Data provided: Tables of distributions and table of Normal Quantiles

MAS6062

The University Of Sheffield.

SCHOOL OF MATHEMATICS AND STATISTICS **Spring Semester 2014–2015**

Bayesian Methods and Clinical Trials **3 hours**

*Candidates may bring to the examination a calculator which conforms to University regulations. Marks will be awarded for your best **five** answers. Total marks 100.*

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1. Consider and AB/BA cross-over trial

a). What are the main advantages and disadvantages over a parallel group trial? **(3 marks)**

b) What is the difference between a paired t-test and a period adjusted t-test for the analysis of this trial? **(1 mark)**

c) How would the results from an analysis of variance compare to a paired t-test and period adjusted t-test? **(1 mark)**

A study has been designed to assess the dose response of three doses of the new drug at 200mg, 400mg and 800mg which will be investigated against placebo. Twenty four patients will be randomised to one of 4 sequences in a Williams Square design

P	200	800	400
200	400	P	800
400	800	200	P
800	P	400	200

d) Describe two aspects of the Williams Square design **(2 marks)**

e) What advantage does this Williams Squared design have over a AB/BA cross-over? **(1 mark)**

f) Due to practical constraints there can only be three periods for this design. Construct the balanced incomplete block design (BIBD) for the treatment sequences to which patients are to be randomised. **(2 marks)**

g) If we wished to compare each dose to Placebo how would a BIBD study change the sample size compared with a design where all subjects received all treatments? **(1 mark)**

Table 1 gives the mean summaries for the pharmacokinetics for a study for one dose.

Table 1- Pharmacokinetic parameters for the active treatment for 200mg

	Geometric Mean
Cmax (units)	15
T1/2 (h)	12*
AUC0-12(units)	82
AUC0-∞ (units)	118

* for T1/2 the value is an arithmetic mean

h) The T1/2 is the elimination half-life. Based on the pharmacokinetics, if this were a single dose study what would be the minimum time between periods to allow for washout for a cross-over study ? **(1 mark)**

i) If the treatment were given as a repeat dose with a dosing interval of τ=12 hours, what would be the predicted values of Cmax and AUC0-τ at steady state? **(2 marks)**

A dose proportionality study was undertaken to assess the dose proportionality of the drug being developed. The results of the analysis of AUC (units) and logDose are shown in Table 2. Both AUC and dose were log transformed for the analysis.

Table 2. Analysis of logAUC against logDose for the assessment of dose proportionality using the Power Method

	b	**SE(b)**	**90% Confidence Interval**
logDose	1.09	0.06	(0.99 to 1.19)

j) Estimate the AUC dose normalised ratio and associated 90% confidence interval per doubling of dose. Comment on the results (**2 marks**)

k) Is there evidence to suggest from AUC that the pharmacokinetics are dose proportional? (**1 mark**)

A new formulation is being developed. The within subject standard deviations on the log scale are: 0.25 for AUC0-inf and 0.30 for Cmax. A bioequivalence study is being planned to demonstrate bioequivalence of the new formulation to the standard formulation. The bioequivalence criteria of (0.80, 1.25) are being used i.e. the 90% Confidence Intervals for both AUC and Cmax must be wholly contained within the interval (0.80, 1.25) to be able to declare bioequivalence. It is also assumed that there is no difference between the means for the test and reference formulations ie μ_T/μ_R =1

l) What sample size would be required to demonstrate bioequivalence assuming: the study is designed with 90% power with a one tailed Type I error rate of 5% **(2 marks)**

You can use the following result for the question

$$n = \frac{2\sigma_W^2 (Z_{1-\beta/2} + Z_{1-\alpha})^2}{(\log_e(\delta))^2}$$

where δ is the criteria limit, $Z_{0.90}$ can be taken as 1.32 and $Z_{0.95}$ can be taken as 1.645.

m) If this is a replicate ABBA/BAAB cross-over study what would the sample size be? **(1 mark)**

2. In a cluster randomised trial of patient centred care in patients with newly diagnosed Type II diabetes, one of the endpoints was the Body Mass Index at one year. General practices were randomised so that the doctors were trained in patient centred care (Group=1) or to Control (Group=0) . Covariates were age and Gender (M=1, F=0). 266 patients took part.

