EXAMINATION PAPER SOLUTION

Statistical tables are attached

Two Hours

UNIVERSITY OF MANCHESTER

Medical Statistics MATH38071

Electronic calculators may be used provided that they cannot store text/transmit or receive information/display graphics

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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 for the paper is 80.

A1.

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

Solution

Concealment refers to the 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.

[1 marks]

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

Solution

Knowledge of the next treatment allocation may influence

a) patient's willingness to join a trial and

b) clinician's determination to recruit a particular patient into trial

both of which may vary according to the characteristic or prognosis of the patient. Knowledge of the next treatment prior to randomisation could therefore lead to the recruitment of patients with different characteristics into each arm of the trial thereby leading to either sampling or allocation bias.

[2 marks]

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

Solution

Two from

a) If the patient knows which treatment they are receiving, they may default from treatment and seek alternatives or they may modify their health related behaviour such as diet or lifestyle. This could cause performance or follow-up bias.

b) If the treating health professionals know the treatment allocation, they may change their expectation of treatment, which might in turn influence the patient's response. It may also influence their choice of additional treatments and care for the patient. This would cause performance bias.

c) If the outcome assessor is aware of treatment allocation, their opinion regarding either treatment could influence the recorded outcome leading to assessment bias.

[3 marks]

[Book work]

[Total mark 6]

A2.

A clinical trial compared a *New* cream to a *Placebo* cream for the treatment of athlete's foot. Using randomisation 78 patients are allocated to the *New* cream and 80 to the *Placebo*. Patients are assessed at the end of the two week treatment period. The infection was eradicated for 58 patients in the *New* cream group and 46 patients in the *Placebo* cream group.

(i) Calculate the point estimate of the difference in the eradication rate of the *New* and *Placebo* treatments.

Solution

The data can be tabulated as follows

	New (T)	Placebo (C)	Total
Success	58(74%)	46 (58%)	104
Failure	20	34	54
Total	78	80	158

The point estimate of the difference in the eradication rates is

$p_T - p_C = 58/78 - 46/80 = \underline{0.1685897}$.

[2 minutes calculation time]

[2 marks]

(ii) Calculate the approximate 95% confidence interval of the difference in the eradication rate of the *New* and *Placebo* treatments, checking the normality assumption.

Solution

Assuming a normal approximation a $(1-\alpha)$ confidence interval can be estimated using

$$p_T - p_C \pm z_{\alpha/2} SE\left[p_T - p_C\right].$$

For the normal approximation to the binomial distribution to be justified we need to check that

$n_T p, n_T(1-p), n_C p$ and $n_C(1-p)$ are all greater than 5 where $p = \dfrac{r_T + r_C}{n_T + n_C}$.

$Min\left[n_T p, n_T(1-p), n_C p, n_C(1-p)\right] = n_T(1-p) = 78 \times \dfrac{54}{158} = 26.7$ so the normal approximation is justified.

The standard error for the difference between two proportions is

$$SE\left[p_T - p_C\right] = \sqrt{\frac{p_T(1-p_T)}{n_T} + \frac{p_C(1-p_T)}{n_C}} = 0.0741559$$

For a 95% confidence interval use $z_{0.025} = 1.96$. Hence the 95% c.i. is

$$p_T - p_C \pm z_{0.025} SE\left[p_T - p_C\right] = 0.1685897 \pm 1.96 \times 0.0741559$$

The 95% confidence interval is <u>0.0232468</u> to <u>0.3139326.</u>

[5 minutes calculation time]

[5 marks]

(iii) Calculate the *Numbers Needed to be Treated* (*NNT*) for one additional eradication and its 95% confidence interval.

Solution

NNT is determined by taking the reciprocal of the rate difference, that is $NNT = 1/(p_T - p_C)$. For this data

$$NNT = \frac{1}{0.1685897} = 5.93$$

Similarly, the 95% confidence limits of *NNT* are 1/ 0.3139326 to 1/0.0232468.

