MATH JUNE 2008 EXAMINATION SOLUTION

A1.

Explain what is meant by *Block randomisation* in a randomised controlled trial.

Solution

Block Randomisation also referred to as *Randomised Permuted Blocks* aims to keep group sizes equal. In block randomisation a random selection of blocks are used with each block containing an equal numbers of each treatment group.

Illustrate this by showing how you might prepare a randomisation list for first twenty patients in a trial with two treatments.

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

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

How might you use block randomisation to improve balance between two treatment groups in 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 strata.

[6 marks]

A2.

A clinical trial compared an analgesics gel with a placebo gel with no active ingredient for the treatment of joint pain. Using randomisation, 30 patients were allocated to the new gel and 30 to the placebo. Patients were assessed at the end of the two-week treatment period. The swelling was eradicated for 21 patients in the new treatment group and 15 patients in the placebo group. An absolute difference in the success rate of the two treatments of 10% was considered to be a clinically important effect.

(i) State the hypotheses you might use to compare the treatments.

Solution

If π_N π_P the population proportions of success in the new and placebo treatment groups the hypotheses that might be used to compare the two treatments is

H_0: $\pi_N = \pi_P$ vs H_0: $\pi_N \neq \pi_P$. [2 marks]

(ii) Carry out a statistical test to compare the treatments specifying the assumptions that are made.

Solution

The data can be tabulated as follows

	New	*Placebo*	*Total*
Success	21(70%)	15(50%)	36
Failure	9	15	24
Total	30	30	60

In order to test this hypothesis a two sample z-test of proportions can be used, which is define as follows. Suppose r_n and r_p are the number of success in each group, p_N p_P the population proportion of success in the new and placebo treatment groups, n_n n_p the in each group. The test statistic is defined as $Z = \dfrac{|p_N - p_P|}{s.e._{null}(p_N - p_P)}$

with $s.e._{null}(p_N - p_P) = \sqrt{p\ (1-p)\left(\dfrac{1}{n_N} + \dfrac{1}{n_P}\right)}$ and $p = \dfrac{r_N + r_P}{n_N + n_P}$

Z can be assumed to be Normally distributed provided $n_N p, n_N(1-p), n_P p\ , n_P(1-p\ )$ are greater than 5. From the table the smallest of these 24 x 30 /60 =12. Hence the normal approximation can be used.

$$p_N - p_P = \frac{r_N}{n_N} - \frac{r_P}{n_P} = \frac{21}{30} - \frac{15}{30} = 0.2,\ \ p = \frac{36}{60}$$

$$s.e._{null}(p_N - p_P) = \sqrt{\frac{36}{60} \times \frac{24}{60}\left(\frac{1}{30} + \frac{1}{30}\right)} = 0.1269$$

Hence $$Z = \frac{|p_A - p_B|}{s.e._{null}(p_A - p_B)} = \frac{0.2}{0.1269} = 1.58$$

For a 5% level two-sided test the critical value of z_α is 1.96.
Alternatively from tables p=0.11 which greater than greater than α =0.05.
Therefore the result is not statistically significant at a 5% level.

[5 marks]

(iii) Comment on the results of the trial.

Solution

The difference in the success rate of the new treatment compared to placebo (treatment effect) observed in this trial is 20%, but this is not statistically in a 5% level two-sided test. Since a 10% improvement in the success rate was considered to be clinically important, it would suggest that the study was under-powered to detect an clinically important effect.

[3 marks]

[Total 10 Marks]

A3. You are asked to advise on the analysis of a double-blind randomised controlled trial of treatments for depression comparing fluoxetine with placebo. The primary outcome measure is the Beck Depression Inventory (***BDI-FU***), which is a continuous outcome measure that is considered to be approximately normally distributed. This same measure has also been recorded at baseline (***BDI-BASE)***. Apparently, ***BDI-FU*** is expected to be strongly correlated with BDI-BASE . The following three statistical analyses are being considered:

- Carry out a t-test comparing ***BDI-FU*** at follow-up.
- Calculate the change from baseline, that is ***BDI-CHG*** = ***BDI-FU*** – ***BDI-BASE***, and then apply a t-test.
- Fit a linear model with ***BDI-FU*** as the dependent variable with co-variates ***BDI-BASE*** and treatment group.