Two analyses were done and the output is are shown below

```
Analysis 1
glm(formula = Bmi1yr ~ age + Gender + Group)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-12.531   -3.422   -0.704    2.884   17.374

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)   34.534      2.208   15.64  < 2e-16 ***
age           -0.111      0.037   -3.00    0.003 **
Gender         3.161      0.725    4.36  1.9e-05 ***
Group          1.833      0.723    2.54    0.012 *
---
```

(Dispersion parameter for gaussian family taken to be 30.6)

Analysis 2

```
geeglm(formula = Bmi1yr ~ age + Gender + Group, id =
praccode, corstr = "exchangeable")

 Coefficients:
            Estimate  Std.err    Wald Pr(>|W|)
(Intercept) 34.31470  2.48866 190.121  < 2e-16 ***
age         -0.10846  0.04154   6.819  0.00902 **
Gender       3.15229  0.79714  15.638 7.67e-05 ***
Group        1.88961  0.77143   6.000  0.01431 *
---

Estimated Scale Parameters:
            Estimate Std.err
(Intercept)    30.09   3.435

Correlation: Structure = exchangeable  Link = identity

Estimated Correlation Parameters:
      Estimate Std.err
alpha  0.02323 0.04361
Number of clusters:   38   Maximum cluster size: 18
```

a) Explain the difference in the two analyses and why one of them is incorrect (**2 marks**)

b) Describe what sort of model is being used in the second analysis and the assumptions it makes**(2 marks**)

c) Explain the term 'exchangeable' in the second analysis (**1 mark)**

d) Contrast the residual standard deviations in the two analyses.(**2 marks**)

e) What is the ICC for these data? Is this a reasonable result? (**2 marks**)

f) Explain what the analyses show in term of whether the intervention was effective and contrast the two analyses (4 **marks**)

g) Explain how the covariates affect BMI. Is a 50 year old woman in the control group expected to be obese at the end of the study? (BMI>30 kh/m^2) (**2 marks**)

h) If $\sigma_W=0.25\sigma_B$, what is ρ, the intracluster correlation coefficient? (**2 marks**)

i) If we were planning a new trial, with an ICC of 0.02, and for a non-clustered trial we needed 200 patients per arm, for a 80% power and 5% significance, for a given effect size how many practices do we need to recruit in a cluster trial with same parameters. Assume we can expect to get the same number per practice as in the example.(3 **marks**)

3. A trial of a new drug for the acute treatment of head injury is being planned in an Emergency Department setting. Many of the patients arriving are quite ill (some unconscious). The primary efficacy outcome is improvement in the patients' quality of life at 1 month.

For a continuous variable the standardised effect size is SES=δ/σ and for a binary variable SES=$\delta/\sqrt{(\pi_1(1-\pi_1)+\pi_2(1-\pi_2))}$ where δ is the difference in means for Normal data or proportions for binary and π_1 and π_2 are the proportions in each group.

For 80 % power and 5% two sided significance, use n per arm =$16/SES^2$ and for 90% power use n per arm $21/SES^2$

a) What are the ethical considerations in recruiting patients into the trial? (**1 mark**)

b) If a mean improvement of 5 units is required for the trial with an anticipated population standard deviation of 20 units what is the evaluable sample size per arm (for 90% power and two sided significance levels of 5%)? If 15% of patients are expected to have dropped out at 3 months what sample size would be required to ensure sufficient numbers of patients? (**2+1 marks**)

c) The investigator reports that due to budget constraints the maximum sample size can only be 300 patients recruited per arm to ensure a sufficient number evaluable. What impact does this new sample size have on the power assuming again 15% of patients are not in the trial at 3 months? (**2 marks**)

Note for the remaining questions take the sample size to be 300 patients recruited per arm to ensure a sufficient number evaluable.

