MATH38071 EXAMINATION SOLUTION (JANUARY 2012)

SECTION A

A1.

Describe three possible sources of bias that can occur in clinical trials and explain how each might be prevented.

Solution

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

A3. A randomised controlled trial is being planned to compare a new treatment (**T**) with a control treatment (**C**)**.** The primary outcome measure is assumed to be continuous and normally distributed. The power to demonstrate a treatment effect τ with a two-sided 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 standard normal distribution.

(i) Suppose that the within treatment group standard deviation (σ) has been estimated to be 15 units and one wishes to detect a treatment effect (τ) of 5 units, estimate the power of a trial with 50 subjects in each treatment group assuming a 5% significance level α.

Solution

Substitution with $\tau = 5$ $\sigma = 15$ $z_{\alpha/2}=1.96$ n=50

$$1-\Phi\left(z_{\alpha/2}-\frac{\tau\sqrt{n}}{\sigma\sqrt{2}}\right)=1-\Phi\left(1.96-\frac{5\sqrt{50}}{15\sqrt{2}}\right)$$

$$=1-\Phi\left(1.96-\frac{25}{15}\right)=1-\Phi(0.29)=1-0.6141=0.3859$$ from tables

The power of the study is 38.6%.

(ii) Making the same assumptions regarding σ, τ and α, determine the sample size required o obtain 90% power.

Solution

$$0.9=1-\Phi\left(z_{\alpha/2}-\frac{\tau\sqrt{n}}{\sigma\sqrt{2}}\right)$$

Substitution with $\tau = 5$ $\sigma = 15$ $z_{\alpha/2} = 1.96$ n=50

$$0.9 = 1 - \Phi\left(1.96 - \frac{\sqrt{n}}{3\sqrt{2}}\right)$$

Therefore $\Phi\left(1.96 - \frac{\sqrt{n}}{3\sqrt{2}}\right) = 0.1$

Taking inverses $\left(1.96 - \frac{\sqrt{n}}{3\sqrt{2}}\right) = \Phi^{-1}(.1)$

From tables $\Phi^{-1}(.1) = -\Phi^{-1}(0.9) = -1.282$

Rearranging gives $\sqrt{n} = 3\sqrt{2}(1.282 + 1.96)$ giving n= 189.2

Therefore the minimum sample size for 90% power is 190 in each group.
[10 marks]

A3.

A team of researchers designing a randomised control trial considers that the age and sex of the patients to be prognostic variables. Explain how you would carry out stratified randomisation stratifying by age and sex.

What are the advantages and disadvantages of stratified randomisation?

Solution

Choose age bands for age strata e.g. 3 age banding (-64, 65-74,75+)

Stratifying by sex and age one would then have 6 age by sex strata

Construct separate randomisation list for each strata using block randomisation.

What are the advantages and disadvantages of stratified randomisation?

Solution

Advantages

Enables balances between treatment on prognostic factors, which increases power and precision.

Disadvantages

Complex to organize and administer - 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 leading to a large number of incomplete blocks and hence imbalance at the end of the trial.

[7 marks]

A4. A clinical researcher has carried out a randomized controlled trial to compare a new treatment (**T**) with a standard treatment (**C**) for patients with arthritis. A 100mm visual analogue pain score has been recorded at baseline (**baseline**) and at follow-up (**followup**) on each patient with lower scores corresponding to improved outcome. The baseline and follow-up data are approximately normally distributed. The researcher carried out a paired t-test analyses comparing baseline and follow-up score separately for each treatment group generating the computer output listed below.

