Statistical tables are attached

Two Hours

UNIVERSITY OF MANCHESTER

Medical Statistics MATH38071

Electronic calculators may be used provided that they cannot store text

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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 on the paper is 80.

A1

(i) In studies investigating the effect of an exposure on health, what is the difference between observational and experimental studies?

Solution

In an observational study the investigator observe subjects and measure variables of interest without assigning exposure to the subjects. The treatment that each subject receives is determined is not control of the investigator.

In an experimental study the investigators apply treatments to experimental units (people, animals, plots of land, etc.) and then proceed to observe the effect of the treatments on the experimental units.

[2 marks]

(i) What is a confounding variable?

Solution

A confounding variable can cause or prevent the outcome of interest, independently of exposure under investigation, but is associated with the factor exposure.

[2 marks]

(ii) Consider an epidemiological study investigating whether high fat consumption causes heart disease. For such a study suggest an example of each of the three types of variable

a) Exposure

b) Outcome

c) Confounding.

Solution

a) Exposure

Daily fat consumption determined from a dietary diary would be an exposure variable.

b) Outcome

There are many possible outcome measures. Examples include (i) clinical symptoms of heart disease (ii) the requirement of treatment for heart disease (iii) electro cardio graphic (ECG) measurements of heart function

c) Confounding.

Smoking or dietary sugar intake are possible confounding variables as both might cause heart disease by a different mechanism but might correlate with dietary sugar intake.

[3 marks]

[Total 7 marks]

A2.

A randomized controlled trial is carried out to compare a new treatment regime (N) with the existing standard treatment (S) for patients. The effectiveness of treatment is assessed by whether the patient is still *infectious after 2 weeks*. The results are summarized in the frequency table below.

		Treatment	
		Standard (S)	*New (N)*
Infectious after 2 weeks	*Yes*	100	70
	No	400	430
Total		500	500

(i) Calculate the rate ratio (RR) of the patient still being *infectious after 2 weeks* with the new treatment (N) compared to the standard treatment (S).

Solution

$$RR = \left(\frac{70/500}{100/500} \right) = 0.7$$

[2 marks]

(ii) Suppose n_T patients are randomized to treatment (T) and n_C to the control (C).Suppose that the number of events in each of the two treatment groups are r_T and r_C with probability parameters π_T and π_C, respectively. The standard error of the $\log_e\left[\hat{RR}\right]$ is

$$\hat{SE}\left[\log_e\left[\hat{RR}\right]\right] = \sqrt{\frac{1}{r_T} - \frac{1}{n_T} + \frac{1}{r_C} - \frac{1}{n_C}}$$

Calculate the 95% confidence interval for rate ratio of being *infectious after 2 weeks*.

Solution

$$\hat{SE}\left[\log_e\left[\hat{RR}\right]\right] = \sqrt{\frac{1}{r_T} - \frac{1}{n_T} + \frac{1}{r_C} - \frac{1}{n_C}} = \sqrt{\frac{1}{70} - \frac{1}{500} + \frac{1}{100} - \frac{1}{500}} = \sqrt{0.020285714} = 0.142427926$$

The $(1-\alpha)$ confidence interval for $\log_e[RR]$ is given by $\log_e[RR] \pm z_{\alpha/2} \times \hat{SE}\left[\log_e\left[\hat{RR}\right]\right]$

For 95% confidence $z_{\alpha/2} = z_{0.025} = 1.96$

Substitution give $-0.3567 \pm 1.96 \times 0.1424$. The 95% confidence interval for $\log_e[RR]$ is therefore -0.6358 to -0.0775.

The confidence interval for the rate ratio is $\exp\left[\log_e[RR] \pm z_{\alpha/2} \times \sqrt{\frac{1}{r_T} - \frac{1}{n_T} + \frac{1}{r_C} - \frac{1}{n_C}}\right]$

Taking exponents the confidence interval for the rate ratio is given by the values of 0.5295 to 0.9254.

[5 marks]

(iii) Is there evidence that the new treatment (N) is better than the standard treatment (S)?

Solution

For the Rate Ratio a null effect is given by 1 . Benefit , that is reduction in being infectious, is given by values below 1. The trial suggests that the new treatment is significantly more effective than the standard treatment as the 95% confidence interval of the RR is (0.53, 0.93) does not include 1.

[2 marks]

[Total 9 marks]

A3.

