Statistics 641, Fall 2013
Homework #6
Solutions

1. Heart patients have a greater risk of a second heart attack (MI) or death immediately following the first MI, then they will later on. Suppose (simplistically) that with standard therapy, the hazard rate λ is constant .10/year during the first 6 months following MI and constant .04/year thereafter. Suppose further that a new treatment is expected to reduce these rates by 25%. We wish to perform a study of patients enrolled immediately following an MI with (uniform) recruitment and followup of either:

   - (i) 1.5 year recruitment, 4 year followup
   - (ii) 2 year recruitment, 3.5 year followup

   (a) Calculate the required number of events to achieve 90% power at $\alpha = 0.05$. Assume equal numbers of patients in each treatment group.

   Schoenfeld's formula gives the number of events required to achieve the desired power is (assume 90% power and $\alpha = 0.05$).

   $$\frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2}{\xi_1\xi_2 \log(r)^2} = \frac{3.24^2}{(1/2)^2 \log .75^2} = 507.4$$

   (b) Compute the required sample size (number of subjects) for each of the two designs. *Hint: You need to compute the probability that a subject will experience an event during the trial. The hazard function will be piecewise linear.*

   To compute the sample size, we need to find the number of subjects required to reach this number of events. There are a couple approaches, the simplest is to use the average hazard. The hazards for the active treatment group is 0.75/year for the first 6 months and 0.03/year thereafter. The average of the control and active hazards is 0.875/year during the first 6 months and 0.035/year thereafter. The cumulative hazard is

   $$\Lambda(t) = \begin{cases} 0.0875t & \text{if } t < 0.5 \\ 0.0875 \times .5 + 0.035(t - .5) = 0.02625 + 0.035t & \text{if } t \geq 0.5 \end{cases}$$

   The probability that a subject experiences an event before time t is $1 - e^{-\Lambda(t)}$.

   If the total length of follow-up is F and the length of the recruitment period is R, then (because $F - R > .5$) the probability of an event is

   $$\begin{aligned} \bar{\rho} &= \frac{1}{R}\int_{F-R}^{F} 1 - e^{-\Lambda(u)} du \\ &= 1 - \frac{e^{-.02625}}{R}\int_{F-R}^{F} e^{-.035u} du \\ &= 1 + \frac{e^{-.02625}}{0.035R}\left(e^{-.035\times F} - e^{-.035\times(F-R)}\right). \end{aligned}$$

   For the two scenarios we have

i. $\bar{\rho} = 0.1305$

ii. $\bar{\rho} = 0.1073$

Therefore, the required number of subjects for each of the two scenarios is:

i. $507.4/0.1305 = 3887$

ii. $507.4/0.1073 = 4727$

2. Suppose that we have a binary outcome, and wish to show superiority of treatment B relative to treatment B. In designing the trial we assumed that the failure rates are $\pi_A = 0.36$ and $\pi_B = 0.30$ in treatment groups A and B respectively.

(a) Find the sample size required to detect the difference in rates above with 90% power at two-sided $\alpha = .05$.

$\bar{\pi} = (.36 + .30)/2 = .33$, so

$$N = \frac{(1.96 + 1.28)^2 \times .33 \times .67 \times 4}{(.36 - .30)^2} = 2579$$

With equal sized groups, use N = 2580, or 1290 per group.

(b) Suppose that the true control rate, π_A is different than expected. For the sample size found in (a),

i. plot power as a function of true π_A for $.07 \leq \pi_A \leq 0.5$ under the assumption of constant risk difference $\pi_A - \pi_B = 0.06$ and

ii. on the same figure, plot power as a function of true π_A under the assumption of constant log-odds ratio $\log(\pi_A/(1 - \pi_A)) - \log(\pi_B/(1 - \pi_B) = 0.272$.

Why do these curves differ in the way that they do?

Power can be found by solving the sample size equation for $Z_{1-\beta}$ and calculating the corresponding value of $1 - \beta$.

$$Z_{1-\beta} = \frac{\sqrt{2780}(\pi_A - \pi_B)}{2\sqrt{\bar{\pi}(1 - \bar{\pi})}} - Z_{1-\alpha/2}$$

so

$$1 - \beta = \Phi\left[\frac{\sqrt{2780}(\pi_A - \pi_B)}{2\sqrt{\bar{\pi}(1 - \bar{\pi})}} - Z_{1-\alpha/2}\right]$$

where Φ is the standard normal CDF.