Results for group = STANDARD TREATMENT (C)

Paired t-test and CI: baseline – followup

```
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
baseline |      20     45.9489    3.024543    13.52617    39.61846    52.27934
followup |      20     42.4291    3.437533    15.37312    35.23426    49.62394
---------+--------------------------------------------------------------------
    diff |      20    3.519793    3.480314    15.56444   -3.764589    10.80418
------------------------------------------------------------------------------
     mean(diff) = mean(baseline - followup)                        t =   1.0113
 Ho: mean(diff) = 0                             degrees of freedom =       19

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.8377         Pr(|T| > |t|) = 0.3246          Pr(T > t) = 0.1623
```

Results for group = NEW TREATMENT (T)

Paired t-test and CI: baseline – followup

```
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
baseline |      20    53.26387    2.715042    12.14204    47.58122    58.94651
followup |      20    42.24397    3.169944    14.17642     35.6092    48.87874
---------+--------------------------------------------------------------------
    diff |      20     11.0199    2.612071    11.68154     5.55277    16.48703
------------------------------------------------------------------------------
     mean(diff) = mean(baseline - followup)                        t =   4.2188
 Ho: mean(diff) = 0                             degrees of freedom =       19

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.9998         Pr(|T| > |t|) = 0.0005          Pr(T > t) = 0.0002
```

Assuming a 5% significance level there is a statistically significant change from baseline to follow-up in treatment **T** but not in treatment **C**. From this the researcher concludes that treatment **T** is significantly more effective than treatment **C** in treating arthritis.

(i) Discuss the flaws in the clinical 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) Describe three methods of analyses that could be used to test whether there was a treatment effect.

Solution

The three possible options are:

(a)Use a two-sample t-test to compare the two treatment groups using the follow-up pain scores **followup.**

(b) Calculate the change in pains-score **change = followup – baseline** then use a two-sample t-test to compare the two treatment groups using the change in pain scores **change.**

(c) Fit a linear model with **followup** as the dependent variable and **baseline** and **treatment** as covariate. The test of the treatment effect is then the test of the coefficient of the covariate **treatment**. Also call analysis of covariance.

(iii) Which of these three analyses would you consider to be most appropriate in this context.

Solution

The expectation of all three estimate are the same due to randomisation, but the linear model analysis is preferable as it give the estimate of the treatment effect with smallest varaince, the efficiency of the trial is increased by reducing the variance of the treatment effect, Carrying out all three analyses is not recommended as they may give contradictory results and cause confusion. Therefore, I would recommend that only one analysis should be included in the statistical analysis plan of the trial and that should be based on the linear model.

[10 marks]

A5. Tabulated below are summary data from a randomised controlled trial comparing a surgical and medical treatment. Some patients randomised to the surgery received the medical treatment, and some patients randomised to medical treatment received surgery.

Survival at 1 year	*Surgical*		*Medical*	
	Received Surgical	*Received Medical*	*Received Surgical*	*Received Medical*
No	15	15	4	26
Yes	105	45	26	124
Total	120	60	30	150

(i) Calculate the point estimates of the treatment effect of surgery compared to medical treatment measured by the proportion surviving at 1 years for (a) Intention-To-Treat, (b) Per-Protocol and (c) As-Treated analyses.

Solution

(a) *Intention-To-Treat* treatment effect *=(105+45)/(120+60)-(26+124)/(30+150)=0.0*

(b) *Per-Protocol* treatment effect *=105/120-124/150=0.048*

(c) *As-Treated* treatment effect*=(105+26)/(150)-(45+124)/210=0. 0.069*

[3 marks]

(ii) Explain why an Intention-To-Treat analysis is usually preferable to a Per-Protocol or an As-Treated analyses in superiority trials.

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 contrast *per-protocol* and *as-treated* analyses may be biased either away from or towards the null hypothesis. 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.

[7 marks]

B1 . A randomised controlled trial is planned to compare a new antibiotic treatment (A) with the current standard therapy (B). At four weeks follow-up it is recorded whether the patients have recovered.

(i) Briefly explain why it is important to estimate sample size in a clinical trial. [2 marks]

Solution

- If the sample size is too small, the trial may lack power to detect a treatment effect that is clinical important.
- If more patients than the minimum to answer the question are recruited, some patients may unnecessarily be exposed to an inferior treatment.

