

Solutions for Specimen Exam paper for MAS367

Section A

1.

A one-sided hypothesis test tests the null hypothesis $H_0: \tau = 0$ against the alternative hypothesis $H_A: \tau > 0$. This may seem appropriate if the anticipated direction of the difference is such that $\hat{\tau} > 0$. However, if you opt for a one-sided test and actually obtain a large negative estimate, i.e. an effect in the opposite direction to that anticipated, then you must be prepared to ascribe this to chance and accept that it provides no evidence whatsoever against $H_0: \tau = 0$. This is incautious and explains why one-sided tests are seldom appropriate in clinical trials.

2.

No. If the true mean difference is greater than or equal to τ_M then there is at least a 90% chance that we will obtain $P < 0.05$. However, for some true mean differences less than τ_M there is a substantial chance of obtaining $P < 0.05$, albeit not as high as 90%. A more formal justification is as follows: the trial has been designed so that the power function $\mathbf{y}(\tau) = \Pr(\text{Reject } H_0 | \text{true difference is } \tau)$ obeys $\mathbf{y}(\tau_M) = 0.9$, but $\mathbf{y}(\tau)$ is clearly continuous so $\mathbf{y}(\tau)$ can be arbitrarily close to 0.9 for τ close to but less than τ_M .

3.

- a) Allocation bias occurs when there is an imbalance between the treatment groups with respect to a prognostic factor.
- b) Stratification and Minimization.
- c) Stratification aims to balance treatment groups in all sub-groups of patients formed by the classification induced by the prognostic factors, whereas minimization aims to produce balance marginally across this classification. More precisely when, e.g. three prognostic factors are at levels i, j and k then stratification aims to make $n_{ijk}^A = n_{ijk}^B$ for all i, j, k (where these are respectively the numbers of patients allocated to A and B in the subgroup). Minimization aims to make $\sum_{i,j} n_{ijk}^A = \sum_{i,j} n_{ijk}^B$ for each k and similarly for i and j .

4.

To show that the analysis is unbiased for τ we must show that $E(\{\bar{X}_2 - \bar{B}_2\} - \{\bar{X}_1 - \bar{B}_1\}) = \tau$. Now the expectation of the mean in group 1 is simply the expectation of an individual component of that mean, namely $\mathbf{m} - \mathbf{m}_B^1$, where \mathbf{m}_B^1 is the mean baseline in group 1. The expectation in group 2 is $\mathbf{m} + \tau - \mathbf{m}_B^2$. Thus the required expectation is the difference of these two. However, by randomization we know that $\mathbf{m}_B^2 = \mathbf{m}_B^1$, hence the result. The efficiency of the analysis is determined by the standard error of $\{\bar{X}_2 - \bar{B}_2\} - \{\bar{X}_1 - \bar{B}_1\}$ which is the square root of $\text{var}(X_2 - B_2) / n_2 + \text{var}(X_1 - B_1) / n_1$ where X_i, B_i are, respectively, generic values of

outcome and baseline for a patient in group i . Now $\text{var}(X_2 - B_2) = \text{var}(X_1 - B_1) = \text{var}(X_1) + \text{var}(B_1) - 2 \text{cov}(X_1, B_1) = 2\mathbf{s}^2(1 - \mathbf{r})$ so the standard error of $\{\bar{X}_2 - \bar{B}_2\} - \{\bar{X}_1 - \bar{B}_1\}$ is the square root of $2\mathbf{s}^2(1 - \mathbf{r})\{n_2^{-1} + n_1^{-1}\}$. The corresponding quantity when the base lines are ignored, i.e. we compare groups using $\bar{X}_2 - \bar{X}_1$, is $\mathbf{s}^2\{n_2^{-1} + n_1^{-1}\}$. So the analysis using change from baseline is more efficient if $2(1 - \mathbf{r}) < 1$.

5.

Comparing those allocated to C with only those who did not withdraw from treatment with I is a comparison of groups not formed by randomization, hence the comparison cannot be claimed to be unbiased. You might wish to perform various analyses of these data, but one analysis which must be performed is the analysis that compares the groups as formed at randomization, which despite its obvious limitations is unbiased. This is the analysis by the dictum of Intention-to-Treat.

