A1.

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

[1 marks]

Solution

Concealment refers to practice of withholding details of the allocated treatment from the participants in a trial (patients, care providers , researchers or statistician) to prevent or reduce bias.

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

Solution

Knowledge of the next treatment allocation may influence

- patient's willingness to participate and
- clinician's determination to recruit into trial leading to sampling and allocation bias.

This may vary due to the characteristic or prognosis of the patient. It is important therefore that the next treatment allocation is concealed from the patient and clinician prior to the decision to join the trials as lack of concealment would therefore undermine randomisation.

[2 marks]

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

Solution

- If the patient knows which treatment they are on they may default from treatment and seek alternative treatments or they may modify their health related behaviour such as diet or lifestyle. Knowledge of treatment may influence the patient's self assessment of outcome particularly for subjective assessments.
- If the treating health professionals know the treatment allocation, they may change their expectation of treatment which might in turn influence the patient response. It may also influence choice of secondary treatments / concomitant.
- If the outcome assessor is aware of treatment, it may influence the measured outcome according to their prejudices. [3 marks]

[Total mark 6]

A2.

In a published report of a randomised trial a new pain relieving drug was compared with a standard drug. Twenty-five patients were allocated to each treatment. Outcome was assessed using a 100 mm visual analogue pain scale with lower scores representing less pain. The mean difference between the new treatment 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.

Solution

The study was underpowered as it failed to detect a clinically important effect of 5 mm reduction as being statistically significant with a 5 % significance level. A larger sample size would be needs for a confirmatory trial.

[2 marks]

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

Solution

The formula for a 95% confidence interval for the difference of two means is given by $\bar{y}_1 - \bar{y}_2 - t_{\alpha/2}(\nu)se(\bar{y}_1 - \bar{y}_2)$ to $\bar{y}_1 - \bar{y}_2 + t_{\alpha/2}(\nu)se(\bar{y}_1 - \bar{y}_2)$ where $s.e.(\bar{y}_1 - \bar{y}_2) = s\sqrt{1/n_1 + 1/n_2}$ and $\nu = n_1 + n_2 - 2$. Considering the difference between the point estimate and either the upper or lower confidence interval $t_{\alpha/2}(\nu)\, se(\bar{y}_1 - \bar{y}_2) = 12.8$. From tables $t_{0.025}(48) = 2.0106$.

Therefore $se(\bar{y}_1 - \bar{y}_2) = 12.8 / 2.0106 = 6.366$. Now

$s = s.e.(\bar{y}_1 - \bar{y}_2) / \sqrt{1/n_1 + 1/n_2} = 6.366 / \sqrt{1/25 + 1/25} = 6.366 \times 5/\sqrt{2} = 22.5$ as an estimate of σ.

[Calculation 4 mins]

[4 marks]

(i) 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 reduction in visual analogue pain scale with a two-sample t-test assuming a two-sided 5% significance level .

Solution

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

For 80% power (1-β)=0.8. giving z_{β}=0.842 τ=5mg/dl σ=22.5.

Therefore sample size per group, $n = \frac{2\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_{\beta}\right)^2 = \frac{2\times 22.5^2}{25}\left(1.960 + 0.842\right)^2 = 317.97$.

Hence the minimum sample size per group is 318

[Calculation 4 mins]

[4 marks]

(ii) 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 target sample size.

Solution

Total number of patients that needs to be randomised = 2 x 317.97/0.8=794.9

Total number that need to be screened =794.9/0.3=2649.666

Hence the number that need to be screened is around 2650.

[Calculation 1 mins]

[3 marks]

[Total mark 13]

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.

Solution

With two treatments, say A and B, one could choose a block size of 4. With this block size there are 6 possible blocks (1) AABB (2) ABAB (3) ABBA (4) BBAA (5) BABA (6) BAAB

To assemble a randomisation list for twenty subjects one would select 5 random numbers between 1- 6 with replacement in sequence, say the numbers 2, 6, 3, 1, 3 from which one could assemble the following list for the first 20 allocations

A,B,A,B/ B,A,A,B/ A,B,B,A/ A,A,B,B/ A,B,B,A

[4 marks]

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

Solution

Block randomisation can be used in conjunction with stratification to obtain balance in a categorical prognostic factor. Separate block randomisation lists are used for each prognostic stratum.

[2 marks]

[Total mark 6]

A4.

A randomised controlled 2-period AB-BA crossover trial compared two treatments to reduce joint inflammation in patients with arthritis. Twenty patients are randomly allocated to receive either A then B or B then A. The compute output below give analysis of joint inflammation score with high score 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 for treatment A compared to treatment B.

