Medical Statistics (MATH38071) Solutions Exercise Sheet 9

(Crossover Trials)

1. An *AB-BA* crossover trial compares the effect of two drugs, *A* and *B*, to preventing gastric bleeding in patients taking pain relieving medication. Eighteen patients are allocated to the sequence *A* then *B* and nineteen to the sequence *B* then *A*.

(i) The statistical output below gives the results of a two-sample t-test of the difference in outcome between period 2 and period 1 for each patient for the two sequences. Is the difference between treatments *A* and *B* statistically significant?

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Two-sample t test with equal variances
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 A then B|      18        1.35    .3511964        1.49    .6090404     2.09096
 B then A|      19        -.36    .3142996        1.37   -1.020319    .3003189
---------+--------------------------------------------------------------------
    diff |               1.71    .4702031                .755437      2.664563
------------------------------------------------------------------------------
    diff = mean(B then A) - mean(A then B)                        t =   3.6367
Ho: diff = 0                                     degrees of freedom =       35

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.9996         Pr(|T| > |t|) = 0.0009          Pr(T > t) = 0.0004
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Solution

Diff = mean(B then A) - mean(A then B) estimates twice the treatment effect of treatment B compared to treatment A. The result of the test $H_0 : \mu_{AB}^d = \mu_{BA}^d$ is the same as $H_0 : \tau = 0$, so there is a statistically significant difference between the two treatments with p=0.0009.

(ii) What is the point estimate and the confidence interval of the treatment effect of *B* compared to *A*?

Solution

The analysis estimates twice the treatment effect of treatment B compared to treatment A.

Hence the point estimate and 95% confidence interval of the effect of treatment B compared to A are obtained by halving the values in the output, giving the treatment effect as 0.85 (95% C.I. 0.38 to 1.33).

(iii) Assuming that high scores correspond to a better outcome, which treatment is better?

Solution

The point estimate of the effect of drug B as compared to drug A is 0.86. Since higher scores correspond to a worse outcome this suggest that drug B is not as effective as drug A.

2. If Y_{ij} is the response for the ith subject during period $\left(j=1,2\right)$, we define a model for an AB-BA crossover trial as follows:

$Y_{i1}=\mu+\xi_i+\varepsilon_{i1}$ for a patient in sequence AB in period 1,

$Y_{i2}=\mu+\tau+\phi+\xi_i+\varepsilon_{i2}$ for a patient in sequence AB in period 2,

$Y_{i1}=\mu+\tau+\xi_i+\varepsilon_{i1}$ for a patient in sequence BA in period 1,

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

where μ is the mean for the sequence AB in period 1 , τ is the treatment effect, ϕ is the period 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.

(i) Define $c_{i1}=Y_{i2}-Y_{i1}$ for sequence AB and $c_{i1}=Y_{i1}-Y_{i2}$ for sequence BA. Let $\overline{c}_{AB}$ and $\overline{c}_{BA}$ be the sample means for sequences AB and BA. Show that $E\left[\frac{\overline{c}_{AB}-\overline{c}_{BA}}{2}\right]=\phi$.

Solution

Substitution from the model above gives

$$E\left[c_i\,|\,i\in AB\right]=E\left[\left(\mu+\tau+\phi+\xi_i+\varepsilon_{ij}\right)-\left(\mu+\xi_i+\varepsilon_{ij}\right)\right].$$

$$=E\left[\left(\tau+\phi+\varepsilon_{ij}\right)+\left(\varepsilon_{ij}\right)\right].$$

Since $E\left[\varepsilon_{ij}\right]=0$, $E\left[c_i\,|\,i\in AB\right]=\tau+\phi$.

Similarly, $E\left[c_i\,|\,i\in BA\right]=E\left[\left(\tau+\varepsilon_{i1}\right)-\left(\phi+\varepsilon_{i2}\right)\right]=\tau-\phi$.

$$E\left[\overline{c}_{AB}\right]=E\left[\frac{\sum_{i\in AB}c_i}{n_{AB}}\right]=\frac{n_{AB}E\left[c_i\,|\,i\in AB\right]}{n_{AB}}=\tau+\phi$$

Similarly

$$E\left[\overline{c}_{BA}\right]=\tau-\phi$$

Hence $E\left[\frac{\overline{c}_{AB}-\overline{c}_{BA}}{2}\right]=\phi$

(ii) From the computer output in question 1 estimate the period effect.

