



The
University
Of
Sheffield.

MAS6012

SCHOOL OF MATHEMATICS AND STATISTICS

Spring Semester 2020–2021

Sampling, Design, Medical Statistics

This is an open book exam.

Answer **all** questions.

You can work on the exam during the 24 hour period starting from 10am (BST), and you must submit your work within 3.5 hours of accessing the exam paper or by the end of the 24 hour period (whichever is earlier).

Late submission will not be considered without extenuating circumstances. Calculations should be performed by hand. A university-approved calculator may be used. The use of any other calculational device, software or service is not permitted. To gain full marks, you will need to show your working.

By uploading your solutions you declare that your submission consists entirely of your own work, that any use of sources or tools other than material provided for this module is cited and acknowledged, and that no unfair means have been used.

Total marks available: 90

- 1 Shoulder surgery is associated with severe postoperative pain, but rapid mobilization is needed for patients to begin their rehabilitation, so effective pain relief is essential. Many operations use a regional nerve block, applied during the surgery, supplemented by patient-controlled-analgesia (PCA) if necessary. Under PCA, a patient can access morphine on demand (within limits).

In a study aimed at assessing the effectiveness of subacromial bursa block (SBB) as a nerve block, the following trial was conducted. Forty shoulder surgery patients were recruited and split at random into two groups of size 20. In the Treated Group T the subjects were treated with SBB during their operation and in Control Group C no treatment was applied. The endpoint of interest was the amount of supplementary morphine (in mg) required during the first 24 hours post-operation.

- (i) The researchers claim they powered their study to give a good (80%) chance of detecting a 1 standard deviation change in mean, if it occurred. Confirm that the proposed sample size (40) was a sensible number to recruit. **(10 marks)**
- (ii) Only 35 patients completed the trial. The trial data (mg of morphine required through PCA) is shown below.

Group	Number	Mean	Standard deviation
T	16	21.2	12.2
C	19	29.7	15.1

What can you conclude about the value of SBB in reducing postoperative pain? **(7 marks)**

- (iii) (a) Suppose that the researchers had wished to compare two different nerve blocks with a control, so needed 3 groups in their trial. What form of analysis would you suggest should be applied in this case? **(2 marks)**
- (b) Suppose instead that the researchers thought that various patient characteristics might affect their response. What form of randomization procedure would you suggest should be applied to split the patients into Groups T and C ? What form of analysis would you suggest should be applied in this case? **(4 marks)**

- 2 A clinical trial was conducted on 32 patients with symptomatic tenosynovial giant cell tumor. Two distinct drugs (Pexidartinib, and Denosumab) were compared. Patients were accordingly randomized into two groups of treatment and followed up. The first group of patients (16 patients) was given (Pexidartinib) Drug A while the second group (16 patients) was given Drug B (Denosumab). The outcome of interest was mortality. Some patients were lost to follow-up; these censored observations and denoted by asterisks(*). The data below show each patient's time until death in months.

	Drug A	Drug B
Patient	Time (months)	Time (months)
1	2.90	3.20
2	9.80*	0.40*
3	1.70*	10.80
4	0.50	5.50*
5	3.10	1.50*
6	4.10*	11.00*
7	3.80	15.80
8	1.50*	0.30
9	2.60*	7.30
10	3.30	8.60
11	15.60	5.00
12	9.50	14.40*
13	8.90	1.60
14	1.30	4.80*
15	2.00	5.90
16	2.40	10.10
Total	73.0	106.2

Table 1: Time to death

- (i) Obtain by hand the Kaplan-Meier (KM) estimate for Drug A up to and including 3.3 months ($t_{(j)} = 3.3$). **(12 marks)**
- (ii) Obtain the median time to death for patients receiving Drug A. **(2 marks)**
- (iii) Assuming exponentially distributed survival times, estimate the mean mortality time accompanied by its respective 95% confidence interval for Drug B. **(8 marks)**

- 3 (i) Investigator 1 conducts an experiment to assess the effect of four specific chemicals on some physiological response of a bacterial organism (called organism 1). It is believed that organism 1 has two strains (distinct populations with different genetic characteristics) and that accounting for the strain in the statistical model might reduce the residual variance in the physiological response. Investigator 1 therefore decides to use a randomised block design in which each chemical is used in each block (strain) exactly once. The linear model they decide to fit (model 1) is

$$\text{model 1 : } E(Y_{ij}) = \mu + \alpha_i + \tau_j \quad (i = 1, 2; j = 1, 2, 3, 4)$$

where i represents the block and j represents the chemical treatment.