[2marks]

(ii) Let n_A and n_B be the number of subjects allocated to each treatment, and r_A and r_B be the numbers of patients that have recovered at 4 weeks for each treatment. The two-sample test of proportions with test statistic T given by

$$T = \frac{|p_A - p_B|}{\sqrt{(p(1-p))(1/n_A + 1/n_B)}}$$

will be used to test the null hypothesis of no treatment effect, where $p_A = r_A/n_A$,

$p_B = r_B/n_B$ and $p = \frac{n_A.p_A + n_B.p_B}{n_A + n_B}$. Assuming that the test statistic T has a normal distribution under the null and alternative hypotheses and using a two-sided test with significance level α, show that the power is approximately

$$1 - \Phi\left(\frac{z_{\alpha/2}.\lambda.\sqrt{\pi(1-\pi)} - |\pi_A - \pi_B|}{\sqrt{\frac{\pi_A(1-\pi_A)}{n_A} + \frac{\pi_B(1-\pi_B)}{n_B}}} \right),$$

where π_A, π_B, and π are the population proportions corresponding to p_A, p_B, and p, $\lambda = \sqrt{1/n_A + 1/n_B}$, and Φ is the cumulative density function of the standard normal distribution.

Solution

Assuming a normal approximation the distribution of T under the null hypothesis is

$N\left(0, \pi(1-\pi)\left(\frac{1}{n_T} + \frac{1}{n_C}\right)\right)$ with critical values $+z_{\alpha/2}$ and $-z_{\alpha/2}$ for an α level two-sided test.

Suppose $\tau = \pi_A - \pi_B$. Therefore the power equals

$$1 - \beta(\alpha, \tau) = \Pr\left(p_A - p_B > z_{\alpha/2}\lambda\sqrt{\pi(1-\pi)}\right) + \Pr\left(p_A - p_B < -z_{\alpha/2}\lambda\sqrt{\pi(1-\pi)}\right)$$

Without loss of generality one can assume $\tau > 0$ so that $\Pr\left(p_A - p_B < -z_{\alpha/2}\lambda\sqrt{\pi(1-\pi)}\right)$ will be negligible.

The distribution of $p_A - p_B$ under the alternate hypothesis is $N\left(\tau, \frac{\pi_A(1-\pi_A)}{n_A} + \frac{\pi_B(1-\pi_B)}{n_B}\right)$.

Therefore

$$1-\beta(\alpha,\tau) = 1-\Phi\left(\frac{z_{\alpha/2}.\lambda.\sqrt{(\pi(1-\pi))} - \tau}{\sqrt{\frac{\pi_A(1-\pi_A)}{n_A} + \frac{\pi_B(1-\pi_B)}{n_B}}}\right).$$

[7 Marks]

(iii) Assuming two equal size groups show that the sample size required for each group to give a power (1-β) is approximately

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

Solution

With $n_A = n_B = n$

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

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

Rearrangement gives

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

Since $\lambda = \sqrt{\frac{2}{n}}$

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

Hence

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

Further rearrangement and replacing δ with $\pi_A - \pi_B$ gives the result

$$n_A = \frac{\left(z_{\alpha/2}.\sqrt{2\left(\pi\left(1-\pi\right)\right)} + z_{\beta}\sqrt{\pi_A\left(1-\pi_A\right)+\pi_B\left(1-\pi_B\right)}\right)^2}{\left(\pi_A-\pi_B\right)^2}.$$

[7 Marks]

(i) The percentage of patients expected to recover in four weeks with the current standard treatment is 50%. Estimate the total sample size that would be need to detect a 10% improvement to 60% with the new treatment assuming a power of 80% and a two-sided 5% significance level.

Solution

From the question π_A=0.6 and π_B=0.5 From tables z_β=0.84 and $z_{\alpha/2}$=1.96

$$\pi = \frac{\pi_A+\pi_B}{2} = \frac{0.6+0.5}{2} = 0.55$$

Substitution gives

$$n_A = \frac{\left(1.96.\sqrt{2\times0.55\times0.45} + 0.84\sqrt{0.6\times0.4+0.5\times0.5}\right)^2}{\left(0.1\right)^2}$$

$$= \frac{\left(1.96\times0.7035+0.84\times0.7\right)^2}{\left(0.1\right)^2} = 386.9$$

The minimum total number patients require for 80% power is approximately 2x387=774.

[Calculation 3 minutes]

[4 Marks]
[Total 20 Marks]

B2.

