Data provided: Formula Sheet, incorporating Critical Values Tables

MAS361

The University Of Sheffield.

SCHOOL OF MATHEMATICS AND STATISTICS **Autumn Semester 2017–18**

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.*

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Do not remove it from the hall

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to be completed by student

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1 If babies are born prematurely, there is a risk that they will be under-developed and suffer a variety of health problems. There is good evidence that mothers who give birth prematurely in one pregnancy will also do so in later pregnancies, so in the following studies, the subjects were mothers who had given birth prematurely in their first pregnancy.

(i) Clinicians designed and conducted a study to assess whether a drug extended pregnancy, by comparing duration of the second pregnancy for two independent groups each of 40 mothers. One group was given the active drug and the other a placebo version. The results of the trial (in weeks) were as follows:

Group	mean	s.d.
Drug	39.1	1.45
Placebo	38.2	1.60

(a) Verify that the trial had an adequate sample size to test for a difference of 1 week, when results expected on the placebo were a mean duration of 38 weeks, with a standard deviation of 1.5 weeks. ***(4 marks)***

(b) Did the trial provide evidence that the drug is beneficial in terms of extending pregnancy? ***(4 marks)***

(ii) When writing up their study, as well as assessing the effect on duration of pregnancy, the clinicians decide to examine whether the drug has any effect on the birthweights of the babies (hoping that longer durations will give the babies more time to develop and hence increase birthweights). Differences in mean birthweight between the two groups give a p-value for the t-test of p=0.03. What should you conclude about the effectiveness of the drug for increasing birthweights? Explain your reasoning. Does this change the way you would evaluate the effect of the drug on pregnancy duration in (i)(b)? ***(6 marks)***

(iii) In fact, it is subsequently revealed that one of the clinicians involved in the trial did not wait until the end of the trial for the formal test of effect of the drug on duration. Instead he looked at all the available data at 3 interim time points, after roughly each quarter of the patients had had their babies. A summary of the t-tests he conducted at these time points is:

Group	Time point 1	Time point 2	Time point 3
Number on Drug	10	20	30
Number on Placebo	9	20	31
p-value	0.081	0.065	0.056

(a) Give 2 reasons why this might have been sensible. ***(2 marks)***

(b) Explain why there might be a problem in adopting this approach. ***(2 marks)***

(c) Was he right to let the trial run its full course? ***(2 marks)***

2 (i) A dermatologist investigating the use of emollient creams in managing dermatitis conducts a 6-week long crossover trial of a new cream versus a standard cream. Patients, who all suffered from a similar form of dermatitis of the hand, were allocated at random to either Group 1 or Group 2 and were instructed to apply the cream supplied (in an unbranded jar) to moisturize their hands twice daily. Group 1 used the new cream for 3 weeks, then reverted to the standard cream, while Group 2 continued with the standard cream for 3 weeks, then trialled the new cream for a further 3 weeks. Patients were encouraged to keep a diary of their impressions of the creams over the 6-week trial period (eg whether they experienced any flare ups or side effects, counting (approximately) the number of skin lesions, reporting the dryness of the skin), but ultimately only recorded whether they preferred their first or second cream (or whether they had no preference). The results are given below, coded as to whether the expressed preference was for new (denoted n), standard (denoted s) or neither (denoted −):

Group	patient	preference
Group 1 new ⟶ standard	1	n
	2	–
	3	n
	4	n
	5	n
	6	–
	7	n
	8	n
	9	n
	10	n
Group 2 standard ⟶ new	11	–
	12	n
	13	n
	14	–
	15	n
	16	s
	17	s
	18	n
	19	s
	20	n

(a) Explain why the creams were provided to patients in unbranded jars. ***(2 marks)***

(b) Comment on the form of response finally used (i.e. that patients kept a diary, but summarized their whole experience into a simple preference). ***(2 marks)***

(c) Show that the trial provides a clear indication that the new cream is preferable. ***(5 marks)***

(d) Show that there is also a suggestion of a period effect. ***(3 marks)***

 Question 2 continued on next page

2 (continued)

(ii) It has been suggested that future similar trials could be shortened to only 3 weeks, by applying the creams simultaneously; one to the patient's left hand and the other to their right hand.