Solution

From the Period 1 output the treatment effect of A compared to B is -10.3 with 95% CI -24.6761 , 4.076101
[2 Marks]

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

Solution

The output gives the two-sample t-test of the differences. This estimates twice the treatment effect of B compared to A. Hence from the output, based of the crossover analysis, the treatment effect of A compared to B is therefore found by

-13.0/2 95% c.i. (-25.68311/2,-.3168945/2) which is

-6.5 with 95% c.i. (-12.84,-0.16)

[Calculation 2 mins]

[3 marks]

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

Solution

Within patient control means that variation between patients is removed in a crossover trial hence sample size may be substantially smaller as illustrated in the above example.

[2 marks]

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

Solution

Two from

- Only applicable to certain types of condition such as stable or chronic diseases. Unsuitable were the condition may resolve.
- More complicated to organize as patients need to be followed for longer and change treatment.
- If a patient withdraws from the trial during period 2, there will be no data for the second period and so the data from the first period cannot be included in the statistical analysis.

[4 marks]

[Total mark 11]

A5.

A randomised controlled trial compared cognitive behavioural therapy (CBT) with standard care (SC) for the treatment of psychosis. Fifty-three 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 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       BPRS
             |          (baseline) (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              Number of obs =      47
-------------+------------------------------           F(  4,    42) =    6.58
       Model |  1156.73783     4  289.184457           Prob > F      =  0.0003
    Residual |  1847.09196    42    43.97838           R-squared     =  0.3851
-------------+------------------------------           Adj R-squared =  0.3265
       Total |  3003.82979    46  65.3006475           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
------------------------------------------------------------------------------
```

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

Solution

At 12 months the mean BPRS for patients receiving CBT and Standard Care were respectively 19.9 and 22.7. There was evidence of a statistically significant treatment effect (p=0.025) with the estimate of the mean treatment effect of CBT as compared to standard Care equal to -4.7 with 95% confidence interval -8.8 to -0.6 after adjustment for baseline BPRS Age and gender.

[4 marks]

[Total mark 4]

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.

Solution

In order to demonstrate that an alternative hypothesis is true, we need to reject a null hypothesis that it is not true. Hence to demonstrate that a new treatment is not inferior, we need to define a null hypothesis that the treatment is inferior, that is $H_0 : \tau < 0$ that can be rejected in favour of an alternative that the treatment is non-inferior, that $H_1 : \tau \geq 0$

[2 marks]

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

Solution

To test whether a new treatment T is non-inferior to a control C one define a limit of non-inferiority $-\tau_N$ say, which can be the minimum clinical non-important difference between the treatment and the control. The hypothesis for testing non-inferiority are then

H_0: $\tau < -\tau_N$ vs H_1: $\tau \geq -\tau_N$

One method for investigating whether a new treatment is non-inferior to a standard treatment is to use a one-sided confidence interval. Where higher values correspond to improved outcome a (1-α) one-sided lower confidence interval for τ is used. If the lower one-sided confidence interval is above the limit of non-inferiority, $-\tau_N$, the null hypothesis is then rejected. It can be shown that if the null hypothesis is rejected according to this condition, the probability of a type 1 error is less than α.

[4 marks]

(iii) Assuming 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, $\lambda = \sqrt{1/n_T + 1/n_C}$, 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.

Solution

With $\tau = 0$ under the alternate hypothesis, substitution of $\tau = 0$ into

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

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