(i) A researcher designing a randomised control trial considers patient's age and gender to be prognostic. Explain how you would carry out stratified randomisation with stratification by age and sex.

Solution

a) Choose age bands for age strata e.g. 3 age banding (-64, 65-74,75+)
b) Stratifying by sex and age one would then have 6 separate age by sex strata.
c) Construct separate randomisation list for each strata using block randomisation.

[5 marks]

(ii) What are the advantages and disadvantages of stratified randomisation?

Solution

Advantages

Enables balances to be maintained between treatment on prognostic factors, which will increases power and precision.

Disadvantages

Complex to organize and administer, which may lead to mistakes.

Unless the study is very large only a small number of prognostic factors can be used as the number of randomisation list is the product of the number of levels for each factor which may lead to a large number of incomplete blocks and hence imbalance at the end of the trial.

[5 marks]

[Total 8 marks]

A4.

The results for a randomised controlled trial comparing a *New* treatment with a *Control* treatment for binary outcome measure (*Recovered after 4 weeks*)are tabulated below. Some patients randomised to the *New* treatment receive the *Control* treatment, but no patients randomised to the *Control* treatment receive the *New* treatment.

	Randomised group		
Recovered after 4 weeks	*New*		*Control*
	Received New	*Received Control*	
Yes	110	5	120
No	40	45	80
Total	150	50	200

Calculate the point estimates of the treatment effect of the *New* treatment compared to the *Control* treatment measured by the proportion of patients who have *Recovered after 4 weeks* for

(i) an *Intention-To-Treat* analysis

(ii) a *Per-Protocol* analysis.

(iii) an As Treated analysis

Solution

(i) *Intention-To-Treat* treatment effect *=(115)/(200)-(120)/(200)= -0.025*

(ii) *Per-Protocol* treatment effect *=110/150-120/200= 0.13333*

(iii) *As-Treated* treatment effect *=110/150-125/250= 0.23333*

[4 marks]

(i) Drawing on the example above explain why an *Intention-To-Treat* analysis is preferable to *Per-protocol* and *As-treated* analyses in a superiority trial.

Solution

Use of *intention-to-treat* biases the statistical analysis towards showing no difference between two treatments. In a superiority trial this is a bias towards the null hypothesis. If we reject the null hypothesis H_o:δ=0 based on an *intention-to-treat* analysis, one can feel confident that the treatment effect is larger in patients that took the treatment. An intention-to-treat analysis is therefore conservative in a superiority trial. In contrast a *per-protocol* and *As-treated* may be biased either away from or towards the null hypothesis depending on the characteristics of the non-compliant patients. In the above example the Intention to treat estimate is very small an negative (2.5 %) where as the per-protocol effect is 13.3% and the as-treated is 23.3%. The disparity between these results is explained by the poor outcome in patients randomised to the new treatment but receiving the control with only 10% recovering.

[4 marks]

[Total marks 8]

A5

In a meta-analysis of *k* trials, 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. The minimum variance estimate is defined by $\hat{\theta}_{MV} = \dfrac{\sum_i^k w_i\hat{\theta}_i}{\sum_i^k w_i}$,

where $w_i = 1/Var\left[\hat{\theta}_i\right]$, and $Var\left[\hat{\theta}_{MV}\right] = \dfrac{1}{\sum_{i=1}^{k}\dfrac{1}{Var\left[\hat{\theta}_i\right]}}$.

The table below summarizes the outcome of two trials comparing a new drug to prevent high blood cholesterol with the current standard drug treatment. The treatment effect for each study $\left(\hat{\theta}_i, i=1,2\right)$ is the difference in mean cholesterol for the two treatments.

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

Study (Date of Publication)	Reduction in cholesterol $\hat{\theta}_i$	$Var\left[\hat{\theta}_i\right]$	w_i
Rahman (2001)	0.36	0.2916	3.43
Chung (2008)	0.68	0.1156	8.65

Solution

The minimum variance estimate $\hat{\theta}_{MV} = \dfrac{\sum_i^k w_i\hat{\theta}_i}{\sum_i^k w_i} = \dfrac{0.36\times 3.43+0.68\times 8.65}{3.43+8.65} = 0.589$

$$Var\left[\hat{\theta}_{MV}\right] = \frac{1}{\sum_i^k w_i} = \frac{1}{3.43+8.65} = 0.08278$$

$$SE\left[\hat{\theta}_{MV}\right] = 0.2877$$

Assuming $\hat{\theta}_{MV}$ is normally distributed the 95% c.i. is $0.589 \pm 1.96\, SE\left[\hat{\theta}_{MV}\right]$, which gives the 95% c.i. to be from 0.0252 to 1.153.

