Two Hours

Statistical tables are attached

UNIVERSITY OF MANCHESTER

MEDICAL STATISTICS

20 January 2016

14:00-16:00

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 two best answers.

The total number of marks for the paper is 80.

Electronic calculators may be used provided that they cannot store text/transmit or receive information/display graphics

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A1.

(i) In the context of randomised controlled trials, explain what is meant by the term *concealment*.

(ii) Why is *concealment* prior to treatment allocation important for randomised controlled trials?

(iii) Give two reasons why it is beneficial to maintain *concealment* after treatment allocation.

[6 marks]

A2.

A clinical trial compared a *New* cream to a *Placebo* cream for the treatment of athlete's foot. Using randomisation 78 patients are allocated to the *New* cream and 80 to the *Placebo*. Patients are assessed at the end of the two week treatment period. The infection was eradicated for 58 patients in the *New* cream group and 46 patients in the *Placebo* cream group.

(i) Calculate the point estimate of the difference in the eradication rate of the *New* and *Placebo* treatments.

(ii) Calculate the approximate 95% confidence interval of the difference in the eradication rate of the *New* and *Placebo* treatments, checking the normality assumption.

(iii) Calculate the *Numbers Needed to be Treated* (*NNT*) for one additional eradication and its 95% confidence interval.

[10 marks]

A3.

In a trial comparing Acupuncture (A) with Homeopathy (H) for patient suffering from chronic headache, patients are allocated to treatment using deterministic minimization controlling for sex and type of head ache (migraine, tension). The numbers of patients with each characteristic for each treatment are given in the table below after eight-nine patients have entered the trial.

Patient Characteristic	Male		Female		Migraine		Tension	
Treatment	(A)	(H)	(A)	(H)	(A)	(H)	(A)	(H)
Number of Patients	19	16	26	28	28	27	17	17

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

(ii) The characteristics of the next two patients entering the trial are (Male, Migraine) followed by (Female, Migraine). Determine the treatment allocation of each patient.

[5 marks]

A4.

A clinical researcher has carried out a randomised controlled trial to compare a new drug treatment (*N*) with the standard drug treatment (*S*) for patients with arthritis. A symptom score has been recorded at baseline (*baseline*) and at follow-up (*followup*) on each patient, with lower scores corresponding to improved outcome. This symptom score is also continuous and normally distributed. Twenty-six patients have been randomised to the new treatment (*N*) and 24 to the standard treatment (*S*) . Using the trial data, the researcher has carried out a separate paired t-test analyses for each treatment group. The statistical output obtained using the statistical package STATA is given below.

Results for NEW TREATMENT (*N*)

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
baseline |      26     55.5602    1.902873    9.702787    51.64116    59.47924
followup |      26     49.8264    1.713542    8.737387     46.2973    53.35551
---------+--------------------------------------------------------------------
    diff |      26    5.733795    1.931726     9.84991     1.75533     9.71226
------------------------------------------------------------------------------
     mean(diff) = mean(baseline - followup)                       t =   2.9682

 Ho: mean(diff) = 0                               degrees of freedom =       25
 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9967         Pr(|T| > |t|) = 0.0065          Pr(T > t) = 0.0033
```

Results for STANDARD TREATMENT (*S*)

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
baseline |      24    56.53192    2.157341    10.56877    52.06912    60.99472
followup |      24    52.85044    2.084191    10.21041    48.53896    57.16191
---------+--------------------------------------------------------------------
    diff |      24    3.681484    3.086131    15.11889   -2.702664    10.06563
------------------------------------------------------------------------------
     mean(diff) = mean(baseline - followup)                       t =   1.1929

 Ho: mean(diff) = 0                               degrees of freedom =       23
 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8775         Pr(|T| > |t|) = 0.2451          Pr(T > t) = 0.1225
```

Because there is a statistically significant change at the 5% level from baseline to follow-up in the new treatment group (*N*) but not in standard group (*S*), the researcher concludes that the new treatment (*N*) is significantly more effective than the standard treatment for treating the symptoms of arthritis.

