Statistical tables are attached

Two Hours

UNIVERSITY OF MANCHESTER

Medical Statistics

17 January 2014

2.00 – 4.00

Electronic calculators may be used provided that they cannot store text

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

Answer **TWO** of the three questions in Section B (40 marks in total). If more than two questions from Section B are attempted, then credit will be given for the best two answers.

The total number of marks on the paper is 80.

SECTION A

Answer **ALL** five questions

A1.

In the context of a clinical trial

(i) What is a *potential* outcome?

(ii) What is a *counter factual* outcome?

(iii) By considering potential outcomes demonstrate why randomization justifies causal inference.

[7 marks]

A2.

In a published report of a randomised trial comparing a drug for reducing blood pressure in patients with a high systolic blood pressure, two groups of 25 patients were compared. The estimated mean difference in systolic blood pressure between the new treatment and the standard treatment was -7 mmHg (95% confidence interval -19.8 to 5.8 mmHg). The p-value for a two-sample t-test is 0.275. A 5 mmHg reduction in systolic blood pressure is considered to be a clinically worthwhile benefit.

(i) Comment on the results of the trial.

(ii) Use the data above to estimate the pooled within group standard deviation.

(iii) A new trial is planned to compare the same two drugs. Using the value of the pooled within group standard deviation determined in (ii) as an estimate of the within group standard deviation σ, calculate the sample size required in each group to have a power equal to 80% to detect a reduction of 5mmHg in systolic blood pressure assuming a 5% two-sided significance level using the formula $n = \frac{2\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_{\beta}\right)^2$.

(iv) It is thought that about 20% of the patients that are randomised will be lost to follow-up, and that only 60% of the patients that are screened for the study will be eligible of whom 50% will consent to join the trial. Estimate the total numbers of patients that need to be screened to obtain the sample size determined in (iii).

[13 marks]

A3.

(i) Show how you might prepare a randomisation list for first twenty patients in a trial with two treatments using Block randomization.

(ii) Gender is thought to be strongly predictive of the success of treatment with women having a better outcome than men. How you might you use block randomisation to improve balance in this characteristic between two treatment groups?

[7 marks]

A4.

(i) Explain the difference between a non-inferiority trial and a superiority trial.

