Specimen Exam paper for MAS367
Time allowed 1½ hours

Section A (40 marks in total, answer all questions)

1.
What is the main argument against using one-sided hypothesis tests in a randomized clinical trial?

[6 marks]

2.
The size of a trial has been determined so that there is a 90% chance of detecting a difference in the means of the treatment groups of t_M at the 5% two-sided significance level. If the trial recruits the specified number of patients and a *P*-value less than 0.05 is obtained, does this mean that the true difference must be at least t_M? Justify your answer.

[7 marks]

3.
a) Explain briefly what is meant by allocation bias
b) Name two methods of allocation that are designed to prevent allocation bias
c) Indicate, briefly, how these methods differ.

[3 marks each part]

4.
Suppose the outcome and baseline measurements on a variable for a patient in a clinical trial are denoted by random variables *X* and *B* respectively, where *X* and *B* each have variance s^2 and the correlation between *X* and *B* is r. Suppose also that the trial has two groups and the means in these groups are, respectively, m and $m + t$. Show that an analysis which compares the groups with respect to change from baseline, $X - B$, is unbiassed for t. Find a condition on r that ensures that an analysis based on $X - B$ is more efficient than one based on *X*.

[10 marks]

5.
Pain from muscle strains generally lasts about two weeks. A trial was performed to compare a fortnight of treatment with one of two types of painkiller for the relief of pain in this condition. One treatment was paracetamol with codeine (*C*) and the other was indomethacin (*I*). About 20% of the patients randomized to *I* complained of stomach pains within two days of starting treatment and had to stop taking the treatment. Your clinical colleague suggests comparing those allocated to *C* with those who completed two weeks taking *I*. What is wrong with this strategy? What comparison should be made? This would be an instance of what dictum?

[8 marks]

Section B (30 marks each question, do two questions)

6.

The outcome in a randomized controlled trial is whether or not a skin disease is cleared within six weeks, i.e. the outcome is a binary variable with values 'cleared' and 'not cleared'. There are two treatments A and B and the investigators anticipate that the probability of achieving clearance in group A is 0.2, and it would be clinically important to know if B achieved a success probability of at least 0.3. The study will comprise two groups of *n* patients and the trial is designed to detect the difference in success probabilities from 0.2 to 0.3 with power of 90% at the 5% two-sided significance level.

a) Determine *n*.

b) Repeat the calculation with success probabilities 0.7 and 0.8. What do you observe about the value obtained here and that in part a)? Explain why you could have anticipated this relationship.

c) Prove that $\arcsin(\sqrt{1-x}) = \frac{1}{2}p - \arcsin(\sqrt{x})$ and explain the relevance of this identity to the results in parts a) and b).

[In this question $\arcsin(y)$, $0<y<1$, is the angle in radians between 0 and ½*p* whose sine is *y*. Also note the table of values below

y	0	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1.00
$\arcsin(\sqrt{y})$	0	0.32	0.46	0.58	0.68	0.79	0.89	0.99	1.11	1.25	1.57

and that if $\Phi(.)$ is the cumulative distribution function of a standard Normal variable, $\Phi(1.96) = 0.975$ and $\Phi(1.28) = 0.9$]

7.

The outcomes and the model for the outcomes on the *i*th patient from an AB/BA crossover trial are as follows:

Sequence	Period 1	Period 2
AB (i=1,…,n)	$x_{i1} = m + p_1 + t_A + x_i + e_{i1}$	$x_{i2} = m + p_2 + t_B + x_i + e_{i2}$
BA (i=n+1,…,2n)	$x_{i1} = m + p_1 + t_B + x_i + e_{i1}$	$x_{i2} = m + p_2 + t_A + x_i + e_{i2}$

where m is the general mean, p_j is the effect of period j (=1,2), the treatment effect of interest is $t = t_A - t_B$ and x_i, e_{ij} are independent residuals with zero mean and variances s_B^2, s^2 respectively.

a) Define $d_i = x_{i1} - x_{i2}$ and let the mean of these in sequence AB be $\bar{d}_{AB}$ and similarly for $\bar{d}_{BA}$. Also let $\bar{x}_{1AB}, \bar{x}_{1BA}$ be the mean responses in period 1 for patients allocated to sequences AB and BA respectively. Show that $\frac{1}{2}(\bar{d}_{AB} - \bar{d}_{BA})$ has the same expectation as $\bar{x}_{1AB} - \bar{x}_{1BA}$ and identify this quantity.
b) Find the variance of $\frac{1}{2}(\bar{d}_{AB} - \bar{d}_{BA})$ and of $\bar{x}_{1AB} - \bar{x}_{1BA}$ and the ratio R of these quantities.
c) If $s_B^2 = 6s^2$ evaluate R and comment on the implication of this value when deciding whether to use a crossover design or a parallel group design.

8.

In a randomized clinical trial to compare two treatments, one treatment is given to the n_1 patients allocated to group 1 and the other to the n_2 patients allocated to group 2. The random variable representing the mean outcome in group *i* (=1,2) is $\overline{X}_i$ and the mean of the baseline measurement of the same variable in group *i* is $\overline{B}_i$. You may assume that $(\overline{X}_i, \overline{B}_i)$ comes from a bivariate Normal distribution with means m_i, n_i for outcome and baseline respectively. They have variances s_X^2 / n_i and s_B^2 / n_i, and $\overline{X}_i, \overline{B}_i$ have correlation r, which are the same in the two groups. Interest is focussed on estimating $m_1 - m_2$.

a) What can be said about the value of $n_1 - n_2$?
b) If the baseline information is ignored what is the expectation of $\overline{X}_1 - \overline{X}_2$?
c) If the baseline means are observed to have values $\overline{b}_1, \overline{b}_2$, then given this information what is the expected value of $\overline{X}_1 - \overline{X}_2$?
d) Define an adjusted treatment mean that, given $\overline{b}_1, \overline{b}_2$, has expectation $m_1 - m_2$ and derive its variance. Comment on the size of the variance relative to that of $\overline{X}_1 - \overline{X}_2$ when baseline information is ignored.

[You may wish to use the following: if (*X*,*Y*) have a bivariate Normal distribution, with means m_X, m_Y and variances s_X^2, s_Y^2 and correlation r then $\mathrm{E}(Y|X = x) = m_Y + \frac{r s_Y}{s_X}(x - m_X)$ and $\mathrm{var}(Y|X = x) = s_Y^2(1 - r^2)$]