MATH38071 EXAMINATION SOLUTION (JANUARY 2010)

SECTION A

A1.

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

Solution

In the context of a clinical trial bias is a factor that deviates the estimate of the treatment effect systematically away from the true estimate.

[1 mark]

(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.

Solution

(ii)_A brief description of any two of the following (i) selection (ii) allocation (iii) performance (iv) follow-up (v) outcome assessment or (vi) analyses biases

[4 marks]
[Total mark 5]

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 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.

Solution

OR= (220x50)/(200x30)= 1.83

[1 minute]

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

Solution

Confidence interval for odds ratio are calculated using

$$\exp\left[\log_e\left[\frac{r_T(n_C-r_C)}{(n_T-r_T)r_C}\right]\pm z_{\alpha/2}\sqrt{\frac{1}{r_T}+\frac{1}{n_T-r_T}+\frac{1}{r_C}+\frac{1}{n_C-r_C}}\right]$$

log(OR)= 0.606

Substitution into the formula with cell frequencies gives

$$\mathrm{SE}\left[\log[\mathrm{OR}]\right]=\sqrt{\frac{1}{r_T}+\frac{1}{n_T-r_T}+\frac{1}{r_C}+\frac{1}{n_C-r_C}}$$

$$=\sqrt{\frac{1}{200}+\frac{1}{50}+\frac{1}{220}+\frac{1}{30}}=0.25075$$

95% c.i. log(OR) is therefore (0.117,1.098).

Taking exponentials give the 95% c.i. for the odds ratio (OR) is (1.124,2.997)

[5 minutes]

(iii) Comment on the results of the trial.

The trial suggest that the 30mg dose is more effect than the 15 mg dose as the odds ratio for immune response or 30mg as compared to 15mg equals 1.83 with 95% confidence interval 1.12 to 3.00.

[10 marks]

A3.

In a clinical trial comparing a psychological treatment (CBT) with the effect of an exercise programme (EX) for patient 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 after sixty-five patients have entered the trial are given in the table below.

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?

Solution

33 CBT 32 Exercise [1 minute]

[1 marks]

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

66th (Male, Moderate)

67th (Female, Moderate)

Determine the treatment allocation of each patient.

Solution Table with total updated after each patient

		Male		Female		Moderate		Severe		Total		Allocated treatment
		(CBT)	(EX)	(CBT)	(EX)	(CBT)	(EX)	(CBT)	(EX)	(CBT)	(EX)	
65	-	18	15	15	17	22	21	11	11			
66	Male, Moderate	18	**16**	15	17	22	**22**	11	11	18+22 =40	15+21 =36	(EX)
67	Female, Moderate									15+22 =37	17+22 =39	(CBT)

The 66th patient is allocated to Exercise (EX) and the 67th to CBT . [4 marks]

[Total 5 marks]

A4.

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

Solution

Usually the aim of a trial is to detect a difference between the treatments under study, testing whether a new treatment is superior to the existing standard treatment or a placebo. Such trials are called *Superiority Trials*. In such a trial the null hypothesis is that the average outcome is the same. *Equivalence trial* are designed to establish that the efficacy of two or more treatments is the same. Therefore in such a trial the null hypothesis is that the average outcome is different.

[3 marks]

(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*.

Solution

Rather than using a formal significance test, statistical analysis of equivalence trials is usually based on the confidence interval of difference between treatments. Equivalence is established by demonstrating that the confidence interval of the difference lies in the specified range ($-\delta_E$, $+\delta_E$). Suppose outcome measure *Y* is continuous and Normally distributed with means μ_C and μ_T for the control and new treatment respectively. Rejection of the null hypothesis that H_0: $|\mu_T-\mu_C|>\delta_E$ against the alternative hypothesis H_1: $|\mu_T-\mu_C|\leq\delta_E$ where the $(1-2\alpha)$ confidence interval is within the interval [$-\delta_E$, $+\delta_E$], will have a type I error of less than α

[4 marks]

(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.

```
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
```

Solution

The printer out gives a 90% confidence interval. This can be used to carry out a 5% level test of equivalence. The question states that a 5mm difference on the visual analogue scale was considered to be the minimum clinically important difference. Therefore ± 5 mm is used as then limits of equivalence. From the printout the 90% confidence interval is (-5.48 to + 7.68) which overlaps both limits equivalence. It is therefore not possible to reject the null hypothesis in a 5% level test.

