A1.

(i) In the context of a randomised controlled trial, explain what is meant by the term *double-blind*.

Solution

This is method to reduce bias in a randomised controlled trial, where neither the study participant nor the experimenters knows which of two treatments the participant is receiving

[2 marks]

(ii) Describe two ways in which a trial being *double blind* might reduce bias?

Solution

Two reasons from: It is advantageous for a trial to be double blind as knowledge of treatment allocation may influence (i) the behaviour of the patient, (ii) the treating health professional or (iii) the assessor of outcome. (i) For example if the patient know which treatment they are receiving it may motivate them to default from treatment or seek alternative treatments. (ii) If the treating health professional know the allocation it may influence choice of secondary treatments. (iii) If the outcome assessor is aware of treatment, allocation there judgement may be bias. For example if may effect a patients self assessment if they know that they have received a placebo or standard treatment.

[2 marks]

(i) Give an example of treatment that cannot be evaluated in a *double-blind* clinical trial.

Solution

Surgery , talking and physical therapies

[1 mark]

[total mark 5]

A2.

A randomised controlled trial is being planned to compare a new treatment (T) and with a control treatment (C)**.** Suppose the primary outcome measure is the continuous and normally distributed. The power to demonstrate a treatment τ with a two-sided two sample t-test is given by the expression $1-\Phi\left(z_{\alpha/2}-\frac{\tau\sqrt{n}}{\sigma\sqrt{2}}\right)$ where σ is the known within treatment group standard deviation, n is the sample size of each of two equal size groups, and Φ is the cumulative density function of a standardised normal distribution.

Suppose one wishes to detect a treatment effect of 5 units and the within treatment group standard deviation has been estimated to be 15 units, estimate the power of a trial with 200 subjects in each treatment group assuming a 5% two-sided significance level.

Solution

$\tau = 5 \quad \sigma = 15 \quad z_{\alpha/2} = 1.96$

$$1-\Phi\left(z_{\alpha/2}-\frac{\tau\sqrt{n}}{\sigma\sqrt{2}}\right)=1-\Phi\left(1.96-\frac{5\sqrt{200}}{15\sqrt{2}}\right)=1-\Phi\left(1.96-\frac{10}{3}\right)=1-\Phi(-1.37)=\Phi(1.37)=0.9147$$

because $\Phi(-1.37)=1-\Phi(1.37)$.

The power of the study is 91.5%

[6 marks]

A3

A clinical researcher has carried out a randomised controlled trial to compare a new drug treatment (T) with a standard drug treatment (C) for patients with arthritis. A pain score has been recorded at baseline (**baseline**) and at follow-up (**followup**) on each patient with lower scores corresponding to improved outcome. The researcher carries out a separate paired t-test analyses for each treatment group generating the computer printed output listed below from the data

Results for group = NEW TREATMENT (T)

Paired t-test and CI: **baseline** – **followup**

	N	Mean	StDev	SE Mean
base	35	36.53	10.31	1.74
followup	35	32.31	12.68	2.14
difference	35	4.22	10.65	1.80

95% CI for mean difference: (0.56,7.87)
T-Test of mean difference = 0 (vs not = 0): T-Value= 2.34 P-value=0.0252

Results for group = STANDARD TREATMENT (C)

Paired t-test and CI: **baseline** – **followup**

	N	Mean	StDev	SE Mean
base	36	36.50	10.92	1.82
followup	36	34.01	11.45	1.91
difference	36	2.51	10.29	1.72

95% CI for mean difference: (-0.98,5.99)
T-Test of mean difference = 0 (vs not = 0): T-Value= 1.46 P-value=0.1530

Because there is a statistically significant change at the 5% level from baseline to follow-up in group T but not in group C, the researcher concludes that treatment T is more effective than treatment C in treating arthritis.

(i) Explain the flaw in the researcher's conclusion.

Solution

A test of within group change does not necessarily measure the effect of treatment. The statistically significant change observed for treatment T may not be due to drug treatment. The

change may have occurred because the condition naturally resolves and we have no way o knowing from these analysis whether the change for treatment T is significantly greater than that for C. A valid statistical analyses of the benefit of the new treatment needs to compare the effect of treatment T compared to the control treatment C. This would be tested by the hypothesis Ho:τ=0 where τ is a measure of the difference in outcome between treatment and control.
[5 marks]

(ii) Use the data from the computer printout to test whether there is a difference between the treatments in terms of the reduction in depression score (**followup - baseline**) stating any assumption you make .