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.

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]

(i) In a crossover trial the treatment effect δ 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 $E\left[\bar{d}_{AB}\right] = E\left[\dfrac{\sum_{i \in AB} d_i}{n_{AB}}\right] = \dfrac{\sum_{i \in AB} E[d_i]}{n_{AB}} = \dfrac{\sum_{i \in AB} E[\phi - \tau + \gamma + \varepsilon_{i2} - \varepsilon_{i1}]}{n_{AB}} = \phi + \gamma - \tau$

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

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

[Book Work]

[4 marks]

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

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

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) The test statistic T_a ,defined as $T_a = \frac{\bar{a}_{AB} - \bar{a}_{BA}}{\hat{S}E\left[\bar{a}_{AB} - \bar{a}_{BA}\right]}$, 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 $\hat{S}E\left[\bar{a}_{AB} - \bar{a}_{BA}\right]$ 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.

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]

(iv) 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]

B3.

In meta-analysis suppose $\hat{\theta}_i$ is an estimate of the treatment effect for the i^{th} study and let $Var\left[\hat{\theta}_i\right]$ be its sampling variance.

(i) For the weight estimate of the overall effect, defined by $\hat{\theta} = \dfrac{\sum_i^k w_i \hat{\theta}_i}{\sum_i^k w_i}$ where w_i are weights, show that $Var\left[\hat{\theta}\right] = \dfrac{\sum_i^k w_i^2 Var\left[\hat{\theta}_i\right]}{\left(\sum_i^k w_i\right)^2}$.

Solution

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

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

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

[Book work]

[4 marks]

(ii) Given that the minimum variance estimator of θ , say $\hat{\theta}_{MV}$, is obtained when $w_i \propto 1/Var\left[\hat{\theta}_i\right]$, show that the minimum variance estimate is equal to

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

Solution

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

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

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

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

as required.

[Book work]
[4 marks]

The table below summarizes the outcome of three trials comparing cholesterol medication for patients for with high blood cholesterol. The treatment effect for each study ($\hat{\theta}_i$, i = 1,2,3) is the difference in mean cholesterol between dietician advice group and doctor advice group. $Var\left[\hat{\theta}_i\right]$ is the sample variance estimate the i^{th} study.

Study	*Difference in blood cholesterol,* $\hat{\theta}_i$	$\hat{Var}\left[\hat{\theta}_i\right]$
Dyson1996	-0.6	0.1
Dunn 2002	-0.7	0.5
Smith 1989	-0.6	0.2

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

Study Number	*Difference in blood cholesterol,* $\hat{\theta}_i$	$\hat{Var}\left[\hat{\theta}_i\right]$	w_i
Dyson1996	-0.6	0.1	10
Dunn 2002	-0.7	0.5	2
Smith 1989	-0.6	0.2	5

$$\hat{\theta}_{MV} = \frac{\sum_i^k w_i \hat{\theta}_i}{\sum_i^k w_i} = \frac{10\times -0.6 + 2\times -0.7 + 5\times 0.6}{10+2+5} = -\frac{10.4}{17} = -0.612$$

$$\hat{Var}\left[\theta_{MV}\right] = \frac{1}{\sum_i^k w_i} = \frac{1}{17}$$

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

$$\hat{\theta}_F \pm 1.96 \times SE\left[\hat{\theta}_F\right] = -0.612 \pm \frac{1.96}{\sqrt{17}}$$

Hence the 95% confidence interval of the overall fixed effect estimate is -1.087 to -0.136.

[Calculation 8 minutes]

[7 marks]

(iii) What do you conclude from the meta-analysis regarding the effectiveness of the drug treatment?

Solution

After pooling the 3 studies there is evidence that the treatment reduces cholesterol.

[1 mark]

(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 is particularly so for smaller studies where sampling variation is larger. This means that the published literature may be unrepresentative leading to bias in meta-analysis estimates of treatment effects.

[3 marks]

(iv) What type of graph might one use to investigate possible publication bias in a meta-analysis?

Solution

A funnel plot.

[1 mark]

[Total mark 20]