

The
University
Of
Sheffield.

**PLEASE LEAVE THIS EXAM PAPER ON YOUR DESK.
DO NOT REMOVE IT FROM THE HALL.**

**Data Provided:
Neaves Tables
Graph Paper**

SCHOOL OF MATHEMATICS AND STATISTICS

MAS461

Autumn Semester 2011-2012

2 Hours

Medical Statistics

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 **THREE** answers.*

Questions 3 and 4 both use the data from a study on chemotherapy but otherwise are independent: either or both can be attempted.

All questions carry equal marks. Total marks 75.

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?
(7 marks)
- (b) What power will her test have if the actual exclusion rate is 20%?
(6 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.
(6 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?
(6 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. **(5 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. **(5 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. **(7 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? **(6 marks)**

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

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

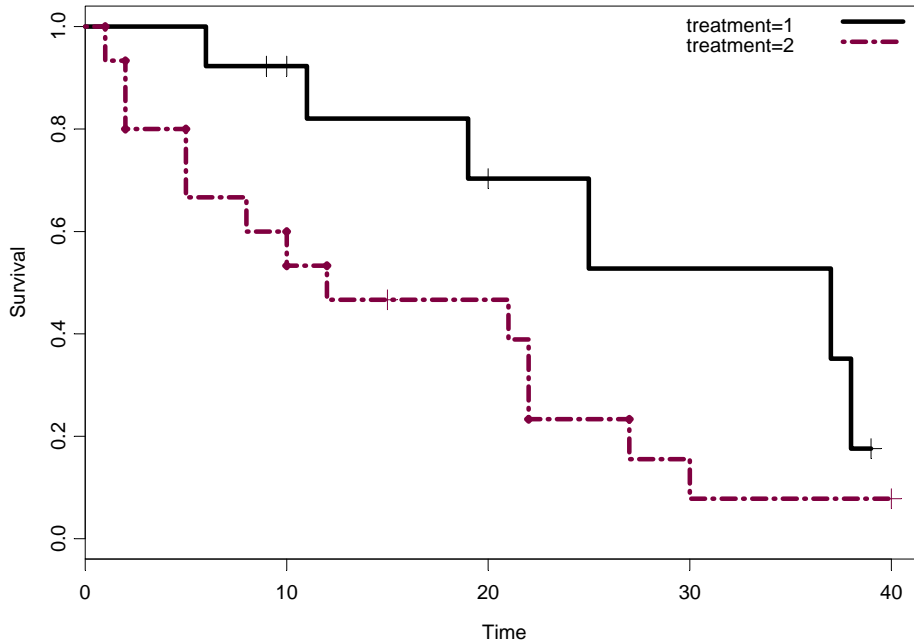
	n.obs	n.max	n.first	events	mean	se(mean)	median
treatment=1	13	13	13	6	28.3	3.79	37
treatment=2	15	15	15	13	15.6	3.11	12

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)
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Call:
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```
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 In a large clinical trial comparing the time to recurrence of disease in leukaemia patients, patients were randomly assigned to receive either treatment AG positive ($X_1 = 1$) or treatment AG negative ($X_1 = 0$). The log (to base 10) white blood count (LWBC) was also recorded as a covariate. A proportional hazards model fitted to the data gave the following results.

variable	regression coefficient	standard error
X_1 : treatment (AG)	-1.12	0.48
X_2 : log white blood count (LWBC)	0.29	0.14

- (a) Specify the form of the proportional hazards model used for this analysis in terms of the baseline hazard function $h_0(t)$ and the covariates.
(2 marks)
- (b) Discuss in detail the effects of these two factors on the time to recurrence of the disease. Providing estimates with 95% confidence intervals for the hazard ratios of AG positive to AG negative and [separately] for an increase of tenfold in the actual white blood count for recurrence of disease at time t .
(8 marks)
- (c) Show diagrammatically the form of the relationship between the survival time and WBC for the two different treatment groups.
(4 marks)

It was thought that the treatment effect might be related to WBC, and to investigate this a further model was fitted which included, in addition to X_1 and X_2 , the interaction term X_1X_2 . The coefficients (and standard errors) for this model were

variable	regression coefficient	standard error
X_1 : treatment (AG)	-1.14	0.43
X_2 : log white blood count (LWBC)	0.10	0.14
X_1X_2 : interaction	0.35	0.15

- (d) Specify the form of the model with the interaction. How does this affect your conclusions (if at all) concerning the effects of treatment and WBC on the time to recurrence of the disease. How does it affect the form of the relationship of survival time with WBC for the two treatment groups?
(7 marks)
- (e) Show diagrammatically the form of the relationship between LWBC and the hazard ratio of AG positive to AG negative for recurrence of disease at time t .
(4 marks)

- 4** 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) Specify a suitable model for these data which incorporates treatment, period and carryover effects.
(1 marks)
- (b) Plot the treatment means for each period.
(3 marks)
- (c) Assess all the evidence that there is a carryover effect from period 1 to period 2.
(6 marks)
- (d) Do the data provide evidence that there is a difference in average response between periods 1 and 2?
(5 marks)
- (e) Assess whether the treatments differ in effect, taking into account the results of your assessments of carryover and period effects.
(6 marks)
- (f) 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).
(4 marks)

Question 4 continued on next page

Question 4 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

End of Question Paper