Medical Statistics (MATH38071) Exercise Sheet 6
(Analysis with Baseline Data)

1. A clinical trial of treatments for chronic back pain allocated 234 patients to either 6 sessions of physiotherapy or a self-help booklet. Treatment was allocated using simple randomisation. The primary outcome was pain measured after 9 months using a 100mm visual analogue scale with 100 representing the worst imaginable pain and 0 representing no pain. Computer output summarizing the results of the trial is listed below. The variables presented are the outcome [VAS_PAIN_9_MONTHS], the pain recorded prior to randomisation [VAS_PAIN_BASELINE] and the treatment group [TRIAL_ARM] coded as 1 if the received physiotherapy and zero if they received a leaflet.

Summary Statistics

	VAS_PAIN_BASELINE			VAS_PAIN_9_MONTHS		
Trial Assignment	mean	sd	N	mean	sd	N
LEAFLET	51.56	22.85	118	35.04	28.41	98
PHYSIOTHERAPY	44.88	18.24	116	26.11	23.49	105

Linear Model : VAS_PAIN_9_MONTHS = b_0+b_1.TRIAL_ARM

Source	SS	df	MS		
Model	4039.1012	1	4039.1012	Number of obs	203
Residual	135682.965	201	675.039628	F(1, 201)	5.98
Total	139722.067	202	691.693399	Prob > F	0.0153
				R-squared	0.0289
				Adj R-squared	0.0241
				Root MSE	25.982

VAS PAIN 9 M	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
TRIAL_ARM	-8.926531	3.649261	-2.45	0.015	-16.12228	-1.730784
Constant	35.04082	2.62453	13.35	0.000	29.86567	40.21596

Linear Model : VAS_PAIN_9_MONTHS = b_0+b_1.TRIAL_ARM + b_2.VAS_PAIN_BASELINE

Source	SS	df	MS		
Model	26232.9875	2	13116.4938	Number of obs	203
Residual	113489.079	200	567.445395	F(2, 200)	23.11
Total	139722.067	202	691.693399	Prob > F	0.0000
				R-squared	0.1878
				Adj R-squared	0.1796
				Root MSE	23.821

VAS PAIN 9 M	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
TRIAL_ARM	-4.176687	3.430938	-1.22	0.225	-10.94214	2.588766
VAS_PAIN_BASE	.5258922	.0840896	6.25	0.000	.3600763	.691708
Constant	7.479774	5.021128	1.49	0.138	-2.421368	17.38092

(i) By examining the output suggest two biases that may affect the results of the trial.

(ii) Suggest two ways in which the design could have been improved to prevent these biases.

(iii) Write down an estimate of the treatment effect of physiotherapy as compared to self-help booklet based on (a) an unadjusted analysis (b) an analysis adjusted for baseline pain, giving the 95% confidence interval and the p-value for the test of the null hypothesis of no treatment effect .

(iv) Briefly comment on the results of these analyses?

2. A researcher has carried out a randomised controlled trial to compare a new treatment (A) with a standard treatment (B) for patients with depression. A depression score has been recorded at baseline (**bprsbase**) and at follow-up (**bprsfu**). Lower scores represent less depression. The researcher generates the printout output listed below from the data.

Results for group = A

Paired T-Test and CI: bprsbase, bprsfu

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Paired T for bprsbase - bprsfu

                  N      Mean     StDev   SE Mean
bprsbase         23     24.35      6.87      1.43
bprsfu           23     20.87      8.45      1.76
Difference       23      3.48      7.10      1.48

95% CI for mean difference: (0.41, 6.55)
T-Test of mean difference = 0 (vs not = 0):
T-Value = 2.35  P-Value = 0.028
```

Results for group = B

Paired T-Test and CI: bprsbase, bprsfu

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Paired T for bprsbase - bprsfu

                  N      Mean     StDev   SE Mean
bprsbase         24     24.33      7.28      1.49
bprsfu           24     22.67      7.63      1.56
Difference       24      1.67      6.86      1.40

95% CI for mean difference: (-1.23, 4.56)
T-Test of mean difference = 0 (vs not = 0):
T-Value = 1.19  P-Value = 0.246
```

Because there is a statistically significant change at the 5% level from baseline to follow-up for group A but not in group B, the researcher concludes that treatment A is more effective than treatment B for treating depression.

