(4 marks)

(c) When she had completed the trial she found that many subjects were unable to give a reliable report of the length of their symptom-free period but were willing to say whether they felt that the treatment was 'effective' or 'non-effective'. Of the 55 subjects receiving the homeopathic remedy 39 reported it as effective whereas of the 49 receiving the placebo 26 reported it as effective. Assess the evidence that the homeopathic remedy is more or less effective than the placebo.

(5 marks)

(d) On further examination of the data she discovers that of the 13 women receiving the homeopathic remedy, 7 found it effective whereas 11 of the 22 men taking the placebo found that effective. Is there evidence that either the men or the women find the homeopathic remedy more or less effective than the placebo?

(5 marks)

2 The table below gives the survival times in weeks of 28 patients with kidney tumours who were randomized to receive either radiation therapy alone or radiation plus chemotherapy.

Radiation alone: 6* 6 9* 10* 11 11* 19 19* 20* 25 37 38 39*
Radiation + chemo: 1 2 2 5 5 8 10 12 15* 21 22 22 27 30 40*
(* indicates a censored observation)

Given below are the results of some statistical analyses of these data.

(a) Without making any assumptions on the form of the survival distributions estimate the median survival times of subjects receiving the two treatments.

(4 marks)

(b) Assuming that the survival times are exponentially distributed $Ex(\lambda_1)$ and $Ex(\lambda_2)$ respectively, estimate λ_1 and λ_2 and calculate approximate 95% confidence intervals for them.

(4 marks)

(c) How would you assess graphically the goodness of fit of the exponential model for these data?

. ***(2 marks)***

(d) Using both a log-rank test and a likelihood ratio test (assuming the exponential model is valid) and appropriate results from the computer output below, assess the effect of chemotherapy on the survival times of these patients.

(5 marks)

(e) If the subjects had not been followed up for more than 20 weeks how would your conclusions based on the likelihood ratio test have been altered?

(5 marks)

********** Analysis of Tumour Survival Times ************

Rows: treatment Columns: censored

	0 censored	1 uncensored	All total
Radiation	114	136	250
	7	6	13
Rad + chemo	55	167	222
	2	13	15
All	169	303	472
	9	19	28

Cell Contents:--
Sum of survival times
N

Question 2 continued on next page

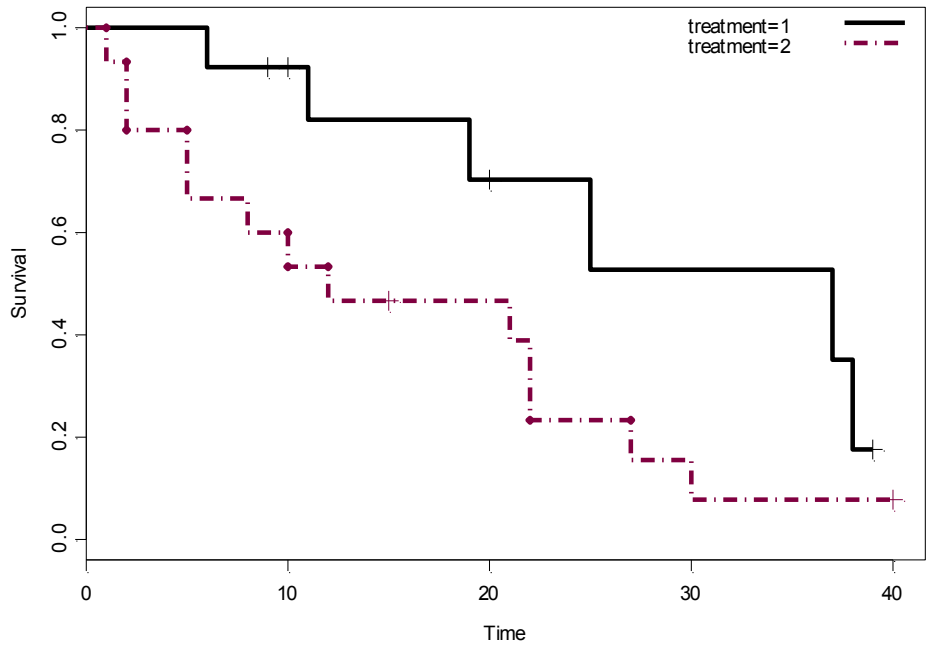
Question 2 continued

```
      *** Nonparametric Survival ***
Call: survfit(formula = Surv(time, censor, type = "right") ~
treatment, type = "kaplan-meier", data = kidneytumour)

            n.obs n.max n.first events mean se(mean) median
treatment=1    13    13      13      6 28.3     3.79     37
treatment=2    15    15      15     13 15.6     3.11     12

                treatment=1
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    6     13       1    0.923  0.0739        0.7890            1
    9     11       0    0.923  0.0739        0.7890            1
   10     10       0    0.923  0.0739        0.7890            1
   11      9       1    0.821  0.1169        0.6206            1
   19      7       1    0.703  0.1477        0.4660            1
   20      5       0    0.703  0.1477        0.4660            1
   25      4       1    0.527  0.1883        0.2620            1
   37      3       1    0.352  0.1907        0.1215            1
   38      2       1    0.176  0.1567        0.0307            1
   39      1       0    0.176  0.1567        0.0307            1

                treatment=2
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    1     15       1   0.9333  0.0644        0.8153        1.000
    2     14       2   0.8000  0.1033        0.6212        1.000
    5     12       2   0.6667  0.1217        0.4661        0.953
    8     10       1   0.6000  0.1265        0.3969        0.907
   10      9       1   0.5333  0.1288        0.3322        0.856
   12      8       1   0.4667  0.1288        0.2717        0.802
   15      7       0   0.4667  0.1288        0.2717        0.802
   21      6       1   0.3889  0.1287        0.2033        0.744
   22      5       2   0.2333  0.1150        0.0888        0.613
   27      3       1   0.1556  0.0995        0.0444        0.545
   30      2       1   0.0778  0.0742        0.0120        0.504
   40      1       0   0.0778  0.0742        0.0120        0.504
```



