Statistical tables are provided

Two Hours

UNIVERSITY OF MANCHESTER

Medical Statistics MATH38071

26 January 2010

14:00 – 16:00

Electronic calculators may be used provided that they cannot store text

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

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

The total number of marks on the paper is 80.

SECTION A

Answer **ALL** five questions

SECTION A

A1.

(i) In the context of clinical trials briefly explain what is meant by the term bias.

(ii) Briefly describe two possible types of bias in clinical trials and for each type suggest a method that might be used to prevent it.

[5 Marks]

A2.

A randomized controlled trial is carried out to compare two doses of a new vaccine for the prevention of H1N1 influenza. The effectiveness of the vaccine is tested by measuring the immune response in the blood measure 9 days following vaccination as this measures successful vaccination and protection against influenza. The results are summarized in the table below.

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Dose		15mg	30mg
Immune Response	Yes	200	220
	No	50	30
n		250	250

(i) Estimate the odds ratio for the effectiveness of 30mg doses as compared to a 15mg doses.

(ii) Calculate the 95% confidence interval of this odds ratio.

(iii) Comment on the results of the trial.

[10 marks]

A3.

In a clinical trial comparing a psychological treatment (CBT) with the effect of an exercise programme (EX) for patients suffering from moderate to severe anxiety, patients are being allocated to treatment using *deterministic minimization* controlling for sex and severity (Moderate, Severe). The numbers of patients with each characteristic for each treatment are given in the table below after sixty-five patients have entered the trial.

Patient Characteristic	Male		Female		Moderate		Severe	
Treatment	(CBT)	(EX)	(CBT)	(EX)	(CBT)	(EX)	(CBT)	(EX)
Number of Patients	18	15	15	17	22	21	11	11

(i) How many patients have been allocated to each treatment?

(ii) The characteristics of the next two patients entering the trial are:

66^{th} (Male, Moderate)

67^{th} (Female, Moderate)

Determine the treatment allocation of both patient.

[5 marks]

A4.

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

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

(iii) A randomised controlled equivalence trial is carried out to test whether a new *generic drug* is as effective as a 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-two patients are randomised to the standard treatment and forty-one to the new generic 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 test whether the new generic drug is equivalent to the current standard drug, specifying the significance level that you have used.

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [90% Conf. Interval]
---------+--------------------------------------------------------------------
Standard |      42        35.2     2.79289        18.1    30.49991    39.90009
Generic  |      41        34.1     2.79551        17.9    29.39278    38.80722
---------+--------------------------------------------------------------------
    diff |               1.1    3.952132               -5.475889    7.675889
------------------------------------------------------------------------------
   diff = mean(Standard) - mean(Generic)                         t =   0.2783
Ho: diff = 0                                     degrees of freedom =       81