d) There is to be safety monitoring of the trial. Due to the mechanism of the drug the Serious Adverse Events are anticipated to occur within 48 hours of treatment. Efficacy will be also assessed with O'Brien-Fleming rules for the efficacy assessments at the interim analyses. There will be 3 interim analyses. Comment on the effect these efficacy analyses will have on the evaluable sample size and why there is an effect (**2 marks**)

e) The randomisation is 1-to-1 and a sample size re-estimation is undertaken half-way through the trial. The total variance observed in the trial is 395 (units) estimated from the two groups combined. What is the estimate of the evaluable sample size now? (**3 marks**)

f) A key secondary outcome is the proportion of patients who have responded well to treatment as assessed by a physician. It is anticipated that 70% of patients on the placebo arm will respond while 80% on the test drug are anticipated to respond. For a

two sided level of statistical significance at 5% is the current trial big enough if a chi-squared test was used in the analysis? (**3 marks**)

g) In the trial above explain the terms: an adverse event, a suspected adverse reaction, a serious adverse event and a suspected unexpected serious adverse reaction (**4 marks**)

h) Explain the terms GCP and ICH-E9 (**2 marks)**

4 Consider the following hierarchical model

$$x_i \sim \mathrm{N}(x_i \,|\, \mu_i, 1/\lambda)\ , \quad \text{independent for } i = 1, \ldots, n$$
$$\pi\left(\mu_i\right) = \mathrm{N}(\mu_i \,|\, \theta, 1/\gamma)\ , \quad \text{independent for } i = 1, \ldots, n$$
$$\pi\left(\lambda\right) = \mathrm{Ga}(\lambda \,|\, a, b)\ , \quad \pi\left(\theta\right) = \mathrm{N}(\theta \,|\, m, 1/p) \quad \text{and} \quad \pi\left(\gamma\right) = \mathrm{Ga}(\gamma \,|\, c, d)\ ,$$

with $\{m, p, a, b, c, d\}$ known constants.

[HINT: The quadratic form $ax^2 + bx + c$ can be written as $a(x + b/(2a))^2 + d$, with d not depending on x.]

(i) Prove that the full conditionals for

(a) μ_i are $\mathrm{N}\left(\mu_i \,|\, m_i^\star, 1/p^\star\right)$ with $p^\star = \lambda + \gamma$ and $m_i^\star = (\lambda x_i + \gamma\theta)/p^\star$. ***(3 marks)***

(b) θ is $\mathrm{N}(\theta \,|\, q^\star, 1/v^\star)$ with $v^\star = n\gamma + p$ and $q^\star = (n\gamma\bar{\mu} + pm)/v^\star$. ***(3 marks)***

(c) λ is $\mathrm{Ga}(\lambda \,|\, a^\star, b^\star)$ with $a^\star = a + n/2$ and $b^\star = b + \dfrac{1}{2}\displaystyle\sum_{i=1}^{n}(x_i - \mu_i)^2$. ***(2 marks)***

(d) γ is $\mathrm{Ga}(\gamma \,|\, c^\star, d^\star)$ with $c^\star = c + n/2$ and $d^\star = d + \dfrac{1}{2}\displaystyle\sum_{i=1}^{n}(\mu_i - \theta)^2$. ***(2 marks)***

(ii) Write pseudo-code of a Gibbs sampler for exploring the posterior of the parameters for this model. ***(10 marks)***

5 A physicist studying the expansion of the universe has two sets of measurements covering the same section of the Milky Way. The difference between these measurements is related to redshift and, if current theory is correct, expected to be very close to zero.

(i) Let $\boldsymbol{d} = \{d_1, \ldots, d_n\}$ be the data available with d_i the i-th observed difference. Assume these are conditionally independent $d_i \sim \mathrm{N}(d_i \mid \mu, 1/\lambda)$, with known precision $\lambda = 0.1$. Derive the posterior distribution of μ using the conjugate prior,

$$\pi(\mu) = \mathrm{N}\left(\mu \,\middle|\, m, \frac{1}{p}\right),$$

and give explicit expressions for its parameters. ***(8 marks)***

(ii) Given the data, the scientist may report a discrepancy (call this decision a_1) or and agreement (decision a_2) with the current theory. If a real discrepancy is reported there is a good chance it would be published in a top journal; if the discrepancy is not real, his career would suffer a major drawback. After some consideration, he believes that the following loss function reflects well his preferences:

$$\mathrm{L}(a_1, \mu) = \begin{cases} 100 & |\mu| \leq 0.5 \\ 0 & |\mu| > 0.5 \end{cases}, \qquad \mathrm{L}(a_2, \mu) = \begin{cases} 0 & |\mu| \leq 0.5 \\ 30 & |\mu| > 0.5 \end{cases}.$$

A set of $n = 150$ measures is taken and the following statistics are recorded:

$$\bar{d} = \frac{1}{n}\sum_{i=1}^{n} d_i = -0.3\,, \quad s_d^2 = \frac{1}{n}\sum_{i=1}^{n}\left(d_i - \bar{d}\right)^2 = 10\,.$$

After elicitation, the scientist's prior parameters are $m = 0$, $p = 0.5$.