Since $1 - \Phi\left(-\tau_N/\sigma\lambda + z_\alpha\right) = \Phi\left(\tau_N/\sigma\lambda - z_\alpha\right)$,

it follows that $1-\beta = \Phi\left(\tau_N/\sigma\lambda - z_\alpha\right)$.

Since $\Phi^{-1}(1-\beta) = z_\beta$, it follows that $z_\beta = \tau_N/\sigma\lambda - z_\alpha$.

Therefore $\frac{\tau_N}{\sigma\lambda} = z_\alpha + z_\beta$

Assuming equal sample sizes n_T=n_C=n so that $\lambda = \sqrt{\frac{2}{n}}$

Substitution gives the $\sqrt{\frac{n}{2}} = \frac{\sigma}{\tau_N}\left(z_\alpha + z_\beta\right)$ leading to

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

[10 marks] [Bookwork]

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 to reject the null hypothesis that the new drug is inferior to the standard drug using a limit of non-inferiority of -3 units and α =0.05 assuming $\tau = 0$ under the alternative hypothesis.

(iv)

Solution

Using the formula $n = \frac{2\sigma^2}{\tau_N^2}\left(z_\alpha + z_\beta\right)^2$, σ=6 , τ_N=3

From tables $z_\beta = z_{0.1} = 1.282$ and $z_\alpha = z_{0.05} = 1.645$.

Hence $n = \frac{2\sigma^2}{\tau_N^2}\left(z_\alpha + z_\beta\right)^2 = \frac{2\times 36}{9}\left(1.645+1.282\right)^2 = 68.5$

Hence the minimum sample size required is 69 per group.

[4 mins]

[4 marks]

[Total mark 20]

B7.

Consider a randomized controlled trial. Suppose the patient population can be divided into three latent sub-groups as follows:

(i) *Compliers*: patients who will comply with the allocated treatment,

(ii) *Always control treatmen*t: patients who will receive control treatment regardless of allocation,

(iii)*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.

Solution

Table of expected means under assumptions of model

	Type	Control Group	New Treatment Group	Proportion In Latent Class
As Randomized	**A**	μ	$\mu + \tau$	$\theta_A = 1-\theta_B - \theta_C$
Always Control	**B**	$\mu+\gamma_B$	$\mu+\gamma_B$	θ_B
Always New Treatment	**C**	$\mu+\gamma_C+\tau$	$\mu+\gamma_C+\tau$	θ_C

τ is the causal effect of treatment

For Intention-to-Treat Estimate

$$\tau_{ITT} = \left[\theta_A(\mu+\tau)+\theta_B(\mu+\gamma_B)+\theta_C(\mu+\gamma_C+\tau)\right]-\left[\theta_A\mu+\theta_B(\mu+\gamma_B)+\theta_C(\mu+\gamma_C+\tau)\right]$$
$$= \theta_A\tau$$

as second and third terms in each bracket cancel.

Hence $\left|\hat{\tau}_{ITT}\right| \le \tau$ which means $\hat{\tau}_{ITT}$ is biased towards zero if $\theta_A < 1$ i.e. if some patients do not comply with treatment.

[5 Marks] [Bookwork]

(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.

Solution

For the Per-Protocol Estimate

$$\tau_{pp} = \left[\frac{\theta_A(\mu+\tau)+\theta_C(\mu+\gamma_C+\tau)}{\theta_A+\theta_C}\right]-\left[\frac{\theta_A\mu+\theta_B\mu+\gamma_B}{\theta_A+\theta_B}\right]$$

$$= \left[\frac{(\theta_A + \theta_C)\mu + \theta_C\gamma_C + (\theta_A + \theta_C)\tau}{\theta_A + \theta_C} \right] - \left[\frac{(\theta_A + \theta_B)\mu + \theta_B\gamma_B}{\theta_A + \theta_B} \right]$$

$$= \tau + \mu + \left[\frac{\theta_C\gamma_C}{\theta_A + \theta_C} \right] - \mu - \left[\frac{\theta_B\gamma_B}{\theta_A + \theta_B} \right]$$

$$= \tau + \left[\frac{\theta_C\gamma_C}{1 - \theta_B - \theta_C + \theta_C} \right] - \mu - \left[\frac{\theta_B\gamma_B}{1 - \theta_B - \theta_C + \theta_B} \right]$$

$$= \tau + \left[\frac{\theta_C\gamma_C}{1 - \theta_B} \right] - \left[\frac{\theta_B\gamma_B}{1 - \theta_C} \right]$$

τ_{PP} is biased by a term involving γ_B and γ_C. Since γ_B and γ_C can be either positive or negative $\hat{\tau}_{PP}$ may be biased either towards or away from zero.

[5 Marks] [Bookwork]

(iii) Tabulated below are summary data from 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 group			
Recovered after 6 weeks	*New Treatment*		*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 assuming

(a) *Intention-To-Treat* and (b) *Per-Protocol*.

Solution

(a) Intention-To-Treat = 144/200 – 136/200= 0.72 - 0.68 = 0.04

(b) *Per-Protocol* = 120/160-120/180=0.75 - 0.667 = 0.083

[2 mins]

[2 marks]

(iv) Briefly explain why an *Intention-To-Treat* analysis is usually preferable to a *Per-protocol* analysis in a superiority trial.

Solution

As we have seen in (i) an intention-to-treat analyses will bias an estimate of the treatment effect towards the estimate of no effect. This means that any effect will be bias towards the null hypothesis of a superiority trial. Hence if we reject the null hypothesis using an intention-to-treat