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.6093         Pr(|T| > |t|) = 0.7815          Pr(T > t) = 0.3907
```

[10marks]

A5

In meta-analysis 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 sampling variance.

(i) For the weighted estimate of the overall 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 $Var\left[\hat{\theta}\right] = \dfrac{\sum_i^k w_i^{\,2}.Var\left[\hat{\theta}_i\right]}{\left(\sum_i^k w_i\right)^2}$.

(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 is

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

[10 marks]

B6 A randomised controlled trial is planned to compare a treatment (T) with the current standard therapy (C). For an outcome measure Y let $\bar{y}_T$, $\bar{y}_C$, μ_T, 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. Define the treatment effect $\tau = \mu_T - \mu_C$ to be estimated by $\bar{d} = \bar{y}_T - \bar{y}_C$. Assume that the null hypothesis of no treatment effect $H_0 : \tau = 0$ 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 treatments respectively. Suppose that patients are to be allocated in the ratio of 1: k such that $n_C = k.n_T$.

(i) Assuming that $\Pr[\text{Reject } H_0 | \ \tau\ ] = \left(1 - \Phi\left(z_{\alpha/2} - \dfrac{\tau}{\sigma\lambda}\right)\right)$, show that the total sample size N required to give a power (1-β) for a two-tailed α size test is

$$N = \frac{(k+1)^2}{k}\frac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2.$$

[8 marks]

(ii) Show that the total sample size N has a minimum when $k = 1$.

[5 marks]

(iii) In a randomised controlled trial it is planned to randomise patients to two treatments using a 1:2 allocation ratio. From previous studies it is know that the pooled within group standard deviation is approximately 6 units. Estimate the total sample size required to detect a treatment effect of 2 units using a two-sided 5% significance level with 90% power.

[3 marks]

(iv) Illustrate how block randomization could be used to randomly allocate treatments to 15 patients with an allocation ratio of 1:2 using a block size of 3.

[4 marks]

[Total 20 marks]

B7

For a parallel group randomised controlled trial comparing a control treatment (C) with a new treatment (T) suppose Y is a continuous normally distributed outcome variable and X is the value of the same variable recorded prior to randomisation. Suppose that τ is the treatment effect such that:

$Y = \mu_y + \varepsilon_y$ and $X = \mu_x + \varepsilon_x$ for treatment C

$Y = \mu_y + \tau + \varepsilon_y$ and $X = \mu_x + \varepsilon_x$ for treatment T.

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

Suppose that $\bar{x}_T$, $\bar{x}_C$, $\bar{y}_T$, and $\bar{y}_C$, are the sample means of X and Y for each treatment. Define $\hat{\tau}(\theta) = (\bar{y}_T - \theta\bar{x}_T) - (\bar{y}_C - \theta\bar{x}_C)$ where θ is any constant.

(i) Show that $E[\hat{\tau}(\theta)] = \tau$.

[4 marks]

(ii) Show that $Var[\hat{\tau}(\theta)] = \lambda^2(\sigma_y^2 + \theta^2\sigma_x^2 - 2\theta\sigma_{xy})$ where $\lambda = \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}$, n_T is the number of patients allocated to the new treatment and n_C is the number allocated to the control treatment.

[7 marks]

(iii) Show that $Var[\hat{\tau}(\theta)]$ has a minimum when $\theta = \frac{\sigma_{xy}}{\sigma_x^2}$.

[4 marks]

(iv) In this setting three statistical analysis might be used to estimated and test the treatment effect:

a) an unadjusted analysis using just the outcome variable Y

b) an analysis based on the change score Y-X or

c) a linear model of the outcome variable Y with treatment group and X as covariates.

What are the implications of the results in (i) and (iii) for the choice between the three analyses?

[3 marks]

(v) Why is it important for randomised controlled trials to have a statistical analysis plan?

[2 marks]

[Total 20 marks]

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

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

$y_{i2} = \mu + \phi + \xi_i + \varepsilon_{i2}$ 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,+

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

where μ is the mean for the sequence BA in period 1 , τ is the treatment effect of A relative to B, ϕ is the period 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. Defining $d_i = y_{i2} - y_{i1}$ let $\bar{d}_{AB}$, μ_{AB}^d, $\bar{d}_{BA}$ and μ_{BA}^d be the sample and population means of these for sequences AB and BA respectively.

(i) Show that $\left(\bar{d}_{BA} - \bar{d}_{AB}\right)/2$ is an unbiased estimator of the treatment effect τ.

[3 marks]

Two drugs used to treat chronic heart-burn were compared in a randomised controlled crossover trial. Eleven patients were allocated to the sequence drug A then drug B and eight patients were allocated to the sequence drug B then drug A. Outcome is assessed at the end of each period using a continuous normally distributed measure of acid-reflux with higher scores representing a worse outcome for the patient. The computer printout below summarizes the sample mean and standard deviation for each sequence and period and gives the results of a two-sample t-test based on the difference in outcome d_i defined above.

```
-------------------------------------------------
Sequence    Period 1          Period 2
            mean  s.d.  n     mean  s.d.  n
-------------------------------------------------
AB          4.92  0.79  11    4.41  0.82  11
BA          4.73  0.67  8     4.51  0.65  8
-------------------------------------------------
Two-sample t test with equal variances
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
      AB |      11       -0.51    0.1537708    0.51     -0.7426227  -0.0573773
      BA |       8       -0.22    0.1555635    0.44     -0.2478492   0.4878492
---------+--------------------------------------------------------------------
    diff |              -0.28    0.2241559               -0.7529276   0.1929276
------------------------------------------------------------------------------
    diff = mean(x) - mean(y)                                      t =  -1.2491
Ho: diff = 0                                     degrees of freedom =       17

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.1143         Pr(|T| > |t|) = 0.2285          Pr(T > t) = 0.8857
------------------------------------------------------------------------------
```

(ii) Using the computer printout estimate the treatment effect for drug A compared to drug B and give the p-value for a two-sided test of the null hypothesis H_0: $\tau = 0$.

[3 marks]

(iii) Define $c_i = y_{i1} - y_{i2}$ for sequence AB and $c_i = y_{i2} - y_{i1}$ for sequence BA. Let μ^c_{AB} μ^c_{BA}, $\bar{c}_{AB}$ and $\bar{c}_{BA}$ be the population and sample means of these for sequences AB and BA respectively. Show that a test of the null hypothesis $H_0 : \mu^c_{AB} = \mu^c_{BA}$ is the same as a test of the period effect, $H_0 : \phi = 0$.

[4 marks]

(iv) Using the computer printout test the null hypothesis $H_0 : \phi = 0$

[4 marks]

(v) Briefly comment on the result of the trial.

[2 marks]

(vi) It is sometimes suggested that the treatment effect τ in a cross-over trial can be estimated by the overall sample mean of the differences c_i , say $\bar{c} = \dfrac{\sum_{i=1}^{N} c_i}{N}$, where N is the total number of subjects in the trial. Using the computer print out estimate the treatment effect of drug A as compared to drug B using this method. Why does this estimate differ from that obtained in part (ii)?

[4 marks]

[Total 20 marks]

END OF EXAMINATION PAPER