Question 2 continued on next page

Question 2 continued

```
survdiff(Surv(time, censor)~treatment,data=kidneytumour)
Call:
survdiff(formula = Surv(time, censor) ~ treatment, data =
     kidneytumour)

                N Observed Expected (O-E)^2/E
treatment=1 13          6     9.99      ?????
treatment=2 15         13     9.01      ?????
 Chisq= ?????  on 1 degrees of freedom, p= ?????
```

3 Given below is a record (edited in places) of an **R** session analysing the results of a randomized double-blind two period crossover trial comparing nicardipine (N) and placebo (P) in patients with Raynard's phenomenon. The data are the number of attacks in two weeks. Patients were randomly allocated to two groups: group 1 received treatment N in period 1 and P in period 2. Group 2 received the treatments in the opposite order.

(a) Plot the treatment means for each period.

(3 marks)

(b) Assess all of the evidence that there is a carryover effect from period 1 to period 2.

(5 marks)

(c) Do the data provide evidence that there is a difference in average response between periods 1 and 2?

(4 marks)

(d) Assess whether the treatments differ in effect, taking into account the results of your assessments of carryover and period effects.

(5 marks)

(e) Which, if any, of the three confidence intervals provided in the analyses below provides a confidence interval for the effect of the treatment with nicardipine on the number of attacks in patients with Raynard's phenomenon? (Justify your answer).

(3 marks)

Question 3 continued on next page

Question 3 continued

Analysis of Crossover trial on Nicardipine

```
***  Summary Statistics for data in:  nicardipine ***
Group:1
          Period1 Period2  Sum PeriodDiffs TreatDiffs
    Mean:   28.83    27.4 56.3        1.42       1.42
 Total N:   12.00    12.0 12.0       12.00      12.00
Std Dev.:    7.66    10.4 17.7        4.60       4.60
-----------------------------------------------
Group:2
          Period1 Period2  Sum PeriodDiffs TreatDiffs
    Mean:   30.87    24.1 54.9        6.80      -6.80
 Total N:   15.00    15.0 15.0       15.00      15.00
Std Dev.:    9.13    14.8 23.0        8.91       8.91

     Welch Modified Two-Sample t-Test
data:  x: Sum with Group = 1 , and y: Sum with Group = 2
t = 0.168, df = 24.9820856374548, p-value = 0.868
alternative hypothesis:  difference in means is not equal to 0
95 percent confidence interval:
 -14.8  17.4
sample estimates:
 mean of x mean of y
      56.3      54.9

     Welch Modified Two-Sample t-Test
data:  x: TreatDiffs with Group = 1 , and y: TreatDiffs with Group =
2
t = 3.09, df = 21.8114860448793, p-value = 0.0053
alternative hypothesis:  difference in means is not equal to 0
95 percent confidence interval:
  2.71 13.73
sample estimates:
 mean of x mean of y
      1.42      -6.8

     Welch Modified Two-Sample t-Test
data:  x: PeriodDiffs with Group = 1 , and y: PeriodDiffs with Group
= 2
t = -2.03, df = 21.8114860448793, p-value = 0.055
alternative hypothesis:  difference in means is not equal to 0
95 percent confidence interval:
 -10.893   0.127
sample estimates:
 mean of x mean of y
      1.42       6.8
```

4 An investigator is studying the dependence of a variable Y on two continuous explanatory variables x_1 and x_2, which have been scaled to lie between -1 and 1. It is known that $EY = 0$ when both $x_1 = 0$ and $x_2 = 0$, and the following model is proposed. Each observation is subject to a measurement error with mean 0 and variance σ^2.

$$EY = \beta_1 x_1 + \beta_2 x_2.$$

The investigator proposes to take four observations, at (-1,0), (1,0), (0,-1) and (0,1). Denote the four observations by $Y_1, \ldots, Y_4$.

