Statistical tables are provided

Two Hours

UNIVERSITY OF MANCHESTER

Medical Statistics

MATH38071

17 January 2012

2pm – 4pm

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

SECTION A

A1

Describe three possible sources of bias that can occur in clinical trials and explain how each might be prevented.

[6 marks]

A2. A randomised controlled trial is being planned to compare a new treatment (**T**) with a control treatment (**C**). The primary outcome measure is assumed to be continuous and normally distributed. The power to demonstrate a treatment effect τ using a two-sided t-test is given by the expression $1-\Phi\left(z_{\alpha/2}-\frac{\tau\sqrt{n}}{\sigma\sqrt{2}}\right)$ 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 standard normal distribution.

(i) Suppose that the within treatment group standard deviation (σ) has been estimated to be 15 units and one wishes to detect a treatment effect (τ) of 5 units, estimate the power of a trial with 50 subjects in each treatment group assuming a 5% significance level α.

(ii) Making the same assumptions regarding σ, τ and α, determine the sample size required obtain 90% power.

[10 marks]

A3.

A team of researchers designing a randomised control trial considers the age and sex of the patients to be prognostic variables. Explain how you would carry out stratified randomisation stratifying by age and sex.

What are the advantages and disadvantages of stratified randomisation?

[7 marks]

A4. A clinical researcher has carried out a randomised controlled trial to compare a new treatment (**T**) with a standard treatment (**C**) for patients with arthritis. A 100mm visual analogue pain score has been recorded at baseline (**baseline**) and at follow-up (**followup**) on each patient with lower scores corresponding to improved outcome. The researcher carried out a paired t-test analyses comparing baseline and follow-up score separately for each treatment group generating the computer output listed below.

Results for group = STANDARD TREATMENT (C)

Paired t-test and CI: baseline - followup

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
baseline	20	45.9489	3.024543	13.52617	39.61846	52.27934
followup	20	42.4291	3.437533	15.37312	35.23426	49.62394
diff	20	3.519793	3.480314	15.56444	-3.764589	10.80418

mean(diff) = mean(baseline - followup) t = 1.0113
Ho: mean(diff) = 0 degrees of freedom = 19

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.8377 Pr(|T| > |t|) = 0.3246 Pr(T > t) = 0.1623

Results for group = NEW TREATMENT (T)

Paired t-test and CI: baseline - followup

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
baseline	20	53.26387	2.715042	12.14204	47.58122	58.94651
followup	20	42.24397	3.169944	14.17642	35.6092	48.87874
diff	20	11.0199	2.612071	11.68154	5.55277	16.48703

mean(diff) = mean(baseline - followup) t = 4.2188
Ho: mean(diff) = 0 degrees of freedom = 19

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.9998 Pr(|T| > |t|) = 0.0005 Pr(T > t) = 0.0002

Assuming a 5% significance level there is a statistically significant change from baseline to follow-up in treatment **T** but not in treatment **C**. From this the researcher concludes that treatment **T** is significantly more effective than treatment **C** in treating arthritis.

(i) Discuss the flaws in the clinical researcher's conclusion.

(ii) Describe three methods of analyses that could be used to test whether there was a treatment effect.

(iii) Which of these three analyses would you consider to be most appropriate in this context?

[10 marks]

A5. Tabulated below are summary data from a randomised controlled trial comparing a surgical and medical treatment for stroke patients. Some patients randomised to the surgery received the medical treatment, and some patients randomised to medical treatment received surgery.

Survival at 1 year	*Surgical*		*Medical*	
	Received Surgical	*Received Medical*	*Received Surgical*	*Received Medical*
No	15	15	4	26
Yes	105	45	26	124
Total	120	60	30	150

(i) Calculate the point estimates of the treatment effect of surgical compared to medical treatment measured by the proportion surviving at 1 years for (a) Intention-To-Treat, (b) Per-Protocol and (c) As-Treated analyses.

(ii) Explain why an Intention-To-Treat analysis is usually preferable to both a Per-Protocol analysis or an As-Treated analysis in superiority trials.

[7 marks]

B1. A randomised controlled trial is planned to compare a new antibiotic treatment (A) with the current standard treatment (B). At four weeks follow-up it is recorded whether the patients have recovered.