Hence, the *NTT* is 5.93 (95% c.i. 3.18 to 43.02).

[2 minutes calculation time]

[3 marks]

[Total mark 10]

A3.

In a trial comparing Acupuncture (A) with Homeopathy (H) for patient suffering from chronic headache, patients are allocated to treatment using deterministic minimization controlling for sex and type of head ache (migraine, tension). The numbers of patients with each characteristic for each treatment are given in the table below after eight-nine patients have entered the trial.

Patient Characteristic	Male		Female		Migraine		Tension	
Treatment	(A)	(H)	(A)	(H)	(A)	(H)	(A)	(H)
Number of Patients	19	16	26	28	28	27	17	17

(i) How many patients have been allocated to each treatment?

[1 marks]

Solution

This is the total of patients receiving a treatment for a factor. 45 patients have received Acupuncture and 44 patients have received Homeopathy.

(ii) The characteristics of the next two patients entering the trial are (Male, Migraine) followed by (Female, Migraine) . Determine the treatment allocation of each patient.

Solution

Table with updated totals

		Male		Female		Migraine		Tension		Total		Alloc. Treat.
		(A)	(H)	(A)	(H)	(A)	(H)	(A)	(H)	(A)	(H)	
89		19	16	26	28	28	27	17	17			
90	Male, Migraine	19	**17**	26	28	18	**18**	27	27	19+28 =47	16+27 =43	(H)

91	Female, Migraine	19	17	**27**	28	**29**	28	17	18	26+28 =54	28+28 =56	(A)

90^{th} patient allocated Homeopathy ,

91^{st} patient allocated Acupuncture.

[3 minutes calculation time]

[4 marks]

[Total mark 5]

A4.

A clinical researcher has carried out a randomised controlled trial to compare a new drug treatment (*N*) with the standard drug treatment (*S*) for patients with arthritis. A symptom score has been recorded at baseline (*baseline*) and at follow-up (*followup*) on each patient, with lower scores corresponding to improved outcome. This symptom score is also continuous and normally distributed. Twenty-six patients have been randomised to the new treatment (*N*) and 24 to the standard treatment (*S*) . Using the trial data, the researcher has carried out a separate paired t-test analyses for each treatment group. The statistical output obtained using the statistical package STATA is given below.

Results for group = NEW TREATMENT (*N*)

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
baseline |      26     55.5602    1.902873    9.702787    51.64116    59.47924
followup |      26     49.8264    1.713542    8.737387     46.2973    53.35551
---------+--------------------------------------------------------------------
    diff |      26    5.733795    1.931726     9.84991     1.75533     9.71226
------------------------------------------------------------------------------
     mean(diff) = mean(baseline - followup)                        t =   2.9682
 Ho: mean(diff) = 0                              degrees of freedom =       25

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9967         Pr(|T| > |t|) = 0.0065          Pr(T > t) = 0.0033
```

Results for group = STANDARD TREATMENT (*S*)

```
Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
baseline |      24    56.53192    2.157341    10.56877    52.06912    60.99472
followup |      24    52.85044    2.084191    10.21041    48.53896    57.16191
---------+--------------------------------------------------------------------
    diff |      24    3.681484    3.086131    15.11889   -2.702664    10.06563
------------------------------------------------------------------------------
     mean(diff) = mean(baseline - followup)                        t =   1.1929
 Ho: mean(diff) = 0                              degrees of freedom =       23