(i) Explain the flaw in this conclusion.

(ii) Based on the information in the output two statistical analyses are possible (a) an unadjusted analysis using `bprsbase` and (b) a change score analysis using `bprsbase – bprsfu` . By inspecting the output explain why the analysis based on change should have greater power than the unadjusted analysis.

(iii) Use the output to test whether treatment A is superior to treatment B using an analysis based on the change score, stating any assumption you make.

3. For a parallel group trial comparing a control treatment (C) with a new intervention (T) suppose *y* is a continuous, normally distributed outcome variable and *x* is the value of the same variable recorded prior to randomisation (at baseline). Suppose that τ is the treatment effect such that

$y = \mu + \varepsilon_y$, $x = \mu_x + \varepsilon_x$ Group C

$y = \mu + \tau + \varepsilon_y$ $x = \mu_x + \varepsilon_x$ Group T.

with $E\left[\varepsilon_x\right] = E\left[\varepsilon_y\right] = 0$, $Var\left[\varepsilon_y\right] = \sigma_y^2$, $Var\left[\varepsilon_x\right] = \sigma_x^2$, and $Cov\left[\varepsilon_x, \varepsilon_y\right] = \sigma_{xy}$

Define $\hat{\tau}(\theta) = \left(\bar{Y}_T - \theta\bar{X}_T\right) - \left(\bar{Y}_C - \theta\bar{X}_C\right)$ for any θ.

(i) Write down an expression for $Var\left[\hat{\tau}(\theta)\right]$

(ii) Assume that $T = \hat{\tau}(\theta) / SE\left[\hat{\tau}(\theta)\right]$ has a normal distribution. A general expression for the power to detect a difference τ_S with a normally distributed test statistic with a two-sided α -size test is

$$\text{Power} = (1\text{-}\beta) = 1 - \Phi\left(z_{\alpha/2} - \frac{\tau_S}{SE[\tau]}\right),$$

Write down an expression for the power of a test statistic $T = \hat{\tau}(\theta) / SE\left[\hat{\tau}(\theta)\right]$ to detect a treatment effect τ_S.

(iii) Assuming that $n_T = n_C = n$, show that the formula for estimating sample size to detect an effect τ_S with the test statistic $T = \hat{\tau}(\theta) / SE\left[\hat{\tau}(\theta)\right]$ and power $(1\text{-}\beta)$ using a two-sided α -size test is

$$n = \frac{2\left(\sigma_Y^2 + \theta^2\sigma_X^2 - 2\theta\sigma_{XY}\right)}{\tau_S^2}\left(z_{\alpha/2} + z_\beta\right)^2$$

(iv) Show that the formula for estimating sample size for with an analysis based on change Y – X is

$$n = \frac{2\left(\sigma_Y^2 + \sigma_X^2 - 2\sigma_{XY}\right)}{\tau_S^2}\left(z_{\alpha/2} + z_\beta\right)^2$$

and for analysis based on a linear model adjusting for a baseline covariate *X* is

$$n = \frac{2\left(\sigma_Y^2\left(1 - \rho_{XY}{}^2\right)\right)}{\tau_S^2}\left(z_{\alpha/2} + z_\beta\right)^2$$

4. In a trial of a new dietary intervention to reduce blood cholesterol a new treatment is compared against the current standard treatment. A 10mg/dl reduction (improvement) in cholesterol levels for the new treatment is considered to be the minimum that would be clinically important for patients. Baseline cholesterol data is being collected on each patient. From a previous trial the within-group standard deviation for cholesterol is estimated to be 60mg/dl at baseline and 50mg/dl at follow-up. The correlation between baseline and follow-up measurements for cholesterol has been estimated to be 0.6. Assuming a two-sided 5% significance level, determine the minimum sample size per group to have 80% power for:
   (i) an unadjusted analysis,
   (ii) an analysis based on change scores, and
   (iii) an analysis based on linear model adjusting for baseline cholesterol.