Statistical tables are provided

Two Hours

UNIVERSITY OF MANCHESTER

Medical Statistics

MATH38071

18 January 2011

14:00 – 16:00

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

A1.

(i) In the context of a randomised controlled trial, 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.

In a published report of a randomised trial a new pain relieving drug was compared with a standard medication. Twenty-five patients were allocated to each treatment group. Outcome was assessed using a 100 mm visual analogue pain scale with lower scores representing less pain. The mean difference between the new drug and the standard treatment was -7 mm (95% confidence interval -19.8 mm to 5.8 mm). The p-value for a two-sample t-test comparing the two treatments was 0.275. A 5 mm reduction in visual analogue pain scores is considered to be a clinically worthwhile benefit.

(i) Comment on the results.

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

(iii) A new trial is planned to test the same two treatments. Using the formula $n = \frac{2\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_{\beta}\right)^2$ and the value of the pooled within group standard deviation determined in (ii), calculate the sample size required in each group to have a power equal to 80% to detect a 5mm change in visual analogue pain scale with a two-sample t-test assuming a two-sided 5% significance level .

(iv) It is thought that about 20% of patients randomised will be lost to follow-up, and that only 30% of patients screened for the study will be eligible and consent to join the new trial. Estimate the numbers of patients that need to be screened to achieve the sample size.

[13 marks]

A3.

(i) Illustrate how you might prepare a randomisation list for the first twenty patients in a trial with two treatments using *block randomisation* with a block size of 4.

(ii) How might block randomisation be used to improve balance between treatment groups for a dichotomous prognostic factor?

[6 marks]

A4.

A randomised controlled *AB-BA* crossover trial compared two treatments to reduce joint inflammation in patients with arthritis. Twenty patients were randomly allocated to receive either *A then B* or *B then A*. The computer output below gives analysis of joint inflammation score with higher scores representing worse inflammation.

Analysis of Period 1

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
A then B |      10        24.0    4.935135    15.60627    12.83595    35.16405
B then A |      10        34.3    4.740019    14.98926    23.57733    45.02267
---------+--------------------------------------------------------------------
    diff |               -10.3    6.842758               -24.6761    4.076101
------------------------------------------------------------------------------
    diff = mean(A then B) - mean(B then A)                        t =  -1.5052
Ho: diff = 0                                     degrees of freedom =       18

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0748         Pr(|T| > |t|) = 0.1496          Pr(T > t) = 0.9252
```

Analysis of Period 2 - Period 1

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
A then B |      10         1.0    3.119829    9.865766   -6.057544    8.057544
B then A |      10       -12.0    5.168279    16.34353   -23.69146   -.3085399
---------+--------------------------------------------------------------------
    diff |                13.0    6.036923               .3168945    25.68311
------------------------------------------------------------------------------
    diff = mean(A then B) - mean(B then A)                        t =   2.1534
Ho: diff = 0                                     degrees of freedom =       18

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9775         Pr(|T| > |t|) = 0.0451          Pr(T > t) = 0.0225
```

(i) Using the analysis for the *Period 1* output give the point estimate and 95% confidence interval of the treatment effect of *treatment A* compared to treatment *B*.

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

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

(iv) Give two limitations of a crossover trial design as compared to a parallel group design.

[11 marks]

A5. A randomised controlled trial compared cognitive behavioural therapy (CBT) with standard care (SC) for the treatment of psychosis. A total of 53 patients were randomised to either treatment. The primary outcome measure was the Brief Psychiatric Rating Scale (BPRS), which was measured at baseline and 12 months follow-up. Lower values represent a better outcome. The statistical analysis plan specified that the treatment effect should be estimated with a linear model adjusting for baseline BPRS, gender and the patient's age at randomisation. The computer output below gives some results from the trial. The treatment allocation was included in the model as an indicator variable *group,* which was coded as 0 for those allocated to standard care (SC) and as 1 for patients allocated to cognitive behavioural therapy (CBT).

Summary statistics: mean, sd, N by categories of: group (Treatment)

Treatment		BPRS (baseline)	BPRS (12 months)
Standard Care	mean	24.46154	22.66667
	sd	7.13992	7.630982
	N	26	24
CBT	mean	26.44444	19.86957
	sd	6.541779	8.454715
	N	27	23

Linear Model: $\text{bprsfu} = \mu + \beta_1.\text{bprsbase} + \beta_2.age + \beta_3.gender + \beta_4.group + \varepsilon$

Source	SS	df	MS		
Model	1156.73783	4	289.184457	Number of obs	47
Residual	1847.09196	42	43.97838	F(4, 42)	6.58
Total	3003.82979	46	65.3006475	Prob > F	0.0003
				R-squared	0.3851
				Adj R-squared	0.3265
				Root MSE	6.6316

bprsfu	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
bprsbase	.7143828	.1455722	4.91	0.000	.4206062	1.008159
age	-.1139789	.084337	-1.35	0.184	-.2841779	.05622
gender	1.008135	2.055901	0.49	0.626	-3.140841	5.157111
group	-4.686154	2.019554	-2.32	0.025	-8.761779	-.6105286
constant	5.10927	4.549531	1.12	0.268	-4.072055	14.2906

Using the computer output comment briefly on the treatment effect of cognitive behavioural therapy compared to standard care.