What advice would you give regarding the choice of statistical analysis to be included in statistical analysis plan justifying that choice?

Solution

All three estimates are unbiased estimators of the treatment effect, but an estimate of the treatment effect based on a linear model has reduced variance compared to an unadjusted analysis and a change analysis particularly as the baseline is strongly correlated with the follow-up assessment. Since the efficiency of the trial is increased by reducing the variance of the treatment effect, the linear model estimate is preferable. 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.

[5 marks]

A4 . Consider a randomized controlled trial. Suppose the patient population can be divided into three latent sub-groups as follows:

- *Compliers*: patients who will comply with the allocated treatment,
- *Always control treatmen*t: patients who will receive control treatment regardless of allocation,
- *Always new treatment*: patients who will receive the new treatment regardless of allocation.

This assumes that there are no defiers, that is patient who will always receive the opposite of the treatment to which they are randomized. Assuming 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 show that

(i) 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

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]

(ii) 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]

[Total 10 Marks]

A5. The Minitab print-out below gives the results of analysis of a randomised controlled 2-period AB-BA crossover trial on 45 patients comparing the effect of eating butter and margarine on total blood fats. Patients are randomised to receive Butter then Margarine or Margarine then Butter

Analysis of Period 1

Two-Sample T-Test and CI

```
Sample              N   Mean   StDev    SE Mean
Butter then Marg    23  6.220  0.870     0.18
Marg then Butter    22  5.910  0.780     0.17


Difference = mu (Butter then Marg) - mu (Marg then Butter)
Estimate for difference:  0.310
95% CI for difference:  (-0.188, 0.808)
T-Test of difference = 0 (vs not =): T-Value = 1.26  P-Value = 0.216  DF = 43
Both use Pooled StDev = 0.8273
```

Analysis of Period 2 - Period 1

Two-Sample T-Test and CI

```
Sample              N    Mean   StDev    SE Mean
Butter then Marg    23  -0.270  0.560     0.12
Marg then Butter    22   0.230  0.590     0.13


Difference = mu (Butter then Marg) - mu (Marg then Butter)
Estimate for difference:  -0.500
95% CI for difference:  (-0.846, -0.154)
T-Test of difference = 0 (vs not =): T-Value = -2.92  P-Value = 0.006  DF = 43
Both use Pooled StDev = 0.5748
```

(i) Using the analysis for *Period 1* output give the estimate and 95% confidence interval of the treatment effect for Margarine as compared to Butter.

Solution

From the Period 1 output the treatment effect of margarine compared to butter is reduction in total blood fats of -0.310 with 95% CI (-0.808, 0.188)

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

Solution

The Minitab output give the two-sample t-test of the differences. This estimates twice the treatment effect. Hence from the output, based of the crossover analysis, the treatment effect of margarine compared to butter is reduction in total blood fats of -0.500/2 95% CI (-0.846/2,-0.154/2) i.e. -0.25 with 95% c.i. (-0.423,-0.077)

(iii) What is the advantage of a crossover design as 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.

(iv) Give one limitation of a crossover design as compared to a parallel group design.

Solution

One 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 during period 2 mean there will be no data for the second period and so the data from the first period cannot be included in the statistical analysis.

[9 marks]

SECTION B

Answer **TWO** of the three questions in this section

B6 A randomised controlled trial is planned to compare a new antibiotic treatment (A) with the current standard therapy (B) for patients with TB. At six months follow-up it is recorded whether the disease is still present in the patient.

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

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) The two-sample test of proportions with statistic z given by

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

will be used to test the null hypothesis of no treatment effect, where n_A, n_B are the number of subjects allocated to each treatment, $p_A = r_A/n_A$, $p_B = r_B/n_B$ with r_A, r_B are the numbers of patients in which TB was absent after 6 months for each treatment and $p = \frac{n_A.p_A + n_B.p_B}{n_A + n_B}$.

