Statistical tables are attached

Two Hours

UNIVERSITY OF MANCHESTER

May 2004 Final Draft

Medical Statistics MT3772

Electronic calculators may be used provided that they cannot store text

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Answer **ALL** six questions in **SECTION A** (50 Marks)

Answer **TWO** of the three questions in **SECTION B** (25 marks each)

The total number of marks on the paper is 100

A1. Explain what is meant by the term stratified randomisation in the context of a randomised controlled clinical trial.
[3 marks]

A2. A clinical trial compared two treatments for athlete's foot, a new ointment and a placebo ointment with no active ingredient. Using randomisation 39 patients are allocated to the new ointment and 40 to the standard ointment. Patients are assessed at the end of the two-week treatment period. The infection was eradicated for 29 patients in the new treatment group and 23 patients in the placebo group. A difference in the success rate of the two treatments of 10% was considered to be clinically important.

(i) State the hypotheses you might use to compare the treatments.

(ii) Carry out a statistical test to compare the treatments specifying the assumptions that are made.

(iii) Comment on the results of the trial.

[10 Marks]

A3.

(i) Explain what is meant by an equivalence trial.

(ii) Outline the statistical analysis one could use to establish whether a new treatment T is equivalent to a control treatment C on a continuous outcome measure Y in a parallel group trial.

(iii) An equivalence trial is carried out to compare a new medication with the current standard medication. To demonstrate equivalent pain relief it was felt that mean pain scores for each group should not differ by more than 5 units. The table below summarizes the pain relief scores for each treatment group with higher pain scores representing greater pain. Test whether the two treatments may be considered to be equivalent.

	Treatment Group					
	New Medication			Standard Medication		
	Mean	S.D.	N	Mean	S.D.	N
Pain Relief	35.2	18.1	171	34.1	17.9	172

[11marks]

A4. A randomised controlled trial of treatments for rheumatoid arthritis compared a new treatment (T) with a standard treatment (C). Outcome is measured by a continuous health activity scale. The table below summaries the outcome in terms of scale broken down by treatment group and age group (<65 years, ≥65 years).

Age Group	<65 years		≥65 years	
Treatment	New Treatment (T)	Control (C)	New Treatment (T)	Control (C)
Mean	1.29	1.47	1.51	1.49
S.D.	0.72	0.74	0.69	0.79
N	124	142	77	63

(i) State the hypothesis you might use to compare the treatment effect in patients less than 65 years of age with the treatment effect in patients of 65 years of age or more and write down a test statistic that could be used to test this.

(ii) Apply this test statistic to assess if there is any evidence of difference in the treatment effect according to age group, stating any assumptions you make.

[9 marks]

A5.

(i) Using asthma as an example, explain the difference between cumulative incidence and prevalence rates.

(ii) An epidemiological study compared asthma prevalence rates in two geographical areas, one with high and one with low atmospheric pollution. Describe two necessary conditions for a factor to be a confounder in this study.

(iii) In the following logistic regression analyses using STATA software, the four variables (asthma, pollution, sclass2 and sclass3) were all coded as 0 or 1 with code 1 indicates presence of asthma, living in a high pollution area, social class 2 and social class 3 respectively. (There were three social classes altogether). Does the data indicate that social class is a confounder? Does the data suggest an effect of pollution on asthma prevalence? What is the estimated odds ratio? Justify your answers.

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Logit estimates                                   Number of obs   =       6117
                                                  LR chi2(1)      =       3.84
                                                  Prob > chi2     =     0.0501
Log likelihood = -2878.4682                       Pseudo R2       =     0.0007
------------------------------------------------------------------------------
    asthma  |    Coef. Std. Err.   z     P>|z|   [95% Conf. Interval]
------------+-----------------------------------------------------------------
  pollution |    .131   .0667     1.96   0.050     -.0001     0.2614
      _cons |  -1.586   .0485   -32.73   0.000    -1.6811    -1.4912
------------------------------------------------------------------------------


Logit estimates                                   Number of obs   =       6117
                                                  LR chi2(3)      =      19.36
                                                  Prob > chi2     =     0.0002
Log likelihood = -2870.7086                       Pseudo R2       =     0.0034

------------------------------------------------------------------------------
    asthma  |    Coef.  Std. Err.   z     P>|z|   [95% Conf. Interval]
------------+-----------------------------------------------------------------
 pollution  |   0.133    .0667     1.99   0.047     .0019    .2638
   sclass1  |   0.127    .0827     1.54   0.125    -.0350    .2892
   sclass2  |   0.315    .0796     3.97   0.000     .1595    .4714
     _cons  |  -1.702    .0601   -28.31   0.000   -1.8199  -1.5843
------------------------------------------------------------------------------
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[12 Marks]

A6.

Consider the problem of estimating $\theta_i = \lambda_{1i}/\lambda_{0i}$, i =1,..,k where λ_{1i} is the death rate in age group i of a group of miners and λ_{0i} is the corresponding rate in the general population which is already known. Data on observed deaths, a_i and corresponding person-years at risk, T_i, i =1,..,k, are available from the miners.

Assuming that the a_i are Poisson distributed and $\theta_i = \theta$ for all i, show that the maximum likelihood estimator of θ is $\dfrac{\sum a_i}{\sum \lambda_{0i} T_i}$.