(i) Briefly explain why it is important to estimate sample size in a clinical trial. [2 marks]

(ii) Let n_A and n_B be the number of subjects allocated to each treatment, and r_A and r_B be the numbers of patients that have recovered at 4 weeks for each treatment. The two-sample test of proportions with test statistic T given by

$$T = \frac{|p_A - p_B|}{\sqrt{\big(p(1-p)\big)\big(1/n_A + 1/n_B\big)}}$$

will be used to test the null hypothesis of no treatment effect (τ) where $p_A = r_A/n_A$, $p_B = r_B/n_B$, and $p = \dfrac{n_A \cdot p_A + n_B \cdot p_B}{n_A + n_B}$. Assuming that the test statistic T has a normal distribution under the null and alternative hypotheses and using a two-sided test with significance level α, show that the power is approximately

$$1 - \Phi\left(\frac{z_{\alpha/2} \cdot \lambda \cdot \sqrt{\pi(1-\pi)} - |\pi_A - \pi_B|}{\sqrt{\dfrac{\pi_A(1-\pi_A)}{n_A} + \dfrac{\pi_B(1-\pi_B)}{n_B}}} \right),$$

where π_A, π_B, and π are the population proportions corresponding to p_A, p_B, and p, $\lambda = \sqrt{1/n_A + 1/n_B}$, and Φ is the cumulative density function of the standard normal distribution. [7 marks]

(iii) Assuming two equal size groups show that the sample size required for each group to give a power (1-β) is approximately

$$n = \frac{\left(z_{\alpha/2}\sqrt{2\pi(1-\pi)} + z_{\beta}\sqrt{\pi_A(1-\pi_A) + \pi_B(1-\pi_B)} \right)^2}{(\pi_A - \pi_B)^2}.$$ [7 marks]

(iv) The percentage of patients expected to recover in four weeks with the current standard treatment is 50%. Estimate the total sample size that would be need to detect a 10% improvement to 60% with the new treatment assuming a power of 80% and a two-sided 5% significance level. [4 marks]

[Total 20 Marks]

B2.

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

$$y_{i1} = \mu + \tau + \xi_i + \varepsilon_{i1} \qquad \text{for a patient in sequence AB in period 1,}$$

$$y_{i2} = \mu + \phi + \gamma + \xi_i + \varepsilon_{i2} \qquad \text{for a patient in sequence AB in period 2,}$$

$$y_{i1} = \mu + \xi_i + \varepsilon_{i1} \qquad \text{for a patient in sequence BA in period 1,}$$

$$y_{i2} = \mu + \tau + \phi + \xi_i + \varepsilon_{i2} \qquad \text{for a patient in sequence BA in period 2.}$$

where μ is the mean for the sequence BA in period 1 , τ 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 of these for sequences AB and BA respectively.

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

[4 marks]

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

[4 marks]

(iii) Let $a_i = y_{i2} + y_{i1}$ and $\bar{a}_{AB}$, μ_{AB}^A, $\bar{a}_{BA}$ and μ_{BA}^A 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?

[2 marks]

[Total mark 20]

B3. In a meta-analysis of randomised controlled trials suppose $\hat{\theta}_i$ is an estimate of the treatment effect for the i^{th} study and let $Var\left[\hat{\theta}_i\right]$ be its sample variance.

(i) For the weighted estimate of the overall treatment effect, defined by $\hat{\theta} = \dfrac{\sum_i^k w_i\hat{\theta}_i}{\sum_i^k w_i}$, where w_i are weights, show that $Var\left[\hat{\theta}\right] = \dfrac{\sum_i^k w_i^2 Var\left[\hat{\theta}_i\right]}{\left(\sum_i^k w_i\right)^2}$. [4 marks]

(ii) Given that the minimum variance estimator of θ, say $\hat{\theta}_{MV}$, is obtained when $w_i \propto 1/Var\left[\hat{\theta}_i\right]$, show that the minimum variance estimate is equal to

$$Var\left[\hat{\theta}_{MV}\right] = \frac{1}{\sum_{i=1}^k \frac{1}{Var\left[\hat{\theta}_i\right]}}$$ [4 marks]

The table below summarizes the outcome of three trials comparing a cholesterol reducing drug with a placebo for the treatment of high cholesterol. The treatment effect for each study ($\hat{\theta}_i$, i = 1,2,3) is the difference in mean cholesterol between treatment and control. $Var\left[\hat{\theta}_i\right]$ is the sample variance estimate for the i^{th} study.

Study	*Difference in blood cholesterol,* $\hat{\theta}_i$	$\hat{Var}\left[\hat{\theta}_i\right]$
Dyson1996	-0.6	0.1
Thomson 2002	-0.7	0.5
Smith 1989	-0.6	0.2

(iii) Compute the minimum variance estimate of the overall treatment effect, $\hat{\theta}_{MV}$, and determine its 95% confidence interval. [7 marks]

(iv) What do you conclude from the meta-analysis regarding the effectiveness of the drug treatment? [1 marks]

(v) In the context of meta-analysis, explain what is meant by the term *publication bias*. [3 marks]

(vi) What type of graph might one use to investigate possible publication bias in a meta-analysis? [1 marks]

[Total mark 20]

END OF EXAMINATION