[6 Marks]

(ii) What can you conclude from the meta-analysis regarding the performance of the new drug?

Solution

There is evidence from the meta-analysis that the new drug gave a greater reduction in blood cholesterol as the 95% confidence interval for reduction is 0.0252 to 1.153 suggesting statistically significant decrease.

[2 Marks]

[Total Mark 8]

B1.

(i) For a binary measure Y let π and p be the population and sample proportions respectively.

Suppose $\gamma = \arcsin\left(\sqrt{\pi}\right)$ and $\hat{\gamma} = \arcsin\left(\sqrt{p}\right)$. Using the approximation formula

$$Var\left[f(x)\right] \cong f'(x)^2\Big|_{x=E[x]} Var[x],$$

show that $Var\left[\hat{\gamma}\right] \cong \frac{1}{4n}$ where n is the sample size.

Solution

With $f(x) = \arcsin\left(\sqrt{x}\right)$, $f'(x) = \frac{d}{dx}\left(\arcsin\left(\sqrt{x}\right)\right) = \frac{1}{\sqrt{1-x}} \cdot \frac{1}{2\sqrt{x}} = \frac{1}{2\sqrt{x(1-x)}}$.

From properties of the binomial distribution $E[p] = \pi$ and $Var\left[p_T\right] = \frac{\pi_T(1-\pi_T)}{n_T}$.

Using the approximate formula $Var\left[f(x)\right] \cong f'(x)^2\Big|_{x=E[x]} Var[x]$

$$Var\left[\hat{\gamma}\right] \cong \frac{1}{4p(1-p)}\Bigg|_{p=E[p]} Var[p] = \frac{1}{4\pi(1-\pi)} \frac{\pi(1-\pi)}{n} = \frac{1}{4n}$$ giving the result.

[Marks 7]

(ii) Consider a parallel group trial with a binary outcome measure with two treatment groups of size n_T and n_C. Suppose π_T, π_C, p_T, and p_C are the population and sample proportions for each treatment. With the treatment effect defined by $\hat{\tau} = \arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)$, show that $SE\left[\hat{\tau}\right] = \sqrt{\frac{1}{4n_T} + \frac{1}{4n_C}}$.

Solution

Since treatment groups are independent,

$$Var\left[\hat{\tau}\right] = Var\left[\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right] = Var\left[\arcsin\left(\sqrt{p_T}\right)\right] + Var\left[\arcsin\left(\sqrt{p_C}\right)\right]$$

Substitution with the result of part (i) gives

$$Var\left[\hat{\tau}\right] = \frac{1}{4n_T} + \frac{1}{4n_C}.$$

Hence, $SE\left[\hat{\tau}\right] = \sqrt{\frac{1}{4n_T} + \frac{1}{4n_C}}$.

[Marks 3]

(iii) For a normally distributed test statistic $T = \dfrac{\hat{\tau}}{SE\left[\hat{\tau}\right]}$ the power to detect a difference τ_D with a two-sided α size test is given by the expression $Power = 1-\Phi\left(z_{\alpha/2} - \dfrac{\tau_D}{SE\left[\hat{\tau}\right]} \right)$. For a test of $H_0 : \pi_T = \pi_C$ vs $H_1 : \pi_T \neq \pi_C$, show that the power to detect a difference between two proportions π_T and π_C can be estimated by $1-\Phi\left(z_{\alpha/2} - \dfrac{\arcsin\left(\sqrt{\pi_T}\right) - \arcsin\left(\sqrt{\pi_C}\right)}{\sqrt{\dfrac{1}{4n_T} + \dfrac{1}{4n_C}}} \right)$, stating any required assumptions.

Solution

With $\hat{\tau} = \arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)$ and $SE\left[\hat{\tau}\right] = \sqrt{\dfrac{1}{4n_T} + \dfrac{1}{4n_C}}$ consider the test statistic $T = \dfrac{\hat{\tau}}{SE\left[\hat{\tau}\right]}$. The effect to be detected on the arc-sine scale is $\tau = \arcsin\left(\sqrt{\pi_T}\right) - \arcsin\left(\sqrt{\pi_C}\right)$.

