MATH38072

Two Hours

Statistical tables are provided

UNIVERSITY OF MANCHESTER

MEDICAL STATISTICS

28 May 2009

14.00 – 16.00

Electronic calculators may be used provided that they conform to University Regulations

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Answer **ALL** five questions in **SECTION A** (40 marks)

Answer **TWO** of the three questions in **SECTION B** (20 marks each)

The total number of marks on the paper is 80

P.T.O.

A1.

(i) In the context of a randomised controlled trial, explain what is meant by the term *double-blind.*

(ii) Briefly describe two ways in which bias might be reduced by a trial being double blind.

(iii) Give an example of treatment that cannot be evaluated in a *double-blind* clinical trial.

[5 marks]

A2.

A randomised controlled trial is being planned to compare a new treatment (T) and with a control treatment (C). Suppose the primary outcome measure is the continuous and normally distributed. The power to demonstrate a treatment effect τ with a two-sided two sample t-test is given by the expression $1-\Phi\left(z_{a/2}-\frac{\tau\sqrt{n}}{\sigma\sqrt{2}}\right)$ where σ is the known within treatment group standard deviation, n is the sample size of each of two equal size groups, and Φ is the cumulative density function of a standardised normal distribution.

Suppose one wishes to detect a treatment effect of 5 units and the within treatment group known standard deviation is 15 units, estimate the power of a trial with 200 subjects in each treatment group.

[6 marks]

A3.

A clinical researcher has carried out a randomised controlled trial to compare a new drug treatment (T) with a standard drug treatment (C) for patients with arthritis. A pain score has been recorded at baseline (variable name = **baseline**) and at follow-up (variable name = **followup**) on each patient with lower scores corresponding to improved outcome. The researcher carries out a separate paired t-test analyses for each treatment group generating the computer printed output listed below from the data.

Results for group = NEW TREATMENT (T)

Paired t-test and CI: **baseline – followup**

	N	Mean	StDev	SE Mean
base	35	36.53	10.31	1.74
followup	35	32.31	12.68	2.14
difference	35	4.22	10.65	1.80

95% CI for mean difference: (0.56,7.87)
T-Test of mean difference = 0 (vs not = 0): T-Value= 2.34 P-value=0.0252

Results for group = STANDARD TREATMENT (C)

Paired t-test and CI: **baseline – followup**

	N	Mean	StDev	SE Mean
base	36	36.50	10.92	1.82
followup	36	34.01	11.45	1.91
difference	36	2.51	10.29	1.72

95% CI for mean difference: (-0.98,5.99)
T-Test of mean difference = 0 (vs not = 0): T-Value= 1.46 P-value=0.1530

Because there is a statistically significant change at the 5% level from baseline to follow-up in group T but not in group C, the researcher concludes that treatment T is more effective than treatment C in treating arthritis.

(i) Explain the flaw in the clinical researcher's conclusion.

(ii) Use the data from the computer printout to test whether there is a difference between the treatments in terms of the reduction in pain score (**followup - base**) stating the assumptions that you make.

[11 marks]

A4.

(i) Tabulated below are summary data for binary outcome measure from a randomised controlled trial comparing a new treatment with a control treatment. Some patients randomised to the new treatment receive the control treatment, but no patients randomised to the control group receive the new treatment.

	Randomised group		
	New Treatment		*Control*
Recovered after 12 weeks	*Received New*	*Received Control*	*Treatment*
Yes	116	13	128
No	9	16	25
Total	125	29	153

Calculate the point estimates of the treatment effect of the new treatment compared to control treatment measured by the proportion of patients who have recovered after 12 weeks for

(a) an *Intention-To-Treat* analysis

(b) a *Per-Protocol* analysis.

(i) Drawing on the above example explain why an *Intention-To-Treat* analysis is preferable to a *Per-protocol* analysis in a superiority trial.

[8 marks]

A5.

(i) Explain the difference between a *fixed effect* and a *random effect* meta-analysis.

(ii) In the context of meta-analysis, explain what is meant by the term *publication bias*.

(iii) How might one investigate possible *publication bias* in a meta-analysis graphically?

[10 marks]

B6.

In a parallel group *equivalence* trial a new treatment T is being compared with a control treatment C on a continuous outcome measure Y. Let $\bar{y}_T$, $\bar{y}_C$, μ_T and μ_C be the sample and population means of Y for each treatment, and σ be the known common within-treatment group standard deviation of Y. Define the treatment effect $\tau = \mu_T - \mu_C$ to be estimated by $\bar{d} = \bar{y}_T - \bar{y}_C$. Define $\lambda = \sqrt{1/n_T + 1/n_C}$ where n_T and n_C are the sample sizes in each group. Suppose that the null hypothesis $H_0 : |\tau| \geq \tau_E$ is rejected if the (1-2α) confidence interval, given by $\bar{d} \pm z_\alpha \lambda \sigma$, is within the interval $(-\tau_E, +\tau_E)$.

(i) Show that

$$\Pr[\text{Reject } H_0 | \tau] = \Phi\left(\frac{(\tau_E - z_\alpha \sigma\lambda - \tau)}{\sigma\lambda}\right) - \Phi\left(\frac{(-\tau_E + z_\alpha \sigma\lambda - \tau)}{\sigma\lambda}\right)$$

where Φ is the cumulative distribution function of the standard normal distribution.