Investigator 1 applies the constraints $\sum_{i=1}^2 \alpha_i = \sum_{j=1}^4 \tau_j = 0$.

- (a) Why does investigator 1 need to apply both constraints $\sum_{i=1}^2 \alpha_i = 0$ and $\sum_{j=1}^4 \tau_j = 0$? **(4 marks)**
- (b) Write down the response vector and design matrix for model 1 with parameters $\mu, \alpha_1, \tau_1, \tau_2$ and τ_3 . **(10 marks)**

- (ii) A bicycle company plans to undertake a survey to estimate the proportion, P , of adults living in England that are considering buying an electric bicycle in the next five years. The company wants to know how many adults to survey so that the width of the 95% confidence interval for P does not exceed a specified value. The company plans to take a simple random sample from the target population. They would prefer a conservative estimate of the sample size. Surveys in Wales and Scotland asking the same question yielded 95% confidence intervals of (0.28, 0.43) and (0.13, 0.35) respectively.

- (a) Describe two ways that the company could sensibly use the confidence intervals from the two previous surveys to estimate the sample size required and quantify what difference these two approaches would have on the estimate of the sample size required. **(8 marks)**
- (b) State any concerns you might have about using these previous confidence intervals to estimate the sample size required. **(2 marks)**

- 4 (i) An investigator is studying the dependence of a variable Y on one continuous explanatory variable x which has been scaled to lie between -1 and 1 . The following model (model 2) is proposed.

$$\text{model 2 : } E(Y) = \beta_0 + \beta_1x + \beta_{11}x^2$$

The investigator proposes the following design (design A) using five design points:

design	design points (x)
A	$\{-1, -1, 0, 1, 1\}$

Use the General Equivalence Theorem to justify whether design A is G-optimal for model 2. You may use the fact that if X is the design matrix for design A under model 2 then

$$(X^T X)^{-1} = \frac{1}{4} \begin{pmatrix} 4 & 0 & -4 \\ 0 & 1 & 0 \\ -4 & 0 & 5 \end{pmatrix}.$$

(8 marks)

- (ii) A survey of undergraduates at a particular university is conducted to estimate how satisfied the undergraduates are (on some arbitrary level) with their degree programme.

(a) If stratified sampling is to be used, suggest a suitable choice of strata. **(1 mark)**

(b) A survey using stratified sampling produced the following data

Stratum	Population size	Sample size	mean
1	5000	50	72
2	2500	50	59
3	2500	30	62

Using an unbiased estimator, estimate the mean satisfaction of undergraduates at this university using the results of the stratified sampling. **(4 marks)**

(c) Suppose a new stratified survey is to be conducted using the same three strata. Let s_i represent the sample standard deviation of stratum i for $i = 1, 2, 3$ and suppose $s_2 = s_3$ and $s_1 > s_2$. What can you say about the sample sizes in the three strata if the Neyman allocation is used? **(4 marks)**

4 (continued)

- (iii) The randomised response technique is used to estimate the proportion of a population with a specific sensitive characteristic. With probability $3/4$ the respondent is asked whether they have the sensitive characteristic. With probability $1/4$ a fair coin is tossed and they are asked whether it lands on a head. An interviewer asking the question is worried that if the respondent answers 'Yes' then the respondent is very likely to have been asked whether they have the sensitive characteristic. Assuming that respondents always answer truthfully, and that the true population proportion with the sensitive characteristic is $1/2$, justify whether the interviewer is correct. **(4 marks)**

End of Question Paper

MAS6012 FORMULA SHEET & 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 Design Formulae

Linear Model formulae

$$\hat{\beta} = (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{X}^T \mathbf{Y} \quad \text{and} \quad \hat{\beta} \sim N\{\beta, \sigma^2 (\mathbf{X}^T \mathbf{X})^{-1}\}$$

Prediction Variance

$$\text{var } \hat{y}(x_0) = \sigma^2 \mathbf{f}(x_0)^T (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{f}(x_0)$$

Standardized Prediction Variance

$$d(\mathbf{x}) = n \mathbf{f}(\mathbf{x})^T (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{f}(\mathbf{x}) = \mathbf{f}(\mathbf{x})^T \mathbf{M}^{-1} \mathbf{f}(\mathbf{x})$$