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8775         Pr(|T| > |t|) = 0.2451          Pr(T > t) = 0.1225
```

Because there is a statistically significant change at the 5% level from baseline to follow-up in the new treatment group (*N*) but not in standard group (*S*), the researcher concludes that the new treatment (*N*) is significantly more effective than the standard treatment for treating the symptoms of arthritis.

(i) What are the flaws in the researcher's conclusion?

Solution

A patient's symptoms may change irrespective of treatment so the statistically significant change observed for treatment *N* may not be due to drug treatment. The change may have occurred because the condition naturally resolved in those patients.

Comparison of p-values of two separate hypothesis test is not a hypothesis test, so we have no way of knowing from these analysis whether the change for treatment *N* is significantly different from that for *S*.

Differences in p-values could relate to differences in sample size or differences in variance rather than differences in the means of the two groups

[4 marks]

(ii) Three other methods of analysis have been suggested to the researcher to test for a treatment effect:

a) Use a two-sample t-test with just the follow-up symptom scores.

b) Calculate the change score, defined as (*followup)* – (*baseline)*, for each patient and then use a two-sample t-test with the change scores.

c) Fit a linear model with follow-up symptom score as the dependent variable and baseline symptom score and a treatment indicator variable as covariates.

Assuming the statistical assumptions of all methods are satisfied, which of these three methods would you recommend to the researcher and why?

Solution

The expectation of all three estimates of the treatment effect are the same due to randomisation. The linear model analysis is preferable as it give the estimate of the treatment effect with smallest expected variance. A smaller variance is beneficial as a treatment effect estimate having smaller variance will give the trial greater power. Therefore, I would recommend the analysis based on the linear model.

[3 marks]

(iii) The researcher suggests carrying out all three statistical analyses on their data. What would you advise and why?

Solution

I would advise the researcher against doing all three analyses as this has the potential to cause analysis bias and might also cause confusion if the test results are contradictory.

[2 marks]

[Reading time 3 minutes]

[Total mark 9]

A5.

(i) Outline the statistical analysis one could use in a parallel group trial to establish whether a new treatment is equivalent to a control treatment for a continuous normally distributed outcome measure *Y*.

Solution

Rather than using a formal significance test, statistical analysis of equivalence trials is often based on the confidence interval of the difference between treatments. Equivalence is established by demonstrating that the confidence interval of the difference lies in a pre-specified interval, say $(-\tau_E, \tau_E)$, called the range of equivalence. Rejection of the null hypothesis that $H_0 : |\tau| \geq \tau_E$ against the alternative hypothesis $H_1 : |\tau| < \tau_E$ where the $(1-2\alpha)$ confidence interval is within the interval $(-\tau_E, \tau_E)$ has a type I error of α or less.

[4 marks]

(ii) A randomised controlled trial is carried out to test whether a *New* generic drug (*N*) is equivalent in effect to current *Standard* drug (*S*) for reducing pain. At follow-up this is measured by a 100 mm analogue scale with higher scores representing greater pain. Eighty-nine patients are randomised to the *New* drug and eighty-eight to the *Standard* drug. The statistical output of the trial is given below. A difference of 5mm has been recommended as the maximum difference between treatments that is not clinically important. Using the statistical output below, test whether the *New* drug (*N*) is equivalent to the current *Standard* drug (*S*) using a 5% significance level.

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
New      |      89        42.3    1.918596        18.1    38.48719    46.11281
Standard |      88        42.2    2.014747        18.9    38.19547    46.20453
---------+--------------------------------------------------------------------
    diff |                 0.1    2.781441               -5.389487    5.589487
------------------------------------------------------------------------------
    diff = mean(New) - mean(Standard)                             t =   0.0360
Ho: diff = 0                                     degrees of freedom =      175

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.5143         Pr(|T| > |t|) = 0.9714          Pr(T > t) = 0.4857
```

Solution

[Reading time 1 minutes]

The statistical output gives a 95% confidence interval appropriate for a 2.5% level test. For a 5% level test of equivalence we need the 90% confidence interval. A (1-α)-size confidence interval for the treatment effect is defined by

$$\left(\bar{y}_N - \bar{y}_S\right) \pm t_{\alpha/2}\left(n_T + n_S - 2\right)\hat{SE}\left[\bar{y}_N - \bar{y}_S\right].$$

From the printout

$\bar{y}_N - \bar{y}_S = 0.1$, $\hat{SE}\left[\bar{y}_N - \bar{y}_S\right] = 2.78$ and $\alpha = 0.1$.