Solution

Since $E\left[\frac{\overline{c}_{AB}-\overline{c}_{BA}}{2}\right]=\phi$, the period effect can be estimated by $\frac{\overline{c}_{AB}-\overline{c}_{BA}}{2}$.

The analysis in the print-out is based on $d_i = Y_{i2} - Y_{i1}$. Suppose $\bar{d}_{AB}$ and $\bar{d}_{BA}$ are the sample means of d_i for the two sequences.

Therefore $\bar{c}_{AB} = \bar{d}_{AB} = 1.35$ and $\bar{c}_{BA} = -\bar{d}_{BA} = -(-0.36) = 0.36$.

Hence $\hat{\phi} = \dfrac{\bar{c}_{AB} - \bar{c}_{BA}}{2} = \dfrac{1.35 - 0.36}{2} = 0.495$

(iii) Test the null hypothesis, $H_0 : \phi = 0$.

Solution

Since $\hat{\phi}$ is the difference of two independent sample means one can test $H_0 : \phi = 0$ by a two sample t-test.

Since the two sequences are independent

$$Var\left[\hat{\phi}\right] = \frac{1}{4} Var\left[\bar{c}_{AB} - \bar{c}_{BA}\right] = \frac{1}{4}\left(Var\left[\bar{c}_{AB}\right] + Var\left[\bar{c}_{BA}\right]\right) = \frac{1}{4}\left(Var\left[\bar{d}_{AB}\right] + Var\left[\bar{d}_{BA}\right]\right)$$

$$= \frac{1}{4} Var\left[\bar{d}_{AB} - \bar{d}_{BA}\right]$$

Therefore $SE\left[\hat{\phi}\right] = \dfrac{1}{2} SE\left[\bar{d}_{AB} - \bar{d}_{BA}\right]$.

Hence $T_c = \dfrac{\hat{\phi}}{SE\left[\hat{\phi}\right]} = \dfrac{\frac{\bar{c}_{AB} - \bar{c}_{BA}}{2}}{\frac{1}{2} SE\left[\bar{c}_{AB} - \bar{c}_{BA}\right]} = \dfrac{\bar{c}_{AB} - \bar{c}_{BA}}{SE\left[\bar{c}_{AB} - \bar{c}_{BA}\right]} = \dfrac{0.99}{0.4702} = 2.105487$.

For a 5% level two-sided test on considers $t_{0.975}(\nu)$where $\nu = n_{AB} + n_{BA} - 2 = 18 + 19 - 2 = 35$. From tables $t_{0.025}(35) = 2.0301$. Since $|T_c| > 2.0301$, we reject the null hypothesis, and so there is evidence of a period effect.

(iv) Comment on the results of (ii) and (iii).

Solution

There was a statistically significant period effect of 0.495, which was statistically significant (p<0.05). The period effect is positives suggesting that the level of gastric bleeding increased over the course of the trial irrespective of treatment.

3. What is a washout period and why might it be important to have one in a cross-over trial?

Solution

A washout period in a crossover trial is a break between treatments to prevent the effect of one treatment being carried forward into the next stage of treatment.

Suppose there are two treatment A and B in the trial. If the effect of treatment A on B is different to the the effect of treatment B on A then one has a carryover effect that biases the estimate of the treatment effect It may be important to have a washout period to prevent a carryover effect.

4. A randomized controlled crossover trial is planned to investigate the effect of substitution of butter by margarine in the diet of patients with high cholesterol. A 0.5 units reduction in cholesterol is considered to be a clinically important difference.

(i) Estimate the sample size required for the cross-over trial if the standard deviation of the differences is 1.5 units, assuming a power of 80% and a 5% two-tailed significance level.

Solution

In a crossover trial sample size is determined by the expression for the total sample size

$$N = \frac{\sigma_d^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$$

For a two-tailed 0.05 level test $z_{\alpha/2} = z_{0.025} = 1.96$

For power (1-β) equal to 80% then $z_\beta = z_{0.2} = 0.84$.

$\tau = 0.5,\ \sigma_d = 1.5$

Applying the formula $N = \frac{1.5^2}{0.5^2}(1.96 + 0.84)^2 = 9 \times 2.8^2 = 70.56$ suggesting a minimum sample size of 71 in total.