[5 marks]

(ii) Show that the sample size required in each treatment group to demonstrate equivalence with power (1-β) is

$$n = \frac{2\sigma^2}{\tau_E^2}\left(z_\alpha + z_{\beta/2}\right)^2$$

[8 marks]

(iii) Suppose the interval [-2, 2] is to be used as the range of equivalence and the within treatment group standard deviation has been estimated to be 4. Determine the sample size per group required to obtain 90% power.

[4 marks]

(iv) Why is patient compliance to randomised treatment important in equivalence trials.

[3 marks]

[Total 20 marks]

B7.

(i) In a trial comparing a new treatment (T) with a control treatment (C) the outcome measure is binary. Suppose that the number of successes in each of the two treatment groups of size n_T and n_C are r_T and r_C with probability parameters π_T and π_C, respectively. Consider the odds ratio defined as $\gamma = \frac{\pi_T(1-\pi_C)}{(1-\pi_T)\pi_C}$ estimated by $\hat{\gamma} = \frac{r_T(n_C - r_C)}{(n_T - r_T)r_C}$. Using the approximate relationship $Var[f(x)] \cong f'(x)^2_{x=E[x]} Var[x]$ show that the variance of the $\log_e$ of the odds ratio is $Var[\log_e \hat{\gamma}] \cong \frac{1}{n_T\pi_T} + \frac{1}{n_T(1-\pi_T)} + \frac{1}{n_C\pi_C} + \frac{1}{n_C(1-\pi_C)}$.

Hence, show that $Var[\log_e \hat{\gamma}]$ can be estimated by $\frac{1}{r_T} + \frac{1}{n_T - r_T} + \frac{1}{r_C} + \frac{1}{n_C - r_C}$.

[8 marks]

(ii) A randomised controlled trial is carried out to compare a new vaccine with a placebo for the prevention of pneumonia. At 12 months follow-up of each subject it is recorded whether pneumonia has occurred. The results are summarized in the table below divided into two age groups.

Age Group		65-74 years (A)		≥75 years (B)	
Treatment		Vaccine	Placebo	Vaccine	Placebo
Pneumonia	Yes	25	75	66	100
	No	5975	5925	3934	3900
n		6000	6000	4000	4000

Estimate the odds ratio of pneumonia infection for vaccine as compared to placebo for each age group.

[3 marks]

(iii) Test the hypothesis that H_0: $\gamma_A = \gamma_B$ vs H_1: $\gamma_A \neq \gamma_B$ where γ_A and γ_B are the odds ratios for vaccine as compared to placebo in the younger and older age groups respectively.

[7 marks]

(iv) What do you conclude regarding the effectiveness of the vaccine in subjects over 75 years as compared to subjects between 65 and 74 years?

[2 marks]

[Total mark 20]

B8.

For an AB/BA crossover trial a model for a continuous outcome y_{ij} of the i^{th} patient in the j^{th} period can be written as

$y_{i1} = \mu + \delta + \xi_i + \varepsilon_{i1}$ for a patient in sequence AB in period 1,
$y_{i2} = \mu + \phi + \gamma + \xi_i + \varepsilon_{i2}$ for a patient in sequence AB in period 2,
$y_{i1} = \mu + \xi_i + \varepsilon_{i1}$ for a patient in sequence BA in period 1,
$y_{i2} = \mu + \delta + \phi + \xi_i + \varepsilon_{i2}$ for a patient in sequence BA in period 2.

where μ is the mean for the sequence BA in period 1 , δ is the treatment effect of A relative to B, ϕ is the effect of the second period relative to the first, γ is the carryover effect, ξ_i is a random variable representing patient i with mean zero and variance σ_B^2 , and ε_{ij} is the error term for patient i in period j assumed to be normally distributed with mean zero and variance σ_ε^2. Let $d_i = y_{i2} - y_{i1}$ and let $\bar{d}_{AB}$, μ_{AB}, $\bar{d}_{BA}$ and μ_{BA} be the sample and population means for sequences AB and BA respectively.

(i) Explain what is meant by the term *carryover effect* and give an example of how a *carryover effect* might occur in a crossover trial.

[4 marks]

(ii) In a crossover trial the treatment effect δ is estimated by $\hat{\delta} = \left(\bar{d}_{BA} - \bar{d}_{AB}\right)/2$. Show that this will be biased if there is a carryover effect.

[4 marks]

(iii) Let $a_i = y_{i2} + y_{i1}$ and $\bar{a}_{AB}$, μ^A_{AB}, $\bar{a}_{BA}$ and μ^A_{BA} be the sample and population means for sequences AB and BA respectively. Show that $E\left[\bar{a}_{AB} - \bar{a}_{BA}\right] = \gamma$.

[4 marks]

(iv) The test statistic T_a, defined as $T_a = \dfrac{\bar{a}_{AB} - \bar{a}_{BA}}{\hat{SE}\left[\bar{a}_{AB} - \bar{a}_{BA}\right]}$, has been suggested as a test of the hypothesis $H_0: \gamma = 0$ vs $H_1: \gamma \neq 0$. What is the limitation of this as a test for carryover effect in a crossover trial? What are the implications of this for the design of crossover trials?

[6 marks]

(v) How might one prevent a carryover effect in a randomised controlled crossover trial to compare two drugs?

[2 marks]

[Total mark 20]

END OF EXAMINATION PAPER

P.T.O.