From tables $t_{\alpha/2}\left(n_T + n_S - 2\right) = t_{0.05}\left(175\right) = 1.6536$

The 90% Confidence interval is $0.1 \pm 1.6536 \times 2.7814$ giving -4.50 to 4.70 .

The question suggests that a 5mm difference on the visual analogue scale was considered to be the maximum difference between treatments that is not clinically important. Therefore the interval $\left(-5,5\right)$ should be used as the range of equivalence. The 90% confidence interval is $\left(-4.50, 4.70\right)$ which is inside the range of equivalence. It is therefore possible to accept the hypothesis that the treatments are equivalent at a 5%significance level .

[3 minutes calculation time]

[6 marks]

[Total marks 10]

B1.

(i) Consider a randomised controlled trial comparing a new treatment (T) with a control treatment (C) with a binary outcome measure. Suppose that n_T and n_C are the sample size of each treatment and that π_T and π_C are the population proportions of a successful outcome. Using standard notation the power $(1-\beta)$ of a two-sample z-test of proportions to detect a treatment effect $\tau = \pi_T - \pi_C$ can be approximated by

$$1-\Phi\left(z_{\alpha/2} - \frac{\tau}{\lambda\sqrt{\pi(1-\pi)}} \right)$$

where $\pi = \frac{n_T.\pi_T + n_C.\pi_C}{n_T + n_C}$ and $\lambda = \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}$. Assuming two equal size groups, show that the sample size required in each group to give a power (1-β) for a two-sided test with significance level α is approximately $n = \frac{2\pi(1-\pi)\left(z_{\alpha/2} + z_\beta\right)^2}{\tau^2}$.

Solution

Using the approximation given

$$\beta = \Phi\left(z_{\alpha/2} - \frac{\tau}{\lambda\sqrt{\pi(1-\pi)}} \right).$$

Taking inverses

$$\Phi^{-1}(\beta) = z_{\alpha/2} - \frac{\tau}{\lambda\sqrt{\pi(1-\pi)}}.$$

Since $\Phi^{-1}(\beta) = -z_\beta$, it follows that $z_\beta + z_{\alpha/2} = \frac{\tau}{\lambda\sqrt{\pi(1-\pi)}}$.

Since groups are of equal size, $\lambda = \sqrt{\frac{2}{n}}$.

Therefore $z_\beta + z_{\alpha/2} = \frac{\tau\sqrt{n}}{\sqrt{2\pi(1-\pi)}}$.

Hence $\left(z_\beta + z_{\alpha/2}\right)\frac{\sqrt{2\pi(1-\pi)}}{\tau} = \sqrt{n}$.

Squaring gives $n = \frac{2\pi(1-\pi)\left(z_{\alpha/2} + z_\beta\right)^2}{\tau^2}$ as required.

[7 Marks]

(ii) For any given τ with $0 < |\tau| < 1$, find the value of π that gives the maximum value of n.

Solution

Maximum of n found by differentiation of $n = \frac{2\pi(1-\pi)\left(z_{\alpha/2} + z_{\beta}\right)^2}{\tau^2}$ w.r.t π.

$$\frac{dn}{d\pi} = \frac{2(1-2\pi)\left(z_{\alpha/2} + z_{\beta}\right)^2}{\tau^2}.$$

This equals zero when $\pi = 0.5$.

$$\frac{d^2}{d\pi^2} n = \frac{-2\left(z_{\alpha/2} + z_{\beta}\right)^2}{\tau^2}$$

Hence, $\pi = 0.5$ gives the maximum of n.

[4 Marks]

(iii) In what circumstance might one apply this result when designing a randomised controlled trial?

Solution

The result might be useful if one was designing a trial with a binary outcome measure but had no idea of the rates for each treatment. If one knew how large a treatment effect $\tau = \pi_T - \pi_C$ one wished to detect, one could apply the above formula for sample size with $\pi = 0.5$ and choice of τ knowing that this is an upper limit of the minimum sample size required to achieve the desired power.