Confidence Regions, σ^2 unknown

$$p^{-1} \hat{\sigma}^{-2} (\hat{\beta} - \beta)^T \mathbf{X}^T \mathbf{X} (\hat{\beta} - \beta) \text{ has an } F_{p, n-p} \text{ distribution, provided } n > p$$

Balanced Incomplete Block Design Notation

- t = number of treatments
- k = number of units in a block
- b = number of blocks
- r = number of applications of each treatment
- λ = number of times each pair of treatments appears together in a block

Balanced Incomplete Block Design Relationships

$$\begin{aligned} t &> k \\ bk &= rt \\ r(k-1) &= \lambda(t-1) \end{aligned}$$

Balanced Incomplete Block Design - Unreduced Design

$$b = \binom{t}{k} \quad r = \binom{t-1}{k-1} \quad \lambda = \binom{t-2}{k-2}$$

Efficiency of Balanced Incomplete Block Design compared to a Randomized Block design

$$\frac{1 - t^{-1}}{1 - k^{-1}}$$

Adding an extra point x

$$|\mathbf{G}^*| = |\mathbf{G}| (1 + \mathbf{f}(x)^T \mathbf{G}^{-1} \mathbf{f}(x))$$

Deleting an existing point x

$$|\mathbf{G}^*| = |\mathbf{G}| (1 - \mathbf{f}(x)^T \mathbf{G}^{-1} \mathbf{f}(x))$$

Adding a new point y and deleting an existing point x

$$|\mathbf{G}_2| = |\mathbf{G}| \left\{ (1 - \mathbf{f}(x)^T \mathbf{G}^{-1} \mathbf{f}(x)) (1 + \mathbf{f}(y)^T \mathbf{G}^{-1} \mathbf{f}(y)) + (\mathbf{f}(x)^T \mathbf{G}^{-1} \mathbf{f}(y))^2 \right\}$$

4 Sample Surveys Formulae

Population variance

$$S^2 = \frac{1}{N-1} \sum_1^N (X_i - \bar{X})^2 = \frac{1}{N-1} \left(\sum_{i=1}^N X_i^2 - N\bar{X}^2 \right)$$

and for a binary characteristic ($X_i = 1$ or 0 for each i),

$$S^2 = \frac{NP(1-P)}{N-1}$$

Variance of sample mean for simple random sampling

$$\text{var } \bar{x} = \left(1 - \frac{n}{N}\right) \frac{S^2}{n}$$

Sample size to achieve given confidence interval width for simple random sampling

$$n \geq \frac{N}{1 + N(d/(2Sz_{\alpha/2}))^2}$$

Stratified estimate of population mean and its variance

$$\bar{x}_{st} = \frac{1}{N} \sum_1^l N_i \bar{x}_i \quad \text{and} \quad \text{var } \bar{x}_{st} = \sum_1^l \left(\frac{N_i}{N}\right)^2 \frac{1-f_i}{n_i} S_i^2$$

Allocation methods

$$\text{Optimal allocation: } n_i \propto \frac{N_i S_i}{\sqrt{c_i}} \quad \text{Neyman allocation: } n_i = \frac{n N_i S_i}{\sum_1^l N_i S_i}$$

Cluster estimate of population mean and its variance

$$\bar{x}_{cl} = \frac{1}{lK} \sum_1^l \sum_1^K x_{ij} \quad \text{and} \quad \text{var } (\bar{x}_{cl}) = \frac{1-f}{l} \frac{1}{L-1} \sum_1^L (\bar{X}_i - \bar{X})^2$$

Regression estimator of population mean and its variance

$$\bar{x}_{lr} = \bar{x} - \hat{\beta}(\bar{y} - \bar{Y}) \quad \text{and} \quad \text{var } \bar{x}_{lr} \simeq \frac{1-f}{n} S_X^2 (1 - \rho^2)$$

Approximate variance of the Peterson estimator, Chapman estimator and approximate variance

n : size of 1st sample, m : size of 2nd sample.

$$\begin{aligned} \widehat{\text{Var}}(\hat{N}_p) &= \frac{mn^2(m-r)}{r^3}, \\ \hat{N}_c &= \frac{(n+1)(m+1)}{r+1} - 1, \\ \widehat{\text{Var}}(\hat{N}_c) &= \frac{(n+1)(m+1)(n-r)(m-r)}{(r+1)^2(r+2)}. \end{aligned}$$

5 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