Suppose that patients are to be allocated in the ratio of k:1 with $n_A = k.n_B$.

Assuming that the test statistic z has a normal distribution under the null and alternative hypotheses and using a two-sided α size test , show that the power

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

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 standard normal cumulative density function.

Solution

For a two-tailed α-level test assuming a normal approximation under the null the power can be written as

$1-\beta(\alpha,\delta) = \Pr\left(\frac{p_A - p_B}{\lambda\sqrt{\pi(1-\pi)}} > z_{\alpha/2}\right) + \Pr\left(\frac{p_A - p_B}{\lambda\sqrt{\pi(1-\pi)}} < -z_{\alpha/2}\right)$ which can be re-written as

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

$\lambda=\sqrt{\frac{1}{n_A}+\frac{1}{n_B}}$.

Suppose $\pi_A-\pi_B=\delta$. Without loss of generality assume that $\delta > 0$. Assuming normality the distribution of p_A-p_B under the alternate hypothesis is $N\left(\delta,\frac{\pi_A(1-\pi_A)}{n_A}+\frac{\pi_B(1-\pi_B)}{n_B}\right)$

Therefore the power

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

where Φ is the standard normal cumulative density function. The last term on the right-hand side is negligible, therefore

$$\beta(\alpha,\delta)\cong\Phi\left(\frac{z_{\alpha/2}.\lambda.\sqrt{\pi(1-\pi)}-\delta}{\sqrt{\frac{\pi_A(1-\pi_A)+k\pi_B(1-\pi_B)}{kn_B}}}\right)$$

[7 Marks]

(iii) Show that the sample size required for each group to give a power β is approximately

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

Solution

With $n_A=k.n_B$

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

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

Rearrangement gives

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

Since $z_{1-\beta} = -z_{\beta}$ and $\lambda = \sqrt{\frac{k+1}{n_A}}$

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

Hence

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

Further rearrangement and substitution of $\delta=\pi_A-\pi_B$ gives the result

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

[7 Marks]

(iv) The investigators planning the randomised controlled trial expect that the proportion of patients that recover in the current standard therapy group (B) will be 50%. An improvement to 65% with the new medication (A) is considered to be clinically important. Estimate the total sample size that would be required using a 2 to 1 allocation ratio (k=2), assuming a power of 80% and a two-sided 5% significance level.

Solution

From the question $\pi_A=0.65$ and $\pi_B=0.5$ From tables $z_{\beta}=0.84$ and $z_{\alpha/2}=1.96$

Since $\pi = \frac{n_A\pi_A + n_B\pi_B}{n_A\pi_A + n_B\pi_B}$

For k=2 $\pi = \frac{k.\pi_A + \pi_B}{k+1} = \frac{2\times 0.65 + 0.5}{3} = 0.6$

Substitution gives

$$n_A = \frac{\left(1.96.\sqrt{0.6\times 0.4\times 3} + 0.84\sqrt{0.65\times 0.35 + 2\times 0.5\times 0.5}\right)^2}{(0.15)^2} = 251.7$$

Since $n_B=n_A/2$, the minimum total number patients require is approximately 252x1.5=378.

[4 Marks]

[Total 20 Marks]

B7.

In a parallel group *non-inferiority* trial a new treatment *T* is being compared with a control treatment *C* on a continuous normally distributed 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, n_T and n_C be the sample sizes, and s be the pooled within-group sample standard deviation of *Y*. Define the treatment effect $\tau = \mu_T - \mu_C$.

