Data provided: Formula Sheet, incorporating Critical Values Tables

MAS461

The University Of Sheffield.

SCHOOL OF MATHEMATICS AND STATISTICS **Autumn Semester 2019–20**

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

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

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1 A doctor proposes using a trial of 200 patients (in two parallel groups of 100 patients each) to test whether a new drug improves response rate above the 55% observed on the current drug.

(i) Check that such a trial would give reasonable power if the new drug improved the response rate to 75% or more. ***(6 marks)***

(ii) He proposes using simple randomization to decide which of the subjects will receive the new drug and which the current drug.

(a) Explain why this might result in unequally sized groups. ***(1 mark)***

(b) Explain why this might be a problem for the verification in (i). ***(1 mark)***

(c) Suggest an alternative method he could use to ensure equal group sizes. ***(1 mark)***

(iii) After a suitable randomization, the trial is conducted and the following data obtained:

	Respond	Do not respond	Total
Current drug	56	44	100
New drug	66	34	100

Test whether the new drug seems to be an improvement on the current drug. ***(4 marks)***

(iv) As part of the general information on the patients in the trial, he notes their sex. Thus he might have represented his data more fully as:

	Male		Female	
	Respond	Do not respond	Respond	Do not respond
Current drug	17	31	39	13
New drug	21	32	45	2

Calculate the response rates for each drug separately for males and females. What problem might this cause for the test in (iii) and why? ***(4 marks)***

(v) Why might analyzing the data using logistic regression help avoid the problem in (iv) and what other benefits might logistic regression offer? ***(3 marks)***

2 A 2-treatment, 2-period crossover trial has been appropriately powered and conducted to compare Formoterol (F) with Salbutamol (S) as a treatment for childhood asthma. The response variable is a measure of lung function and high values of the response are good. Six patients receive the drugs in each order and the trial data are organized in the following manner:

2 (continued)

Variable name	Gp1Per1	Gp1Per2	Gp2Per1	Gp2Per2
Group	1	1	2	2
Period	1	2	1	2
Treatment	F	S	S	F

Summary statistics for the variables are given in the following table:

Variable	Gp1Per1	Gp1Per2	Gp2Per1	Gp2Per2
Mean	341.67	312.5	283.33	345.83
St dev	57.417	68.684	105.388	70.881

(i) Plot the treatment means for each period and make a preliminary graphical assessment of the trial's findings. ***(5 marks)***

(ii) Additional variables are constructed in `R` as follows:

```
Gp1Ave<-0.5*(Gp1Per1+Gp1Per2)
Gp2Ave<-0.5*(Gp2Per1+Gp2Per2)
Gp1Diff12<-Gp1Per1-Gp1Per2
Gp2Diff12<-Gp2Per1-Gp2Per2
Gp1Diff21<-Gp1Per2-Gp1Per1
Gp2Diff21<-Gp2Per2-Gp2Per1
```

The following 4 tests, described in R notation, are available to allow an analysis of the trial.

```
TEST 1
> t.test(Gp1Per1,Gp2Per1)

TEST 2
> t.test(Gp1Ave,Gp2Ave)

TEST 3
> t.test(Gp1Diff12,Gp2Diff12)

TEST 4
> t.test(Gp1Diff12,Gp2Diff21)
```

Explain how the collection of tests might be used to analyze the trial. In your answer, state clearly what effect each test is designed to detect and, by providing a flow chart or otherwise, explain the circumstances and order in which the tests are used. ***(8 marks)***

2 (continued)

(iii) The following edited R output is obtained from running the tests:

```
TEST 1
> t.test(Gp1Per1,Gp2Per1)

Welch Two Sample t-test

data:  Gp1Per1 and Gp2Per1
t = 1.1906, df = 7.7279, p-value = 0.2691
alternative hypothesis: true difference in means is not equal to 0

TEST 2
> t.test(Gp1Ave,Gp2Ave)

Welch Two Sample t-test

data:  Gp1Ave and Gp2Ave
t = 0.28865, df = 8.9373, p-value = 0.7794
alternative hypothesis: true difference in means is not equal to 0

TEST 3
> t.test(Gp1Diff12,Gp2Diff12)

Welch Two Sample t-test

data:  Gp1Diff12 and Gp2Diff12
t = 3.9196, df = 9.5488, p-value = 0.003134
alternative hypothesis: true difference in means is not equal to 0

TEST 4
> t.test(Gp1Diff12,Gp2Diff21)

Welch Two Sample t-test

data:  Gp1Diff12 and Gp2Diff21
t = -1.4253, df = 9.5488, p-value = 0.1859
alternative hypothesis: true difference in means is not equal to 0
```

What does the *R* output tell you about any differences between Formoterol and Salbutamol treatments? Explain how you reach your conclusion.