[3 Marks]

(iv) A randomized controlled trial is planned to compare a new antibiotic treatment (*T*) with the current standard control therapy (*C*) for patients with a chronic respiratory infection. At 6 months follow-up it is recorded whether the patient has recovered. The researcher knows that π_C is not greater than 30% and wishes to detect a 10% increase in the recovery rate with a two-sided 5% significance level. It is anticipated that 20% of patients randomised will be lost to follow-up. Assuming π_C does not exceed 30%, what is the minimum number of patients that would need to be randomised to be certain of having 90% power?

Solution

From tables $z_{\alpha/2} = z_{0.025} = 1.960$, $z_{\beta} = z_{0.1} = 1.282$. The maximum of n occurs when $\pi = 0.5$.

The sample size *n* will therefore be monotone increasing for π_C for $\pi_C \le 0.3$ where $\pi_C < \pi_T$.

Hence maximum will occur when $\pi_C = 0.3$. Therefore $\pi = \frac{\pi_C + \pi_T}{2} = \frac{0.3 + (0.3 + 0.1)}{2} = 0.35$

Hence

$$n_{\max} = \frac{2\pi(1-\pi)\left(z_{\alpha/2} + z_{\beta}\right)^2}{\tau^2} = \frac{2 \times 0.35 \times 0.65 \times (1.960 + 1.282)^2}{0.01} = 478.23.$$

This is the number of subjects that need to be followed up per group.

Minimum sample size of subjects that need to be randomised $= \frac{2n_{\max}}{0.8} = \frac{956.46}{0.8} = 1195.5$

To be certain of having 90% power to detect a 10% difference is 1196 subjects need to be randomised.

[4 minutes calculation time]

[4 marks]

(v) Give two reasons why it is important to estimate sample size in a clinical trial.

Solution

a) If the sample size is too small, the trial may lack power to detect a treatment effect that is clinical important.

b) If more patients than the minimum to answer the question are recruited, some patients may be exposed unnecessarily to an inferior treatment.

[2 marks]

[Total 20 Marks]

B2.

For an *AB*/*BA* crossover trial a standard model for a continuous outcome y_{ij} for the i^{th} patient in the j^{th} period is

$y_{i1} = \mu + \tau + \xi_i + \varepsilon_{i1}$ 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, and ϕ is the period effect, with ξ_i and ε_{ij} being two independent random variables with $\xi_i \sim N\left[0, \sigma_B^2\right]$ and $\varepsilon_{ij} \sim N\left[0, \sigma_\varepsilon^2\right]$. Defining $d_i = y_{i2} - y_{i1}$, let $\bar{d}_{AB}$ and $\bar{d}_{BA}$ be the sample means of d_i for sequences *AB* and *BA* respectively.

(i) Under this data generating model, show that $\hat{\tau}_C = \frac{\bar{d}_{BA} - \bar{d}_{AB}}{2}$ is an unbiased estimator of the treatment effect, τ.

Solution

For sequence *AB*

$E\left[d_i\right] = E\left[y_{i2} - y_{i2}\right] = E\left[\left(\mu + \phi + \xi_i + \varepsilon_{i2}\right) - \left(\mu + \tau + \xi_i + \varepsilon_{i1}\right)\right] = \phi - \tau$ since $E\left[\xi_i\right] = E\left[\varepsilon_{ij}\right] = 0$

Hence

$$E\left[\bar{d}_{AB}\right]=E\left[\frac{\sum_{i=1}^{n_{AB}}d_i}{n_{AB}}\right]=\frac{\sum_{i=1}^{n_{AB}}E\left[d_i\right]}{n_{AB}}=\tau-\phi$$

