**Medical Statistics (MATH38071) Solutions 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 represents a clinically important benefit.

(i) Comment on the results of the trial.

**Solution**

The study was underpowered as it failed to detect a clinically important effect of 11mg/dl as being statistically significant. The sample size needed to be larger to detect an effect of 10mg/dl.

(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*.

**Solution**

From the formula for a confidence interval

$$l = \bar{y}_T - \bar{y}_C - t_{\alpha/2}(\nu) SE\left[\bar{y}_T - \bar{y}_C\right]$$

$u = \bar{y}_T - \bar{y}_C + t_{\alpha/2}(\nu) SE\left[\bar{y}_T - \bar{y}_C\right]$ where $SE\left[\bar{y}_T - \bar{y}_C\right] = s\sqrt{1/n_T + 1/n_C}$ .

It follows that

$$w = u - l = 2.t_{\alpha/2}(\nu) s\sqrt{1/n_T + 1/n_C} .$$

Therefore

$$s = \frac{w}{2.t_{\alpha/2}(\nu)\sqrt{1/n_T + 1/n_C}}$$

(iii) Use the data above to calculate the pooled within-group standard deviation, *s*.

**Solution**

From tables $t_{0.025}(198) \cong 1.972$. $n_T = n_C = 100$ , $w = 25 - (-3) = 28$

From (ii) $s=\dfrac{w}{2.t_{\alpha/2}(\nu)\sqrt{1/n_T+1/n_C}}=\dfrac{28}{2\times 1.972\sqrt{1/100+1/100}}=\dfrac{14\sqrt{50}}{1.972}=\underline{50.2}$

(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 $\sigma$, 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 .

**Solution**

The formula from the notes is $n=\dfrac{2\sigma^2}{\tau^2}\left(z_{\alpha/2}+z_\beta\right)^2$.

From tables $z_{\alpha/2}$ =1.96 for $\alpha$=0.05

For 90% power (1-$\beta$)=0.9. giving $z_\beta=z_{0.1}=1.2816$

From question $\tau$=10mg/dl

From part (ii) $\sigma$=s=50.2 .

Therefore sample size per group,

$$n=\frac{2\sigma^2}{\tau^2}\left(z_{\alpha/2}+z_\beta\right)^2=\frac{2\times(50.2)^2}{100}(1.96+1.2816)^2=529.6\ .$$

Hence the minimum sample size to detect a difference of 10mg/dl with 90% power is <u>530</u> per group.

(v) Part (iv) estimate 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 and 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

**Solution**

(a) If the proportion lost to follow-up is L and the number needed for analysis is N then the number need to be randomised = N/(1-L). With L= 0.15 and N equals to 2x529.6=1059.2, the number that need to be randomised =1059.2/0.85=<u>1246.1</u>. So 1247 patients would need to be randomised.

(b) Similarly if the rates of eligibility=E and the rate of consent is C, the number that need to be screened=N/((1-L)xCxE)=1059.2/(0.85x0.5x2/3)=3738.35, which suggest that 3739 patients would need to be screened to yield the target sample size.

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

**Solution**

The formula in the notes is used

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

From the question

Significance level $\alpha = 0.05$ giving $z_{\alpha/2} = 1.96$

Power1-β=0.9 giving $z_\beta = z_{0.1} = 1.2816$

Control proportion is $\pi_C = 0.2$

If the rate of complications is halved, $\pi_T = 0.1$.Hence $\tau = \pi_T - \pi_C = 0.1$ Assuming $\pi = \frac{(\pi_T + \pi_C)}{2}$ under $H_0 : \tau = 0$, $\pi_T = 0.15$.