(4 marks)

2 (continued)

(iv) Suppose it was later discovered that two subjects from Group 2 had not in fact completed their Period 2 treatment correctly, because they found it had unwanted side effects.

(a) What is the name for this problem with the trial data? ***(1 mark)***

(b) What problems does it cause for the analysis you have done and how might they be resolved?
[Note: You need not actually carry out any new analysis you suggest.] ***(2 marks)***

3 A clinical trial was conducted on 14 patients with leukemia. Patients were randomized into two treatment groups and followed up. One group of 7 patients was given Drug A and the second group of 7 patients was given Drug B. The outcome of interest was mortality. Four patients were lost to follow-up; these censored observations are denoted by asterisks (*). The data below show each patient's time until death in months.

Patient	Drug A Time (months)	Drug B Time (months)
1	8.3*	22.7*
2	16.6	2.8
3	0.5	23.2
4	23.0	8.0
5	8.0	3.5
6	5.9*	6.7*
7	28.0	11.5
Total	90.3	78.4

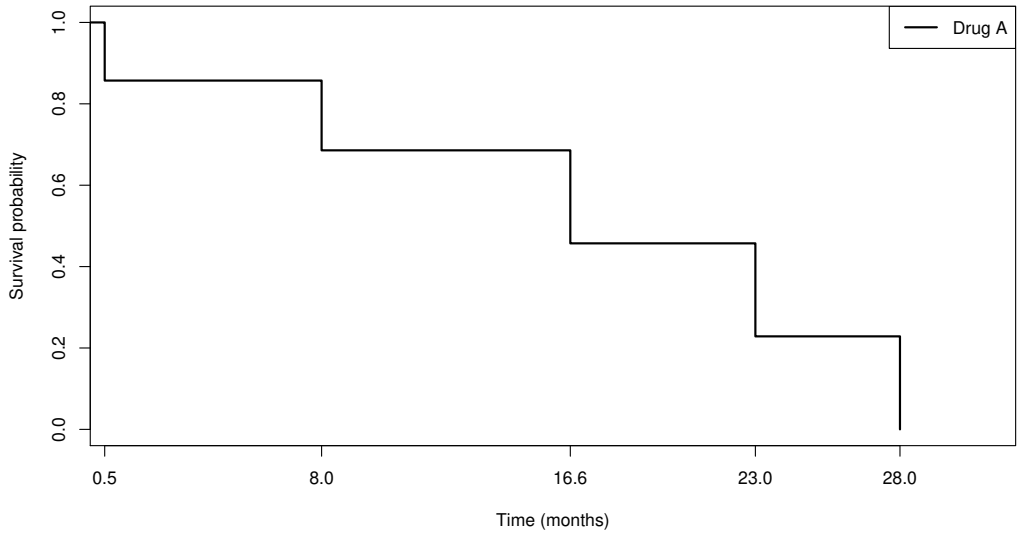
In the *R* output below, a Kaplan-Meier analysis is shown (status=1 if death; status=0 if censored), with the results for Drug B omitted.

```
> Leuk.sv <- Surv(time, status, type = "right")
> summary(survfit(Leuk.sv ~ drug))
Call: survfit(formula = Leuk.sv ~ drug)

                drug=A
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  0.5      7       1    0.857   0.132       0.6334            1
  8.0      5       1    0.686   0.186       0.4026            1
 16.6      3       1    0.457   0.224       0.1748            1
 23.0      2       1    0.229   0.197       0.0423            1
 28.0      1       1    0.000     NaN           NA           NA
```

3 (continued)

The Kaplan-Meier estimate of the survivor function for Drug A is displayed in the following figure.



(i) Obtain, by hand, the Kaplan-Meier (KM) estimate of the survivor function for Drug B and sketch the corresponding plot. ***(6 marks)***

(ii) Estimate the value of the survivor function for both Drugs A and B at 9 months using the corresponding KM estimates. ***(2 marks)***

(iii) Without making any model assumptions, a doctor argues that because the KM estimate of the survivor function for Drug A at 18 months is less than 0.5, then the estimate of the median time to death is 18 months. Do you agree with this statement? Justify your answer. ***(2 marks)***

(iv) If someone was interested in fitting a parametric model to the survival times for each drug, explain whether an Exponential distribution would seem appropriate. ***(2 marks)***

(v) Assuming the survival time for Drug A is Exponentially distributed, estimate the mean time to death accompanied by an approximate 95% confidence interval. ***(2 marks)***

3 (continued)

(vi) The partially-completed table below shows the number at risk, number of deaths and expected number of deaths, at separate time points for each drug.