Similarly for sequence *BA*

$$E\left[d_i\right]=E\left[y_{i2}-y_{i1}\right]=E\left[\left(\mu+\phi+\tau+\xi_i+\varepsilon_{i2}\right)-\left(\mu+\xi_i+\varepsilon_{i1}\right)\right]=\phi+\tau\,.$$

$$E\left[\bar{d}_{BA}\right]=E\left[\frac{\sum_{i=1}^{n_{BA}}d_i}{n_{BA}}\right]=\frac{\sum_{i=1}^{n_{BA}}E\left[d_i\right]}{n_{BA}}=\phi+\tau\,.$$

Hence

$$E\left[\hat{\tau}_C\right]=E\left[\frac{\bar{d}_{BA}-\bar{d}_{AB}}{2}\right]=\frac{\left(\tau+\phi\right)-\left(\phi+\tau\right)}{2}=\tau\,.$$

[Book Work]

[3 marks]

(ii) Using standard notation the total sample size required to detect a treatment effect δ using a two sample t-test with two equal size groups, power $\left(1-\beta\right)$ and a two-sided significance level α is given by the formula $\frac{4\sigma^2}{\delta^2}\left(z_{\alpha/2}+z_\beta\right)^2$. Show that the total sample size for a cross-over trial to detect a treatment effect τ using a two sample t-test with equal numbers in each sequence, power $\left(1-\beta\right)$ and a two-sided significance level α is $N_C=\frac{2\sigma_\varepsilon^2}{\tau^2}\left(z_{\alpha/2}+z_\beta\right)^2$.

Solution

Total sample size is $\frac{4\sigma^2}{\delta^2}\left(z_{\alpha/2}+z_\beta\right)^2$.

For sequence *AB*

$Var\left[d_i\right]=Var\left[\left(\mu+\phi+\xi_i+\varepsilon_{i2}\right)-\left(\mu+\tau+\xi_i+\varepsilon_{i1}\right)\right]=Var\left[\varepsilon_{i2}-\varepsilon_{i1}\right]=Var\left[\varepsilon_{i1}\right]+Var\left[\varepsilon_{i2}\right]=2\sigma_\varepsilon^2$ as $\mathrm{cov}\left[\varepsilon_{i1},\varepsilon_{i2}\right]=0$. Similarly for sequence *BA* $Var\left[d_i\right]=2\sigma_\varepsilon^2$.

Since $\bar{d}_{BA}-\bar{d}_{AB}$ estimates 2τ, we replace δ with 2τ and σ^2 with $2\sigma_\varepsilon^2$ in the above formula giving

$$N_C=\frac{4\times2\sigma_\varepsilon^2}{4\tau^2}\left(z_{\alpha/2}+z_\beta\right)^2=\frac{2\sigma_\varepsilon^2}{\tau^2}\left(z_{\alpha/2}+z_\beta\right)^2 \text{ as required.}$$

[Book Work]

[3 marks]

(iii) Show that the total sample size for a parallel group trial based on first period of the trial is

$$N_P = \frac{4\left(\sigma_B^2 + \sigma_\varepsilon^2\right)}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2.$$

Solution

$Var\left[y_{i1}\right] = Var\left[\mu + \tau + \xi_i + \varepsilon_{i1}\right] = Var\left[\xi_i + \varepsilon_{i1}\right] = \sigma_B^2 + \sigma_\varepsilon^2$ as $\text{cov}\left[\xi_i, \varepsilon_{i1}\right] = 0$. We can replace σ^2 with $\sigma_B^2 + \sigma_\varepsilon^2$ and δ with τ in $\frac{4\sigma^2}{\delta^2}\left(z_{\alpha/2} + z_\beta\right)^2$. Therefore $N_P = \frac{4\left(\sigma_B^2 + \sigma_\varepsilon^2\right)}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$

[3 marks]

(iv) The relative efficiency of a crossover design compared to a parallel group design can be defined as $RE = \frac{N_P}{N_C}$. Show that $RE = 2\left(1 + \frac{\sigma_B^2}{\sigma_\varepsilon^2}\right)$.