(a) Prove that the scientist should report a discrepancy if and only if

$$\frac{100}{130} < \mathrm{P}[|\mu| \leq 0.5 \mid \boldsymbol{d}]\,.$$

(5 marks)

(b) Which is the scientist's optimal decision?
[Additional information, if Z has a standard Gaussian distribution, $\mathrm{P}[Z \leq 0.826] = 0.795$ and $\mathrm{P}[Z \leq 3.112] = 0.999$.] ***(7 marks)***

6 Let x_i be the number of complaints filed to a consumer agency in a given day, and let $\mathbf{x} = \{x_1, \ldots, x_n\}$ be a random sample obtained from the agency's records. Assuming that $\mathrm{Po}(x_i \mid \lambda)$ is a suitable model:

(i) (a) Prove that the posterior from the non-informative (improper) prior $\pi(\lambda) \propto \lambda^{-1}$ is a Gamma distribution and write down the posterior parameters explicitly. ***(3 marks)***

(b) Prove that $\pi(\lambda) = \mathrm{Ga}(\lambda \mid a, b)$ is a conjugate prior and write down the posterior parameters explicitly. ***(2 marks)***

(ii) It is further assumed that the distribution of the x_i arise from a process where the distribution of the waiting time to the next complaint, t, is exponential with the same rate parameter λ.

(a) Using your results in (i) (a), prove that the predictive distribution of t is

$$f(t \mid \boldsymbol{x}) = n^s s (n + t)^{-(s+1)} , \quad \text{where} \quad s = \sum_{i=1}^{n} x_i .$$

(5 marks)

(b) The agency's manager claims that it is more likely that the next complaint will be filed before midday than not; *i.e.* $t \leq 1/2$. Does the sample $\boldsymbol{x} = \{0, 2, 1, 4, 3, 4, 3, 0, 2, 1\}$ provide evidence to support this statement? ***(5 marks)***

(iii) (a) Using your results in (i)(b), prove that the predictive distribution of y, the number of complaints filed in next day is

$$f(y \mid \boldsymbol{x}) = \frac{b^{\star a^\star}}{y!} \frac{\Gamma(a^\star + y)}{(b^\star + 1)^{(a^\star + y)}} ,$$

with $\{a^\star, b^\star\}$ the parameters of the posterior distribution. ***(5 marks)***