		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	0.5	7	7	14	1	0	1	1/2	1/2
2	2.8	6	7	13	0	1	1	6/13	7/13
3	3.5	6	6	12	0	1	1	1/2	1/2
4	8.0								
5	11.5								
6	16.6								
7	23.0	2	1	3	1	0	1	2/3	1/3
8	23.2	1	1	2	0	1	1	1/2	1/2
9	28.0	1	0	1	1	0	1	1	0
Total					$O_A = 5$	$O_B = 5$		$E_A = 5.84$	$E_B = 4.16$

(a) Complete the missing rows ($i = 4, 5, 6$).
You do not need to copy the entire table onto your answer book but only the missing rows. ***(4 marks)***

(b) Perform a non-parametric comparison of the two survival distributions at the 5% level. ***(2 marks)***

4 Relapsing-remitting multiple sclerosis (RRMS) is a serious disease of the central nervous system. RRMS patients typically present with symptoms, followed by remission, possibly followed by relapse. A clinical trial was conducted on 150 patients to compare two treatments for RRMS, Extavia and Avonex. Patients were randomly allocated to treatments and followed up for 4 years for a potential relapse. Patients still in remission after the end of study were considered right-censored. The data are stored in `RRSM` and coding for the different variables is shown below:

Coding:

Sex:	0 = male; 1 = female
Age:	age of patient centred on 35 years (i.e. 30 year old is -5)
Time:	time until relapse (years)
Treatment:	0 = Extavia; 1 = Avonex
Status:	0 = censored; 1 = relapse

4 (continued)

(i) An analysis was implemented in R producing the following output:

```
> RRMS.sv <- Surv(Time, Status)
>
> RRMS.fit1 <- survreg(RRMS.sv ~Sex+Age+Treatment, dist="exponential")
> summary(RRMS.fit1)

Call:
survreg(formula = RRMS.sv ~ Sex + Age + Treatment, dist = "exponential")
               Value Std. Error     z       p
(Intercept)  0.77301    0.16881  4.58 4.7e-06
Sex         -0.12475    0.19577 -0.64 0.52398
Age          0.03466    0.00982  3.53 0.00042
Treatment   -0.61445    0.19586 -3.14 0.00171

Scale fixed at 1

Exponential distribution
Loglik(model)= -147.3   Loglik(intercept only)= -159.4
Chisq= 24.34 on 3 degrees of freedom, p= 2.1e-05
Number of Newton-Raphson Iterations: 5
n= 150
```

(a) Describe the analysis performed and write down the form of the fitted model for the time to relapse using appropriate notation. *(4 marks)*

(b) Based on the analysis, would you say that Extavia seems to be more effective than Avonex? Justify your answer. *(2 marks)*

(c) Estimate the expected time to relapse for a 28 year old female assigned to Extavia. *(2 marks)*

(ii) An alternative analysis was conducted by another statistician, who presented the following results:

```
> RRMS.fit2 <- coxph(RRMS.sv ~Sex+Age+Treatment)
> summary(RRMS.fit2)
Call:
coxph(formula = RRMS.sv ~ Sex + Age + Treatment)

  n= 150, number of events= 106

              coef exp(coef) se(coef)      z Pr(>|z|)
Sex         0.12999   1.13881  0.19771  0.657 0.510897
Age        -0.03356   0.96700  0.01019 -3.295 0.000986 ***
Treatment  0.58730   1.79913  0.20093  2.923 0.003467 **
---
```

4 (continued)

(a) Write down the fitted model in terms of the baseline hazard function $h_0(t)$, the covariates and the parameter estimates. Why are such models called semi-parametric? *(3 marks)*

(b) Using the R output, describe in detail the effects of sex, treatment and age on time to relapse. *(4 marks)*

(c) How would you assess whether the statistician's approach of using the proportional hazards model was appropriate? *(2 marks)*

(d) Based on the model fitted, estimate the hazard ratio comparing two males, 33 and 43 years old respectively, both taking Avonex. Would this hazard ratio estimate change if both individuals were females instead? Justify your answer. *(3 marks)*

End of Question Paper

STANDARD FORMULAE FOR MEDICAL STATISTICS (INCLUDING TABLES OF CRITICAL 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