(a) Explain why this could still be regarded as a form of crossover trial. ***(2 marks)***

(b) Explain what key benefit (other than giving quicker results) this would offer over the format used in (i). ***(2 marks)***

(c) What problems might arise if the patients did not all have the same dominant hand (i.e. some were right handed, others left handed)? ***(2 marks)***

(d) What further modification of the trial format could you suggest to overcome the problem in (c)? Would it have any effect on your analysis? ***(2 marks)***

3 A food manufacturer wants to test out a new diet program which they claim helps people lose weight more quickly. To analyse their claim they randomly allocate participants to either their new diet plan (plan A with 9 participants) or the current plan of a competitor (plan B with 8 participants). The table below shows the time taken until the participants lose 5kg in weight. An asterisk denotes a right censored observation where contact with the participant was lost before the participant lost the 5kg.

	New Plan A Time (weeks)	Competitor Plan B Time (weeks)
	1	2
	2	4
	5*	8
	6	9*
	7*	12
	14	15
	15*	23*
	22	23
	36	
Total	108	96

(i) Estimate the value of the survivor function for the new diet plan at 25 weeks via Kaplan-Meier. ***(5 marks)***

(ii) Using your Kaplan-Meier estimate, write down an estimate for the median time for a participant on the new plan to lose 5kg. ***(2 marks)***

Note: You are not required to work out the Kaplan-Meier estimates for the competitor plan.

 Question 3 continued on next page

3 (continued)

(iii) It is suggested that the times to lose the weight in each group are exponentially distributed with rates λ_A and λ_B respectively. Under this assumption:

(a) Estimate λ_A and λ_B and hence the mean time to lose 5kg with approximate 95% confidence intervals. ***(4 marks)***

(b) How might you assess this assumption of exponentially distributed times? ***(2 marks)***

(iv) Using an exponential model as in (iii), perform a likelihood ratio test to assess whether there is a difference between the diet plans in terms of the time taken to lose 5kg. ***(4 marks)***

(v) The advertising authority is concerned about the possibility that the censoring may be informative. Explain what this means and give two possible reasons that could have led to informative censoring in this study. ***(3 marks)***

4 (i) A new treatment is being trialled for lung cancer. 703 patients who presented with lung cancer were randomly allocated to either the new or standard treatment and followed up until either death or censoring. The information stored on each patient was:

time:	time until death/censoring (years)
status:	failure indicator (1 = death; 0 = censored)
sex:	Female or Male
drug:	New or Standard

The following R analysis was performed:

```
> lcancer.surv <- Surv(time, status)
>
> lcancer.fit <- coxph(lcancer.surv ~ sex + drug)
> summary(lcancer.fit)
Call:
coxph(formula = lcancer.surv ~ sex + drug)

  n= 703, number of events= 703

                coef exp(coef) se(coef)     z Pr(>|z|)
sexMale      0.30019   1.35012  0.08017 3.744 0.000181 ***
drugStandard 0.42560   1.53052  0.07680 5.542    3e-08 ***
---

             exp(coef) exp(-coef) lower .95 upper .95
sexMale          1.350     0.7407     1.154     1.580
drugStandard     1.531     0.6534     1.317     1.779

Concordance= 0.556  (se = 0.012 )
Rsquare= 0.059   (max possible= 1 )
Likelihood ratio test= 43.04  on 2 df,   p=4.516e-10
Wald test            = 43.01  on 2 df,   p=4.58e-10
Score (logrank) test = 43.49  on 2 df,   p=3.606e-10
```

(a) What type of model is fitted in `lcancer.fit`? Specify the form of the hazard for an individual given their sex and drug treatment. Make sure to describe your notation carefully. ***(4 marks)***

