Sample Size Reference, Fleiss [1981] book

1) Based on Normal Distribution (1-Sample)

Suppose $y_1, y_2, \ldots, y_n$ are from a normal distribution (μ, σ^2), σ^2 known

- Test $H_0 : \mu = \mu_0$ against $H_1 : \mu = \mu_1 > \mu_0$

- Require 1-sided Type I error α and Type II error β

- Reject H_0 when $z = \frac{(\overline{y} - \mu_0)}{\sigma/\sqrt{n}} > z_\alpha,$ where $\overline{y} = \frac{\sum_{i=1}^{n} y_i}{n}$ and z_α is $100(1-\alpha)$th percentile of standard normal distribution with mean 0 and variance 1

- Power $= \Pr\{z > z_\alpha \text{ under } H_1\} = 1 - \beta$

$$= \Pr\{(\overline{y} - \mu_0)\sqrt{n}/\sigma > z_\alpha \text{ under } H_1\}$$

$$= \Pr\{\overline{y} > (\sigma z_\alpha + \sqrt{n}\,\mu_0)/\sqrt{n} \text{ under } H_1\}$$

$$= \Pr\{\sqrt{n}(\overline{y} - \mu_1)/\sigma > z_\alpha - \sqrt{n}\,(\mu_1 - \mu_0)/\sigma\}$$

$$= 1 - \beta$$

- Which implies $z_\alpha - \frac{\sqrt{n}(\mu_1 - \mu_0)}{\sigma} = -z_\beta$

$$(z_\alpha + z_\beta)\sigma/(\mu_1 - \mu_0) = \sqrt{n}$$

$$n = (z_\alpha + z_\beta)^2\sigma^2/(\mu_1 - \mu_0)^2$$

- Let $\Delta = (\mu_1 - \mu_0)$, then $n = \frac{(z_\alpha + z_\beta)^2\sigma^2}{\Delta^2}$

- Now suppose $y_1, y_2, \ldots, y_n$ are dichotomous such that $y_i = \begin{cases} 1 & \text{if positive response} \\ 0 & \text{if negative response} \end{cases}$

Then $E\{y_i\} = \pi = \Pr\{y_i = 1\}$. $V\{y_i\} = \pi(1 - \pi)$.

So for $H_0 : \pi = \pi_0$ against $H_1 : \pi = \pi_1$, use

$$n = \frac{(z_\alpha + z_\beta)^2\{\text{Max}[\pi_0(1 - \pi_0), \pi_1(1 - \pi_1)]\}}{(\pi_1 - \pi_0)^2}$$

2) <u>Based on Wald Statistic (2-Sample)</u>

Suppose two groups are to be compared for the probabilities of favorable response. Suppose the number favorable in samples from the respective groups have independent binomial distributions

- Let p_i be proportion favorable in ith group for which corresponding sample size is n_i. Let $\pi_i = E\{p_i\}$ be probability of favorable in population represented by sample for ith group

- Test $H_0 : \pi_1 = \pi_2$ vs. $H_1 : (\pi_1 - \pi_2) = \Delta > 0$ with 1-sided Type I Error α and Type II Error β

- Wald Statistic rejection region for H_0 is

$$z_W = \frac{(p_1 - p_2)}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}} > z_\alpha,$$

where z_α is $100(1-\alpha)$th percentile of standard normal distribution

- Power $= \Pr\{z_W > z_\alpha \text{ under } H_1\} = 1 - \beta$

$$= \Pr\left\{ \frac{(p_1 - p_2)}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}} > z_\alpha \text{ under } H_1 \right\}$$

$$= \Pr\left\{ \frac{(p_1 - p_2) - (\pi_1 - \pi_2)}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}} > z_\alpha - \frac{(\pi_1 - \pi_2)}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}} \right\}$$

- Which implies

$$z_\alpha - \frac{(\pi_1 - \pi_2)}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}} \approx z_\alpha - \frac{(\pi_1 - \pi_2)}{\sqrt{\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}}} = -z_\beta$$

or $$n_1 = \frac{(z_\alpha + z_\beta)^2 \left\{ \pi_1(1-\pi_1) + \frac{\pi_2(1-\pi_2)}{n_2/n_1} \right\}}{(\pi_1 - \pi_2)^2}$$

$$= \frac{(z_\alpha + z_\beta)^2 \left\{ \pi_1(1-\pi_1) + \frac{\pi_2(1-\pi_2)}{k} \right\}}{(\pi_1 - \pi_2)^2},$$

where $(n_2/n_1) = k$ or $n_2 = kn_1$

3) Based on Counterpart to Pearson χ^2 Statistic (2-Sample)

- Fisher's exact test results are better approximated if sample size is based on continuity corrected counterpart to Pearson chi-square statistic.

a) For equal sample size in both groups, meaning $n_1 = n_2 = n$ (i.e., $k = 1$):