End of Question Paper

SOME DISCRETE DISTRIBUTIONS

Name	**Context**	**Notation**	**p.f.** $p(x \mid \theta)$	$\mathrm{E}[X \mid \theta]$	$\mathrm{Var}[X \mid \theta]$	**Applications**	**Comments**
Uniform (discrete)	Set of k equally likely outcomes (usually, not necessarily, the integers)	$\mathrm{U}(1, ..., k)$	$p(x) = 1/k$ $\mathcal{X} = \{1, ..., k\}$	$\frac{k+1}{2}$	$\frac{k^2-1}{12}$	Dice	
Bernoulli trial	Expt. with two outcomes: 'success' w.p. θ and 'failure' w.p. $1-\theta$ $X \equiv$ no. successes	$\mathrm{Ber}(x \mid \theta)$	$p(x) = \theta^x(1-\theta)^{1-x}$ $\mathcal{X} = \{0, 1\}$ $\Theta = (0, 1)$	θ	$\theta(1-\theta)$	Coins, constituent of more complex distributions	
Binomial	$X \equiv$ no. successes in n ind. $\mathrm{Ber}(x \mid \theta)$ trials	$\mathrm{Bi}(x \mid n, \theta)$	$p(x) = \binom{n}{x}\theta^x(1-\theta)^{n-x}$ $\mathcal{X} = \{0, 1, 2, ..., n\}$ $\Theta = (0, 1)$	$n\theta$	$n\theta(1-\theta)$	Sampling with replacement	$\mathrm{Bi}(x \mid 1, \theta) \equiv \mathrm{Ber}(x \mid \theta)$
Geometric	$X \equiv$ no. failures until 1st success in sequence of ind. $\mathrm{Ber}(x \mid \theta)$ trials	$\mathrm{Ge}(x \mid \theta)$	$p(x) = \theta(1-\theta)^x$ $\mathcal{X} = 0, 1, 2, ...$ $\Theta = (0, 1)$	$\frac{1-\theta}{\theta}$	$\frac{1-\theta}{\theta^2}$	Waiting times (for single events)	Alternative formulation in terms of $Y \equiv$ no. of trials to 1st success ($Y = X+1$)
Negative binomial (or Pascal)	$X \equiv$ no. failures to m-th success in sequence of ind. $\mathrm{Ber}(x \mid \theta)$ trials. Generalisation of Geometric	$\mathrm{NB}(x \mid m, \theta)$	$p(x) = \binom{m+x-1}{x}\theta^m(1-\theta)^x$ $\mathcal{X} = 0, 1, 2, ...$ $\Theta = (0, 1)$	$\frac{m(1-\theta)}{\theta}$	$\frac{m(1-\theta)}{\theta^2}$	Waiting times (for compound events)	$\mathrm{NB}(x \mid 1, \theta) \equiv \mathrm{Ge}(x \mid \theta)$
Poisson	Arises empirically or via Poisson Process (PP) for counting events. For PP rate ν the no. of events in time $t \sim \mathrm{Po}(x \mid \nu t)$. Also as an approx. to the Binomial	$\mathrm{Po}(x \mid \lambda)$	$p(x) = \frac{e^{-\lambda}\lambda^x}{x!}$ $\mathcal{X} = 0, 1, 2, ...$ $\Lambda = \mathbb{R}^+$	λ	λ	Counting events occurring 'at random' in space or time	$\mathrm{Bi}(x \mid n, \theta) \equiv \mathrm{Po}(x \mid n\theta)$ if n large, θ small

