Data provided: Formula Sheet, incorporating Critical Values Tables

The University Of Sheffield.

MAS361

SCHOOL OF MATHEMATICS AND STATISTICS **Autumn Semester 2016–17**

Medical Statistics **2 hours**

*Candidates may bring to the examination a calculator that conforms to University regulations. All questions will be marked, but credit will be given for only the best **THREE** answers. All questions carry equal marks. Total marks 60.*

Please leave this exam paper on your desk
Do not remove it from the hall

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to be completed by student

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1 The data below come from an RCT of a possible new drug for treatment of hypertension in diabetics (adapted from Altman (1995); original data from Hommel *et al.* (1986)). Systolic blood pressures of 16 patients before and after one week's treatment with Captopril or Placebo are given in mmHg.

	Captopril				Placebo		
	Baseline	After 1 week	Change		Baseline	After 1 week	Change
1	147	137	-10	1	133	139	6
2	129	120	-9	2	129	134	5
3	158	141	-17	3	152	136	-16
4	164	137	-27	4	161	151	-10
5	134	140	6	5	154	147	-7
6	155	144	-11	6	141	137	-4
7	151	134	-17	7	156	149	-7
8	141	123	-18				
9	153	142	-11				
Mean	148.0	135.3	-12.7	Mean	146.6	141.9	-4.7
SD	11.43	8.43	8.99	SD	12.29	6.94	7.91

(i) Explain what is meant by an RCT and what advantages they have. ***(4 marks)***

(ii) The authors of the original study performed paired t tests on the data in each group. They found a significant change in pressure in the Captopril group (t=4.24, df=8, p=0.003), but not in the Placebo group (t=1.57, df=6, p=0.17). They then concluded that therefore 'Captopril represents a valuable new drug for treating hypertension in diabetics'.

(a) What is wrong with their analysis? ***(3 marks)***

(b) Suggest a better analysis, explaining your reasoning. Perform the test you suggest and explain what conclusions can be drawn about the effects of Captopril in such patients. ***(8 marks)***

(iii) In the trial the group sizes are unbalanced (Captopril:Placebo is 9:7 rather than 8:8).

(a) What effect is this likely to have on the effectiveness of the trial? ***(2 marks)***

(b) Specify a mechanism by which one could ensure a balanced allocation of the 16 patients. Give details of how it could be applied. ***(3 marks)***

2 The data in this question come from a study of adverse reactions in recipients of bone marrow transplants for treatment of leukaemia (adapted from Altman (1995); original data from Bagot *et al.* (1988)). The study concerned 37 transplants in which 20 recipients went on to develop an adverse reaction while 17 did not. Possible explanatory factors which were also recorded were: type of leukaemia (coded AML, ALL or CML), recipient and donor ages (in years), whether the donor had ever been pregnant (coded 1= Yes, 0=No) and a continuous chemical index (Index) reflecting condition at the time of transplant.

(i) Use the data below to assess whether type of leukaemia is associated with occurrence of an adverse reaction.

	Type of leukaemia		
	AML	ALL	CML
Reaction	5	4	8
No reaction	6	12	2

(4 marks)

(ii) Use the data below to assess whether donor pregnancy is associated with occurrence of an adverse reaction. Give the relative risk of developing a reaction for a transplant from a donor who has ever been pregnant versus one who has not and a 95% confidence interval for this relative risk.

	Pregnancy	
	Yes	No
Reaction	8	9
No reaction	2	18

(7 marks)

(iii) A logistic regression analysis of the full data set, using the stepwise method and a 5% level of significance to assess whether to retain a variable, gave the output below. Here the response has been coded 1=adverse reaction occurred, 0=no adverse reaction occurred; leukaemia type was recoded by use of 2-level dummy variables for presence of each of ALL and CML; and only main effects were considered.

Variable	Coefficient	SE	z	p-value
CML	2.251	1.106	2.035	0.04
Pregnancy	2.496	1.101	2.266	0.02
Index	1.488	0.720	2.067	0.04

(a) Explain why a logistic regression analysis might be preferable to analyses of the types in parts (i) and (ii). ***(2 marks)***

(b) Use the output above to calculate the probability of an adverse reaction for a patient age 20, with ALL and an Index of 0.9, receiving a donation from a donor age 25 who had been pregnant. ***(4 marks)***

(c) Use the output above to calculate the odds ratio for risk of adverse reaction following a transplant from a donor who has been pregnant versus one who has not. Compare your answer with that in (ii).