Assuming $\hat{\tau}$ is normally distributed substitution in to $1-\Phi\left(z_{\alpha/2} - \dfrac{\tau_D}{SE\left[\hat{\tau}\right]} \right)$ gives

$$\text{Power} = 1-\Phi\left(z_{\alpha/2} - \frac{\arcsin\left(\sqrt{\pi_T}\right) - \arcsin\left(\sqrt{\pi_C}\right)}{\sqrt{\dfrac{1}{4n_T} + \dfrac{1}{4n_C}}} \right).$$

[Marks 4]

(iv) Hence, show that two groups of size

$$n = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2}{2\left(\arcsin\left(\sqrt{\pi_T}\right) - \arcsin\left(\sqrt{\pi_C}\right)\right)^2}$$

will have power $\left(1\text{-}\beta\right)$ to detect a difference between π_T and π_C with a two-sided test α size test.

Solution

Assuming $n_T = n_C$

$$\text{Power=}1\text{-}\beta = 1-\Phi\left(z_{\alpha/2} - \left(\arcsin\left(\sqrt{\pi_T}\right) - \arcsin\left(\sqrt{\pi_C}\right)\right).\sqrt{2n} \right)$$

Hence $\beta = \Phi\left(z_{\alpha/2} - \left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right).\sqrt{2n}\right)$

Taking inverses $-z_\beta = z_{\alpha/2} - \left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right).\sqrt{2n}$

Rearrangement gives

$$\sqrt{2n} = \frac{z_{\alpha/2} + z_\beta}{\left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right)}$$

Hence $n = \dfrac{\left(z_{\alpha/2} + z_\beta\right)^2}{2\left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right)^2}$ as required.

[Marks 6]

B2.

In a parallel group *non-inferiority* trial a new treatment *T* is being compared with a control treatment *C* using a normally distributed outcome measure *Y*. Suppose that large values of *Y* represent a worse outcome for the patient. Let $\bar{y}_T$, $\bar{y}_C$, μ_T and μ_C be the sample and population means for each treatment, n_T and n_C be the sample sizes, and let σ and s be the population and sample standard deviation , respectively. 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 not be appropriate in a non-inferiority trial.

Solution

To demonstrate that an alternative hypothesis is true, we need to reject a null hypothesis. Hence to demonstrate that a new treatment is not inferior, we need to define a null hypothesis that the treatment is inferior rather than a null hypothesis that is zero.

[3 marks]

(ii) Suppose that the null hypothesis $H_0 : \mu_T - \mu_C \geq \tau_N$ is rejected if the (1-α) single sided confidence interval for $\hat{\tau}$ is less than τ_N . Stating any assumptions, show that

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

where Φ is the cumulative distribution function of the standard normal distribution and $\lambda = \sqrt{1/n_T + 1/n_C}$.

Solution

Assuming a normal approximation to the t-distribution and a known standard deviation σ , the (1-α) single sided confidence interval for $\hat{\tau}$ is given by $\hat{\tau} + z_\alpha \sigma\lambda$. H_0 will be rejected provided $\hat{\tau} + z_\alpha \sigma\lambda < \tau_N$. Therefore

$$\Pr\left[\text{Reject } H_0 \middle| \tau\right] = \Pr\left[\hat{\tau} + z_\alpha \sigma\lambda < \tau_N\right] = \Pr\left[\hat{\tau} < \tau_N - \sigma\lambda z_\alpha\right] = \Pr\left[\frac{\hat{\tau}}{\sigma\lambda} < \frac{\tau_N}{\sigma\lambda} - z_\alpha\right].$$

Since $\hat{\tau}$ is $N\left[\tau, \sigma^2\lambda^2\right]$, it follows that $\Pr\left[\text{Reject } H_0 \middle| \tau\right] = \Phi\left(\left(\frac{\tau_N}{\sigma\lambda} - z_\alpha\right) - \frac{\tau}{\sigma\lambda}\right)$ as required.

[5 marks]

(iii) Show that $\Pr\left[\text{Reject } H_0 \middle| \tau\right]$ has a maximum under H_0 when $\tau = \tau_N$. Hence, show that this procedure has a type I error less than α .