(b) Describe the findings of the analysis. ***(4 marks)***

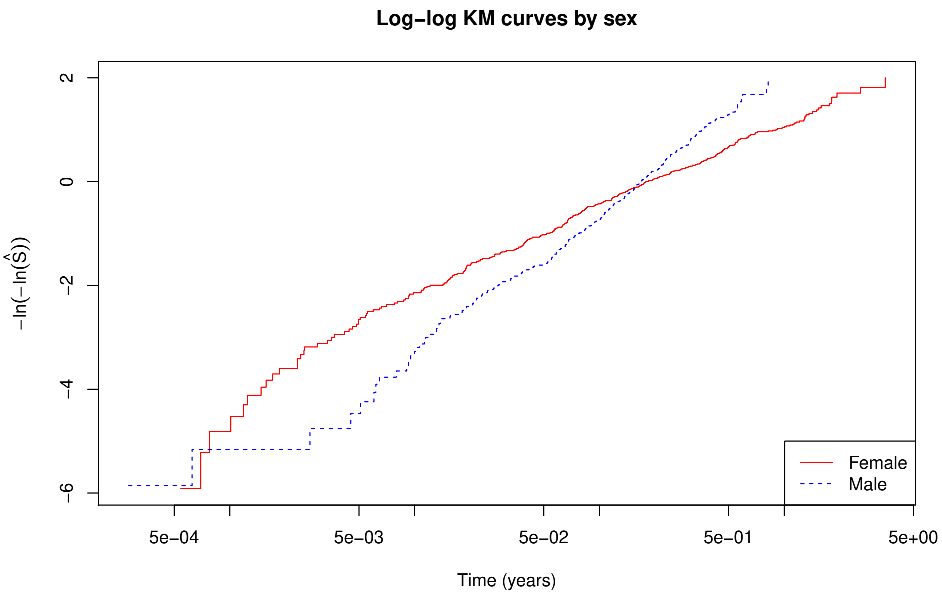
 Question 4 continued on next page

4 (continued)

(c) A statistician has performed some further analysis as shown below

```
> lcancer.fit2 <- coxph(lcancer.surv ~ drug + strata(sex))
> plot(survfit(lcancer.fit2),fun="cloglog")
```

which produced the following plot:



Does this plot raise any concerns regarding the suitability of the initial analysis? Justify your decision. ***(3 marks)***

(ii) A group of 126 elderly patients were studied to determine potential risk factors for hip fractures. The study investigators collected data on each patient's sex (male or female); age (measured in years); and whether they exercised (true or false).

 Question 4 continued on next page

4 (continued)

The patients were studied for a period of 5 years to see whether they fractured their hip in that time. Coding for the different variables is shown below:

failtime:	time until hip fracture (years)
status:	fracture indicator (1 = hip fracture observed; 0 = no hip fracture observed)
sex:	Female or Male
age:	uncentred age of patient (years)
exercise:	True or False

An R analysis is provided below:

```
> hip.surv <- Surv(failtime, status)
>
> hipfrac.fit <- survreg(hip.surv ~ sex + age + exercise, dist = "exponential")
> summary(hipfrac.fit)

Call:
survreg(formula = hip.surv ~ sex + age + exercise, dist = "exponential")
               Value Std. Error     z        p
(Intercept)   3.8820      0.902  4.30 1.68e-05
sexMale       0.6163      0.181  3.41 6.40e-04
age          -0.0279      0.010 -2.78 5.51e-03
exerciseTRUE  0.3775      0.183  2.06 3.89e-02

Scale fixed at 1

Exponential distribution
Loglik(model)= -367.3   Loglik(intercept only)= -380.5
Chisq= 26.39 on 3 degrees of freedom, p= 7.9e-06
Number of Newton-Raphson Iterations: 5
n= 126
```

(a) What type of model is fitted in `hipfract.fit`? Write down the model fitted for the time T until hip fracture for an individual given their age, sex and exercise status. Make sure to describe your notation carefully. ***(5 marks)***

(b) Briefly describe the results of the analysis in terms of the effects of age, sex and exercise upon time to hip fracture. ***(4 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