[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 weight 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 $Var\left[\hat{\theta}\right] = \dfrac{\sum_i^k w_i^2 . Var\left[\hat{\theta}_i\right]}{\left(\sum_i^k w_i\right)^2}$.

Solution

$$Var\left[\hat{\theta}\right] = Var\left[\frac{\sum_i^k w_i . \hat{\theta}_i}{\sum_i^k w_i}\right] = \frac{1}{\left(\sum_i^k w_i\right)^2} Var\left[\sum_i^k w_i . \hat{\theta}_i\right].$$

Since the studies are independent, it follows that $Var\left[\sum_i^k w_i . \hat{\theta}_i\right] = \sum_i^k w_i^2 . Var\left[\hat{\theta}_i\right]$.

Hence $Var\left[\hat{\theta}\right] = \dfrac{\sum_i^k w_i^2 . Var\left[\hat{\theta}_i\right]}{\left(\sum_i^k w_i\right)^2}$.

[Book work]

[5 marks]

(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 estimate is equal to

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

Solution

Given that the minimum variance estimator is obtained when $w_i \propto 1/Var\left[\hat{\theta}_i\right]$ without loss of generality one can assume 1/Var[θ_i] for w_i . This gives

$$\hat{Var}[\theta_{MV}] = \frac{\sum_{i}^{k}\left(\frac{1}{Var\left[\hat{\theta}_i\right]}\right)^2 .Var\left[\hat{\theta}_i\right]}{\left(\sum_{i}^{k}\frac{1}{Var\left[\hat{\theta}_i\right]}\right)^2} = \frac{\sum_{i}^{k}\frac{1}{Var\left[\hat{\theta}_i\right]}}{\left(\sum_{i}^{k}\frac{1}{Var\left[\hat{\theta}_i\right]}\right)^2} = \frac{1}{\sum_{i}^{k}\frac{1}{Var\left[\hat{\theta}_i\right]}}$$

as required.

[Book work]

[5 marks]
[Total mark 10]

SECTION B

B6 A randomised controlled trial is planned to compare a treatment (A) with the current standard therapy (B). For an outcome measure *Y* let $\bar{y}_A, \bar{y}_B, \mu_A, \mu_B$ 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*. Assume that the null hypothesis of no treatment effect $H_0 : \mu_A = \mu_B$ will be tested by the statistic $T = \frac{\bar{y}_A - \bar{y}_B}{s\lambda}$, with $\lambda = \sqrt{1/n_A + 1/n_B}$ where n_A and n_B are the number of subjects allocated to the treatments respectively. Suppose that patients are allocated in the ratio of 1: k such that $n_B = k.n_A$.

(i) Assuming that sample size

$$\Pr[\text{Reject } H_0 | \ \tau\ ] = \left(1 - \Phi\left(z_{\alpha/2} - \frac{\tau}{\sigma\lambda}\right)\right) + \Phi\left(-z_{\alpha/2} - \frac{\tau}{\sigma\lambda}\right).$$

Show that the total sample size *N* required to give a power $(1-\beta)$ 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]

Solution

The second term in equation [1] is negligible, therefore

$$Power = 1 - \beta(\alpha, \tau) \cong 1 - \Phi\left(z_{\alpha/2} - \frac{\tau}{\sigma\lambda}\right)$$

Since $\Phi^{-1}(\beta) = -z_\beta$ it follows that $-z_\beta = z_{\alpha/2} - \frac{\tau}{\sigma\lambda}$

giving $\frac{\tau}{\sigma\lambda} = z_{\alpha/2} + z_\beta$.