Section B

6.

a) It would be acceptable to quote the formula $n = \frac{(z_b + z_{\frac{1}{2}\alpha})^2}{2(\arcsin \sqrt{p_A} - \arcsin \sqrt{p_B})^2}$ provided that the quantities involved were identified correctly. Using 0.2 and 0.3 for the two proportions we obtain $n = \frac{(1.28 + 1.96)^2}{2(\arcsin \sqrt{0.3} - \arcsin \sqrt{0.2})^2} = \frac{5.25}{(0.58 - 0.46)^2} = 365$

[10 marks]

b) Repeating the calculation with proportions 0.7 and 0.8 gives

$n = \frac{(1.28 + 1.96)^2}{2(\arcsin \sqrt{0.8} - \arcsin \sqrt{0.7})^2} = \frac{5.25}{(1.11 - 0.99)^2} = 365$. This could have been

anticipated because a trial that can detect a change in success probabilities from 0.2 to 0.3 with given power and at a given significance level can also be thought of as detecting a change in failure probabilities from 0.8 to 0.7. Determining the sample size using proportion 0.2 and 0.3 must therefore give the same sample size as using the proportions 1-0.2 and 1-0.3, i.e. 0.8 and 0.7.

[10 marks]

c) Let $q = \arcsin(\sqrt{x})$, then $x = \sin^2 q$, so $1 - x = 1 - \sin^2 q = \cos^2 q = \sin^2(\frac{1}{2}\pi - q)$, so $q = \frac{1}{2}\pi - \arcsin(\sqrt{1-x}) = \arcsin(\sqrt{x})$ hence the result. It follows from this identity that $(\arcsin \sqrt{p_A} - \arcsin \sqrt{p_B})^2 = (\arcsin \sqrt{1-p_A} - \arcsin \sqrt{1-p_B})^2$ so sample size determinations based on comparing success proportions must agree with those based on the corresponding failure proportions.

[10 marks]

7.

a) The expectation of $\frac{1}{2}(\bar{d}_{AB} - \bar{d}_{BA})$ is equal to that of $\frac{1}{2}(d_1 - d_{2n})$ (or any two ds one from each sequence). Now

$$E[\frac{1}{2}d_1] = \frac{1}{2}(m + p_1 + t_A - m - p_2 - t_B) = \frac{1}{2}(p_1 - p_2 + t), \text{ and}$$

$$E[\frac{1}{2}d_{2n}] = \frac{1}{2}(p_1 - p_2 - t), \text{ so required expectation is } \tau. \text{ Also}$$

$$E[\bar{x}_{1AB} - \bar{x}_{1BA}] = (m + p_1 + t_A - m - p_1 - t_B) = t, \text{ as required.}$$

[10 marks]

b) As the differences in the two sequences are independent

$$\text{var}[\frac{1}{2}(\bar{d}_{AB} - \bar{d}_{BA})] = \frac{1}{4} \{ \text{var}(\bar{d}_{AB}) + \text{var}(\bar{d}_{BA}) \} \text{ and } \text{var}(\bar{d}_{AB}) = \text{var}(d_1) / n = 2s^2 / n,$$

$$\text{var}(\bar{d}_{BA}) = \text{var}(d_{2n}) / n = 2s^2 / n, \text{ so } \text{var}[\frac{1}{2}(\bar{d}_{AB} - \bar{d}_{BA})] = \frac{1}{4} \{ \frac{2s^2}{n} + \frac{2s^2}{n} \} = \frac{s^2}{n}.$$

Again $\bar{x}_{1AB}, \bar{x}_{1BA}$ are independent, so $\text{var}[\bar{x}_{1AB} - \bar{x}_{1BA}] = \text{var}[\bar{x}_{1AB}] + \text{var}[\bar{x}_{1BA}]$ and this is equal to

$$\text{var}[x_1] / n + \text{var}[x_{2n}] / n = (s_B^2 + s^2) / n + (s_B^2 + s^2) / n = 2(s_B^2 + s^2) / n. \text{ Hence}$$

$$R = 2\{1 + (\mathbf{s}_B^2 / \mathbf{s}^2)\}.$$

[14 marks]

- c) If $\mathbf{s}_B^2 = 6\mathbf{s}^2$ then $R=14$. Thus if we chose to perform a parallel group trial (essentially use period 1 data only) then the standard error of the estimator of the effect of treatment would be $\sqrt{14} = 3.74$ times greater than that you would obtain using a crossover design if the between-patient variance was six times the within-patient variance. Thus if there is the opportunity to run a crossover trial and there is substantially greater variation between patients than within, then a crossover trial can pay very worthwhile dividends.