Solution

The maximum of this can be obtained by differentiation w.r.t. τ. The derivative is

$\frac{d}{d\tau}\Pr\left[\text{Reject } H_0 |\ \tau\right] = -\frac{1}{\sigma\lambda}\phi\left(\left(\frac{\tau_N}{\sigma\lambda} - z_\alpha\right) - \frac{\tau}{\sigma\lambda}\right)$ where ϕ is the standard normal density function.

Since $\phi > 0$ for finite values, it follows that $\Pr\left[\text{Reject } H_0 |\ \tau\right]$ is monotone decreasing with τ. Hence the type I error rate, which is $\Pr\left[\text{Reject } H_0 |\ \tau\right]$ when $\tau \geq \tau_N$, has a maximum when $\tau = \tau_N$.

Setting $\tau = \tau_N$

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

Since the type I error has a maximum when $\tau = \tau_N$ the type I error is therefore less than or equal to α.

[7 marks]

(i) A randomised controlled non-inferiority trial is carried out to test whether a *New* drug is as effective as a current *Standard* drug for controlling pain. Outcome is measured on a continuous scale with high scores representing greater pain. Eighty patients are randomised to the *New* treatment and 78 to the *Standard* treatment. The statistical output is given below.

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
     New |      80        45.9     2.62738        23.5    40.67033    51.12967
Standard |      78        46.1    2.581592        22.8    40.95939    51.24061
---------+--------------------------------------------------------------------
combined |     158    45.99873    1.836423    23.08348    42.37145    49.62602
---------+--------------------------------------------------------------------
    diff |                -.2     3.68486               -7.478658    7.078658
------------------------------------------------------------------------------
    diff = mean(New) - mean(Standard)                             t =  -0.0543
Ho: diff = 0                                     degrees of freedom =      156