(3 marks)

3 An engineering firm is testing a new method of making drill bits (the cutting tool used on a drill). In a trial comparing two methods, *New* and *Standard*, 19 drill bits were tested to destruction. Follow-up was censored prior to failure in 5 of the bits. The table below shows the times until failure in weeks. An asterisk denotes a censored observation.

	New Time (weeks)	Standard Time (weeks)
	1	2*
	4	5
	11*	7
	15*	10
	16	12
	32	13
	34	14
	52*	17*
	85	27
		27
Total	250	134

(i) Assuming that the censoring is for reasons unrelated to drill bit breakage, estimate the value of the survivor function at 20 weeks using Kaplan-Meier estimates separately in each group. ***(6 marks)***

Note: You are not required to work out the Kaplan-Meier estimates beyond this time in either group.

(ii) It is suggested that the survival times in each group are exponentially distributed. Under this assumption, estimate the value of the survivor function in each group at 20 weeks. ***(4 marks)***

Hint: For an exponential distribution with rate λ, then $S(t) = e^{-\lambda t}$.

(iii) How would you decide if the estimate found in part (ii) was appropriate? ***(2 marks)***

(iv) (a) It was decided to compare the two manufacturing methods using a log-rank test. Complete the first two rows of the following table (where the new technique is denoted as group A and the standard technique group B). ***(3 marks)***

 Question 3 continued on next page

3 (continued)

Do not copy out more than the first two rows onto your solution paper.

		Number at risk			Number of deaths			Expected number of deaths	
i	t_i	r_{Ai}	r_{Bi}	r_i	d_{Ai}	d_{Bi}	d_i	e_{Ai}	e_{Bi}
1	1								
2	4								
3	5	7	9	16	0	1	1	7/16	9/16
4	7	7	8	15	0	1	1	7/15	8/15
5	10	7	7	14	0	1	1	7/14	7/14
6	12	6	6	12	0	1	1	6/12	6/12
7	13	6	5	11	0	1	1	6/11	5/11
8	14	6	4	10	0	1	1	6/10	4/10
9	16	5	3	8	1	0	1	5/8	3/8
10	27	4	2	6	0	2	2	8/6	4/6
11	32	4	0	4	1	0	1	1	0
12	34	3	0	3	1	0	1	1	0
13	85	1	0	1	1	0	1	1	0
Total								8.95	5.05

(b) Discuss whether the data provide evidence of a difference in the failure time between the methods. ***(3 marks)***

(v) If censoring in this study was due to the operator noticing a hairline crack in the drill bit, briefly discuss the appropriateness of using the above failure times to assess the success of the new manufacturing technique. ***(2 marks)***

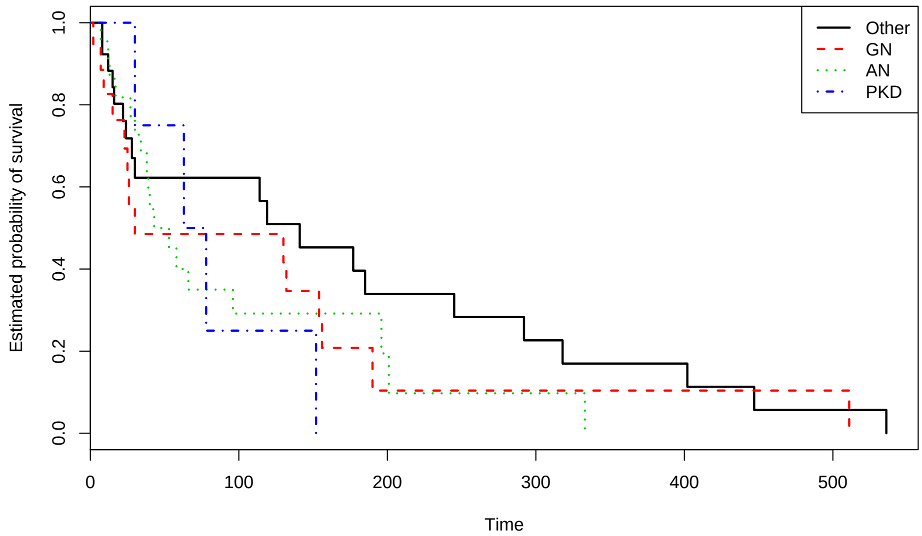
4 McGilchrist and Aisbett (1991) reported a trial on kidney disease patients using portable dialysis equipment. When an infection is found in a dialysis patient, the catheter they currently have needs to be removed and the infection cleared up. Once this is done a new catheter is inserted. McGilchrist and Aisbett investigated the recurrence time to infection, from the time of insertion of this new catheter. Catheters were removed for reasons other than infection, in which case the observation was right censored. Primary interest was in whether the disease type affected recurrence time.