[6 marks]

8.

- a) By randomization $\mathbf{n}_1 - \mathbf{n}_2 = 0$ [5 marks]

- b) If baselines are ignored, $E[\bar{X}_1 - \bar{X}_2] = \mathbf{m}_1 - \mathbf{m}_2$ [3 marks]

- c) \bar{X}_1, \bar{B}_1 are bivariate Normal, so by the result stated in the question,

$$E(\bar{X}_1 | \bar{B}_1 = \bar{b}_1) = \mathbf{m}_1 + \frac{r\mathbf{s}_X}{\mathbf{s}_B}(\bar{b}_1 - \mathbf{n}_1). \text{ Similarly we obtain}$$

$E(\bar{X}_2 | \bar{B}_2 = \bar{b}_2) = \mathbf{m}_2 + \frac{r\mathbf{s}_X}{\mathbf{s}_B}(\bar{b}_2 - \mathbf{n}_2)$. As the outcome is clearly independent of the baseline in the other group, the conditional value of the baseline value in the other group can be added to the conditioning event in each expectation without changing its value, so we can subtract these two expectations to obtain

$$E(\bar{X}_1 - \bar{X}_2 | \bar{B}_1 = \bar{b}_1, \bar{B}_2 = \bar{b}_2) = \mathbf{m}_1 - \mathbf{m}_2 + \frac{r\mathbf{s}_X}{\mathbf{s}_B}(\bar{b}_1 - \bar{b}_2), \text{ where we have used the result from a).}$$

- d) Clearly, from the above and conditional on \bar{b}_1, \bar{b}_2 , $\bar{X}_1 - \bar{X}_2 - \frac{r\mathbf{s}_X}{\mathbf{s}_B}(\bar{b}_1 - \bar{b}_2)$ has expectation $\mathbf{m}_1 - \mathbf{m}_2$, so this is the adjusted mean. Given the values of the baseline means the adjustment term in this expression is fixed, so the variance of the adjusted mean is the variance of $\bar{X}_1 - \bar{X}_2$, conditional on the baseline means.

Thus, taking into account the independence of \bar{X}_1, \bar{X}_2 we have:

$$\text{var}(\bar{X}_1 - \bar{X}_2 - \frac{r\mathbf{s}_X}{\mathbf{s}_B}(\bar{b}_1 - \bar{b}_2) | \bar{b}_1, \bar{b}_2) = \text{var}(\bar{X}_1 - \bar{X}_2 | \bar{b}_1, \bar{b}_2) = \text{var}(\bar{X}_1 | \bar{b}_1) + \text{var}(\bar{X}_2 | \bar{b}_2)$$

and from the second result stated in the question we obtain

$$\text{var}(\bar{X}_1 | \bar{b}_1) = \frac{\mathbf{s}_X^2}{n_1}(1 - \mathbf{r}^2) \text{ with a similar expression for group 2. Hence}$$

$\text{var}(\bar{X}_1 - \bar{X}_2 | \bar{b}_1, \bar{b}_2) = \mathbf{s}_X^2(\frac{1}{n_1} + \frac{1}{n_2})(1 - \mathbf{r}^2)$. If the baseline information is ignored then $\text{var}(\bar{X}_1 - \bar{X}_2) = \mathbf{s}_X^2(\frac{1}{n_1} + \frac{1}{n_2})$ thus $\text{var}(\bar{X}_1 - \bar{X}_2 | \bar{b}_1, \bar{b}_2) = \text{var}(\bar{X}_1 - \bar{X}_2)(1 - \mathbf{r}^2)$, so if we take account of baseline information in this way we obtain an estimate of treatment effect that cannot exceed that obtained if we ignore the baseline values, and is smaller by a factor $1 - \mathbf{r}^2$. Thus we obtain a reduction in variance unless $\mathbf{r} = 0$. As, in fact, values of \mathbf{r} around 0.5 to 0.8 are common, valuable reductions are usually obtained.