Substitution gives $n = \frac{\left(1.96\sqrt{2\times 0.15\times 0.85} + 1.2816\sqrt{0.2\times 0.8 + 0.1\times 0.9}\right)^2}{0.1^2} = 265.8$

Therefore the minimum sample size per group for the required power is 266

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 $(\pi_T - \pi_C)$ is

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

where $\pi_T$ and $\pi_C$ are the proportions under the alternative hypothesis, and $\pi$ is the proportion under the null defined as

**Solution**

From derivation of the formula for sample size for a binary outcome in notes

$$Power = 1 - \beta(\alpha,\delta) = 1 - \Phi\left(\frac{z_{\alpha/2}.\lambda.\sqrt{(\pi(1-\pi))} - \tau}{\sqrt{\frac{\pi_T(1-\pi_T)}{n_T} + \frac{\pi_C(1-\pi_C)}{n_C}}}\right).$$

Since $\Phi^{-1}(\beta) = -z_\beta$, it follows that

$$-z_\beta = \frac{z_{\alpha/2}.\lambda.\sqrt{\left(\pi\left(1-\pi\right)\right)} - \tau}{\sqrt{\frac{\pi_T\left(1-\pi_T\right)}{n_T} + \frac{\pi_C\left(1-\pi_C\right)}{n_C}}}$$ with $\tau = \pi_T - \pi_C$.

If $n_T = kn_C$, then $\lambda = \sqrt{\frac{1}{kn_C} + \frac{1}{n_C}} = \sqrt{\frac{k+1}{kn_C}}$.

Substitution gives and rearrangement gives

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

Rearrangement gives

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

Further rearrangement gives

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

Hence the total sample size,

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

4. A simpler formula 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 $\alpha$ and power (1-$\beta$) 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 $\pi$, where $\pi = \left(\frac{\pi_T + \pi_C}{2}\right)$, and $\tau$, show that for any given $\tau$ with $0 < |\tau| < 1$, $n$ has a maximum when $\pi$ equals 0.5.

**Solution**

Since $\pi = \left(\frac{\pi_T + \pi_C}{2}\right)$ rearrangement gives $\pi_C = 2\pi - \pi_T$.

Substitution $\tau = \pi_T - \pi_C = \pi_T - \left(2\pi - \pi_T\right) = 2\left(\pi_T - \pi\right)$.

Rearrangement gives $\pi_T = \pi + \frac{\tau}{2}$. Hence $\pi_C = \pi - \frac{\tau}{2}$.

Substitution in the formula for *n* given in the question gives

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

Maximum found by differentiation of $n$ with respect to $\pi$

$$\frac{dn}{d\pi} = \frac{\left(z_{\alpha/2} + z_\beta\right)^2}{\tau^2}\left(\left(1 - \pi - \frac{\tau}{2}\right) - \left(\pi + \frac{\tau}{2}\right) - \left(\pi - \frac{\tau}{2}\right) + \left(1 - \pi + \frac{\tau}{2}\right)\right)$$

$= \frac{\left(z_{\alpha/2} + z_\beta\right)^2}{\tau^2}\left((1-2\pi) - (2\pi - 1)\right) = \frac{\left(z_{\alpha/2} + z_\beta\right)^2}{\tau^2}\left((2 - 4\pi)\right)$, which equals zero when $\pi = 0.5$.

$\frac{d^2 n}{d\pi^2} = -4\frac{\left(z_{\alpha/2} + z_\beta\right)^2}{\tau^2} < 0$ so the maximum occurs when $\pi = \left(\frac{\pi_T + \pi_C}{2}\right)$ equals 0.5

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

**Solution**

The result might be useful if one was designing a trial for which one did not know the rates for each treatment, that is $\pi_T$ and $\pi_C$ but did know how large a treatment effect $\tau\left(=\pi_T - \pi_C\right)$ one wished to detect. One would apply the above formula with $\pi = 0.5$ and choice of $\tau$ and know that this is an upper limit of the required sample size. [Note that this approach to sample size estimation was probably used in the smoking cessation trial (Quist-Paulsen P Gallefoss F Randomised controlled trial of smoking cessation intervention after admission for coronary heart disease BMJ 2003;327:1254.) as the paper does not specify $\pi_T$ and $\pi_C$ in the section on sample size.]