The data are stored in `dialysis` and coding for the different variables is shown below:

Coding:
time: time until recurrence (weeks)
status: censoring indicator (1 = recurrence; 0 = censoring)
age: age of patient (yrs)
sex: 0 = Female, 1 = Male
disease type, four possible types: GN, AN, PKD, and Other

(i) Briefly describe what procedure the following R code implements and what the plot that it produces tells you.

```
> attach(dialysis)
> dialysis.surv <- Surv(time, status)
>
> dialysisfit.raw <- survfit(dialysis.surv ~ disease)
> plot(dialysisfit.raw, col=c(1:4), lty=c(1:4),lwd=2,xlab="Time",
+   ylab="Estimated probability of survival")
> legend("topright",levels(disease),col=c(1:4),lty=c(1:4),lwd=2)
```



(4 marks)

4 (continued)

(ii) A more in depth analysis was performed below:

```
> dialysis.fit <- survreg(dialysis.surv ~ sex + age + disease,
+   dist = "exponential")
> summary(dialysis.fit)

Call:
survreg(formula = dialysis.surv ~ sex + age + disease, dist = "exponential")
               Value Std. Error      z        p
(Intercept)  5.20601     0.4126 12.617 1.71e-36
sex         -1.74338     0.3126 -5.578 2.44e-08
age          0.00235     0.0112  0.210 8.34e-01
diseaseGN   -0.08935     0.4040 -0.221 8.25e-01
diseaseAN   -0.59722     0.3934 -1.518 1.29e-01
diseasePKD  -0.21870     0.6424 -0.340 7.34e-01

Scale fixed at 1

Exponential distribution
Loglik(model)= -312.4   Loglik(intercept only)= -326.5
Chisq= 28.07 on 5 degrees of freedom, p= 3.5e-05
Number of Newton-Raphson Iterations: 5
n= 74

>
> anova(dialysis.fit)
        Df   Deviance Resid. Df    -2*LL     Pr(>Chi)
NULL    NA         NA        73 652.9310           NA
sex      1 24.9099653        72 628.0211 6.007110e-07
age      1  0.2971188        71 627.7239 5.856943e-01
disease  3  2.8642543        68 624.8597 4.130315e-01
```

Describe this analysis making sure you explain:

(a) The type of model fitted; the statistical representation of the model; and the coding of the variables; ***(5 marks)***

(b) What the effects of the different variables are on recurrence; and if disease type is seen to make a difference. ***(5 marks)***

(iii) Using the model output in part (ii), predict the expected recurrence time for a 40yr old male with disease type 'Other'. ***(4 marks)***

(iv) Write down one benefit to a clinician that this model provides that a proportional hazards model would not. Similarly write down one benefit of a proportional hazards model. ***(2 marks)***

End of Question Paper

STANDARD FORMULAE FOR MEDICAL STATISTICS (INCLUDING TABLES OF CRTICAL VALUES)

1 Clinical Trials Formulae

Two Sample t-Test — Separate variances form $r = min(n_1, n_2)$

$$t_r = |\frac{\bar{X_1} - \bar{X_2}}{\sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}}|$$

Two Sample t-Test — Pooled variance form $r = n_1 + n_2 - 2$

$$t_r = |\frac{\bar{X_1} - \bar{X_2}}{\sqrt{\frac{(n_1-1)S_1^2+(n_2-1)S_2^2}{n_1+n_2-2}(\frac{1}{n_1} + \frac{1}{n_2})}}|$$

Sample Size Calculations — Two sample test for proportions NB number in each group

$$n \simeq \frac{\theta_2(1-\theta_2) + \theta_1(1-\theta_1)}{(\theta_2 - \theta_1)^2}[\Phi^{-1}(\beta) + \Phi^{-1}(\alpha/2)]^2$$

Sample Size Calculations — Two sample test for means NB number in each group

$$n \simeq \frac{2\sigma^2}{(\mu_2 - \mu_1)^2}[\Phi^{-1}(\beta) + \Phi^{-1}(\alpha/2)]^2$$