(i) Find the least squares estimators of β_1 and β_2, verify that they are unbiased, and give their variances in terms of σ^2 only. ***(5 marks)***

(ii) By examining the form of your estimators in part (i) (rather than by considering the design matrix), briefly explain why β_1 and β_2 are orthogonal to each other for the chosen design. ***(2 marks)***

(iii) Show that this design is neither D-optimal nor G-optimal, by using the General Equivalence Theorem. ***(4 marks)***

(iv) Suggest an alternative design, with four observations, that is D-optimal. Justify your suggestion. ***(6 marks)***

(v) If the A-optimality criterion is to be used, is your design in part (iv) better than the original proposed design? Justify your answer. ***(3 marks)***

5 An experiment is to be carried out to investigate the effect of three diets and three drugs on blood pressure. Nine volunteers are recruited to the study, and are grouped by weight into three blocks of three. A design is chosen based on the following Latin square.

A	B	C
C	A	B
B	C	A

The following model is to be fitted to the data.

$$EY_{ij} = \mu + \theta_i + \phi_j + \psi_{\kappa(i,j)},$$

with $i = 1, 2, 3$ representing block, $j = 1, 2, 3$ representing diet, and $\psi_{\kappa(i,j)}$ representing the effect of the drug given to the individual on diet j in block i (so that $\kappa(i, j) = 1, 2$ or 3.) The constraints

$$\sum_{i=1}^{3} \theta_i = \sum_{j=1}^{3} \phi_j = \sum_{k=1}^{3} \psi_k = 0,$$

are applied.

(i) Write this model in matrix notation, and explain, with justification, which groups of parameters are orthogonal to each other. ***(7 marks)***

(ii) Suppose the experiment is to be extended to investigate the effect of three different exercise regimes, in addition to drug, diet and weight. State how you would allocate exercise regimes to volunteers using a second Latin square that is orthogonal to the first. State how you would modify the original model, and give the extra columns of the design matrix.
(7 marks)

(iii) In an alternative experiment, the effect of the three diets are to be considered only, but volunteers will still be blocked by weight. If blocks of size two are to be used, how many volunteers are required for the smallest possible balanced incomplete block design? For the smallest possible such design, list which diets should be used in each block. ***(3 marks)***

If there are four diets to compare, can a balanced incomplete block design be used with 8 blocks of size 3? Justify your answer. ***(3 marks)***

6 (i) A small survey has been conducted to estimate the proportion of the population in favour of raising the female retirement age. The sex of each participant in the survey was recorded, and the results are given below.

	males	females
in favour	23	15
against	18	44

If the sample was drawn using simple random sampling, suggest two different estimates of the population proportion in favour of raising the female retirement age. Briefly explain your reasoning. ***(3 marks)***

(ii) An opinion poll is to be taken to estimate the proportion of the adult population in Scotland who are in favour of Scotland leaving the United Kingdom. If a simple random sample is to be used, how large would the sample need to be to ensure that a 90% confidence interval for the true proportion was no wider than 0.1? You may ignore the finite population correction. ***(5 marks)***

(iii) 100 motors have various different ages, all of which are known. It is believed that the remaining lifetime of each motor will be dependent on the motor's age. Five motors are selected at random, their ages are noted and their remaining lifetimes are observed by running them continuously until failure. Let Y_i be the age of the i-th motor, and X_i be the remaining lifetime of the i-th motor. The following summary statistics are observed.

$$\sum_{i=1}^{100} Y_i = 9024, \qquad \sum_{i=1}^{5} y_i = 350, \qquad \sum_{i=1}^{5} x_i = 4646,$$

$$\sum_{i=1}^{5} (x_i - \bar{x})(y_i - \bar{y}) = -13754, \qquad \sum_{i=1}^{5} (y_i - \bar{y})^2 = 13960,$$

where $(x_1, y_1), \ldots, (x_5, y_5)$ are the observed age and remaining lifetime for 5 randomly selected motors.

Suggest two possible estimates of $\bar{X}$, explaining your reasoning. Without referring explicitly to the formulae of your estimators, give an intuitive explanation for the discrepancy between the two estimates. ***(6 marks)***

6 (continued)

(iv) A survey is to be taken to estimate the mean starting wage of individuals following completion of a new training course. Two pilot studies have been conducted. In the first study, a simple random sample of size 20 was used, and the following summary statistics were observed.

$$\sum_{i=1}^{20} x_i = 564.9, \qquad \sum_{i=1}^{20} x_i^2 = 16131.2,$$

where each x_i is measured in £1000.

In the second study, cluster sampling was used. Courses are run at different training centres around the country, with 10 students at each centre. Two training centres were selected as the clusters. The following summary statistics were observed.

$$\sum_{j=1}^{10} x_{1j} = 258.7, \qquad \sum_{j=1}^{10} x_{1j}^2 = 6714.3,$$

$$\sum_{j=1}^{10} x_{2j} = 305.0, \qquad \sum_{j=1}^{10} x_{2j}^2 = 9319.2,$$

where x_{ij} is observation j within cluster i.

Based on the pilot survey data, would you recommend the use of cluster sampling or simple random sampling for the new survey? Briefly explain your reasoning. ***(6 marks)***

End of Question Paper