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.4784         Pr(|T| > |t|) = 0.9568          Pr(T > t) = 0.5216
```

A difference of 5 mm was considered by researchers to be clinically important difference between treatments. Using a 5% significance level, test whether the *New* drug is non-inferior to the *Standard* drug.

Solution

Since higher score represent greater pain to test non-inferiority consider the null hypothesis $H_0 : \mu_T - \mu_C \geq 5mm$. This can be tested at a 5% level by considering the 95% one-sided confidence interval $\bar{y}_T - \bar{y}_C + z_\alpha \lambda s$.

From tables

$z_\alpha = 1.645$

λs is the SE = 3.68486

$\bar{y}_N - \bar{y}_C = -0.20$.

So the one-sided upper interval is -0.20 +1.645x3.6848 = 5.862. Since this is above 5mm , the null hypothesis cannot be rejected.

[5 Marks]

[Total 20 Marks]

B3.

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,

$y_{i2} = \mu + \phi + \gamma + \xi_i + \varepsilon_{i2}$ 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 effect of the second period relative to the first, γ is the carryover 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. Let $d_i = y_{i2} - y_{i1}$ and let $\bar{d}_{AB}$, μ_{AB}, $\bar{d}_{BA}$ and μ_{BA} be the sample and population means of these for sequences AB and BA respectively.

(i) Explain what is meant by the term *carryover effect*.

Solution

The effect of either treatment in the first period of a cross-over trial may carry over to the second period. If there is a difference in the carryover for the two drug sequences, this is the called the *carryover effect*.

[2 marks]

(i) In a crossover trial the treatment effect τ is estimated by $\hat{\tau} = \left(\bar{d}_{BA} - \bar{d}_{AB}\right)/2$. Show that this will be biased if there is a carryover effect.

Solution

For sequence AB $d_i = y_{i2} - y_{i1} = \phi - \tau + \gamma + \varepsilon_{i2} - \varepsilon_{i1}$

Therefore $E\left[\bar{d}_{AB}\right] = E\left[\dfrac{\sum_{i\in AB} d_i}{n_{AB}}\right] = \dfrac{\sum_{i\in AB} E\left[d_i\right]}{n_{AB}} = \dfrac{\sum_{i\in AB} E\left[\phi - \tau + \gamma + \varepsilon_{i2} - \varepsilon_{i1}\right]}{n_{AB}} = \phi + \gamma - \tau$

Similarly, for sequence BA, $d_i = y_{i2} - y_{i1} = \phi + \tau + \varepsilon_{i2} - \varepsilon_{i1}$.

Therefore $E\left[\bar{d}_{BA}\right] = \phi + \tau$

Hence $E\left[\hat{\tau}\right] = E\left[\dfrac{\bar{d}_{BA} - \bar{d}_{AB}}{2}\right] = \tau - \dfrac{\gamma}{2}$

So the treatment effect is biased by $\gamma/2$.

[Book Work] [4 marks]

(ii) Let $a_i = y_{i2} + y_{i1}$ and $\bar{a}_{AB}$, μ_{AB}^{A}, $\bar{a}_{BA}$ and μ_{BA}^{A} be the sample and population means for sequences AB and BA respectively. Show that $E\left[\bar{a}_{AB} - \bar{a}_{BA}\right] = \gamma$.

Solution

For sequence AB

$$a_i = y_{i2} + y_{i1} = 2\mu + \phi + \tau + \nu + 2\xi_i + \varepsilon_{i2} + \varepsilon_{i1}$$

Therefore

$$E\left[\bar{a}_{AB}\right] = E\left[\frac{\sum_{i\in AB} a_i}{n_{AB}}\right] = \frac{\sum_{i\in AB} E\left[a_i\right]}{n_{AB}} = 2\mu + \phi + \tau + \gamma$$

For sequence BA

$$a_i = y_{i2} + y_{i1} = 2\mu + \phi + \tau + 2\xi_i + \varepsilon_{i2} + \varepsilon_{i1}$$

$$E\left[\bar{a}_{BA}\right] = E\left[\frac{\sum_{i\in BA} a_i}{n_{BA}}\right] = \frac{\sum_{i\in BA} E\left[a_i\right]}{n_{BA}} = 2\mu + \phi + \tau$$

Subtraction gives $E\left[\bar{a}_{AB} - \bar{a}_{BA}\right] = \gamma$ as required.

[4 marks]

(iii) Show that $Var\left[\bar{a}_{BA} - \bar{a}_{AB}\right] = \left(4\sigma_B^2 + 2\sigma_\varepsilon^2\right)\left(\frac{1}{n_{BA}} + \frac{1}{n_{AB}}\right)$

Solution

For either sequence

$$Var\left[a_i\right] = Var\left[2\xi_i + \varepsilon_{i2} + \varepsilon_{i1}\right] = 4Var\left[\xi_i\right] + Var\left[\varepsilon_{i1}\right] + Var\left[\varepsilon_{i2}\right] = 4\sigma_B^2 + 2\sigma_\varepsilon^2$$

Therefore $Var\left[\bar{a}_{AB}\right] = \frac{4\sigma_B^2 + 2\sigma_\varepsilon^2}{n_{AB}}$ and $Var\left[\bar{a}_{BA}\right] = \frac{4\sigma_B^2 + 2\sigma_\varepsilon^2}{n_{BA}}$.

Hence $Var\left[\bar{a}_{BA} - \bar{a}_{AB}\right] = Var\left[\bar{a}_{BA}\right] + Var\left[\bar{a}_{AB}\right] = \left(4\sigma_B^2 + 2\sigma_\varepsilon^2\right)\left(\frac{1}{n_{BA}} + \frac{1}{n_{AB}}\right)$, as required.

[4 marks]

(iv) The test statistic T_a, defined as $T_a = \frac{\bar{a}_{AB} - \bar{a}_{BA}}{\hat{SE}\left[\bar{a}_{AB} - \bar{a}_{BA}\right]}$, has been suggested as a test of the hypothesis H_0: $\gamma = 0$ vs H_1: $\gamma \neq 0$. What is the limitation of this as a test for carryover effect in a crossover trial?

Solution

The advantage of a crossover trial is that the between subject variance σ_B^2, which is generally larger than the within subject variance σ_ε^2, is removed from the test of the treatment effect. The weakness of the T_a test of carryover effect is that $\hat{SE}\left[\bar{a}_{AB} - \bar{a}_{BA}\right]$ includes the between subject variance σ_B^2. The statistical test T_a will therefore have low power in the circumstance when such a test might be used.

[2 marks]

(v) What are the implications of (iv) for the design of crossover trials?

Solution

The implication of this for the design of crossover trials is that they are usually only advisable in circumstance where the possibility of a carryover effect can be discounted for scientific reasons or by virtue of the design.

[2 marks]

(vi) How might one prevent a carryover effect in a randomised controlled crossover comparing two drug?

Solution

One way of preventing a carryover effect is to have a "washout period" between the two treatments to allow any residual effect of the first treatment to be eliminated before starting the second treatment.

[2 marks]

[Total marks 20]