Medical Statistics (MATH38071) Exercise Sheet 4
(Sample Size Estimation)

1. In a published report of a randomised controlled trial comparing a dietary intervention to reduce blood cholesterol with a control treatment, two groups of 100 patients were recruited. The treatment effect was the difference in the mean reduction (improvement) in blood cholesterol. The point estimate of the treatment effect was 11mg/dl with a 95% confidence interval -3mg/dl to 25mg/dl. The p-value for a two-sample t-test was 0.12 and was interpreted using a 5% significance level. The researchers consider that a 10mg/dl reduction in cholesterol levels represented a clinically important benefit.

(i) Comment on the results of the trial.

(ii) Suppose *w* is the width of the confidence interval (*u*-*l*) where *u* and *l* are the upper and lower confidence limits for the difference of means. Using the formula for a confidence interval for the difference of means, write down an expression for the pooled within-group standard deviation as a function of *w*,

(iii) Use the data above to calculate *s*.

(iv) A new trial is planned to test the same intervention against the same control group. Using the value of *s* from (iii) as an estimate of σ, calculate the minimum sample size per treatment group required to have a power of 90% to detect a reduction of 10mg/dl reduction in cholesterol levels for the dietary intervention assuming a two-sided test with 5% significance level .

(v) Part (iv) estimated the numbers need for statistical analysis. It is thought that about 15% of patients randomised will be lost to follow-up, and that only 50% of patients screened for the study will be eligible. Of those two thirds will consent to join the trial and be randomised. Estimate the numbers of patients that need to be (a) randomised and (b) screened for this trial.

2. A clinical trial is planned of an intervention to reduce post-operative complications. The rate of complication is thought to be 20%. It is felt that the intervention would only be worthwhile if this rate was halved. Estimate the sample size required per group to have a power of 90% to detect such a reduction using a two-sample z-test of proportions with two-sided 5% significance level

3. In a parallel group trial, patients are randomised in the ratio of 1 to k into two groups so that $n_T = kn_C$. The primary outcome is a binary variable and the two groups are to be compared using a two-sample z-test of proportions with a two-sided test and significance level α . Show that the total sample size $N = n_T + n_C$ required to have power (1-β) to detect a treatment effect equal to $\tau \left(= \pi_T - \pi_C\right)$ is

$$N = \frac{(1+k)\left(z_{\alpha/2}\sqrt{\pi(1-\pi)(1+k)} + z_\beta\sqrt{\pi_T(1-\pi_T) + k\pi_C(1-\pi_C)}\right)^2}{k\left(\pi_T - \pi_C\right)^2}$$

where π_T and π_C are the proportions under the alternative hypothesis, and π is the proportion under the null.

4. A simpler formula sometimes used for estimating the sample size *n* for each of two equal sized groups to detect a treatment effect of magnitude $\tau\left(=\pi_T-\pi_C\right)$ using a two group z-test of proportions with a two-sided significance level α and power (1-β) is

$$n=\frac{\left(z_{\alpha/2}+z_{\beta}\right)^2\left(\left(\pi_T\right)\left(1-\pi_T\right)+\left(\pi_C\right)\left(1-\pi_C\right)\right)}{\tau^2}$$

(i) By expressing the above result as a function of π, where $\pi=\left(\frac{\pi_T+\pi_C}{2}\right)$, and τ, show that for any given τ with $0<|\tau|<1$, n has a maximum when $\pi=0.5$.

(ii) How might you apply this result if you were designing a randomised trial?

5.

(i) Consider $\gamma=\arcsin\left(\sqrt{\pi}\right)$ and $\hat{\gamma}=\arcsin\left(\sqrt{p}\right)$ where π is the population proportion and p is the sample proportion from a sample of size n. Use the delta method (see notes) to show that

$$Var\left[\hat{\gamma}\right]\cong\frac{1}{4n}.$$

(iii) Consider now a parallel group trial with a binary outcome measure with two treatment groups of size n_T and n_C. Suppose π_T, π_C, p_T, and p_C are the population and sample proportions for each group respectively. With the treatment effect $\hat{\tau}_{as}=\arcsin\left(\sqrt{p_T}\right)-\arcsin\left(\sqrt{p_C}\right)$, show that

$$SE\left[\hat{\tau}_{as}\right]=\sqrt{\frac{1}{4n_T}+\frac{1}{4n_C}}.$$

(iv) Considered a test statistic $T=\frac{\tau}{SE[\tau]}$ assumed to be a normally distributed test under $H_0:\tau=0$ and $H_1:\tau\neq 0$. A general expression for a power to detect a difference τ_D is with a two-sided α size test is $\text{Power} = (1\text{-}\beta)=1-\Phi\left(z_{\alpha/2}-\frac{\tau_D}{SE[\tau]}\right)$

Assuming the test statistic defined as $T_{as}=\frac{\hat{\tau}_{as}}{SE\left[\hat{\tau}_{as}\right]}$ is approximately normally distributed, write down an expression for power to test $H_0:\pi_T=\pi_C$ vs $H_0:\pi_T\neq\pi_C$.

(v) Hence, show that two groups of size $n=\frac{\left(z_{\alpha/2}+z_{\beta}\right)^2}{2\left(\arcsin\left(\sqrt{p_T}\right)-\arcsin\left(\sqrt{p_C}\right)\right)^2}$

will have a power of $(1\text{-}\beta)$ to detect a difference between π_T and π_C with a two-sided test using the test statistic T_{as} with significance level α.

(vi) Recalculate the sample size in question 3 using this formula.

6. Assuming equal size groups, suppose the total sample size for a power $(1-\beta)$ using a significance level α using a two-sided two-sample t-test is N. Suppose that there is imbalance in treatment group sizes due to simple randomisation with $n_T = kn_C$ where n_T and n_C are the number of subjects allocated to each treatments with $N = n_T + n_C$. Show that the power equals

$$1-\Phi\left(z_{\alpha/2}-\left(\frac{2\sqrt{k}}{k+1}\right)\left(z_{\alpha/2}+z_{\beta}\right)\right).$$

7. A randomised controlled trial is planned to compare a treatment (*T*) with the current standard therapy (*C*). Suppose $\lambda = \sqrt{1/n_T + 1/n_C}$ where n_T and n_C are the number of subjects allocated to the treatments respectively. Suppose that patients are allocated in the ratio of $1:k$ such that $n_T = kn_C$.

(i) Assuming that $\Pr[\text{Reject H}_0 | \ \tau \ ] = \left(1-\Phi\left(z_{\alpha/2}-\frac{\tau}{\sigma\lambda}\right)\right)+\Phi\left(-z_{\alpha/2}-\frac{\tau}{\sigma\lambda}\right)$ show that the total sample size required to give a power $(1-\beta)$ for a two-tailed two-sample t-test with significance level α is

$$N(k)=\frac{(k+1)^2}{k}\frac{\sigma^2}{\tau^2}\left(z_{\alpha/2}+z_{\beta}\right)^2.$$

(ii) Hence show that $N(k)=N(1)\left(1+\frac{(k-1)^2}{4.k}\right)$.