- Rejection region is:

$$z_P = \frac{(p_1 - p_2) - \frac{1}{n}}{\sqrt{\frac{2\overline{p}(1-\overline{p})}{n}}} > z_\alpha, \quad \text{where } \overline{p} = \frac{p_1 + p_2}{2}$$

- Power $= \Pr\{z_P > z_\alpha \text{ under } H_1\} = 1 - \beta$

$$= \Pr\left\{ \frac{(p_1 - p_2) - \frac{1}{n}}{\sqrt{\frac{2\overline{p}(1-\overline{p})}{n}}} > z_\alpha \text{ under } H_1 \right\}$$

$$= \Pr\left\{ (p_1 - p_2) > \frac{1}{n} + z_\alpha \sqrt{\frac{2\overline{p}(1-\overline{p})}{n}} \text{ under } H_1 \right\}$$

$$= \Pr\left\{ (p_1 - p_2) - (\pi_1 - \pi_2) > \frac{1}{n} - (\pi_1 - \pi_2) + z_\alpha \sqrt{\frac{2\overline{p}(1-\overline{p})}{n}} \text{ under } H_1 \right\}$$

$$= \Pr\left\{ \frac{(p_1 - p_2) - (\pi_1 - \pi_2)}{\sqrt{\frac{\pi_1(1-\pi_1)}{n} + \frac{\pi_2(1-\pi_2)}{n}}} > \right.$$

$$\left. \frac{\frac{1}{n} - (\pi_1 - \pi_2) + z_\alpha \sqrt{\frac{2\overline{p}(1-\overline{p})}{n}}}{\sqrt{\frac{\pi_1(1-\pi_1)}{n} + \frac{\pi_2(1-\pi_2)}{n}}} \right\}$$

- Which implies that

$$-z_\beta = \frac{\frac{1}{n} - (\pi_1 - \pi_2) + z_\alpha \sqrt{\frac{2\overline{p}(1-\overline{p})}{n}}}{\sqrt{\frac{\pi_1(1-\pi_1)}{n} + \frac{\pi_2(1-\pi_2)}{n}}} \approx \frac{\frac{1}{n} - (\pi_1 - \pi_2) + z_\alpha \sqrt{\frac{2\overline{\pi}(1-\overline{\pi})}{n}}}{\sqrt{\frac{\pi_1(1-\pi_1)}{n} + \frac{\pi_2(1-\pi_2)}{n}}}$$

or

$$-z_\beta \sqrt{\frac{\pi_1(1-\pi_1)}{n} + \frac{\pi_2(1-\pi_2)}{n}} = \frac{1}{n} - (\pi_1 - \pi_2) + z_\alpha \sqrt{\frac{2\overline{\pi}(1-\overline{\pi})}{n}}$$

or

$$\frac{\left[z_\alpha \sqrt{2\overline{\pi}(1-\overline{\pi})} + z_\beta \sqrt{\pi_1(1-\pi_1) + \pi_2(1-\pi_2)}\right]}{(\pi_1 - \pi_2)} = \left\{ \sqrt{n} - \frac{1}{(\pi_1 - \pi_2)\sqrt{n}} \right\}$$

- Let $n' = \frac{\left[z_\alpha \sqrt{2\overline{\pi}(1-\overline{\pi})} + z_\beta \sqrt{\pi_1(1-\pi_1) + \pi_2(1-\pi_2)}\right]^2}{(\pi_1 - \pi_2)^2}$

- Then $n' = \left\{ \sqrt{n} - \frac{1}{(\pi_1 - \pi_2)\sqrt{n}} \right\}^2$

$$= n - \frac{2}{(\pi_1 - \pi_2)} + \frac{1}{n(\pi_1 - \pi_2)^2}$$

- Which implies

$$n^2 - \left(\left(n' + \frac{2}{(\pi_1 - \pi_2)}\right) n + \frac{1}{(\pi_1 - \pi_2)^2}\right) = 0$$

- Thus, $n = \frac{n' + \frac{2}{(\pi_1 - \pi_2)} + \sqrt{\left(n' + \frac{2}{(\pi_1 - \pi_2)}\right)^2 - \frac{4}{(\pi_1 - \pi_2)^2}}}{2}$

$$= \frac{n'}{2} + \frac{1}{(\pi_1 - \pi_2)} + \frac{1}{2}\sqrt{n'^2 + \frac{4n'}{(\pi_1 - \pi_2)}}$$

$$= \frac{n'}{2}\left\{1 + \sqrt{1 + \frac{4}{n'(\pi_1 - \pi_2)}}\right\} + \frac{1}{(\pi_1 - \pi_2)}$$

$$= \frac{n'}{2}\left\{\left[1 + \sqrt{1 + \frac{4}{n'(\pi_1 - \pi_2)}}\right]^2 \left(\frac{1}{2}\right) - \frac{2}{n'(\pi_1 - \pi_2)}\right\} + \frac{1}{(\pi_1 - \pi_2)}$$

$$= \frac{n'}{4}\left[1 + \sqrt{1 + \frac{4}{n'(\pi_1 - \pi_2)}}\right]^2 \text{ where } \pi_1 > \pi_2$$