[4 marks]

B6.

In a parallel group *non-inferiority* trial a new treatment T is compared to a control treatment C using a continuous outcome measure Y with higher scores corresponding to a better outcome. Let μ_T and μ_C be the means of Y for each treatment, n_T and n_C be the two sample sizes, and σ be the common within-group standard deviation of Y. Define $\tau = \mu_T - \mu_C$ as the treatment effect.

(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.

(ii) Outline how one could test whether the new treatment T is non-inferior to the control treatment C.

(iii) Assume that $\Pr[\text{Reject } H_0|\tau] = 1 - \Phi\left(\frac{-\tau_N + z_\alpha \sigma\lambda - \tau}{\sigma\lambda}\right)$ where $-\tau_N$ is the limit of non-inferiority, $\lambda = \sqrt{1/n_T + 1/n_C}$, z_α is the standard normal deviate for an upper tail probability α and Φ is the cumulative distribution function of the standard normal distribution. Show that the sample size per group required to demonstrate non-inferiority with a power (1-β), is

$$n = \frac{2\sigma^2}{\tau_N^2}\left(z_\alpha + z_\beta\right)^2$$

assuming $\tau = 0$ under the alternative hypothesis.

(iv) In a proposed non-inferiority trial, comparing a new drug with a standard drug, outcome is to be assessed using a continuous measure. The within-group standard deviation is thought to be approximately 6 units. Estimate the minimum sample size required to have 90% power using a limit of non-inferiority of -3 units and α=0.05 assuming $\tau = 0$ under the alternative hypothesis.

[20 marks]

B7.

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 treatment*: patients who will receive control treatment regardless of allocation,
- *Always new treatment*: patients who will receive the new treatment regardless of allocation.

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.

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

(iii) Tabulated below are summary data from a randomised controlled trial comparing two treatments . Some patients allocated to the *New* treatment received the *Control* and some patients allocated *Control* received the *New* treatment.

	Randomised Groups			
Recovered after 6 weeks	*New*		*Control*	
	Received New	*Received Control*	*Received New*	*Received Control*
Yes	120	24	16	120
No	40	16	4	60
Total	160	40	20	180

Calculate the point estimates of the treatment effect of *New* treatment compared to the *Control* treatment measured by the proportion recovered after 6 weeks for a

(a) *intention-to-treat* analysis and

(b) *per-protocol* analysis.

(iv) Briefly explain why an *intention-to-treat* analysis is preferable to *per-protocol* in a superiority trial.

(v) What are the implications of (iv) for the conduct of randomised controlled trials?

(vi) For the data in (iii) calculate the point estimates of the *Compliance Average Causal Effect* for *New* treatment compared to the *Control* treatment.

[20 marks]

B8.

(i) In a trial n_T patients are randomised to a new treatment (T) and n_C to the control treatment (C). and the outcome measure is binary. Suppose that the number of successes in each of the two treatment groups are r_T and r_C with probability parameters π_T and π_C. Consider the rate ratio of treatment compared to control defined as $RR = \frac{\pi_T}{\pi_C}$ and estimated by $\hat{RR} = \frac{r_T n_C}{n_T r_C}$.

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

$$Var\left[\log_e\left[\hat{RR}\right]\right] = \frac{1}{n_T\pi_T} - \frac{1}{n_T} + \frac{1}{n_C\pi_C} - \frac{1}{n_C}.$$

Hence show that the 95% confidence interval for the rate ratio is given by the values of

$$\exp\left[\log_e\left[\hat{RR}\right] \pm 1.96 \times \sqrt{\frac{1}{r_T} - \frac{1}{n_T} + \frac{1}{r_C} - \frac{1}{n_C}}\right].$$

A systematic review of trials of a new vaccine to prevent pneumonia has identified two randomised trials that compare the *New* vaccine with a *Standard* vaccine. The table below summarises the data from the two trials.

Trial	*New Vaccine*		*Standard Vaccine*		*Rate Ratio*
(i)	*Number (n_T)*	*Cases (r_T)*	*Number (n_C)*	*Cases (r_C)*	*(RR)*
A	5000	50	5000	100	0.5
B	3000	35	3000	50	0.7

(ii) Obtain a 95% confidence interval of the rate ratio for each trial.

(iii) The inverse-variance pooled estimate is given by $\hat{\theta} = \frac{\sum_i w_i \hat{\theta}_i}{\sum_i w_i}$ where $w_i = 1/Var\left[\hat{\theta}_i\right]$. By setting $\hat{\theta}_i = \log_e\left(\hat{RR}\right)$, compute the inverse-variance pooled estimate of the rate ratio for *New* vaccine as compared to *Standard* vaccine.

[20 marks]

END OF EXAMINATION PAPER