Solution

A two-sample t-test could be carried out by comparing the mean differences for the two treatments. This assumes that

(i) patient outcomes are independent,

(ii) within patient differences are normally distributed, and

(iii) equal population standard deviation for the two treatment.

For a two sample t-test

$$T=\frac{\bar{d}_T-\bar{d}_C}{s.e.\left(\bar{d}_T-\bar{d}_C\right)} \textbf{ where } s.e.\left(\bar{d}_T-\bar{d}_C\right)=s\sqrt{1/n_T+1/n_C} \textbf{ and } s=\sqrt{\frac{\left(n_T-1\right).s_T^2+\left(n_C-1\right).s_C^2}{n_C+n_C-2}}$$

The relevant data can be summarized as follows.

	N	$\bar{d}$	s.d.
Treatment T	35	4.22	10.65
Treatment C	36	2.51	10.29

$$s=\sqrt{\frac{\left(n_T-1\right).s_T^2+\left(n_C-1\right).s_C^2}{n_C+n_C-2}}=10.469$$

$$s.e.\left(\bar{d}_T-\bar{d}_C\right)=s\sqrt{1/n_T+1/n_C}=2.486$$

$$T=\frac{\bar{d}_T-\bar{d}_C}{s.e.\left(\bar{d}_T-\bar{d}_C\right)}=\frac{\left(4.22-2.51\right)}{2.486}=0.687$$

For a 5% size test of H_0: δ=0 vs H_1: $\delta\neq0$, compare T with $t_{0.025}(45)$. From statistical table $t_{0.025}(69) \approx t_{0.025}(70)$ =1.99. Hence there is insufficient evidence to reject the null hypothesis of no treatment effect.

[6 Marks]

[Total mark 11]

A4.

(i) Tabulated below are summary data for binary outcome measure from a randomised controlled trial comparing a new treatment with a control treatment. Some patients randomised to the new treatment receive the control treatment, but no patients randomised to the control group receive the new treatment.

	Randomised group		
Recovered after 12 weeks	*New*		*Control*
	Received New	*Received Control*	
Yes	116	13	128
No	9	16	25
Total	125	29	153

Calculate the point estimates of the treatment effect of new treatment compared to control treatment measured by the proportion of patients who have recovered after 12 weeks for

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

(b) a *Per-Protocol* analysis.

Solution

(a) *Intention-To-Treat* treatment effect *=(116+13)/(125+29)-(128)/(153)= 0.838- 0.837=0.001*
(b) *Per-Protocol* treatment effect *=116/122-128/153= 0.928-0.837=0.091*

[4 marks]

(i) Drawing on the above example why an *Intention-To-Treat* analysis is preferable to *Per-protocol* 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* 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 effect is very small (0.1 %) where as the per-protocol effect is 8%. This is explained by the poor outcome in patients randomised to the new treatment but receiving the control with only 45% recovering. An *Intention-to-treat* analysis may also be thought

of as the pragmatic estimate as it estimates the effect of treatment taking account of non-compliance.

[4 marks]

[Total marks 8]

A5.

(i) Explain the difference between a *fixed effect* and a *random effect* meta-analysis.

Solution

The Fixed-Effect Analysis assumes that the studies all estimate the same overall effect of treatment say θ and that the departure of $\hat{\theta}_i$ from θ is due to sampling variation. *The Random-Effects Analysis* assumes that the studies are sampled from a larger population of studies and that θ_i is a random variable.

[3 marks]

(iv) In the context of meta-analysis, explain what is meant by the term *publication bias*.

Solution

Studies in which an intervention is not found to have a statistically significant effect are sometimes never published whereas studies that demonstrate an effect may be more likely to be published. This means that the published literature may be unrepresentative leading to bias in meta-analysis estimates of treatment effects

[3 marks]

(v) How might one investigate publication bias graphically?

Solution

Publication bias is more likely for small studies than large studies. One way of investigating whether publication bias is present is to construct a funnel plot in which the treatment effect of each study is plotted against the sample size. If there is no publication bias the plot will be symmetric about the line representing the overall treatment effect. If there is publication bias, the funnel plot will be asymmetric about this line with treatment effects in smaller studies tending to be larger than in bigger studies. Answer will probably give a sketch graph illustration.

