



The
University
Of
Sheffield.

SCHOOL OF MATHEMATICS AND STATISTICS

**Autumn Semester
2018–19**

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 clinician investigating treatments for Parkinson's disease conducts a small, double blind, crossover trial of a promising new drug against a placebo. Patients were allocated at random to either Group 1 or Group 2, where Group 1 received the treatments in the order Drug then Placebo, while Group 2 received first Placebo then Drug. The first treatment was applied for 4 weeks (Period 1), then patients swapped to their second treatment for a further 4 weeks (Period 2). A score was given for each period based on average symptom severity over the 4 weeks (low values are good). The results are given below (data adapted from Hunter *et al.*, 1970):

Group	Patient	Period 1 Score	Period 2 Score
Group 1 Drug \rightarrow Placebo	1	8.75	8.75
	2	10.50	9.75
	3	15.00	18.50
	4	21.00	21.50
Group 2 Placebo \rightarrow Drug	5	22.00	18.00
	6	15.00	13.00
	7	14.00	13.75
	8	22.75	21.50

- (i) Explain what is meant by a 'double blind' trial and why this is used. *(2 marks)*
- (ii) Assuming each Group's data is Normally distributed and that there is no carryover effect from Period 1 to Period 2,
- (a) provide an estimate of the drug's effect. *(5 marks)*
- (b) assess whether this treatment effect is statistically significant. *(5 marks)*
- (iii) For each of the assumptions stated in (ii), explain how you could test whether the assumption held and how you would proceed if it were violated. [You do not need to carry out any of the analyses you suggest.] *(4 marks)*
- (iv) Give two reasons why it is considered so important to minimize sample sizes in clinical trials. *(2 marks)*
- (v) Crossover trials are typically used, because they are more efficient than a similarly-sized parallel group study due to the correlation between observations made on the same patient. If this study is deemed as efficient as a study using a total of 24 patients in 2 (equal) parallel groups, how large is the correlation between Period 1 and 2 observations on a single patient? *(2 marks)*

- 2 (i) Which of the following trial designs:
- 2-period, 2-treatment crossover
 - sequential
 - parallel group
 - factorial

would be most appropriate for investigating the relative benefits of ‘stomach stapling surgery’ and ‘support from a dietician’ in treatment of obesity? Explain your reasoning. *(4 marks)*

- (ii) Explain the following terms in the context of randomization in clinical trials:
- (a) balance *(1 mark)*
- (b) simple randomization *(1 mark)*
- (c) block randomization *(1 mark)*

- (iii) Patients involved in a clinical trial of an active drug (D) against a placebo (P) are known to differ in three important characteristics: gender (M or F), disease form (I, II, or III) and smoking status (y or n). A minimization approach is being used to allocate patients to treatments. The first 10 patients to arrive for the trial have been allocated as follows:

Patient	Gender	Disease form	Smoking status	Allocation
1	M	I	y	D
2	M	III	y	P
3	F	III	y	D
4	F	I	n	P
5	M	I	n	D
6	M	II	n	P
7	M	III	n	D
8	M	III	n	P
9	F	I	y	P
10	F	III	y	D

If the next patient to arrive has characteristics M, II, n, show whether they should be allocated to D or P. [You need not use the probabilistic version of minimization.] *(5 marks)*

- (iv) A study has been conducted to compare a RAST (radioallergosorbent) test and a new, simpler, cheaper multi-RAST, or MAST, test of allergy. The data are categorized test responses and given in the following table (from Brostoff *et al.*):

		RAST					Total
		Negative	Weak	Moderate	High	Very high	
MAST	Negative	86	3	14	0	2	105
	Weak	26	0	10	4	0	40
	Moderate	20	2	22	4	1	49
	High	11	1	37	16	14	79
	Very high	3	0	15	24	48	90
Total		146	6	98	48	65	363

2 (continued)

- (a) By calculating the κ statistic, assess how well the MAST test agrees with the RAST test. *(6 marks)*
- (b) Since the categories are ordered, how might we refine our idea of whether the tests ‘agree’? [You need not carry out any revised analysis you suggest.] *(2 marks)*

3 21 patients with acute myeloid leukemia were randomised to one of two forms of treatment and followed up until death. The data below show the times until death in months. 6 patients were lost to follow up before death was observed, these censored observations are denoted by asterisks in the table.

Treatment	Time to Death/Censored Times (months)										Total Time in Study	
	1*	1	3	6	7	13*	18	20	28	35		
New											132	
Standard	1	2*	5	10*	11	12	21	26*	43	46*	52	229