[end of book work]

If $n_B = k.n_A$, then $\lambda = \sqrt{1/n_A + 1/kn_A} = \sqrt{(k+1)/kn_A}$

Therefore $\frac{\tau}{\sigma}\sqrt{\frac{kn_a}{(k+1)}} = z_{\alpha/2} + z_\beta$. Rearrangement gives

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

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

Hence the total sample size $n = n_a + kn_a = \frac{(k+1)^2}{k}\frac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$

[8 marks]

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

Solution

To find the minimum differentiate with respect to k.

$$\frac{dn}{dk} \propto \frac{d}{dk}\left(k + 2 + \frac{1}{k}\right) = 1 - \frac{1}{k^2}$$

Equating derivative to zero to find turning point gives $\left(k^2 - 1\right) = 0$ gives k=1

Since the second derivative is positive, this must be a minimum. k=1 corresponds to an equal allocation ratio.

[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.

Solution

For α=0.05 from tables $z_{\alpha/2}$ =1.96.

For 90% power (1-β)=0.9. giving z_β=1.2816 τ=2mg/dl σ=6.

Therefore total sample size $N = \frac{(k+1)^2}{k}\frac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2 = \frac{(2+1)^2}{2}\frac{6^2}{2^2}(1.96 + 1.28)^2 = 425.15$

Hence the minimum total sample size is 426

[4 minutes]

[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.

Solution

First one defines the possible block. For 2 treatment and a block size of 3, the possible blocks are (1) AAB, (2) ABA and (3) BAA

A sequence of pseudo random intergers from 1 to 3 in order that the blocks can be selected.

For 15 patient we need 5 blocks of 3 . Suppose the five random numbers are say 1,3,2,2,1 then the allocation sequence for the first 15 patient would be AAB, BAA, ABA, ABA, AAB

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

Suppose $\bar{x}_T$, $\bar{x}_C$, $\bar{y}_T$, and $\bar{y}_C$, are the sample means of X and Y for each treatment.
Let $D = Y - X$ with $\bar{d}_C$ and $\bar{d}_T$ the sample means of treatment C and treatment T respectively.
Define $\hat{\tau}(\theta) = (\bar{y}_T - \theta\bar{x}_T) - (\bar{y}_C - \theta\bar{x}_C)$.

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

Solution

Define $\hat{\tau}(\theta) = (\bar{y}_T - \theta\bar{x}_T) - (\bar{y}_C - \theta\bar{x}_C)$.

Values of θ equal to 0 , 1 and β correspond to the treatment effect in an unadjusted, change and adjusted model analyses.

Now $E\left[\hat{\tau}(\theta)\right] = E\left[\bar{y}_T - \bar{y}_C\right] - \theta E\left[\bar{x}_T - \bar{x}_C\right]$

Since $E\left[\bar{y}_T - \bar{y}_C\right] = \tau + \beta E\left[\bar{x}_T - \bar{x}_C\right]$, it follows that

$$E\left[\hat{\tau}(\theta)\right] = \tau + (\beta - \vartheta) E\left[\bar{x}_T - \bar{x}_C\right]$$

Randomisation means that $E\left[\bar{x}_T\right] = E\left[\bar{x}_C\right]$.

Therefore $E\left[\hat{\tau}(\theta)\right] = \tau$.