Standard Error for Natural Logarithm of Relative Risk

$$s.e[(log_e(RR)] = \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}$$

Standard Error for Natural Logarithm of Odds Ratio

$$s.e[(log_e(OR)] = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

2 Survival Analysis Formulae

Exponential Distributions — MLE of rate λ with censoring The mle

$$\hat{\lambda} = \frac{\sum_{i=1}^{n} \delta_i}{\sum_{i=1}^{n} t_i} = \frac{\Delta}{\mathcal{T}} \qquad var(\hat{\lambda}) \approx \frac{\hat{\lambda}^2}{\sum_{i=1}^{n} \delta_i}.$$

For any (differentiable, monotonic) function $g(\cdot)$,

$$var(g(\hat{\lambda})) \approx \left[\{g'(\lambda)\}^2 var(\lambda)\right]_{\lambda=\hat{\lambda}}.$$

so e.g.

$$var(\frac{1}{\hat{\lambda}}) = var(\hat{\mu}) \approx \frac{\hat{\mu}^2}{\sum_{i=1}^{n} \delta_i}$$

Exponential Distributions — MLE test

$$W = \frac{\hat{\lambda}_1 - \hat{\lambda}_2}{\sqrt{\frac{\hat{\lambda}_1^2}{\Delta_1} + \frac{\hat{\lambda}_2^2}{\Delta_2}}} \approx N(0,1).$$

Exponential Distributions — LRT test

$$2\left\{\Delta_1 \log \frac{\Delta_1}{\mathcal{T}_1} + \Delta_2 \log \frac{\Delta_2}{\mathcal{T}_2} - (\Delta_1 + \Delta_2) \log \frac{\Delta_1 + \Delta_2}{\mathcal{T}_1 + \mathcal{T}_2}\right\} \approx \chi_1^2$$

Log-rank Statistic

$$LR = \frac{(O_1 - E_1)^2}{E_1} + \frac{(O_2 - E_2)^2}{E_2} \sim \chi_1^2$$

3 Tables of Percentage Points (also known as Quantiles or Critical Values) for Three Standard Distributions

The tables contain values of quantiles q such that $P[X \leq q] = p$ for various probabilities p when X has the specified distribution (which may depend on particular degrees of freedom ν). In these tables, p has been expressed as a percentage rather than a decimal. The relevant R commands for generating the q are also shown. For the $N(0,1)$ distribution, the tabulated function is also known as the Φ^{-1} function.

STANDARD NORMAL DISTRIBUTION PERCENTAGE POINTS
`qnorm(`p`)` where p is percentage, e.g. for 95%, $p = 0.95$

	60.0%	66.7%	75.0%	80.0%	87.5%	90.0%	95.0%	97.5%	99.0%	99.5%	99.9%
qnorm	0.253	0.431	0.674	0.842	1.150	1.282	1.645	1.960	2.326	2.576	3.090

CHI-SQUARED PERCENTAGE POINTS
`qchisq(`p, ν`)` where p is percentage, e.g. for 95%, $p = 0.95$

ν	60.0%	66.7%	75.0%	80.0%	87.5%	90.0%	95.0%	97.5%	99.0%	99.5%	99.9%
1	0.708	0.936	1.323	1.642	2.354	2.706	3.841	5.024	6.635	7.879	10.828
2	1.833	2.197	2.773	3.219	4.159	4.605	5.991	7.378	9.210	10.597	13.816
3	2.946	3.405	4.108	4.642	5.739	6.251	7.815	9.348	11.345	12.838	16.266
4	4.045	4.579	5.385	5.989	7.214	7.779	9.488	11.143	13.277	14.860	18.467
5	5.132	5.730	6.626	7.289	8.625	9.236	11.070	12.833	15.086	16.750	20.515
6	6.211	6.867	7.841	8.558	9.992	10.645	12.592	14.449	16.812	18.548	22.458
7	7.283	7.992	9.037	9.803	11.326	12.017	14.067	16.013	18.475	20.278	24.322
8	8.351	9.107	10.219	11.030	12.636	13.362	15.507	17.535	20.090	21.955	26.125
9	9.414	10.215	11.389	12.242	13.926	14.684	16.919	19.023	21.666	23.589	27.877
10	10.473	11.317	12.549	13.442	15.198	15.987	18.307	20.483	23.209	25.188	29.588