Solution

$$RE = \frac{N_P}{N_C} = \frac{\frac{4\left(\sigma_B^2 + \sigma_\varepsilon^2\right)}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2}{\frac{2\sigma_\varepsilon^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2} = \frac{4\left(\sigma_B^2 + \sigma_\varepsilon^2\right)}{2\left(\sigma_\varepsilon^2\right)} = 2\left(1 + \frac{\sigma_B^2}{\sigma_\varepsilon^2}\right)$$

[2 marks]

(v) What is the minimum value of *RE*?

Solution

Since σ_B^2 and σ_ε^2 are variances, neither can be negative. The minimum value of RE will therefore occur when $\sigma_B^2 = 0$. The minimum value of *RE* is therefore 2.

[2 marks]

(vi) What is the implication of parts (iv) and (v) for the sample size of patients for a cross-over trial design as compared to a parallel group design?

Solution

Since *RE* is the ratio of the sample sizes, *RE* having a minimum of 2 means that the maximum size of a cross-over trial is half that of the corresponding parallel group trial. Typically σ_B^2 will be larger than σ_ε^2. For example if $\sigma_B^2 = 2\sigma_\varepsilon^2$ the relative efficient $RE = 2\left(1 + \frac{2\sigma_\varepsilon^2}{\sigma_\varepsilon^2}\right) = 6$, indicating that a crossover trial design would only require a sixth of the number of patients required for a parallel group trial. A crossover design is therefore much more efficient in terms of sample size of patients than a parallel group design.

[3 marks]

(vii) Describe two situations in which a cross-over design may be not be suitable.

Solution

Crossover trials are not suitable

a) where there is a possibility that the data cannot be obtained in period 2. This can occur due to the condition resolving during period 1 thereby making treatment in period 2 unnecessary.

b) if there is the possibility of a carry-over effect from period 1 that could bias the treatment effect in period 2. A carry-over effect can occur if there is a residual effect of the treatment from period 1 in period 2 and this is dependent on the treatment received in period 1.

[4 marks]

[Total mark 20]

B3.

Consider a meta-analysis of *k* trials. Suppose $\hat{\theta}_i$ is an estimate of the treatment effect for the i^{th} trial and let $Var\left[\hat{\theta}_i\right]$ be its sampling variance.

(i) For the weighted 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]

[3 marks]

(ii) 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 variance of estimator 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 $w_i = 1/Var\left[\hat{\theta}_i\right]$. This gives

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

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

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

as required.

[Book work]

[3 marks]

The table below summarizes the outcome of three randomised trials comparing *dietary advice* with *usual treatment* for patients with diabetes. The treatment effect for each study ($\hat{\theta}_i$, i = 1,2,3) is the difference in mean blood sugar levels for the two treatments with lower values representing a benefit of treatment. $Var\left[\hat{\theta}_i\right]$ is the sample variance estimate of the i^{th} study.

Study	*Difference in blood sugar,* $\hat{\theta}_i$		$Var\left[\hat{\theta}_i\right]$
	*Mean Difference**	*(95% c.i.)*	
Smith (1995)	-1.2	(-2.5,0.1)	0.4
Cohen (2002)	1.4	(-1.4,4.2)	2.0
Iqbal (2007)	-1.5	(-3.3,0.3)	0.8

* *dietary advice - treatment as usual*.

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

Solution

Study Number	Mean Difference $\hat{\theta}_i$	$Var\left[\hat{\theta}_i\right]$	$w_i = 1/Var\left[\hat{\theta}_i\right]$
Smith (1995)	-1.2	0.4	2.5
Cohen (2002)	1.4	2.0	0.5
Iqbal (2007)	-1.5	0.8	1.25

$$\hat{\theta}_{MV} = \frac{\sum_i^k w_i \hat{\theta}_i}{\sum_i^k w_i} = \frac{2.5 \times -1.2 + 0.5 \times 1.4 + 1.25 \times 1.5}{2.5 + 0.5 + 1.25} = -\frac{4.175}{4.25} = -0.9821$$

$$\hat{Var}\left[\hat{\theta}_{MV}\right] = \frac{1}{\sum_i^k w_i} = \frac{1}{4.25}$$