[4 marks]

[Total mark 10]

B6. In a parallel group *equivalence* trial a new treatment *T* is being compared with a control treatment *C* on a continuous 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, and σ be the known common within-treatment group standard deviation of *Y*. Define the treatment effect $\tau = \mu_T - \mu_C$ to be estimated by $\bar{d} = \bar{y}_T - \bar{y}_C$. Define $\lambda = \sqrt{1/n_T + 1/n_C}$ where n_T and n_C are the sample sizes in each group. Suppose that the null hypothesis $H_0 : |\tau| \geq \tau_E$ is rejected if the (1-2α) confidence interval, given by $\bar{d} \pm z_\alpha \lambda\sigma$, is within the interval ($-\tau_E$, $+\tau_E$) .

(i) Show that

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

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

Solution

H_0 will be rejected provided $\bar{d} + z_\alpha\lambda\sigma \leq \tau_E$ and $\bar{d} - z_\alpha\lambda\sigma \geq -\tau_E$

Hence H_0 will be rejected $\bar{d} \leq \tau_E - z_\alpha\lambda\sigma$ and $\bar{d} \geq -\tau_E + z_\alpha\lambda\sigma$, which is equivalent to is in the range $[\tau_E - z_\alpha\lambda\sigma, -\tau_E + z_\alpha\lambda\sigma]$

$\Pr(\text{Reject } H_0|\tau) = \Pr\left(\bar{d} \leq \tau_E - \sigma\lambda t_\alpha\right) - \Pr\left(\bar{d} < -\tau_E + \sigma\lambda t_\alpha\right)$

The distribution of $\bar{d}/\sigma\lambda$ *is* non-central t-distribution. If we assume a normal approximation, $\bar{d}$ has a distribution N($\tau, \sigma^2\lambda^2$ and replace t_α with z_α.

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

[Book Work]

[5 marks]

(ii) Show that the sample size required in each treatment group to demonstrate equivalence with a power (1-β) is

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

Solution

$$\text{Using } \Pr(\text{Reject } H_0|\tau) = \Phi\left(\frac{(\tau_E - \sigma\lambda z_\alpha) - \tau}{\sigma\lambda}\right) - \Phi\left(\frac{(-\tau_E + \sigma\lambda z_\alpha) - \tau}{\sigma\lambda}\right)$$

Under the alternate hypothesis τ=0, so the power

$$1-\beta = \Phi\left(\tau_E/\sigma\lambda - z_\alpha\right) - \Phi\left(-\tau_E/\sigma\lambda + z_\alpha\right)$$

Since $\Phi\left(-\tau_E/\sigma\lambda + z_\alpha\right) = 1-\Phi\left(\tau_E/\sigma\lambda - z_\alpha\right)$ it follows that

$$1-\beta = 2\Phi\left(\tau_E/\sigma\lambda - z_\alpha\right) - 1.$$

Rearrangement gives

$$1-\beta/2 = \Phi\left(\tau_E/\sigma\lambda - z_\alpha\right).$$

Since $\Phi^{-1}\left(1-\beta/2\right) = z_{\beta/2}$, it follows that $z_{\beta/2} = \dfrac{\tau_E}{\sigma\lambda} - z_\alpha$.

Hence $\dfrac{\tau_E}{\sigma\lambda} = z_\alpha + z_{\beta/2}$

Assuming equal sample size $n_T = n_C = n$, then $\lambda = \sqrt{\dfrac{2}{n}}$.

Hence $\sqrt{\dfrac{n}{2}} = \dfrac{\sigma}{\tau_E}\left(z_\alpha + z_{\beta/2}\right)$.

Rearrangement gives

$$n = \frac{2\sigma^2}{\tau_E^2}\left(z_\alpha + z_{\beta/2}\right)^2 \text{ as required.}$$

[Book Work]

[8 marks]

(iii) Suppose the interval [-2,2] is to be used as the range of equivalence and the within treatment group standard deviation has been estimated to be 4 . Determine the sample size per group required to obtain 90% power.

Solution

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

Substitution with $\delta=2$ $\sigma=4$ and $\alpha=0.05$ $\beta=0.1$.
From table $z_\alpha = z_{0.05}=1.645$ and $z_{\beta/2} = z_{0.05}=1.645$

Substitution gives

$$n = \frac{2\sigma^2}{\tau_E^2}\left(z_\alpha + z_{\beta/2}\right)^2 = \frac{2\times 4^2}{2^2}\left(1.645+1.646\right)^2 = 86.59$$

Therefore the minimum sample size is 87 in each group.