[4 marks]

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

Solution

Consider $\hat{\tau}(\theta) = (\bar{y}_T - \theta\bar{x}_T) - (\bar{y}_{\boldsymbol{C}} - \theta\bar{x}_C)$

$$Var\left[\hat{\tau}(\theta)\right] = Var\left[(\bar{y}_T - \bar{y}_C) - \theta(\bar{x}_T - \bar{x}_C)\right]$$

$$= Var\left[\bar{y}_T - \bar{y}_C\right] + Var\left[\theta\left((\bar{x}_T - \bar{x}_C)\right)\right] - 2Cov\left[\bar{y}_T - \bar{y}_C, \theta(\bar{x}_T - \bar{x}_C)\right]$$

$$Var\left[\bar{y}_T - \bar{y}_C\right] + \theta^2 Var\left[\bar{x}_T - \bar{x}_C\right] - 2.\theta.Cov\left[\bar{y}_T - \bar{y}_C, \bar{x}_T - \bar{x}_C\right] \text{ [1]}$$

Considering the first term

$$Var\left[\bar{y}_T - \bar{y}_C\right] = Var\left[\bar{y}_T\right] + Var\left[\bar{y}_C\right] - 2Cov\left[\bar{y}_T, \bar{y}_C\right]$$

Since treatment groups are independent $Cov\left[\bar{Y}_T, \bar{Y}_C\right] = 0$.

Therefore $Var\left[\bar{y}_T - \bar{y}_C\right] = Var\left[\bar{y}_T\right] + Var\left[\bar{y}_C\right]$.

Since observations are independent $Var\left[\bar{y}_T\right] = \frac{\sum_{i \in T} Var\left[y_T\right]}{n_T^2} = \frac{\sum_{i \in T} \sigma_Y^2}{n_T^2} = \frac{\sigma_Y^2}{n_T}$.

Similarly $Var\left[\bar{y}_C\right] = \frac{\sigma_Y^2}{n_C}$.

Therefore $Var\left[\bar{y}_T - \bar{y}_C\right] = \lambda^2 \sigma_Y^2$ where $\lambda = \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}$.

Similarly $Var\left[\bar{x}_T - \bar{x}_C\right] = \lambda^2 \sigma_X^2$ and $Cov\left[\bar{y}_T - \bar{y}_C, \bar{x}_T - \bar{x}_C\right] = \lambda^2 \sigma_{XY}$.

Substitution into [1] gives $Var\left[\hat{\tau}(\theta)\right] = \lambda^2\left(\sigma_y^2 + \theta^2 \sigma_X^2 - 2\theta\sigma_{XY}\right)$

[7 marks]

(iii) Show that $Var\left[\hat{\tau}(\theta)\right]$ has a minimum when $\theta = \beta$.

Solution

Differentiation with respect to θ gives

$$\frac{\partial}{\partial\theta} Var\left[\hat{\tau}(\theta)\right] = \lambda^2\left(2\theta\sigma_x^2 - 2\sigma_{xy}\right).$$

This equals zero when $\theta = \sigma_{xy}/\sigma_x^2$.

The second derivative $\frac{\partial^2}{\partial\theta^2} Var\left[\hat{\tau}(\theta)\right] = 2\lambda^2\sigma_x^2$.

As this is positive , it follows that $Var\left[\hat{\tau}(\theta)\right]$ *has a minimum when* $\theta = \sigma_{xy}/\sigma_x^2$.

[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?

Solution

Values of θ equal to 0 , 1 and β correspond to the treatment effect in an unadjusted, change and linear adjusted model analyses. All three estimates are unbiased, but an estimate of the treatment effect based on a linear model smaller variance compared to an unadjusted analysis or a change analysis. Reducing the variance of the treatment effect estimate increases the power of the analysis. As a consequence if a baseline variable is thought to be correlated with outcome, an analysis adjusting for baseline is recommended, and where the baseline value of the outcome is recorded a linear model analysis is superior to an analysis based on change.

[3 marks]

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

A statistical analysis should be prepared prior to beginning the analysis. There can be many different ways in which the outcome from a randomised controlled trial can be analysed. For example 3 possible analysis were considered in (iv). These analyses may give results that are more or less supportive of the investigators' opinion . Unless the analysis is pre-specified the investigators may present that which is closest to their opinion, instead of the best analysis.

[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, 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.

Solution

Let $\bar{d}_{AB} = \frac{\sum d_i}{n_{AB}}$, μ_{AB} , $\bar{d}_{BA} = \frac{\sum d_i}{n_{BA}}$ and μ_{BA}, the sample and population means for sequences AB and BA.