(i) Explain why a significance test of the hypothesis $H_0 : \tau = 0$ vs $H_1 : \tau < 0$ would be an inappropriate in a non-inferiority trial. [3 marks]

Solution

In order to demonstrate that an alternative hypothesis is true, we need to reject a null hypothesis. Hence to demonstrate that a new treatment is not inferior, we need to define a null hypothesis that the treatment is inferior rather than a null hypothesis that is zero.
[4 marks]

(ii) Suppose that the null hypothesis $H_0 : \mu_T - \mu_C \le -\tau_N$ is rejected if the (1-α) single sided confidence interval, given by $\bar{y}_T - \bar{y}_C - z_\alpha \lambda s$ with $\lambda = \sqrt{1/n_T + 1/n_C}$, is greater than $-\tau_N$. Show that

$$\Pr[\text{Reject } H_0|\tau] = 1 - \Phi\left(-\frac{(\tau_N + \tau)}{s\lambda} + z_\alpha \right)$$

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

Solution

Assuming a normal approximation H_0 will be rejected provided $\hat{\tau} > -\tau_N + s\lambda z_\alpha$. Therefore

$$\Pr(\text{Reject } H_0|\tau) = \Pr\left(\hat{\tau} > -\tau_N + s\lambda z_\alpha\right) = 1 - \Pr\left(\hat{\tau} \le -\tau_N + s\lambda z_\alpha\right) = 1 - \Pr\left(\frac{\hat{\tau}}{s\lambda} < -\frac{\tau_N}{s\lambda} + z_\alpha\right)$$

Assuming $\hat{\tau}$ is $N[\tau, s^2\lambda^2]$, it follows that $\Pr[\text{Reject } H_0|\tau]$

$$= 1 - \Phi\left(\left(-\frac{(\tau_N)}{s\lambda} + z_\alpha\right) - \frac{(\tau)}{s\lambda}\right) = 1 - \Phi\left(-\frac{(\tau_N + \tau)}{s\lambda} + z_\alpha\right) \text{ as required}$$

[7 marks]

(iii) Show that $\Pr[\text{Reject } H_0|\tau]$ has a maximum under H_0 when $\tau = -\tau_N$. Hence show that this procedure has a type I error $\le \alpha$.

Solution

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

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

Since $\phi > 0$ for finite values, it follows that $\Pr(\text{Reject } H_0|\delta)$ is monotone increasing for τ. Hence the type I error rate has a maximum when $\tau = -\tau_N$. Substitution in to

$$\Pr[\text{Reject } H_0|\tau] = 1 - \Phi\left(-\frac{(\tau_N - \tau_N)}{s\lambda} + z_\alpha \right) = 1 - \Phi\left(z_\alpha\right) = \alpha$$

[6 marks]

(v) A randomised controlled non-inferiority trial is carried out to test whether a new generic drug is as effective as a current standard drug for controlling pain measured by a 100 mm analogue scale. Fifty patients are randomised to the standard treatment and 52 to the new generic treatment. The Minitab output is given below.

Two-Sample T-Test and CI

```
Sample                       N  Mean   StDev    SE Mean
Current standard drug        50  65.5   18.5      2.6
New generic drug             52  66.1   18.8      2.6

Difference = mu (Current standard drug) - mu (New generic drug)
Estimate for difference:  -0.60
Standard Error (SE) for difference:    3.69
95% CI for difference:  (-7.93, 6.73)
T-Test of difference = 0 (vs not =):
              T-Value = -0.16  P-Value = 0.871  DF = 100
Both use Pooled StDev = 18.6536
```

A difference of 10 mmHg was considered by researchers to be clinically important. Using a 5% significance level, test whether the new medication is non-inferior to the current standard drug .

Solution

Since higher score represent greater pain to test non-inferiority consider the null hypothesis $H_0 : \mu_T - \mu_C \geq 10$. This can be tested at a 5% level by considering the 95% one-sided confidence interval $\overline{y}_T - \overline{y}_C + z_\alpha \lambda s$.

$z_\alpha = 1.64$

λs is the SE = 3.69

$\overline{y}_T - \overline{y}_C = 0.60$.

So the one-sided interval is 0.6 +1.64x3.69 = 6.65. Since this is below 10, the null hypothesis can be rejected.

