ST520: Statistical Principles of Clinical Trials

HW 4 Solutions

Problem 1

(a) Let Y_{1j} be the blood pressure (in mm) of patient j using the new treatment, and let Y_{2j} denote the blood pressure of patient j using placebo. We assume the following statistical model:

$$Y_{2j} \overset{iid}{\sim} N(\mu_2, \sigma^2), j = 1, \ldots, n_2$$
$$Y_{1j} \overset{iid}{\sim} N(\mu_2 + \Delta, \sigma^2), j = 1, \ldots, n_1$$

Our null hypothesis is then $H_0 : \Delta \geq 0$, and our alternative hypothesis is $H_A : \Delta < 0$. The clinically important difference is $\Delta_A = 5$.

(b) Because we are comparing the difference in mean responses among two groups, the test statistic here would be a T-statistic. Let n be the total number of patients, so that $n_1 = 2n/3$ patients are assigned to the new treatment and $n_2 = n/3$ patients are assigned to the placebo. Let $\bar{Y}_{1+} = \frac{1}{n_1}\sum_{j=1}^{n_1} Y_{1j}$ and $\bar{Y}_{2+} = \frac{1}{n_2}\sum_{j=1}^{n_2} Y_{2j}$ be the sample mean responses among patients under the new treatment and placebo, respectively. Because we assume both treatments have the same variance, we use the pooled variance estimator in the denominator. We would calculate the statistic as

$$T = \frac{\bar{Y}_{1+} - \bar{Y}_{2+}}{s_Y(\frac{1}{n/3} + \frac{1}{2n/3})^{1/2}} = \frac{\bar{Y}_1 - \bar{Y}_2}{s_Y(\frac{9}{2n})^{1/2}}$$

where $s_Y^2 = \frac{\sum_{j=1}^{n_2}(Y_{2j} - \bar{Y}_{2+})^2 + \sum_{j=1}^{n_1}(Y_{1j} - \bar{Y}_{1+})^2}{n_1 + n_2 - 2}$ is the pooled sample variance.

(c) Based on this test statistic, we want the probability that we reject H_0 to be at least 0.8 at the clinically significant difference, i.e. when $\Delta = \Delta_A = 5$, using a level $\alpha = 0.025$ one-sided test. We calculate $Z_\alpha = 1.96$ and $Z_\beta = 0.842$. Then we want

$$\frac{5}{25(\frac{9}{2n})^{1/2}} = Z_{0.20} + Z_{0.025}$$
$$\Rightarrow n = \frac{(Z_{0.20} + Z_{0.025})^2(25^2)(9/2)}{5^2} = 883.3$$

Therefore, we need at least $\boxed{n = 882}$ patients, corresponding to $n_1 = 294$ patients in the new treatment arm and $n_2 = 588$ in the placebo arm, to obtain the power to detect the clinical difference given using a one-sided test at the 0.025 level of significance.

(d) If we instead randomized with equal allocation, we would instead have $n_1 = n_2 = n/2$. Consequently, the test statistic would instead be $T = \frac{\bar{Y}_2 - \bar{Y}_1}{s_Y(\frac{1}{n/2} + \frac{1}{n/2})^{1/2}} = \frac{\bar{Y}_2 - \bar{Y}_1}{s_Y(\frac{4}{n})^{1/2}}$, so we would obtain $n = \frac{(Z_{0.20} + Z_{0.025})^2(25^2)(4)}{5^2} = 785.1$, or $\boxed{n = 786}$ patients instead. This corresponds to $n_1 = n_2 = 393$ patients in each arm.

Problem 2

(a) It appears that both groups have similar variances. Our test statistic is then

$$T = \frac{\bar{Y}_{1+} - \bar{Y}_{2+}}{s_p(\frac{1}{n_1} + \frac{1}{n_2})^{1/2}}, s_p^2 = \frac{(n_1-1)s_1^2 + (n_2-1)s_2^2}{n_1+n_2-2}$$

Using the data given, the test statistic is $T = -2.756$.

(b) The test statistic T has a normal distribution under the null hypothesis. Our p-value is then $P(T < -2.756) = 0.00289$. There is enough evidence to reject H_0: the new drug is ineffective. We can conclude that the new drug is effective.

Problem 3

(a) Let p_1 be the proportion of surviving patients (after six months) initially assigned to treatment 1, and let p_2 be the same quantity for treatment 2. Let n_1 and n_2 be the total number of patients allocated to treatments 1 and 2, respectively. Lastly, let the true probability of survival under each treatment be π_1 and π_2. We want to test $H_0 : \pi_1 = \pi_2$, and our alternative is $H_A : \pi_1 > \pi_2$.

We assume that the two treatments will have equal patient populations, so $n_1 = n_2 = n/2$ here.

Then our test statistic is

$$T = \frac{p_1 - p_2}{\{(\frac{1}{n_1} + \frac{1}{n_2})\bar{p}(1-\bar{p})\}^{1/2}} = \frac{\sqrt{n}(p_1 - p_2)}{\{4\bar{p}(1-\bar{p})\}^{1/2}}$$

where $\bar{p} = \frac{X_1+X_2}{n_1+n_2}$. We need $\frac{n^{1/2}(0.1)}{\{4(0.85)(0.15)\}^{1/2}} = Z_{0.05/2} + Z_{0.10}\left\{\frac{0.8(0.2)+0.9(0.1)}{2(0.85)(0.15)}\right\}$. This leads us to $n = \frac{4(0.85)(0.15)(1.96+1.28(0.98)^{1/2})^2}{0.1^2} = 531.7$, so we need at least $\boxed{532}$ patients to obtain the power required for the 0.05-level two-sided test. This corresponds to $n_1 = n_2 = 266$ patients in each treatment arm.

(b) If we were to use the arcsine square root transformation, our test statistic would be

$$T' = \frac{\sin^{-1}(\sqrt{p_1}) - \sin^{-1}(\sqrt{p_2})}{\sqrt{\frac{1}{4(n/2)} + \frac{1}{4(n/2)}}} = \sqrt{n}(\sin^{-1}(\sqrt{p_1}) - \sin^{-1}(\sqrt{p_2}))$$

We need $\sqrt{n}(\sin^{-1}(\sqrt{0.9}) - \sin^{-1}(\sqrt{0.8})) = Z_{0.05/2} + Z_{0.10} = 3.24$, or $n = \frac{3.24^2}{(\sin^{-1}(\sqrt{0.9}) - \sin^{-1}(\sqrt{0.8}))^2} = 521.9$, so we would need at least $\boxed{522}$ patients to obtain the power required. This corresponds to $n_1 = n_2 = 261$ patients for each treatment arm.

Problem 4

(a) The test statistic using the proportions test is $T = \frac{(\frac{54}{73} - \frac{63}{77})}{\sqrt{\frac{117}{150}(1-\frac{117}{150})(\frac{1}{73}+\frac{1}{77})}} = -1.153$. This gives a p-value of $P(|Z| > T) = \boxed{0.249}$.

(b) The test statistic using the arcsine square root transformation is $T = \frac{\sin^{-1}(\sqrt{\frac{54}{73}}) - \sin^{-1}(\sqrt{\frac{63}{77}})}{\sqrt{\frac{1}{4(73)} + \frac{1}{4(77)}}} = -1.155$. This gives a p-value of $P(|Z| > T) = \boxed{0.248}$.

(c) Based on these results, one might conclude that there is no significant evidence of a treatment difference at the 0.05 level of significance.

(d) Compared to the trial in question 3, the sample size in this clinical trial is too small. This leads to the weak power of this test. The conclusion that there is no significant difference between the two treatments is not guaranteed by enough power.