Worksheet 2 MAS367
Blindness, Placebos and Analysis

1. Patients who have undergone surgery for bladder reconstruction often suffer from excessive levels of mucous in their urine. It is thought that cranberry juice might thin the mucous and thereby alleviate the problems faced by these patients. A trial is proposed in which patients are randomized to drinking either a carton of cranberry juice or a carton containing the same volume of distilled water every day for a month. At the end of the trial a suitable outcome is measured. Clearly, it is impossible to arrange for the trial to be blind. Does this matter: i) if the outcome is the patient's assessment of their improvement (e.g. on a scale of much worse, worse, the same, better, much better) and ii) if the outcome is the amount of mucin secreted in their urine in a given 24 hour period?

2. The following data are from a small trial about pain relief in patients who undergo thoracotomy (an operation which opens the chest cavity). Post-operatively patients find it painful to breath properly and how well they can breath is a reasonable measure of pain relief. The measure of how well they can breath used in this study was the Peak Expiratory Flow rate (PEFR): the larger the PEFR the better the pain relief. All patients received the standard pain relief regimen and in addition had infusions of drug into the fluid surrounding the spinal cord. In group 1 the infusion was saline (i.e. a fluid expected to have no analgesic properties) and in group 2 the anaesthetic fentanyl was used (Data kindly made available by Dr ID Conacher, Freeman Hospital).

	Peak Expiratory flow in litres/min.	
Treatment (1=saline, 2=fentanyl)	Baseline (immediately post-op.)	One hour post-op.
1	90	110
1	150	150
1	80	80
1	140	130
1	60	60
1	150	120
1	180	180
1	250	260
1	60	100
1	170	180
2	100	180
2	130	300
2	120	200
2	150	220
2	190	260
2	150	310
2	100	170
2	170	210
2	100	250
2	100	250

(The data can be downloaded in a Minitab worksheet from http://www.mas.ncl.ac.uk/~njnsm/mas367/tutor.htm)

Ignoring the baseline information test the null hypothesis that the treatment has had no effect on the PEFR. Estimate the difference in the effects of the two treatments. Between what limits would you expect this difference to lie?

3. Suppose that the outcome measurement from a clinical trial is a random variable X which has mean μ in the control group (C) and mean $\mu+\tau$ in the new treatment group (T) and standard deviation σ in both groups. Suppose further that the measurement of the same quantity at the start of the trial, the baseline, is a random variable B which by randomization will have the same mean μ_B and standard deviation σ_B in both groups The correlation between B and X is ρ, assumed to be the same in both groups. It has been shown in lectures that an analysis which compares the groups on the basis of the change from baseline (i.e. compares X-B between the groups) gives a narrower confidence interval than the analysis based on X alone provided that $\rho > ½$. This result assumed that $\sigma = \sigma_B$. Find the corresponding condition when this assumption is not made.

4. An RCT is conducted to compare a control group C (with N_C patients) with a treated group T (with N_T patients) in which the outcome, x_i, and baseline, b_i are assumed to be related by the following model (ε_is are independent Normal errors with zero mean and common variance)

$x_i = \mu + \gamma b_i + \varepsilon_i$ in group C

$x_i = \mu + \tau + \gamma b_i + \varepsilon_i$ in group T

The estimators of the parameters μ, τ, γ, namely $\hat{\mu}, \hat{\tau}, \hat{\gamma}$ are the values of the parameters which minimize:

$$S(\mu,\tau,\gamma) = \sum_{i \text{ in T}} (x_i - \mu - \tau - \gamma b_i)^2 + \sum_{i \text{ in C}} (x_i - \mu - \gamma b_i)^2$$

a) By differentiation show that the estimators satisfy the following:

$$\begin{pmatrix} N & N_T & N\bar{b} \\ N_T & N_T & N_T\bar{b}_T \\ N\bar{b} & N_T\bar{b}_T & S^0_{bb} \end{pmatrix} \begin{pmatrix} \hat{\mu} \\ \hat{\tau} \\ \hat{\gamma} \end{pmatrix} = \begin{pmatrix} N\bar{x} \\ N_T\bar{x}_T \\ S^0_{bx} \end{pmatrix},$$

where $N = N_T + N_C$, $\bar{b}, \bar{b}_T$ are the means of the b_i over both groups or in group T respectively, with similar definitions for $\bar{x}, \bar{x}_T$. Also $S^0_{bb} = \sum b_i^2$, $S^0_{bx} = \sum x_i b_i$ with both summations taken over all patients in the study.

b) Show that for any value of $\hat{\gamma}$ the first two rows of the above matrix equation is satisfied by $\hat{\mu} = \bar{x}_C - \hat{\gamma}\bar{b}_C$, $\hat{\tau} = (\bar{x}_T - \bar{x}_C) - \hat{\gamma}(\bar{b}_T - \bar{b}_C)$, with the obvious definitions for $\bar{x}_C, \bar{b}_C$.

c) Hence show that:

$$\hat{\gamma} = \frac{\sum_{i \text{ in T}} (x_i - \bar{x}_T)(b_i - \bar{b}_T) + \sum_{i \text{ in C}} (x_i - \bar{x}_C)(b_i - \bar{b}_C)}{\sum_{i \text{ in T}} (b_i - \bar{b}_T)^2 + \sum_{i \text{ in C}} (b_i - \bar{b}_C)^2}$$

5. Re-analyse the data in question 2 but this time do not ignore baseline information. Use analysis of covariance in Minitab to compare treatments with baseline value as the covariate. What now is the *P*-value for the comparison of the treatments? What is the difference in the adjusted treatment means? (remember to use Results… to display means corresponding to the treatment term and Graphs can be useful to check whether the assumption of Normal residuals is reasonable). Repeat the analysis, still using baseline as a covariate but with outcome equal to the difference between the value at one-hour post op. and baseline. Comment on the differences and similarities between the analyses.