Now

$E\left[\bar{d}_{AB}\right] = E\left[\frac{\sum d_i}{n_{AB}}\right] = \phi - \tau$ and $E\left[\bar{d}_{BA}\right] = E\left[\frac{\sum d_i}{n_{BA}}\right] = \phi + \tau$.

Therefore $E\left[\bar{d}_{BA} - \bar{d}_{AB}\right] = 2\tau$.

Hence $\hat{\tau} = \frac{\bar{d}_{BA} - \bar{d}_{AB}}{2}$ is an unbiased estimator of 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.

```
-------------------------------------------------
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 as compared to drug B and give the p-value for a two-sided test of the null hypothesis H_0: $\tau = 0$.

Solution

From the printout $\bar{d}_{BA} - \bar{d}_{AB}$ equals 0.28

$$\hat{\tau} = \frac{\bar{d}_{BA} - \bar{d}_{AB}}{2} = \frac{0.28}{2} = 0.14 \ .$$

[1 minutes]

The p-value of the two-side test of H_0: $\tau = 0$ is 0.2285

[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, $H_0 : \phi = 0$.

Solution

$$\mu^c_{AB} = E\left[y_{i1} - y_{i2}\right] = E\left[\left(\mu + \tau + \varepsilon_{i2}\right) - \left(\mu + \phi + \varepsilon_{i1}\right)\right] = \tau - \phi$$

$$\mu^c_{BA} = E\left[y_{i2} - y_{i1}\right] = E\left[\left(\mu + \phi + \tau + \varepsilon_{i2}\right) - \left(\mu + \varepsilon_{i1}\right)\right] = \phi + \tau$$

Therefore $\mu^C_{BA} - \mu^C_{AB} = -2\phi$.

Hence the test H_0: $\mu^c_{AB} = \mu^c_{BA}$ is equivalent to a test of the period effect $H_0 : \phi = 0$.

[4 marks]

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

Solution

The hypothesis H_0: ϕ=0 vs. H_1: $\phi \neq 0$ can be tested using a two-sample t-test of the means of the differences $H_0 : \mu^c_{AB} = \mu^c_{BA}$.

Now $\mu^c_{AB} = -\mu^d_{AB}$ =0.51 and $\mu^c_{BA} = \mu^d_{BA}$ =-0.22

$$\hat{SE}\left[\bar{c}_{BA} - \bar{c}_{AB}\right] = \hat{SE}\left[\bar{d}_{BA} - \bar{d}_{AB}\right] = 0.229$$

Therefore $T_C = \dfrac{0.51 - (-0.22)}{0.229} = 3.19$

From tables $t_{\alpha/2}\left(n_1 + n_2 - 2\right) = t_{0.05}\left(16\right) = 2.12$ Therefore one can reject the null hypothesis that H_0: ϕ=0
[3 minutes]

[4 marks]

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

Solution

The treatment effect of drug A compared to drug B is 0.14 suggesting theat patients receiving drug B have a slightly better outcome than those receiving drug A, but from the test of the hypothesis H_0: $\tau = 0$

there is no evidence of a treatment effect. In contrast there is evidence of a period effect. From inspection of the data in the table one can see that gastric reflux levels reduce for both sequences.

[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 $\bar{c} = \frac{\sum_{i=1}^{N} c_i}{N}$, 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)?

Solution

$$\bar{c} = \frac{\sum_{i=1}^{N} c_i}{N} = \frac{n_{AB} \times \bar{c}_{AB} + n_{BA} \times \bar{c}_{BA}}{n_{AB} + n_{BA}} = \frac{11 \times 0.51 + 8 \times -0.22}{19} = \frac{3.85}{19} = 0.202 .$$

[2 minutes]

The estimate differs from that in part (ii) due to the period effect which biases this estimator.

[4 marks]

[Total 20 marks]