STUDENT'S t PERCENTAGE POINTS

`qt(`p, ν`)` where p is percentage, e.g. for 95%, $p = 0.95$

ν	60.0%	66.7%	75.0%	80.0%	87.5%	90.0%	95.0%	97.5%	99.0%	99.5%	99.9%
1	0.325	0.577	1.000	1.376	2.414	3.078	6.314	12.706	31.821	63.657	318.31
2	0.289	0.500	0.816	1.061	1.604	1.886	2.920	4.303	6.965	9.925	22.327
3	0.277	0.476	0.765	0.978	1.423	1.638	2.353	3.182	4.541	5.841	10.215
4	0.271	0.464	0.741	0.941	1.344	1.533	2.132	2.776	3.747	4.604	7.173
5	0.267	0.457	0.727	0.920	1.301	1.476	2.015	2.571	3.365	4.032	5.893
6	0.265	0.453	0.718	0.906	1.273	1.440	1.943	2.447	3.143	3.707	5.208
7	0.263	0.449	0.711	0.896	1.254	1.415	1.895	2.365	2.998	3.499	4.785
8	0.262	0.447	0.706	0.889	1.240	1.397	1.860	2.306	2.896	3.355	4.501
9	0.261	0.445	0.703	0.883	1.230	1.383	1.833	2.262	2.821	3.250	4.297
10	0.260	0.444	0.700	0.879	1.221	1.372	1.812	2.228	2.764	3.169	4.144
11	0.260	0.443	0.697	0.876	1.214	1.363	1.796	2.201	2.718	3.106	4.025
12	0.259	0.442	0.695	0.873	1.209	1.356	1.782	2.179	2.681	3.055	3.930
13	0.259	0.441	0.694	0.870	1.204	1.350	1.771	2.160	2.650	3.012	3.852
14	0.258	0.440	0.692	0.868	1.200	1.345	1.761	2.145	2.624	2.977	3.787
15	0.258	0.439	0.691	0.866	1.197	1.341	1.753	2.131	2.602	2.947	3.733
16	0.258	0.439	0.690	0.865	1.194	1.337	1.746	2.120	2.583	2.921	3.686
17	0.257	0.438	0.689	0.863	1.191	1.333	1.740	2.110	2.567	2.898	3.646
18	0.257	0.438	0.688	0.862	1.189	1.330	1.734	2.101	2.552	2.878	3.610
19	0.257	0.438	0.688	0.861	1.187	1.328	1.729	2.093	2.539	2.861	3.579
20	0.257	0.437	0.687	0.860	1.185	1.325	1.725	2.086	2.528	2.845	3.552
21	0.257	0.437	0.686	0.859	1.183	1.323	1.721	2.080	2.518	2.831	3.527
22	0.256	0.437	0.686	0.858	1.182	1.321	1.717	2.074	2.508	2.819	3.505
23	0.256	0.436	0.685	0.858	1.180	1.319	1.714	2.069	2.500	2.807	3.485
24	0.256	0.436	0.685	0.857	1.179	1.318	1.711	2.064	2.492	2.797	3.467
25	0.256	0.436	0.684	0.856	1.178	1.316	1.708	2.060	2.485	2.787	3.450
26	0.256	0.436	0.684	0.856	1.177	1.315	1.706	2.056	2.479	2.779	3.435
27	0.256	0.435	0.684	0.855	1.176	1.314	1.703	2.052	2.473	2.771	3.421
28	0.256	0.435	0.683	0.855	1.175	1.313	1.701	2.048	2.467	2.763	3.408
29	0.256	0.435	0.683	0.854	1.174	1.311	1.699	2.045	2.462	2.756	3.396
30	0.256	0.435	0.683	0.854	1.173	1.310	1.697	2.042	2.457	2.750	3.385
35	0.255	0.434	0.682	0.852	1.170	1.306	1.690	2.030	2.438	2.724	3.340
40	0.255	0.434	0.681	0.851	1.167	1.303	1.684	2.021	2.423	2.704	3.307
45	0.255	0.434	0.680	0.850	1.165	1.301	1.679	2.014	2.412	2.690	3.281
50	0.255	0.433	0.679	0.849	1.164	1.299	1.676	2.009	2.403	2.678	3.261
55	0.255	0.433	0.679	0.848	1.163	1.297	1.673	2.004	2.396	2.668	3.245
60	0.254	0.433	0.679	0.848	1.162	1.296	1.671	2.000	2.390	2.660	3.232
∞	0.253	0.431	0.674	0.842	1.150	1.282	1.645	1.960	2.326	2.576	3.090