Statistical tables are provided

Two Hours

UNIVERSITY OF MANCHESTER

Date: Wednesday 4th June 2008

Time: 1400 to 1600

Medical Statistics MT38072

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

Answer **ALL** five questions

A1.

Briefly explain what is meant by *Block randomisation*.

Illustrate this by showing how you might prepare a randomisation list for first twenty patients in a trial with two treatments.

How might you use block randomisation to improve balance between two treatment groups in a dichotomous prognostic factor?

[6 Marks]

A2.

A clinical trial compared an analgesics gel with a placebo gel with no active ingredient for the treatment of joint pain. Using randomisation, 30 patients were allocated to the new gel and 30 to the placebo. Patients were assessed at the end of the two-week treatment period. The swelling was eradicated for 21 patients in the new treatment group and 15 patients in the placebo group. An absolute difference in the success rate of the two treatments of 10% was considered to be a clinically important effect.

(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 you make.

(iii) Comment on the results of the trial.

[10 Marks]

A3.

You are asked to advise on the analysis of a double-blind randomised controlled trial of treatments for depression comparing fluoxetine with placebo. The primary outcome measure is the Beck Depression Inventory (***BDI-FU***), which is a continuous outcome measure that is considered to be approximately normally distributed. This same measure has also been recorded at baseline (***BDI-BASE)***. Apparently, ***BDI-FU*** is expected to be strongly correlated with BDI-BASE . The following three statistical analyses are being considered:

- Carry out a t-test comparing ***BDI-FU*** at follow-up.
- Calculate the change from baseline, that is ***BDI-CHG*** = ***BDI-FU*** – ***BDI-BASE***, and then apply a t-test.
- Fit a linear model with ***BDI-FU*** as the dependent variable with co-variates ***BDI-BASE*** and treatment group.

What advice would you give regarding the choice of statistical analysis to be included in statistical analysis plan justifying that choice?

[5 Marks]

A4.

Consider a randomized controlled trial. Suppose the patient population can be divided into three latent 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 randomized. Assuming 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, show that:

(i) An *intention-to-treat* estimate of the treatment effect is biased towards the null hypothesis of no treatment effect.

(ii) A *per-protocol* estimate of the treatment effect may be biased either towards or away from the null hypothesis of no treatment effect.

[10 Marks]

A5.

The Minitab print-out below gives the results of analysis of a randomised controlled 2-period AB-BA crossover trial on 45 patients comparing the effect of eating butter and margarine on total blood fats. Patients are randomised to receive Butter then Margarine or Margarine then Butter.

Analysis of Period 1

Two-Sample T-Test and CI

```
Sample              N   Mean   StDev    SE Mean
Butter then Marg    23  6.220  0.870     0.18
Marg then Butter    22  5.910  0.780     0.17


Difference = mu (Butter then Marg) - mu (Marg then Butter)
Estimate for difference:  0.310
95% CI for difference:  (-0.188, 0.808)
T-Test of difference = 0 (vs not =): T-Value = 1.26  P-Value = 0.216  DF = 43
Both use Pooled StDev = 0.8273
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Analysis of Period 2 - Period 1

Two-Sample T-Test and CI

```
Sample              N    Mean   StDev    SE Mean
Butter then Marg    23  -0.270  0.560     0.12
Marg then Butter    22   0.230  0.590     0.13


Difference = mu (Butter then Marg) - mu (Marg then Butter)
Estimate for difference:  -0.500
95% CI for difference:  (-0.846, -0.154)
T-Test of difference = 0 (vs not =): T-Value = -2.92  P-Value = 0.006  DF = 43
Both use Pooled StDev = 0.5748
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(i) Using the analysis for *Period 1* output give the estimate and 95% confidence interval of the treatment effect for Margarine as compared to Butter.

(ii) Using the analysis for *Period 2 – Period 1* give the estimate and 95% confidence interval of the treatment effect for Margarine as compared to Butter.

(iii) What is the advantage of a crossover design as compared to a parallel group design?

(iv) Give one limitation of a crossover design as compared to a parallel group design.

[9 Marks]

SECTION B

Answer **TWO** of the three questions in this section

B6.

A randomised controlled trial is planned to compare a new antibiotic treatment (A) with the current standard therapy (B) for patients with TB. At six months follow-up it is recorded whether the disease is still present in the patient.

(i) Why it is important to estimate sample size in a clinical trial. [2 Marks]

(ii) The two-sample test of proportions with statistic z given by

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

will be used to test the null hypothesis of no treatment effect, where n_A, n_B are the number of subjects allocated to each treatment, $p_A = r_A/n_A$, $p_B = r_B/n_B$ with r_A, r_B are the numbers of patients in which TB was absent after 6 months for each treatment and $p = \frac{n_A.p_A + n_B.p_B}{n_A + n_B}$.

Suppose that patients are to be allocated in the ratio of k:1 with $n_A = k.n_B$.