[3 Marks]

[Total 20 Marks]

B8.

In meta-analysis suppose $\hat{\theta}_i$ is an estimate of the treatment effect for the i^{th} study, assumed to be normally distributed, and let $Var\left[\hat{\theta}_i\right]$ let be its sampling variance. The fixed effect estimator $\hat{\theta} = \dfrac{\sum_i^k w_i\hat{\theta}_i}{\sum_i^k w_i}$, where w_i are weights, with $Var\left[\hat{\theta}\right] = \dfrac{\sum_i^k w_i{}^2.Var\left[\hat{\theta}_i\right]}{\left(\sum_i^k w_i\right)^2}$.

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

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

[12 Marks]

Solution

Without loss of generality one can apply the constraint that $\sum_{i=1}^k w_i = 1$.

Define $G(w_1, w_2, ..., w_k) = \sum_{i=1}^k w_i - 1$.

In the Lagrange Multiplier Method one defines

$$H(w_1, w_2, ..., w_k, \lambda) = F(w_1, w_2, ..., w_k) - \lambda G(w_1, w_2, ..., w_k)$$

The minimum of F subject to the constraint G is found by equating the partial derivatives of $H(w_1, w_2, ..., w_k, \lambda)$ with respect to each w_i and equating to zero. For the jth study

$$\frac{\partial H}{\partial w_j}(w_1, w_2, ..., w_k, \lambda) = \frac{\partial}{\partial w_j}\sum_{i=1}^k w_i{}^2.Var\left[\hat{\theta}_i\right] - \lambda\frac{\partial}{\partial w_j}\left(\sum_{i=1}^k w_i - 1\right)$$

Hence $\dfrac{\partial H}{\partial w_j}(w_1, w_2, ..., w_k) = 2w_j Var\left[\hat{\theta}_j\right] - \lambda = 0$ giving $w_j = \lambda \Big/ \left(2Var\left[\hat{\theta}_i\right]\right)$ for any j=1..k.

Assuming $Var\left[\hat{\theta}_j\right]$>0 , the second derivatives of H w.r.t. w_i are positive so this must be a minima.

Taking λ=1, $w_i = 1 \Big/ Var\left[\hat{\theta}_i\right]$. Hence

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

The table below summarizes the outcome of three trials comparing dietary advice given by a dietician with that given by a doctor 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 group. $Var\left[\hat{\theta}_i\right]$ is the sample variance estimate the i^{th} study.

Study	*Reduction in blood cholesterol,* $\hat{\theta}_i$	$\hat{Var}\left[\hat{\theta}_i\right]$
Dyson1996	0.34	0.0289
Thomson 2002	0.18	0.0729
Smith 1989	0.27	0.0676

(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	*Reduction in cholesterol* $\hat{\theta}_i$	$\hat{Var}\left[\hat{\theta}_i\right]$	W_i	$W_i\,\hat{\theta}_i$
Dyson1996	0.34	0.0289	34.60	11.76
Thomson 2002	0.18	0.0729	13.72	2.47
Smith 1989	0.27	0.0676	14.79	3.99
		Σ	63.11	18.23

The minimum variance estimate $\hat{\theta}_{MV} = \dfrac{\sum_i^k w_i\hat{\theta}_i}{\sum_i^k w_i} = \dfrac{18.23}{63.11} = 0.2888$

$$Var\left[\hat{\theta}_{MV}\right] = \frac{1}{\sum_i^k w_i} = \frac{1}{63.11} = 0.0158$$

$$SE\left[\hat{\theta}_{MV}\right] = \sqrt{0.0158} = 0.1258$$

Hence the 95% c.i. is $0.289 \pm 1.96\, SE\left[\hat{\theta}_{MV}\right]$, which gives the 95% to be from 0.042 to 0.536.

[6 Marks]

(iii) What do you conclude from the meta-analysis?

Solution

There is evidence from the meta-analysis dietary advice given by a dietician is more effective than dietary advice given by a doctor.

[2 Marks]

[Total 20 Marks]