5. The relative efficiency of a crossover trial compared to a parallel group trial can be defined by

$$RE = \frac{Var\left[\hat{\tau}_{PGT}\right]}{Var\left[\hat{\tau}_{CT}\right]}.$$

(i) Consider the model for an *AB-BA* crossover trial defined in Q2. For $\hat{\tau}_{CT} = \frac{\bar{d}_{AB} - \bar{d}_{BA}}{2}$ show that

$$Var\left[\hat{\tau}_{CT}\right] = \frac{\sigma_\varepsilon^2}{2}\left(\frac{1}{n_{AB}} + \frac{1}{n_{BA}}\right).$$

Solution

$$\text{Var}\left[\hat{\tau}_{CT}\right] = Var\left[\frac{\bar{d}_{AB} - \bar{d}_{BA}}{2}\right] = \frac{1}{4}\left(Var\left[\frac{\sum_{i\in AB} d_i}{n_{AB}}\right] + Var\left[\frac{\sum_{i\in BA} d_i}{n_{BA}}\right]\right) = \frac{1}{4}\left(Var\left[d_i\right]\left(\frac{1}{n_{AB}} + \frac{1}{n_{BA}}\right)\right)$$

Now $Var\left[d_i\right] = Var\left[\varepsilon_{i1}\right] + Var\left[\varepsilon_{i2}\right] = 2\sigma_\varepsilon^2$. Substitution gives $Var\left[\hat{\tau}_{CT}\right] = \frac{\sigma_\varepsilon^2}{2}\left(\frac{1}{n_{AB}} + \frac{1}{n_{BA}}\right)$

(ii) A parallel group trial corresponds to the first period of an *AB-BA* crossover trial from which a treatment effect can be estimated by $\hat{\tau}_{PGT} = \bar{y}_{BA}(1) - \bar{y}_{AB}(1)$, where $\bar{y}_{AB}(1)$ and $\bar{y}_{BA}(1)$ are the sample means of y_{i1} for each sequence. Show that $\text{Var}\left[\hat{\tau}_{PGT}\right] = \left(\sigma_B^2 + \sigma_\varepsilon^2\right)\left(\frac{1}{n_{AB}} + \frac{1}{n_{BA}}\right)$.

Solution

$$Var\left[y_{i1}\right] = Var\left[\xi_i + \varepsilon_{i1}\right] = Var\left[\xi_i\right] + Var\left[\xi_i\right] = \sigma_B^2 + \sigma_\varepsilon^2$$

$\text{Var}\left[\hat{\tau}_{PGT}\right] = Var\left[\bar{y}_{BA}(1) - \bar{y}_{AB}(1)\right] = Var\left[\bar{y}_{BA}(1)\right] + Var\left[\bar{y}_{AB}(1)\right]$ by independence of groups.

$$Var\left[\bar{y}_{AB}(1)\right] = Var\left[\frac{\sum_{i \in AB} y_{i1}}{n_{AB}}\right] = \frac{1}{n_{AB}} Var\left[y_{i1}\right] = \frac{1}{n_{AB}}\left(\sigma_B^2 + \sigma_\varepsilon^2\right)$$

Hence $\text{Var}\left[\hat{\tau}_{PGT}\right] = \left(\sigma_B^2 + \sigma_\varepsilon^2\right)\left(\frac{1}{n_{AB}} + \frac{1}{n_{BA}}\right)$.

(iii) Hence, show that $RE = 2\left(1 + \frac{\sigma_B^2}{\sigma_\varepsilon^2}\right)$.

Solution

$$RE = \frac{Var\left[\hat{\tau}_{PGT}\right]}{Var\left[\hat{\tau}_{CT}\right]} = \frac{\left(\sigma_B^2 + \sigma_\varepsilon^2\right)\left(\frac{1}{n_{AB}} + \frac{1}{n_{BA}}\right)}{\frac{\sigma_\varepsilon^2}{2}\left(\frac{1}{n_{AB}} + \frac{1}{n_{BA}}\right)} = 2\left(1 + \frac{\sigma_B^2}{\sigma_\varepsilon^2}\right)$$ as required.