[4 marks]

(iv) Explain why patient compliance to treatment is particularly important in an equivalence trial.

Solution

If patients do not comply with treatment or switch treatments in a clinical trial the outcome for the treatment groups will tend to closer together than if patients complied with treatment. In a

superiority trial this is a bias against rejecting the null hypothesis, whilst in an equivalence trial this is a bias towards the alternative hypothesis. Hence poor compliance in an equivalence trial can undermine the conclusion that two treatments have equivalent efficacy

[3 marks]
[total 20 marks]

B7

(i) (i) In a trial comparing a new treatment (T) with a control treatment (C) the outcome measure is binary. Suppose that the number of successes in each of the two treatment groups of size n_T and n_C are r_T and r_C with probability parameters π_T and π_C, respectively.

Consider the odds ratio defined as $\gamma = \frac{\pi_T(1-\pi_C)}{(1-\pi_T)\pi_C}$ estimated by $\hat{\gamma} = \frac{r_T(n_C - r_C)}{(n_T - r_T)r_C}$. Using the approximate relationship $Var\left[f(x)\right] \cong f'(x)^2_{x=E[x]} Var[x]$ show that the variance of the $\log_e$ of the odds ratio is $Var\left[\log_e \hat{\gamma}\right] \cong \frac{1}{n_T\pi_T} + \frac{1}{n_T(1-\pi_T)} + \frac{1}{n_C\pi_C} + \frac{1}{n_C(1-\pi_C)}$.

Hence, show that $Var\left[\log_e \hat{\gamma}\right]$ can be estimated by $\frac{1}{r_T} + \frac{1}{n_T - r_T} + \frac{1}{r_C} + \frac{1}{n_C - r_C}$.

Solution

$$\frac{d}{d\pi}\left(\ln\frac{\pi}{1-\pi}\right) = \frac{(1-\pi)}{\pi}.\frac{1}{(1-\pi)^2} \text{ and } Var(\pi) = \frac{\pi(1-\pi)}{n}.$$

Then using approximation,

$$Var\left(\ln\frac{\pi}{(1-\pi)}\right) \approx \left[\frac{d}{d\pi}\left(\ln\frac{\pi}{1-\pi}\right)\right]^2 Var(\pi) = \frac{1}{n\pi(1-\pi)} = \frac{1}{n\pi} + \frac{1}{n(1-\pi)}.$$

Hence
$$Var\left(\ln\left[\frac{\pi_T(1-\pi_C)}{(1-\pi_T)\pi_C}\right]\right) = Var\left(\ln\frac{\pi_T}{1-\pi_T}\right) + Var\left(\ln\frac{\pi_C}{1-\pi_C}\right)$$
$$= \frac{1}{n_T\pi_T} + \frac{1}{n_T(1-\pi_T)} + \frac{1}{n_C\pi_C} + \frac{1}{n_C(1-\pi_C)}$$

Replacing observed cell frequencies r_T, r_C, $n_T - r_T$ and $n_C - r_C$ for $n_T\pi_T$, $n_C\pi_C$, $n_T(1-\pi_T)$ and $n_C(1-\pi_C)$ gives $\frac{1}{r_T} + \frac{1}{n_T - r_T} + \frac{1}{r_C} + \frac{1}{n_C - r_C}$

[8 marks]

(ii) A randomised controlled trial is carried out to compare a new vaccine with a placebo for the prevention of pneumonia. At 12 months follow-up it is recorded whether pneumonia has occurred for each subject . The results are summarized in the table below broken by two age groups.

Age Group		65-74 years (A)		≥75 years (B)	
Treatment		Vaccine	Placebo	Vaccine	Placebo
Pneumonia	Yes	25	75	66	100
	No	5975	5925	3934	3900
n		6000	6000	4000	4000

Estimate the odds ratio of pneumonia infection for vaccine as compared to placebo for each age group.

Solution

Substituting the observed cell frequencies

$$\hat{\gamma}_A = \frac{r_{TA}\left(n_{CA} - r_{CA}\right)}{\left(n_{TA} - r_{TA}\right) r_{CA}} = \frac{25 \times 5952}{5975 \times 75} = 0.332$$

$$\hat{\gamma}_B = \frac{r_{TB}\left(n_{CB} - r_{CB}\right)}{\left(n_{TB} - r_{TB}\right) r_{CB}} = \frac{66 \times 3900}{3934 \times 100} = 0.654$$

[3 marks]

(iii) Test the hypothesis that H_0: $\gamma_A = \gamma_B$ vs H_1: $\gamma_A \neq \gamma_B$ where γ_A and γ_B are the odds ratios for vaccine as compared to placebo in the younger and older age groups respectively.