Assuming that the test statistic z has a normal distribution under the null and alternative hypotheses and using a two-sided α size test , show that the power

$$1-\beta(\alpha,\tau) \cong 1-\Phi\left(\frac{z_{\alpha/2}.\lambda.\sqrt{\pi(1-\pi)} - \tau}{\sqrt{\frac{\pi_A(1-\pi_A)}{n_A} + \frac{\pi_B(1-\pi_B)}{n_B}}}\right),$$

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 standard normal cumulative density function. [7 Marks]

(iii) Show that the sample size required for group A to give a power (1-β) is approximately

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

(iv) The investigators planning the randomised controlled trial expect that the proportion of patients that recover in the current standard therapy group (B) will be 50%. An improvement to 65% with the new medication (A) is considered to be clinically important. Estimate the total sample size that would be required using a 2 to 1 allocation ratio (k=2), assuming a power of 80% and a two-sided 5% significance level. [4 Marks]

[Total 20 Marks]

B7.

In a parallel group *non-inferiority* trial a new treatment *T* is being compared with a control treatment *C* using a continuous normally distributed 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, n_T and n_C be the sample sizes, and s be the pooled within-group sample standard deviation of *Y*. Define the treatment effect $\tau = \mu_T - \mu_C$.

(i) Explain why a significance test of the hypothesis $H_0 : \tau = 0$ vs $H_1 : \tau < 0$ would be inappropriate in a non-inferiority trial.

[4 Marks]

(ii) Suppose that the null hypothesis $H_0 : \mu_T - \mu_C \leq -\tau_N$ is rejected if the (1-α) single sided confidence interval, given by $\bar{y}_T - \bar{y}_C - z_\alpha \lambda s$ with $\lambda = \sqrt{1/n_T + 1/n_C}$, is greater than $-\tau_N$. Show that

$$\Pr[\text{Reject } H_0 | \tau] = 1 - \Phi\left(-\frac{(\tau_N + \tau)}{s\lambda} + z_\alpha \right)$$

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

[7 Marks]

(iii) Show that $\Pr[\text{Reject } H_0 | \tau]$ has a maximum under H_0 when $\tau = -\tau_N$. Hence show that this procedure has a type I error $\leq \alpha$. [6 Marks]

(iv) A randomised controlled non-inferiority trial is carried out to test whether a new generic drug is as effective as a current standard drug for controlling pain measured by a 100 mm analogue scale with higher scores representing greater pain. Fifty patients are randomised to the standard treatment and 52 to the new generic treatment. The Minitab output is given below.

Two-Sample T-Test and CI

Sample	N	Mean	StDev	SE Mean
Current standard drug	50	65.5	18.5	2.6
New generic drug	52	66.1	18.8	2.6

```
Difference = mu (Current standard drug) - mu (New generic drug)
Estimate for difference:  -0.60
Standard Error (SE) for difference:    3.69
95% CI for difference:  (-7.93, 6.73)
T-Test of difference = 0 (vs not =):
             T-Value = -0.16  P-Value = 0.871  DF = 100
Both use Pooled StDev = 18.6536
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A difference of 10 mmHg was considered by researchers to be the minimum that was clinically important. Using a 5% significance level test whether the new medication is non-inferior to the current standard drug . [3 Marks]

[Total 20 Marks]

B8.

In meta-analysis suppose $\hat{\theta}_i$ is an estimate of the treatment effect for the i^{th} study, assumed to be normally distributed, and let $Var\left[\hat{\theta}_i\right]$ be its sampling variance. The fixed effect estimator

$\hat{\theta} = \dfrac{\sum_i^k w_i \hat{\theta}_i}{\sum_i^k w_i}$, where w_i are weights, with $Var\left[\hat{\theta}\right] = \dfrac{\sum_i^k w_i^2 . Var\left[\hat{\theta}_i\right]}{\left(\sum_i^k w_i\right)^2}$.

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

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

[12 Marks]

The table below summarizes the outcome of three trials comparing dietary advice given by a dietician with that given by a doctor for patients for with high blood cholesterol. The treatment effect for each study ($\hat{\theta}_i$, i = 1,2,3) is the difference in mean cholesterol between dietician advice group and doctor advice group. $Var\left[\hat{\theta}_i\right]$ is the sample variance estimate the i^{th} study.

Study	*Difference in blood cholesterol,* $\hat{\theta}_i$	$\hat{Var}\left[\hat{\theta}_i\right]$
Dyson1996	-0.34	0.0289
Thomson 2002	-0.18	0.0729
Smith 1989	-0.27	0.0676

(ii) Compute the minimum variance estimate of the overall treatment effect, $\hat{\theta}_{MV}$, and determine its 95% confidence interval stating any assumptions that you make. [6 Marks]

(iii) What do you conclude from the meta-analysis? [2 Marks]

[Total 20 Marks]

End of Examination Paper