Medical Statistics (MATH38071) 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?

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

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

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Two-sample t test with equal variances
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         |     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(A then B) - mean(B then A)                        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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2. If Y_{ij} is the outcome for the *i*th 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 $\bar{c}_{AB}$ and $\bar{c}_{BA}$ be the sample means of c_{i1} for sequences *AB* and *BA*. Show that $E\left[\left(\bar{c}_{AB}-\bar{c}_{BA}\right)/2\right]=\phi$.

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

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

(iv) Briefly comment on the results of (ii) and (iii).

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

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. 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.

5.

(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

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

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

(iii) The relative efficiency of a crossover design compared to a parallel group design can be defined by $RE = \frac{Var\left[\hat{\tau}_{PGT}\right]}{Var\left[\hat{\tau}_{CT}\right]}$. Show that $RE = 2\left(1 + \frac{\sigma_B^2}{\sigma_\varepsilon^2}\right)$.

(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 crossover trial is $N_C = \frac{2\sigma_\varepsilon^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)$.

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

(vi) Show that $\frac{N_{PGT}}{N_C} = RE$.

6. A randomised 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.

(ii) Estimate the relative efficient (RE) (See Q 5) of a cross-over trial design compared to a parallel group design for this treatment comparison.

(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 the sample size for a parallel group trial comparing the same two treatments.