Solution

This can be tested using the test statistic

$$T_{AB} = \frac{\log_e \hat{\gamma}_A - \log_e \hat{\gamma}_B}{SE\left[\log_e \hat{\gamma}_A - \log_e \hat{\gamma}_B\right]} = \frac{\log_e \hat{\gamma}_A - \log_e \hat{\gamma}_B}{\sqrt{Var\left[\log_e \hat{\gamma}_A\right] + Var\left[\log_e \hat{\gamma}_B\right]}}$$

From (i) $\hat{Var}\left[\log_e \hat{\gamma}\right] = \frac{1}{r_T} + \frac{1}{n_T - r_T} + \frac{1}{r_C} + \frac{1}{n_C - r_C}$

$$T_{AB} = \frac{\log_e \hat{\gamma}_A - \log_e \hat{\gamma}_B}{\sqrt{\frac{1}{r_{TA}} + \frac{1}{n_{TA} - r_{TA}} + \frac{1}{r_{CA}} + \frac{1}{n_{CA} - r_{CA}} + \frac{1}{r_{TB}} + \frac{1}{n_{TB} - r_{TB}} + \frac{1}{r_{CB}} + \frac{1}{n_{CB} - r_{CB}}}}$$

$$= \frac{\log_e 0.332 - \log_e 0.654}{\sqrt{\frac{1}{25} + \frac{1}{5975} + \frac{1}{75} + \frac{1}{5925} + \frac{1}{66} + \frac{1}{3934} + \frac{1}{100} + \frac{1}{3900}}} = \frac{-0.678}{\sqrt{0.07910}} = \frac{-0.678}{0.2812} = -2.41$$

From normal distribution tables p= 0.015.
Hence we can reject the null hypothesis

[7 marks]

(iv) What do you conclude regarding the effectiveness of the vaccine in subjects over 75 years as compared to subjects between 65 and 74 years.

Solution

There is evidence that the vaccine is more effective in younger subjects than older subjects.

[2 marks]
[Total mark 20]

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

$y_{i1} = \mu + \delta + \xi_i + \varepsilon_{i1}$ 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,
$y_{i2} = \mu + \delta + \phi + \xi_i + \varepsilon_{i2}$ for a patient in sequence BA in period 2.

where μ is the mean for the sequence BA in period 1 , δ 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* and give an example of how the *carryover effect* might occur in a crossover trial.

Solution

The effect of 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 then this is the called the carryover effect. This might occur if one drug remains in the body for longer after completion of treatment than the other drug. [4 marks]

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

Solution

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

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

For sequence BA $d_i = y_{i2} - y_{i1} = \phi + \delta + \varepsilon_{i2} - \varepsilon_{i1}$

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

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

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

[Book Work]

[4 marks]

(iii) Let $a_i = y_{i2} + y_{i1}$ and $\bar{a}_{AB}, \mu^A_{AB}, \bar{a}_{BA}$ and μ^A_{BA} 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

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

Therefore

$$E\left[\bar{a}_{AB}\right] = E\left[2\mu + \phi + \delta + \gamma + 2\xi_i + \varepsilon_{i2} + \varepsilon_{i1}\right] = 2\mu + \phi + \delta + \gamma$$

For sequence BA

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

$$E\left[\bar{a}_{BA}\right] = E\left[2\mu + \phi + \delta + 2\xi_i + \varepsilon_{i2} + \varepsilon_{i1}\right] = 2\mu + \phi + \delta$$

Subtraction gives $E\left[\bar{a}_{AB} - \bar{a}_{BA}\right] = \gamma$ 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? 3 What are the implications of this for the design of crossover trials?

Solution

The advantage of a crossover trial is that the between subject variance σ^2_B, which is generally larger than the within subject variance σ^2_ε, 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^2_B. The statistical test T_a will therefore have low power in the circumstance when such a test might be used. [3 marks]

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.

[3 marks]

(v) How one might prevent a carryover effect in a randomised controlled crossover to compare two medications?

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]