(ii) A randomised controlled non-inferiority trial is carried out to test comparing a *new* drug with the current *standard* drug for controlling pain. At follow-up this is measured by a 100 mm analogue scale with higher scores representing greater pain. Forty-nine patients are randomised to the new treatment and fifty one to the standard treatment. The statistical computer package output is given below. A difference of 5 mm was considered by researchers to be the minimum that was clinically important. Using the results in the output below, test whether the *new* drug is non-inferior to the *standard* drug specifying the significance level used.

```
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [90% Conf. Interval]
---------+--------------------------------------------------------------------
NEW      |      49        45.1    2.171429        15.2    41.45803    48.74197
STANDARD |      51        46.9    2.282457        16.3    43.07482    50.72518
---------+--------------------------------------------------------------------
combined |     100      46.018      1.5717      15.717    43.40836    48.62764
---------+--------------------------------------------------------------------
    diff |              -1.8    3.154794               -7.038697    3.438697
------------------------------------------------------------------------------
    diff = mean(NEW) - mean(STANDARD)                             t =  -0.5706
Ho: diff = 0                                     degrees of freedom =       98
    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.2848         Pr(|T| > |t|) = 0.5696          Pr(T > t) = 0.7152
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[9 marks]

A5.

Inferential statistical tests comparing treatment groups at baseline are quite often seen in published reports of randomised controlled trials. Why are such tests not recommended when reporting the results of randomised controlled trials?

[4 marks]

SECTION B

Answer **TWO** of the three questions

B6.

Consider a parallel group trial with treatment (*T*) and control (*C*). For an 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. Let *s* and σ be the common within-group sample and population standard deviation of *Y*. Assume that the null hypothesis of no treatment effect $H_0 : \mu_T - \mu_C = 0$ will be tested by the statistic $T = \dfrac{\bar{y}_T - \bar{y}_C}{s\lambda}$, with $\lambda = \sqrt{1/n_T + 1/n_C}$ where n_T and n_C are the number of subjects allocated to the respective treatments.

(i) Assuming a normal approximation to the *t*-distribution, what is the distribution of T when $\mu_T - \mu_C = \tau$? [2 marks]

(ii) Show that $\Pr[\text{Reject } H_0 \mid \tau\ ] \cong \left(1 - \Phi\left(z_{\alpha/2} - \dfrac{\tau}{\sigma\lambda}\right)\right)$. [3 marks]

(iii) Assuming equal size groups $(n_T = n_C)$, show that the total sample size required to give a power $(1-\beta)$ for a two-tailed α size test is

$$N = 4\frac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_{\beta}\right)^2.$$ [6 marks]

(iv) Suppose the total sample size to give a power $(1-\beta)$ using a test size α assuming equal group size is equal to N. Following treatment allocation there is an imbalance in group sizes with $n_T = kn_C$ and $n_T + n_C = N$. Show that the power of the trial is equal to

$$1 - \Phi\left(z_{\alpha/2} - \left(\frac{2\sqrt{k}}{k+1}\right)\left(z_{\alpha/2} + z_{\beta}\right)\right).$$ [6 marks]

(v) Suppose sample size for a trial has been estimated to give 80% power assuming a two-tailed test size of 5% and equal size groups $(n_T = n_C)$. Determine the power the trial will have if the allocation ratio *k* = 1.2, and comment briefly on the result. [3 marks]

[Total 20 marks]

B7.

Consider a randomised controlled trial. Suppose the patient population can be divided into three sub-groups as follows:

Compliers: patients who will comply with the allocated treatment,

*Always control treatmen*t: patients who will receive control treatment regardless of allocation,

Always new treatment: patients who will receive the new treatment regardless of allocation.

This assumes that there are no defiers, that is patient who will always receive the opposite of the treatment to which they are randomised. Assume that the proportion and characteristics of *Compliers, Always control treatment, Always new treatment* is the same in both arms and that randomization can only affect the outcome through the receipt of treatment.

(i) Show that an *Intention-To-Treat* estimate of the treatment effect is biased towards the null hypothesis of no treatment effect. [4 marks]

(ii) Show that an *As-Treated* estimate of the treatment effect may be biased either towards or away from the null hypothesis of no treatment effect. [5 marks]

The table below summarizes the outcome of patients from randomised controlled trial comparing two treatments according to randomized group and treatment received. Some patients allocated to the *New* treatment received the *Control* treatment and some patients allocated to *Control* treatment received the *New* treatment.

	Randomised Group			
	New Treatment		*Control*	
Recovered after 6 weeks	*Received New*	*Received Control*	*Received New*	*Received Control*
Yes	360	72	48	360
No	120	48	12	180
Total	480	120	60	540

(iii) For the outcome measure Recovered after 6 weeks, calculate the point estimate of the treatment effect of the *New* treatment compared to the *Control* treatment assuming

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

(b) an*As-Treated analysis*.

[2 marks]

(iv) Explain why an *Intention-To-Treat* estimate is preferable to an *As-Treated* estimate in a superiority trial. [3 marks]

[Continued]

(v) What are the implications of this for the conduct of randomised controlled trials? [2marks]

(vi) Calculate the point estimates of the C*ompliance Average Causal Effect* of *New* treatment compared to *Control*. [4 marks]

[Total 20 marks]

B8.

(i) Suppose that in a clinical trial n_T patients are randomized to treatment (*T*) and n_C to the control(*C*). The outcome measure is binary. Suppose that the number of events in each of the two treatment groups are r_T and r_C with probability parameters π_T and π_C, respectively.

Consider the odds ratio for the treatment effect of *T* compared to *C* defined by $OR = \frac{\pi_T(1-\pi_C)}{(1-\pi_T)\pi_C}$.

Using the approximate relationship $Var\left[f(X)\right] \cong f'(X)^2_{X=E[X]} Var\left[X\right]$, show that

$$Var\left[\log_e\left[OR\right]\right] \approx \frac{1}{n_T\pi_T} + \frac{1}{n_T(1-\pi_T)} + \frac{1}{n_C\pi_C} + \frac{1}{n_C(1-\pi_C)}. \qquad \text{[7 marks]}$$

(ii) Hence show that the $(1-\alpha)$ confidence interval for the odds ratio is given by the values of

$$\exp\left[\log_e\left[\frac{r_T(n_C-r_C)}{(n_T-r_T)r_C}\right] \pm z_{\alpha/2} \times \sqrt{\frac{1}{r_T} + \frac{1}{(n_T-r_T)} + \frac{1}{r_C} + \frac{1}{(n_C-r_C)}}\right]. \qquad \text{[4 marks]}$$

A systematic review of trials of vaccines to prevent influenza has identified two randomized trials that compare the *New* vaccine with a *Standard* vaccine. The table below summarizes the data from the two trials giving the number of subjects who had or not had influenza in the 12 months following vaccination by intervention group for each of the two trials.

	New Vaccine			*Standard Vaccine*		
	Influenza		N	Influenza		N
Trial	Yes	No		Yes	No	
A	50	500	550	100	450	550
B	30	200	230	50	180	230

(iii) For each trial determine $\log_e\left[OR\right]$ and $\hat{SE}\left[\log_e\left[OR\right]\right]$. [4 marks]

(iv) Suppose θ_i is the treatment effect for the i^{th} trial. The inverse-variance pooled estimate is given by $\hat{\theta} = \frac{\sum_i w_i\hat{\theta}_i}{\sum_i w_i}$ where $w_i = 1/Var\left[\hat{\theta}_i\right]$ with $Var\left[\hat{\theta}\right] = \frac{1}{\sum_i w_i}$. By setting $\hat{\theta}_i = \log_e\left[OR_i\right]$, compute the pooled estimate of the odds ratio for *New* vaccine as compared to *Control*.

[5 marks]

[Total 20 marks]

END OF EXAMINATION PAPER