(i) What are the flaws in the researcher's conclusion?

(Continued)

(ii) Three other methods of analysis have been suggested to the researcher to test for a treatment effect:

a) Use a two-sample t-test with just the follow-up symptom scores.

b) Calculate the change score, defined as (*followup)* – (*baseline)*, for each patient and then use a two-sample t-test with the change scores.

c) Fit a linear model with follow-up symptom score as the dependent variable and baseline symptom score and a treatment indicator variable as covariates.

Assuming the statistical assumptions of all methods are satisfied, which of these three methods would you recommend to the researcher and why?

(iii) The researcher suggests carrying out all three statistical analyses on their data. What would you advise and why?

[9 marks]

A5.

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

(ii) A randomised controlled trial is carried out to test whether a *New* generic drug (*N*) is equivalent in effect to current *Standard* drug (*S*) for reducing pain. At follow-up this is measured by a 100 mm analogue scale with higher scores representing greater pain. Eighty-nine patients are randomised to the *New* drug and eighty-eight to the *Standard* drug. The statistical output of the trial is given below. A difference of 5mm has been recommended as the maximum difference between treatments that is not clinically important. Using the STATA statistical output below, test whether the *New* drug (*N*) is equivalent to the current *Standard* drug (*S*) using a 5% significance level.

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
New      |      89        42.3    1.918596        18.1    38.48719    46.11281
Standard |      88        42.2    2.014747        18.9    38.19547    46.20453
---------+--------------------------------------------------------------------
    diff |                 0.1    2.781441               -5.389487    5.589487
------------------------------------------------------------------------------
    diff = mean(New) - mean(Standard)                             t =   0.0360
Ho: diff = 0                                     degrees of freedom =      175