5.

(i) Consider $\gamma = \arcsin\left(\sqrt{\pi}\right)$ and $\hat{\gamma} = \arcsin\left(\sqrt{p}\right)$ where $\pi$ 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 $Var\left[\hat{\gamma}\right] \cong \frac{1}{4n}$.

**Solution**

Using the *Delta Method* approximation in the notes $Var\left[f(x)\right] \cong f'(x)^2\Big|_{x=E[x]} Var[x]$

With $f(x) = \arcsin\left(\sqrt{x}\right)$, $f'(x) = \frac{d}{dx}\left(\arcsin\left(\sqrt{x}\right)\right) = \frac{1}{\sqrt{1-x}}.\frac{1}{2\sqrt{x}} = \frac{1}{2\sqrt{x(1-x)}}$

.

From properties of the binomial distribution $E[p]=\pi$ and $Var[p_T]=\dfrac{\pi_T(1-\pi_T)}{n_T}$ .

Hence $Var[\hat{\gamma}]\cong \left.\dfrac{1}{4p(1-p)}\right|_{x=E[x]} Var[p]=\dfrac{1}{4\pi(1-\pi)}\dfrac{\pi(1-\pi)}{n}=\dfrac{1}{4n}$ giving the result.

(ii) Consider now a parallel group trial with a binary outcome measure with two treatment groups of size $n_T$ and $n_C$. Suppose $\pi_T$, $\pi_C$, $p_T$, and $p_C$ are the population and sample proportions.

With the treatment effect $\hat{\tau}_{as}=\arcsin\left(\sqrt{p_T}\right)-\arcsin\left(\sqrt{p_C}\right)$, show that $SE[\hat{\tau}_{as}]=\sqrt{\dfrac{1}{4n_T}+\dfrac{1}{4n_C}}$ .

**Solution**

Since treatment groups are independent,

$$Var[\hat{\tau}_{as}]=Var\left[\arcsin\left(\sqrt{p_T}\right)-\arcsin\left(\sqrt{p_C}\right)\right]=Var\left[\arcsin\left(\sqrt{p_T}\right)\right]+Var\left[\arcsin\left(\sqrt{p_C}\right)\right]$$

Substitution with the result of part (i) give

$$Var[\hat{\tau}_{as}]=\frac{1}{4n_T}+\frac{1}{4n_C}.$$

Hence $SE[\hat{\tau}_{as}]=\sqrt{\dfrac{1}{4n_T}+\dfrac{1}{4n_C}}$ .

(iii) Considered a test statistic $T=\dfrac{\tau}{SE[\tau]}$ 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 $\tau_D$ is with a two-sided $\alpha$ size test is $\text{Power} = (1\text{-}\beta)=1-\Phi\left(z_{\alpha/2}-\dfrac{\tau_D}{SE[\tau]}\right)$

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

**Solution**

Substitution gives

$$\text{Power} = (1\text{-}\beta)=1-\Phi\left(z_{\alpha/2}-\frac{\arcsin\left(\sqrt{p_T}\right)-\arcsin\left(\sqrt{p_C}\right)}{\sqrt{\dfrac{1}{4n_T}+\dfrac{1}{4n_C}}}\right)$$

(iv) Hence, show 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 power $(1\text{-}\beta)$ to detect a difference between $\pi_T$ and $\pi_C$ with a two-sided test using the test statistic $T_{as}$ with significance level $\alpha$.