Since $\sqrt{1 + x} \approx 1 + \frac{x}{2}$ for small $x > 0$,

$$n \approx \frac{n'}{4}\left[1 + 2\left\{1 + \left(\frac{1}{2}\right)\frac{4}{n'(\pi_1 - \pi_2)}\right\} + 1 + \frac{4}{n'(\pi_1 - \pi_2)}\right]$$

$$= n' + \frac{2}{(\pi_1 - \pi_2)}$$

- In summary,

$$n = \frac{n'}{4}\left[1 + \sqrt{1 + \frac{4}{n'|\pi_1 - \pi_2|}}\right]^2 \approx n' + \frac{2}{|\pi_1 - \pi_2|}$$

where

$$n' = \frac{\left[z_\alpha\sqrt{2\overline{\pi}(1-\overline{\pi})} + z_\beta\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}\right]^2}{(\pi_1-\pi_2)^2}$$

for which $\overline{\pi} = \frac{\pi_1+\pi_2}{2}$, and z_α and z_β are the $100(1-\alpha)$th and $100(1-\beta)$th percentiles of $N(0,1)$

b) For a specified sample size of n per group, power to test $H_0 : \pi_1 = \pi_2$ against $H_1 : (\pi_1 - \pi_2) = \Delta > 0$ is determined via

$$n' = n - \frac{2}{|\pi_1-\pi_2|}$$

$$z_\beta = \frac{|\pi_1-\pi_2|\sqrt{n'} - z_\alpha\sqrt{2\overline{\pi}(1-\overline{\pi})}}{\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}}$$

- Thus,

$$\text{Power} = \Pr\left\{\text{Std. Normal} \leq \frac{|\pi_1-\pi_2|\sqrt{n'} - z_\alpha\sqrt{2\overline{\pi}(1-\overline{\pi})}}{\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}}\right\}$$

c) For two-sided tests, apply methods here with $\frac{\alpha}{2}$

d) For alternatives H_1, specify $(\pi_1 - \pi_2)$ with π_1 directly

- Specify π_2 and θ for $\pi_1 = \pi_2 + \theta(1-\pi_2)$ and so

$(\pi_1 - \pi_2) = \theta(1-\pi_2)$, or $\theta = \frac{(\pi_1-\pi_2)}{(1-\pi_2)}$

- Specify π_2 and odds ratio $\psi = \frac{\pi_1(1-\pi_2)}{\pi_2(1-\pi_1)}$

$$\frac{\pi_1}{(1-\pi_1)} = \psi \frac{\pi_2}{(1-\pi_2)} \text{ or } \pi_1 = \frac{\psi \frac{\pi_2}{(1-\pi_2)}}{1+\psi \frac{\pi_2}{(1-\pi_2)}}$$

$$\pi_1 = \frac{\psi\pi_2}{(1-\pi_2)+\psi\pi_2} \text{ and } \pi_1 - \pi_2 = \frac{\psi\pi_2}{(1-\pi_2)+\psi\pi_2} - \pi_2$$

$$\text{or } \pi_1 - \pi_2 = \frac{\psi\pi_2 - \pi_2(1-\pi_2) - \psi\pi_2^2}{(1-\pi_2)+\psi\pi_2} = \frac{(\psi-1)\pi_2(1-\pi_2)}{(\psi-1)\pi_2+1}$$

e) For general situation with n_1 subjects in Group 1 and $n_2 = kn_1$ in Group 2

$$n_1' = \frac{\left[z_\alpha\sqrt{(k+1)\overline{\pi}(1-\overline{\pi})} + z_\beta\sqrt{k\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}\right]^2}{k(\pi_1-\pi_2)^2}$$

$$n_1 = \frac{n_1'}{4}\left[1 + \sqrt{1 + \frac{2(k+1)}{n_1' k|\pi_1-\pi_2|}}\right]^2$$

$$\approx n_1' + \frac{(k+1)}{k|\pi_1-\pi_2|},$$

where $\overline{\pi} = \frac{(\pi_1+k\pi_2)}{(1+k)}$

f) For the situation with n subjects in one group which corresponds to π_1, the sample size to test π_2 as a null hypothesis is given by #5 above with $k = \infty$, i.e.:

$$n_1' = \frac{\left[z_\alpha\sqrt{\pi_2(1-\pi_2)}+z_\beta\sqrt{\pi_1(1-\pi_1)}\,\right]^2}{(\pi_1-\pi_2)^2}$$

$$n_1 = \frac{n_1'}{4}\left[1 + \sqrt{1 + \frac{2}{n'|\pi_1-\pi_2|}}\,\right]^2$$

<u>Example of sample size calculations:</u> Suppose a clinical trial is being planned to compare a test treatment, an active control treatment, and placebo for the healing of ulcers. Suppose the expected healing rates are $\pi_1 = 0.45$ for placebo, $\pi_2 = 0.68$ for the active control, and $\pi_3 = 0.82$ for the test treatment.

a) What sample size per treatment is needed to have 0.80 power for the comparison between the test treatment and the active control at the two-sided $\alpha = 0.05$ significance level (given that the sample sizes are equal for these two treatments).