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.5143         Pr(|T| > |t|) = 0.9714          Pr(T > t) = 0.4857
```

[10 marks]

B1.

(i) Consider a randomised controlled trial comparing a new treatment (*T*) with a control treatment (*C*) with a binary outcome measure. Suppose that n_T and n_C are the sample size of each treatment and that π_T and π_C are the population proportions of a successful outcome. Using standard notation the power $(1-\beta)$ of a two-sample z-test of proportions to detect a treatment effect $\tau = \pi_T - \pi_C$ can be approximated by

$$1-\Phi\left(z_{\alpha/2} - \frac{\tau}{\lambda\sqrt{\pi(1-\pi)}} \right)$$

where $\pi = \frac{n_T.\pi_T + n_C.\pi_C}{n_T + n_C}$ and $\lambda = \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}$. Assuming two equal size groups show that the sample size required in each group to give a power (1-β) for a two-sided test with significance level α is approximately $n = \frac{2\pi(1-\pi)\left(z_{\alpha/2} + z_\beta\right)^2}{\tau^2}$. [7 marks]

(ii) For any given τ with $0 < |\tau| < 1$, find the value of π that gives the maximum value of n. [4 marks]

(iii) In what circumstance might one apply this result when designing a randomised controlled trial? [3 marks]

(iv) A randomized controlled trial is planned to compare a new antibiotic treatment (*T*) with the current standard control therapy (*C*) for patients with a chronic respiratory infection. At 6 months follow-up it is recorded whether the patient has recovered. The researcher knows that π_C is not greater than 30% and wishes to detect a 10% increase in the recovery rate with a two-sided 5% significance level. It is anticipated that 20% of patients randomised will be lost to follow-up. Assuming π_C does not exceed 30%, what is the minimum number of patients that would need to be randomised to be certain of having 90% power? [4 marks]

(v) Give two reasons why it is important to estimate sample size in a clinical trial. [2 marks]

[Total 20 marks]

B2.

For an *AB*/*BA* crossover trial a standard model for a continuous outcome y_{ij} for the i^{th} patient in the j^{th} period is

$y_{i1} = \mu + \tau + \xi_i + \varepsilon_{i1}$ 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, and ϕ is the period effect, with ξ_i and ε_{ij} being two independent random variables with $\xi_i \sim N\left[0, \sigma_B^2\right]$ and $\varepsilon_{ij} \sim N\left[0, \sigma_\varepsilon^2\right]$. Defining $d_i = y_{i2} - y_{i1}$ let $\bar{d}_{AB}$ and $\bar{d}_{BA}$ be the sample means of d_i for sequences *AB* and *BA* respectively.

(i) Under this data generating model, show that $\hat{\tau}_C = \dfrac{\bar{d}_{BA} - \bar{d}_{AB}}{2}$ is an unbiased estimator of the treatment effect, τ. [3 marks]

(ii) Using standard notation the total sample size required to detect a treatment effect δ using a two sample t-test with two equal size groups, power $(1-\beta)$ and a two-sided significance level α is given by the formula $\dfrac{4\sigma^2}{\delta^2}\left(z_{\alpha/2} + z_\beta\right)^2$. Show that the total sample size for a cross-over trial to detect a treatment effect τ using a two sample t-test with equal numbers in each sequence, power $(1-\beta)$ and a two-sided significance level α is $N_C = \dfrac{2\sigma_\varepsilon^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$.

[3 marks]

(iii) Show that the total sample size for a parallel group trial based on first period of the trial is $N_P = \dfrac{4\left(\sigma_B^2 + \sigma_\varepsilon^2\right)}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$. [3 marks]

(iv) The relative efficiency of a crossover design compared to a parallel group design can be defined as $RE = \dfrac{N_P}{N_C}$. Show that $RE = 2\left(1 + \dfrac{\sigma_B^2}{\sigma_\varepsilon^2}\right)$. [2 marks]

(v) What is the minimum value of *RE*? [2 marks]

(vi) What is the implication of parts (iv) and (v) for the sample size of patients for a cross-over trial design as compared to a parallel group design? [3 marks]

(vii) Describe two situations in which a cross-over design may be not be suitable. [4 marks]

[Total marks 20]

B3.

Consider a meta-analysis of *k* trials. Suppose $\hat{\theta}_i$ is an estimate of the treatment effect for the i^{th} trial and let $Var\left[\hat{\theta}_i\right]$ be its sampling 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 $Var\left[\hat{\theta}\right] = \dfrac{\sum_i^k w_i^2 Var\left[\hat{\theta}_i\right]}{\left(\sum_i^k w_i\right)^2}$. [3 marks]

(ii) 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 variance of this estimator is equal to

$$Var\left[\hat{\theta}_{MV}\right] = \frac{1}{\sum_{i=1}^k \frac{1}{Var\left[\hat{\theta}_i\right]}}.$$ [3 marks]

The table below summarizes the outcome of three randomised trials comparing *dietary advice* with *usual treatment* for patients with diabetes. The treatment effect for each study ($\hat{\theta}_i$, i = 1,2,3) is the difference in mean blood sugar levels for the two treatments with lower values representing a benefit of treatment. $Var\left[\hat{\theta}_i\right]$ is the sample variance estimate of the i^{th} study.

Study	*Difference in blood sugar,* $\hat{\theta}_i$		$Var\left[\hat{\theta}_i\right]$
	*Mean Difference**	*(95% c.i.)*	
Smith (1995)	-1.2	(-2.5,0.1)	0.4
Cohen (2002)	1.4	(-1.4,4.2)	2.0
Iqbal (2007)	-1.5	(-3.3,0.3)	0.8

* *dietary advice - treatment as usual*.

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

(iv) Illustrate the three studies and the pooled result using a sketch of a forest plot. [5 marks]

(v) What do you conclude from the meta-analysis regarding the effectiveness of *dietary advice*? [2 marks]

[Total marks 20]

End of Examination Paper