[5 Marks]

B7.

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 of these for sequences AB and BA respectively.

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

(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 .

(iii) Show that $Var\left[\hat{\delta}\right] = \frac{\sigma_\varepsilon^2}{2}\left(\frac{1}{n_{BA}} + \frac{1}{n_{AB}}\right)$ where n_{AB} and n_{BA} are the number of patients in each sequence.

(iv) 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 $E\left[\bar{a}_{AB} - \bar{a}_{BA}\right] = \gamma$.

(v) Derive an expression for $Var\left[\bar{a}_{AB} - \bar{a}_{BA}\right]$.

(vi) The test statistic T_a ,defined as $T_a = \frac{\bar{a}_{AB} - \bar{a}_{BA}}{\hat{SE}\left[\bar{a}_{AB} - \bar{a}_{BA}\right]}$, has been suggested as a test of the hypothesis H_0:γ = 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?

(vii) In a randomised controlled crossover to compare two medications, explain how one might prevent a carryover effect?

[25 Marks]

B8. Give two reasons why it is important to estimate sample size in a randomised controlled trial.

For a parallel group trial comparing a control treatment (Group C) with a new intervention (Group T) suppose y is a continuous, normally distributed outcome variable and x is the value of the same variable recorded at baseline prior to randomisation. Suppose that δ is the treatment effect such that

$y = \mu + \varepsilon_y$, $x = \mu_x + \varepsilon_x$ Group C

$y = \mu + \delta + \varepsilon_y$, $x = \mu_x + \varepsilon_x$ Group T.

with $E\left[\varepsilon_x\right] = E\left[\varepsilon_y\right] = 0$, $Var\left[\varepsilon_y\right] = \sigma_y^2$, $Var\left[\varepsilon_x\right] = \sigma_x^2$, and $Cov\left[\varepsilon_x, \varepsilon_y\right] = \sigma_{xy}$

(i) Let $d = y - x$ with $\bar{d}_C$ and $\bar{d}_T$ the sample means of Group C and Group T respectively. Show that $E\left[\bar{d}_T - \bar{d}_C\right] = \delta$ and $Var\left[\bar{d}_T - \bar{d}_C\right] = \lambda^2\left(\sigma_Y^2 + \sigma_X^2 - 2\sigma_{XY}\right)$ where $\lambda = \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}$ and n_T and n_C are the number of patients in each treatment group.

(ii) For the test statistic $T = \frac{\bar{d}_T - \bar{d}_C}{\hat{SE}\left[\bar{d}_T - \bar{d}_C\right]}$, write down an expression for the power of the test to detect a treatment effect τ, given a two-tailed alternative hypothesis and assuming that the test statistic T has a normal distribution under the null and the alterative hypotheses.

(iii) Assuming a two-tailed α size test, show that the sample size required for each of two equal size groups is $n = \frac{2\left(\sigma_Y^2 + \sigma_X^2 - 2\sigma_{XY}\right)}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$ to give a power β.

(iv) In a trial of an anti-hypertensive medication, the patient's outcome is to be assessed by systolic blood pressure. From previous studies it is known that amongst patients that would be eligible for the trial $\sigma_X^2 = \sigma_Y^2 = 400$ mmHg^2 and σ_{XY}=300 mmHg^2. Calculate the minimum sample size required in each of two equal sized groups to have a power of at least 80% power to detect a difference of 5 mmHg between the two treatment where the statistical analysis is based on change in blood pressure assuming a 0.05 size test .

[25 Marks]

B3. Consider a population of which a proportion q are exposed to a suspected carcinogenic substance, the remainder being unexposed. The cumulative incidence rates of cancer in the exposed and unexposed parts of the population over a time interval (0,t) are π_1 and π_0 respectively. Consider three different study designs to estimate $\ln(\gamma)$, where $\gamma = \frac{\pi_1(1-\pi_0)}{(1-\pi_1)\pi_0}$. In design **A**, random samples of size m are chosen from each of the exposed and unexposed parts of the population, in design **B** random samples of size m are chosen from people with and people without cancer at time t, and in design **C** a random sample of size $2m$ is chosen from the population as a whole. Assume that, in all designs, the variance of $\ln(\hat{\gamma})$ can be approximated by $\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}$ where a, b, c, and d are the frequencies in the cells of the observed 2x2 table.

(i) Give expressions for the proportions of the whole population in the four cells formed by cross-classifying exposure status and cancer status at t.

(ii) Use the results in (i) to estimate the numbers of subjects in the four cells under each of the three designs.

(iii) Show that the relative efficiency of design **A** compared to **C** for estimating $\ln(\gamma)$ is given by $\frac{1}{4q(1-q)}$ under H_0: $\pi_1 = \pi_0 = \pi$. Assuming that H_0 is true, in what type of population will design **A** would be more efficient than design **C**?

(iv) Show that the relative efficiency of design **B** compared to **A** for estimating $\ln \gamma$ is given by $\frac{q(1-q)}{\pi(1-\pi)}$ when $\pi_1 = \pi_0 = \pi$. Assuming that H_0 is true, $q < ½$ and $\pi < ½$, what does the study organiser need to know about the population to decide which of these two designs is more efficient?

[25 Marks]