For the general situation with n_1 subjects in Group 1 and $n_2 = kn_1$ subjects in Group 2:

$$n_1' = \frac{\left[z_\alpha \sqrt{(k+1)\,\overline{\pi}\,(1-\overline{\pi})} + z_\beta \sqrt{k\,\pi_1\,(1-\pi_1) + \pi_2\,(1-\pi_2)}\,\right]^2}{k(\pi_1 - \pi_2)^2}$$

$$n_1 = \frac{n_1'}{4}\left[1 + \sqrt{1 + \frac{2(k+1)}{n_1' k |\pi_1 - \pi_2|}}\right]^2 \approx \; n_1' + \frac{(k+1)}{k|(\pi_1 - \pi_2)|}$$

where $\overline{\pi} = \frac{(\pi_1 + k\pi_2)}{(1+k)}$

For our problem, $k = 1$, so $\overline{\pi} = \frac{(\pi_2+\pi_3)}{2} = \frac{(0.68 + 0.82)}{2} = 0.75$

$$n' = \frac{\left[1.96\sqrt{2\,(0.75)(0.25)} + 0.84\sqrt{0.68\,(0.32) + 0.82\,(0.18)}\,\right]^2}{(0.68 - 0.82)^2} = 148.8$$

and

$$n = \frac{148.8}{4}\left[1 + \sqrt{1 + \frac{4}{148.8|0.68 - 0.82|}}\right]^2$$
$= 162.8 \approx 163$ per group

b) What sample size is needed to provide 0.80 power for the comparison between the active control and placebo at the two-sided $\alpha = 0.05$ significance level in a research design where twice as many patients receive active control as placebo?

n_1 patients get placebo

$n_2 = 2n_1$ patients get active drug $\quad \Rightarrow k = 2$

$$\overline{\pi} = \frac{(\pi_1 + k\pi_2)}{(k+1)} = \frac{(0.45 + (2)0.68)}{3} = 0.60$$

$$n_1' = \frac{\left[1.96\sqrt{3\,(0.60)(0.40)} + 0.84\sqrt{2(0.45)\,(0.55) + 0.68\,(0.32)}\,\right]^2}{2(0.45 - 0.68)^2}$$

$$= 53.2$$

and

$$n_1 = \frac{53.2}{4}\left[1 + \sqrt{1 + \frac{6}{2(53.2)\left|0.45 - 0.68\right|}}\,\right]^2$$

$= 59.5 \approx 60$ patients in placebo group and
120 patients in active group

c) For a study design with sufficient sample size to address both (a) and (b), and with twice as many patients for each of test treatment and active control as for placebo, what is the power for the statistical test to compare test treatment with placebo at the two-sided $\alpha = 0.05$ significance level (Hint: for this study, the sample size for active control will be the larger of the values from (a) and (b), the sample size for test treatment will be the same as that for the active control, and the sample size for placebo will be half as large as that for the active control).

$n_1 = 82$ placebo group $\qquad z_\beta = ?$
$n_3 = 163$ test treatment

Solving for z_β :

$$\bar{\pi} = \frac{(0.45 + (2)0.82)}{3} = 0.70$$

$$82 \approx n_1' + \frac{3}{2|(0.45 - 0.82)|} \qquad \Rightarrow n_1' = 78$$

$$78 = \frac{\left[1.96\sqrt{3\,(0.70)(0.30)} + z_\beta\sqrt{2(0.45)\,(0.55) + 0.82\,(0.18)}\right]^2}{2(0.45 - 0.82)^2}$$

$$\Rightarrow z_\beta = 3.824$$

So the power would be $> 99\%$.

d) Suppose the rate of an adverse event is 1% in the treatment group. How many subjects are needed to have 90% power at the one-sided $\alpha = 0.025$ level that the rate of the adverse event is less than 3%?

$$n' = \frac{\left[1.96\sqrt{(.03)(1-.03)} + 1.282\sqrt{(.01)(1-.01)}\right]^2}{(.01-.03)} = 534$$

$$n = \frac{(534)}{4}\left[1 + \sqrt{1 + \frac{2}{(534)\left|.01-.031\right|}}\right]^2 = 583$$