Assuming normality the 95% c.i. of the overall treatment effect is given by

$$\hat{\theta}_{MV} \pm z_{0.025} \times SE\left[\hat{\theta}_{MV}\right] = -0.9821 \pm \frac{1.96}{\sqrt{4.25}}$$

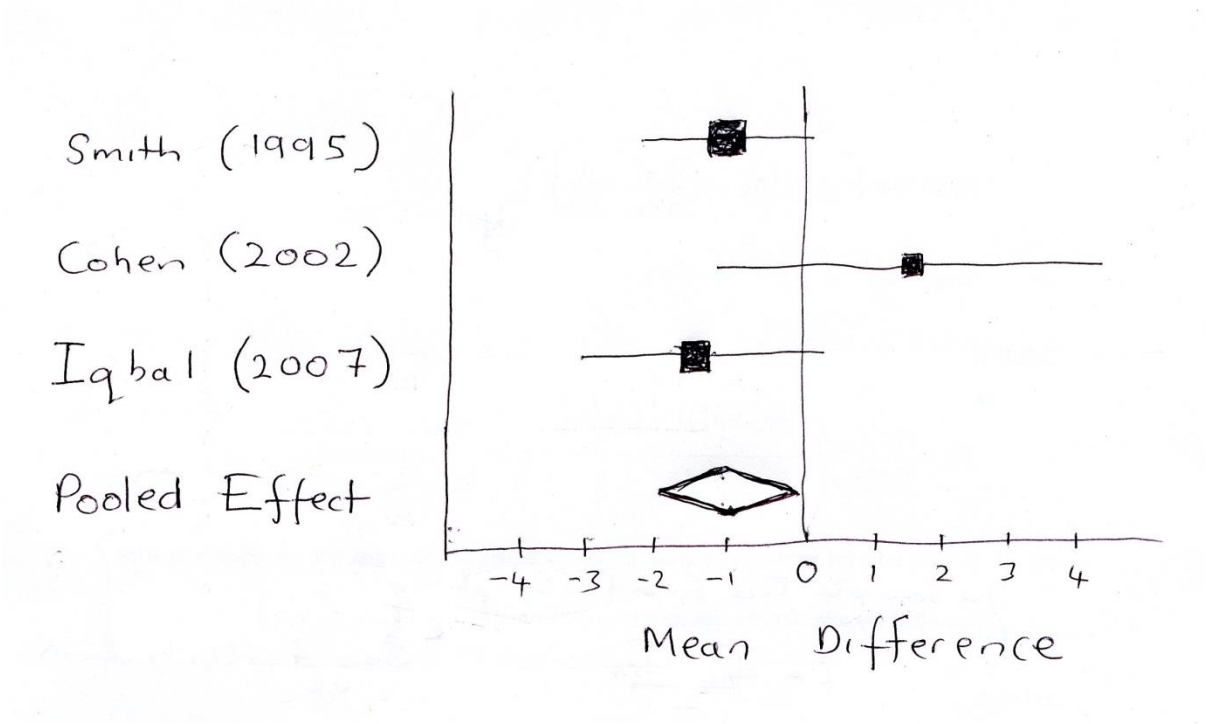
Hence, the 95% confidence interval of the overall treatment effect estimate is <u>-1.9331 to -0.0316</u>.

[Calculation time 7 minutes]

[7 marks]

(iii) Illustrate the three studies and the pooled result using a sketch of a forest plot

Solution



[Time 5 minutes]

[5 marks]

(iv) What do you conclude from the meta-analysis regarding the effectiveness of dietary advice?

Solution

After pooling the three trials there is evidence that *dietary advice* is beneficial by reducing blood sugar levels compared to *usual treatment* for patients with diabetes as the 95% confidence interval of the treatment effect is -1.93 to -0.032.

[2 mark]

[Total mark 20]