Given below are the results of a Kaplan-Meier preliminary analysis of the data in *R*

```
> Leuk.sv <- Surv(Time, Status, type = "right")
> # Find KM estimate
> KMest <- survfit(Leuk.sv ~ type)
> summary(KMest)
Call: survfit(formula = Leuk.sv ~ type)
```

```

                                type=New
time n.risk n.event survival std.err lower 95% CI upper 95% CI
  1     10      1    0.900  0.0949   0.7320    1.000
  3      8      1    0.787  0.1340   0.5641    1.000
  6      7      1    0.675  0.1551   0.4303    1.000
  7      6      1    0.562  0.1651   0.3165    1.000
 18      4      1    0.422  0.1737   0.1883    0.945
 20      3      1    0.281  0.1631   0.0903    0.876
 28      2      1    0.141  0.1286   0.0234    0.844
 35      1      1    0.000    NaN           NA           NA

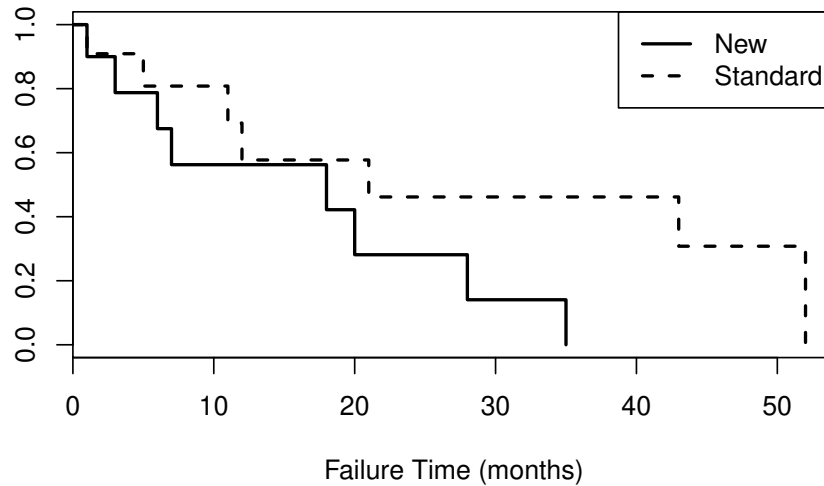
```

```

                                type=Standard
time n.risk n.event survival std.err lower 95% CI upper 95% CI
  1     11      1    0.909  0.0867   0.754    1.000
  5      9      1    0.808  0.1225   0.600    1.000
 11      7      1    0.693  0.1498   0.453    1.000
 12      6      1    0.577  0.1634   0.331    1.000
 21      5      1    0.462  0.1666   0.228    0.936
 43      3      1    0.308  0.1677   0.106    0.895
 52      1      1    0.000    NaN           NA           NA

```

3 (continued)



(i) Without making any model assumptions, estimate the median failure times for the two treatments. *(3 marks)*

(ii) Using the (partially edited) output below, perform a non-parametric comparison of the two survival distributions.

```
> survdiff(Leuk.sv ~ as.factor(type))
```

Call:

```
survdiff(formula = Leuk.sv ~ as.factor(type))
```

	N	Observed	Expected	(O-E) ² /E	(O-E) ² /V
as.factor(type)=New	10	8	5.38	?????	2.23
as.factor(type)=Standard	11	7	9.62	?????	2.23

Chisq= ??? on ? degrees of freedom, p= ???

(4 marks)

(iii) It is suggested that the survival times for the two treatments 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 failure times with approximate 95% confidence intervals. *(4 marks)*

(b) Use the likelihood ratio test to assess whether there is a difference in the failure time distribution of the two components. *(4 marks)*

(c) Do the assumptions of Exponential survival distributions seem plausible? Explain your answer. *(2 marks)*

(iv) If it was known that the censored patients had in fact been moved to a hospice for end-of-life care how might this affect the suitability of the analysis suggested above? *(3 marks)*

- 4 (i) In a study for an engineering company, 100 drill batteries were constructed and then randomised to two different test environments — use on wood and use on brick. Time until the battery ran out was studied as the survival time of interest. Drills still operating at the conclusion of the study were considered right-censored. The data are stored in `drill` and coding for the different variables is shown below.

Coding:

env: test environment (0 = wood; 1 = brick)
 time: battery life in hours
 status: indicator of failure (1) or censoring (0)

Some R analysis was performed with the output shown below:

```
> fit <- survreg(Surv(time, status) ~ env, data=drill,
+ dist="exponential")
> summary(fit)
```

Call:

```
survreg(formula = Surv(time, status) ~ env, data = drill,
+ dist = "exponential")
```

	Value	Std. Error	z	p
(Intercept)	-1.327	0.141	-9.38	<2e-16
env	0.405	0.200	2.02	0.043

Scale fixed at 1

Exponential distribution

Loglik(model)= 12.5 Loglik(intercept only)= 10.4

Chisq= 4.07 on 1 degrees of freedom, p= 0.044

Number of Newton-Raphson Iterations: 4

n= 100

- (a) Describe the analysis performed and the final model for T , the battery life, for both the wood and brick test environments. *(4 marks)*
- (b) Is there evidence that the test environment makes a significant difference to battery life? Does the battery last longer when used on wood or brick? *(2 marks)*
- (c) Estimate the mean battery life for a drill used on wood; and the mean battery life for a drill used on brick. *(2 marks)*

4(continued)

- (ii) A cohort study to investigate diet was carried out on a group of men. Before entering the study each individual was asked for their smoking and drinking habits; and whether they were vegetarian or not. Their weights were also recorded (kg) and centred around 75 kg (i.e. 85 would be coded as 10 and 70 as -5). The outcome of interest was all-cause mortality. A Cox proportional hazards model was fitted to the data and the output is shown below:

Variable	Coefficient	Standard Error
Smoking Habits		
Smoker	Reference	—
Non-smoker	-0.25	0.03
Drinking Status		
Regular Drinker	Reference	—
Occasional Drinker	-0.15	0.34
Never Drink	-0.33	0.08
Weight (centred on 75 kgs as baseline)		
	0.0004	0.0001
Vegetarian		
Yes	Reference	—
No	-0.32	0.31

Table: Log hazard ratio coefficients of mortality with standard errors

- (a) Write down the model fitted. *(4 marks)*
- (b) Describe in detail the effects of these variables on survival. *(5 marks)*
- (c) Using the model, calculate the estimate of the hazard ratio comparing
- A smoker weighing 83kg who denotes themselves as regular drinker and who **is** a vegetarian;
 - A non-smoker weighing 71kg who denotes themselves as a non-drinker and who **is not** a vegetarian.

(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 $r = \min(n_1, n_2)$

$$t_r = \left| \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}} \right|$$

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

$$t_r = \left| \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2} \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}} \right|$$

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

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

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

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

so e.g.

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

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%
<code>qnorm</code>	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, nu)` 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
 $qt(p, \nu)$ 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