SOME CONTINUOUS DISTRIBUTIONS

Name	**Notation**	**p.d.f.** $f(x \mid \theta)$	$\mathrm{E}[X \mid \theta]$	$\mathrm{Var}[X \mid \theta]$	**Applications**	**Comments**
Uniform (continuous)	$\mathrm{Un}(x \mid \alpha, \beta)$	$f(x) = \dfrac{1}{\beta - \alpha}$ $\mathcal{X} = [\alpha, \beta]$ $\Theta = \{(\alpha, \beta) \in \mathbb{R}^2 \,:\, \alpha < \beta\}$	$\dfrac{\alpha + \beta}{2}$	$\dfrac{(\beta - \alpha)^2}{12}$	Rounding errors $\mathrm{Un}(x \mid -1/2, 1/2)$. Simulating other distributions from $\mathrm{Un}(x \mid 0, 1)$	
Exponential	$\mathrm{Ex}(x \mid \lambda)$	$f(x) = \lambda e^{-\lambda x}$ $\mathcal{X} = \mathbb{R}_+$ $\Lambda = \mathbb{R}_+$	$\dfrac{1}{\lambda}$	$\dfrac{1}{\lambda^2}$	Inter-event times for Poisson Process. Models lifetimes of non-ageing items.	Also parameterised in terms of $1/\lambda$. $\mathrm{Ga}(x \mid 1, \lambda) \equiv \mathrm{Ex}(x \mid \lambda)$
Gamma	$\mathrm{Ga}(x \mid \alpha, \beta)$	$f(x) = \dfrac{\beta^\alpha x^{\alpha-1} e^{-\beta x}}{\Gamma[\alpha]}$ $\mathcal{X} = \mathbb{R}_+$ $\Theta = \{(\alpha, \beta) \in \mathbb{R}^2 \,:\, \alpha > 0, \beta > 0\}$	$\dfrac{\alpha}{\beta}$	$\dfrac{\alpha}{\beta^2}$	Times between k events for Poisson Process. Lifetimes of ageing items.	Also parameterised in terms of $1/\beta$ $\mathrm{Ga}(x \mid 1, \lambda) \equiv \mathrm{Ex}(x \mid \lambda)$, $\mathrm{Ga}(x \mid \nu/2, 1/2) \equiv \chi^2_{(\nu)}(x)$
Beta	$\mathrm{Be}(x \mid \alpha, \beta)$	$f(x) = \dfrac{x^{\alpha-1}(1-x)^{\beta-1}}{\mathrm{B}(\alpha, \beta)}$ $\mathcal{X} = (0, 1)$ $\Theta = \{(\alpha, \beta) \in \mathbb{R}^2 \,:\, \alpha > 0, \beta > 0\}$	$\dfrac{\alpha}{\alpha + \beta}$	$\dfrac{\alpha\beta(\alpha + \beta)^{-2}}{(\alpha + \beta + 1)}$	Useful model for variables with finite range. Also as a Bayesian conjugate prior.	$\mathrm{Be}(x \mid 1, 1) \equiv \mathrm{Un}(x \mid 0, 1)$ $\mathrm{Be}(x \mid \alpha, \beta)$ is reflection about $\frac{1}{2}$ of $\mathrm{Be}(x \mid \beta, \alpha)$. Can transform $\mathrm{Be}(x \mid \alpha, \beta)$ on [0, 1] to any finite range $[a, b]$ by $Y = (b - a)X + a$
Normal (Gaussian)	$\mathrm{N}\big(x \,\big\vert\, \mu, \sigma^2\big)$	$f(x) = \dfrac{1}{\sigma\sqrt{2\pi}} \exp\left[-\dfrac{1}{2}\left(\dfrac{x - \mu}{\sigma}\right)^2\right]$ $\mathcal{X} = \mathbb{R}$ $\Theta = \{(\mu, \sigma^2) \in \mathbb{R}^2 \,:\, \sigma^2 > 0\}$	μ	σ^2	Empirically and theoretically (via CLT etc.) a good model in many situations. Often parameterised in terms of the precision $\lambda = 1/\sigma^2$	$Y = aX + b \sim \mathrm{N}\big(y \,\big\vert\, a\mu + b, a^2\sigma^2\big)$ $Z = \frac{X - \mu}{\sigma} \sim \mathrm{N}(z \mid 0, 1)$ $\mathrm{P}[X \in (u, v)] = \mathrm{P}\left[Z \in \left(\frac{u - \mu}{\sigma}, \frac{v - \mu}{\sigma}\right)\right]$
Chi-square	$\chi^2_{(\nu)}(x)$	$f(x) = 2^{-\nu/2}\Gamma(\nu/2)^{-1} x^{\nu/2-1} e^{-x/2}$ $\mathcal{X} = \mathbb{R}_+ \,;\quad \Theta = \mathbb{R}_+$	ν	2ν	Sum of squares of ν standard normals	$\chi^2_{(\nu)}(x) \equiv \mathrm{Ga}(x \mid \nu/2, 1/2)$
Student t	$\mathrm{St}(x \mid \mu, \lambda, \nu)$	$f(x) = \Gamma[(\nu + 1)/2] / \Gamma[\nu/2] \left(\dfrac{\lambda}{\nu\pi}\right)^{1/2}$ $\big(1 + \lambda(x - \mu)^2/\nu\big)^{-(\nu+1)/2}$ $\mathcal{X} = \mathbb{R}\ \Theta = \mathbb{R}_+$	μ (if $\nu > 1$)	$\lambda^{-1}\dfrac{\nu}{\nu - 2}$ (if $\nu > 2$)	Useful alternative to Normal for variables with heavy tails.	If $X \sim \mathrm{N}(x \mid 0, 1)$ and $Y \sim \chi^2_{(\nu)}(y)$ independent then $\frac{X}{\sqrt{Y/\nu}} \sim \mathrm{t}_\nu$. $\mathrm{t}_1 \equiv$ Cauchy. $\mathrm{t}^2_\nu \equiv \mathrm{F}_{1,\nu}$. If $Y = \sqrt{\lambda}(x - \mu)$ then $Y \sim t_1(y)$