**Solution**

Assuming $n_T = n_C$

$$\text{Power} = (1\text{-}\beta) = 1 - \Phi\left(z_{\alpha/2} - \left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right).\sqrt{2n}\right)$$

Hence $\beta = \Phi\left(z_{\alpha/2} - \left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right).\sqrt{2n}\right)$

Taking inverses $-z_\beta = z_{\alpha/2} - \left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right).\sqrt{2n}$

Rearrangement gives

$$\sqrt{2n} = \frac{z_{\alpha/2} + z_\beta}{\left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right)}$$

Hence $n = \dfrac{\left(z_{\alpha/2} + z_\beta\right)^2}{2\left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right)^2}$ as required

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

From question 3

Significance level $\alpha = 0.05$ giving $z_{\alpha/2} = 1.96$

Power1-β=0.9 giving $z_\beta = z_{0.1} = 1.2816$

Control proportion is $\pi_C = 0.2$ , $\pi_T = 0.1$. Hence

$$\arcsin\left(\sqrt{\pi_C}\right) = \arcsin\left(\sqrt{0.2}\right) = 0.4636$$

$$\arcsin\left(\sqrt{\pi_T}\right) = \arcsin\left(\sqrt{0.1}\right) = 0.3218$$

Hence $n = \dfrac{\left(z_{\alpha/2} + z_\beta\right)^2}{2\left(\arcsin\left(\sqrt{p_T}\right) - \arcsin\left(\sqrt{p_C}\right)\right)^2} = \dfrac{(1.96 + 1.2816)^2}{2(0.3218 - 0.4636)^2} = 260.94$

The arcsine formula gives 261 per group whereas the proportion based method gave 266.

6. Assuming equal group size suppose the total sample size for a power $(1-\beta)$ using a test size $\alpha$ 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

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

**Solution**

Consider first equal sample size, from notes the total sample size assuming equal allocation is ,

$N = 4\frac{\sigma^2}{\tau^2}\left( z_{\alpha/2} + z_\beta \right)^2$.

Rearrangement gives $\frac{\tau}{\sigma} = \frac{2}{\sqrt{N}}\left( z_{\alpha/2} + z_\beta \right)$ (1)

Consider unequal sample size with $n_T = kn_C$ and $n_T + n_C = N$.

Since $n_T + n_C = N$, it follows that $n_C = N/(k+1)$ and $n_T = kN/(k+1)$

Hence $\lambda = \sqrt{1/n_T + 1/n_C} = \sqrt{\frac{k+1}{Nk} + \frac{k+1}{N}} = \frac{1+k}{\sqrt{kN}}$. (2)

From notes $Power = 1 - \Phi\left( z_{\alpha/2} - \frac{\tau}{\sigma\lambda} \right)$ where $\Phi$ is the cumulative distribution function of the standardised normal distribution.

Substitution with (1) and (2) gives

$$Power = 1 - \Phi\left( z_{\alpha/2} - \frac{\frac{2}{\sqrt{N}}\left( z_{\alpha/2} + z_\beta \right)}{\frac{(1+k)}{\sqrt{kN}}} \right) = 1 - \Phi\left( z_{\alpha/2} - \left( \frac{2\sqrt{k}}{k+1} \right)\left( z_{\alpha/2} + z_\beta \right) \right)$$ as required.

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 $\alpha$ size test is

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

**Solution**

The second term in equation  is negligible, therefore $Power = 1 - \beta(\alpha,\tau) \cong 1 - \Phi\left(z_{\alpha/2} - \frac{\tau}{\sigma\lambda}\right)$

Since $\Phi^{-1}(\beta) = -z_\beta$ it follows that $-z_\beta = z_{\alpha/2} - \frac{\tau}{\sigma\lambda}$

giving $\frac{\tau}{\sigma\lambda} = z_{\alpha/2} + z_\beta$ .

If $n_T = kn_C$ , then $\lambda = \sqrt{1/n_C + 1/kn_C} = \sqrt{(k+1)/kn_C}$

Therefore $\frac{\tau}{\sigma}\sqrt{\frac{kn_C}{(k+1)}} = z_{\alpha/2} + z_\beta$ .

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

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

Hence the total sample size $N(k) = n_C + kn_C = \frac{(k+1)^2}{k}\frac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$ as required.

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

**Solution**

Substituting k=1 gives $N(1) = 4\frac{\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_\beta\right)^2$

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