(iv) Starting from the formula for the sample size of a parallel group trial with two equal size arms, show that the total sample size for a cross-over trial is $N_C = \frac{2\sigma_\varepsilon^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)$

Solution

For a parallel group trial, the sample size per arm is given by

$n = \frac{2\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)$ (see notes). Hence the total sample size is $\frac{4\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)$.

The difference of the means for the two sequences estimates twice the treatment effect. The variance of the difference $Var\left[d_i\right] = 2\sigma_\varepsilon^2$. Hence

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

(v) Starting from the formula for a parallel group trial show that the total sample size for a parallel group trial is $N_{PGT} = \frac{4\left(\sigma_B^2 + \sigma_\varepsilon^2\right)}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$.

Solution

The total sample size for a parallel group trial is $\frac{4\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)$. Since $Var\left[y_{i1}\right] = \sigma_B^2 + \sigma_\varepsilon^2$.

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

(vi) Hence, show that $\frac{N_{PGT}}{N_C} = RE$

$$\frac{N_{PGT}}{N_C} = \frac{4\left(\sigma_B^2 + \sigma_\varepsilon^2\right)}{2\left(\sigma_\varepsilon^2\right)} = 2\left(1 + \frac{\sigma_B^2}{\sigma_\varepsilon^2}\right) = RE$$

(vii) What is the implication of the relative efficiency for the sample size of patients for a cross-over trial as compared to a parallel group trial?

Solution

It has been shown in (vi) that the relative efficiency is the ratio of the sample sizes. Given that the RE is likely to be large in circumstance where one might conduct a cross-over trial, this implies that cross-over trials will tend to be much smaller assuming other design parameters (τ, α, β) are equal. For example when $\sigma_B^2 = 2\sigma_\varepsilon^2$ the relative efficient was 6, which implies that the sample size of a cross-over trial will be 1/6 of the corresponding parallel group trial.

6. A randomized controlled crossover trial is used to assess whether thyroxin treatment is effective in patients with symptoms of hypothyroidism. Patients have been randomised to either placebo then thyroxin (PT) or thyroxin then placebo(TP). The table below summarizes the sample mean and standard deviation (s.d.) of the free thyroxin (pmol/l) in the blood.

Sequence	*Period 1*		*Period 2*		*Period 2 – Period 1*		*N*
	Mean	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	
PT	16.1	6.3	19.2	6.9	3.1	3.4	20
TP	18.4	6.4	18.3	7.2	-0.1	3.5	20

(i) Using the model defined by question 2 estimate (a) σ_ε^2 and (b) σ_B^2 from the summary data above.

Solution

(a) From question 5 $Var\left[d_i\right]=2\sigma_\varepsilon^2$. $Var\left[d_i\right]$ can be estimated by the pooled sample variance of the treatment differences s_d^2.

$$s_d^2=\frac{\left(n_{PT}-1\right)s_{d_{PT}}^2+\left(n_{TP}-1\right)s_{d_{TP}}^2}{n_{PT}+n_{TP}-2}=\frac{19\times3.5^2+19\times3.4^2}{38}=11.905$$

Hence $\sigma_\varepsilon^2=11.9/2=5.9525$.

(b) From above $Var\left[y_{i1}\right]=\sigma_B^2+\sigma_\varepsilon^2$. $Var\left[y_{i1}\right]$ can be estimated by the pooled sample variance of the period 1 data, say $s^2=\frac{\left(n_1-1\right).s_1^2+\left(n_2-1\right).s_2^2}{n_1+n_2-2}=\frac{6.4^2+6.3^2}{2}=40.325$.

Hence $\sigma_B^2=s^2-s_d^2/2=40.325-5.9525=34.3725$.

(ii) Hence estimate the relative efficient (RE) of a cross-over trial design compared to a parallel group design for this treatment comparison.

Solution

$$RE=2\left(1+\frac{\sigma_B^2}{\sigma_\varepsilon^2}\right)=2\left(1+\frac{40.325}{5.9525}\right)=13.5489$$

(iii) What is the implication of the result of (ii) for the sample size of patients of a future cross-over trial comparing these two treatments as compared to that for a parallel group trial comparing the same treatment?

Solution

It has been shown in Q5 (vi) that the relative efficiency is also the ratio of the sample sizes. Based on this data the ratio of the sample size for a parallel group trial to a crossover trials is therefore approximately 13.5. Hence for trials comparing the same treatments the sample size of a crossover trial can be much smaller than a parallel group trial.