analysis, we can be more confident that the true treatment effect is at least as large as that observed. In contrast a per-protocol analyses may bias the estimate of the treatment effect either away or towards the null hypothesis of no effect as seen in (ii)

[2 marks]

(v) What are the implications of this for the conduct of randomised controlled trials.

Solution

If statistical analyses of a randomized clinical trial are to be based on intention-to-treat, we need outcome data on all patients. The implications of this are that researchers running trials should endeavour to get outcome data on all patients, irrespective of whether they receive the treatment to which they are randomized.

[3 marks]

(vi) Calculate the point estimates of the C*ompliance Average Causal Effect* of *New* treatment compared to *Control* treatment.

Solution

From above $\tau_{ITT} = \theta_A \tau$ where θ_A is the proportion of subjects that accept randomised treatment and τ is the causal effect of treatment or the C*ompliance Average Causal Effect* . $\theta_A = 1-\theta_B - \theta_C$ where θ_B is the proportion of patients that will always receive and the control θ_C the proportion who will always receive the newactive treatment.

θ_B can be estimated from the new treatment arm and θ_C always the control arm.

Hence θ_A =1-20/200 -40/200=0.7

Hence the C*ompliance Average Causal Effect* of *New* treatment compared to *Control* treatment,
τ=0.04/0.7=0.057

[3 marks]

[Total mark 20]

B8.

(i) In a trial n_T patients are randomised to a new treatment (T) and n_C to the control treatment (C). 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, respectively.

Consider the rate ratio 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 confidence interval for the rate ratio is given by the values of

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

[10 marks]

Solution

$$Var\left[\log_e \left[\hat{RR} \right] \right] = Var\left[\log_e \left[\frac{\pi_T}{\pi_C} \right] \right]$$

$$= Var\left[\log_e [\pi_T] - \log_e [\pi_C] \right]$$

$$= Var\left[\log_e [\pi_T] \right] + Var\left[\log_e [\pi_C] \right] (*)$$

because treatment groups are independent.

Approximate standard errors can be calculated using the *Delta Methods*, which is based on a Taylor Series approximation. This states that

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

Considering $f(\pi_T) = \log_e [\pi_T]$, $f'(\pi) = \frac{1}{\pi_T}$.

Since $Var[\pi_T] = \frac{\pi_T (1-\pi_T)}{n}$,

$$Var\left[\log_e [\pi_T] \right] = \left(\frac{1}{\pi_T} \right)^2 \frac{\pi_T (1-\pi_T)}{n_T} = \frac{(1-\pi_T)}{n_T \pi_T} = \frac{1}{n_T \pi_T} - \frac{1}{n_T}.$$

Similar

$$Var\left[\log_e [\pi_C] \right] = \left(\frac{1}{n_C \pi_C} - \frac{1}{n_C} \right)$$

Substitution in the equation (*) above give $Var\left[\log_e [RR] \right] = \frac{1}{n_T \pi_T} - \frac{1}{n_T} + \frac{1}{n_C \pi_C} - \frac{1}{n_C}$

Substitution with observed frequencies

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

Confidence interval for $\log_e\left[RR\right]$ is given by

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

Hence the confidence interval for the rate ratio is given by the values of

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

[10 marks] [Bookwork]

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.

Solution

For trial A $\hat{SE}\left[\log_e\left[\hat{RR}\right]\right]=\sqrt{\frac{1}{50}-\frac{1}{5000}+\frac{1}{100}-\frac{1}{5000}}=0.172$

Confidence interval given by the values of $\exp\left[\log_e\left[0.5\right]\pm 1.96\times 0.172\right]$ i.e.0.357 to 0.700

For trial A $\hat{SE}\left[\log_e\left[\hat{RR}\right]\right]=\sqrt{\frac{1}{35}-\frac{1}{3000}+\frac{1}{50}-\frac{1}{3000}}=0.229$

Confidence interval given by the values of $\exp\left[\log_e\left[0.7\right]\pm 1.96\times 0.219\right]$ i.e 0.456 to 1.075

[5 marks]

(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 *Control* vaccine.

Solution

For A $w_A = 1/Var\left[\hat{RR}_A\right]$=1/0.172^2=33.80, $\log_e\left(\hat{RR}_A\right) = -0.693$

For B $w_B = 1/Var\left[\hat{RR}_B\right]$=1/0.219^2=20.85, $\log_e\left(\hat{RR}_B\right) = -0.357$

Hence pooled log(rate ratio) = $= \dfrac{\sum_i w_i \log_e\left(\hat{RR}_i\right)}{\sum_i w_i}$

$$= \frac{w_A \log_e\left(\hat{RR}_A\right) + w_B \log_e\left(\hat{RR}_B\right)}{w_A + w_B}$$

$$= \frac{33.80 \times (-0.693) + 20.85 \times (-0.357)}{33.80 + 20.85}$$

=-0.564

Hence pooled rate ratio equal = exp(-0.564)=0.568

[5 marks]

[Total mark 20]