If we choose π_A, and fix the risk difference to be 0.06, we have

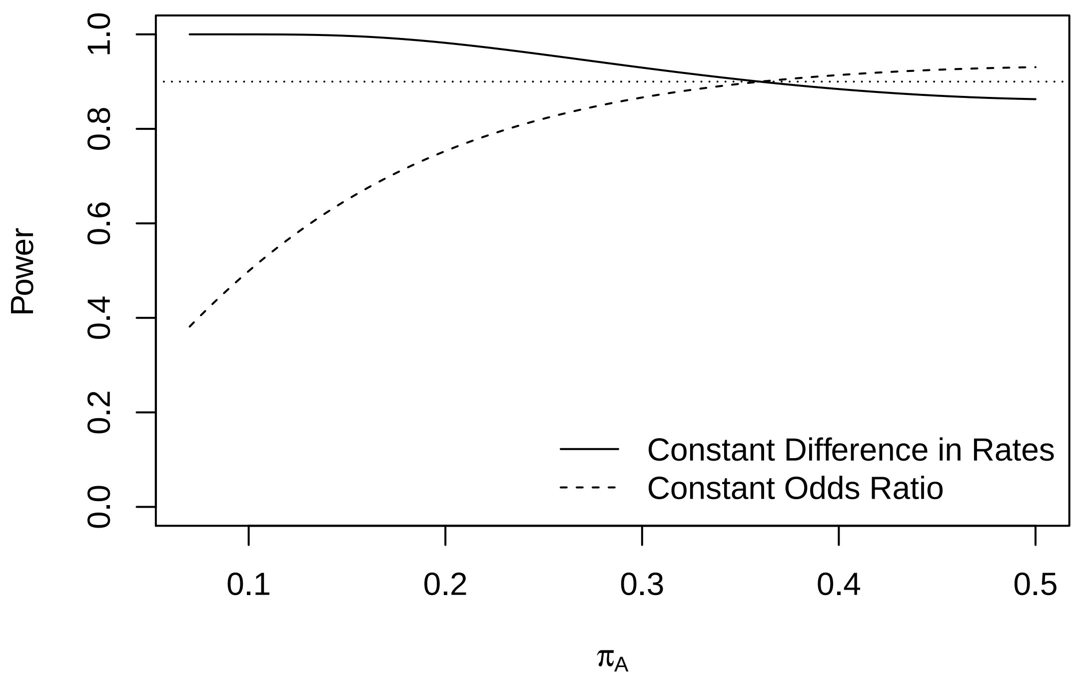
$$1 - \beta = \Phi\left[\frac{\sqrt{2780} \times 0.06}{2\sqrt{(\pi_A - .03)(1.03 - \pi_A)}} - Z_{1-\alpha/2}\right]$$

If we choose π_A, and fix the odds-ratio to be $.3 \times .64/.7 \times .36 = 0.7619$, we have that

$$\frac{\pi_B}{1-\pi_B} = \frac{0.7619\pi_A}{1-\pi_A} \qquad \text{and solving for } \pi_B, \qquad \pi_B = \frac{0.7619\pi_A}{1-.2381\pi_A}$$

R code:

```
> pA <- 7:50/100
> pBi <- pA -.06
> pBii <- exp(-.272)*pA/(1+(exp(-.272)-1)*pA)
> pBari <- pA-.03
> pBarii <- (pA+pBii)/2
> plot(pA, pnorm(sqrt(2580)*.06/2/sqrt(pBari*(1-pBari))-1.96),
+   type="l",ylim=c(0,1), ylab="Power",xlab=expression(pi[A]))
> lines(pA, pnorm(sqrt(2580)*sqrt(pBarii*(1-pBarii))*.272/2-1.96),
+   lty=2)
> abline(h=.9,lty=3)
> legend("bottomright", bty="n", lty=1:2, c("Constant Difference in Rates", "Constant Odds
```



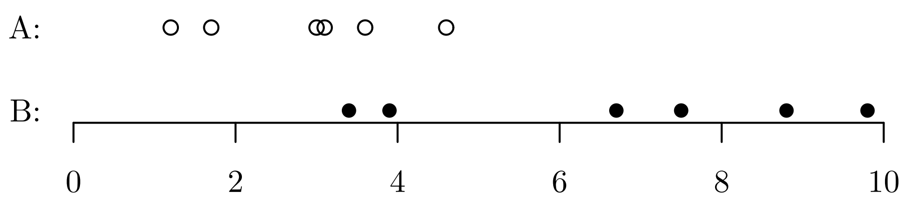
As in the previous problem, for fixed risk difference, the variability in $\widehat{\pi}_A - \widehat{\pi}_B$ decreases as $\widehat{\pi}_A$ decreases, so the standardized difference, $|\pi_A - \pi_B|/\sqrt{\widehat{\pi}_A - \widehat{\pi}_B}$ increases, with a corresponding increase in power. On the other hand, for fixed OR, the standardized difference, $|\log(OR)|/\sqrt{\text{Var}(\log(\widehat{OR}))}$ decreases with decreasing π_A, with a corresponding decrease in power.

3. Suppose that we observe the following continuous responses for groups A and B.

A: 3.0, 1.7, 4.6, 3.6, 1.2, 3.1
B: 3.9, 6.7, 7.5, 3.4, 8.8, 9.8

Let $\widehat{\mu}$ be then difference in means, $\widehat{\mu} = \bar{X}_B - \bar{X}_A$. Compute a one-sided p-value under the randomization distribution generated by the random allocation rule ($N_A = N_B$). (Note that you don't need to generate the entire randomization distribution for $\widehat{\mu}$.) Compare to p-values from a two-sample t-test and Wilcoxon rank-sum test (since these are two-sided by default, you'll need to divide the p-values by 2).

First, we have $\widehat{\mu} = 6.683 - 2.867 = 3.817$. A plot of the data shows that most of the observations in group B are well to the right of the observations in group A.



There are only small number of treatment allocations that produce a more extreme mean difference than the one observed, specifically, we need only consider allocations such that the mean in group B is larger than the observed mean, 6.683. These are enumerated below:

Allocated to B	mean
3.9, 4.6, 6.7, 7.5, 8.8, 9.8	6.883
3.6, 4.6, 6.7, 7.5, 8.8, 9.8	6.833
3.4, 4.6, 6.7, 7.5, 8.8, 9.8	6.800
3.1, 4.6, 6.7, 7.5, 8.8, 9.8	6.750
3.0, 4.6, 6.7, 7.5, 8.8, 9.8	6.733*
3.6, 3.9, 6.7, 7.5, 8.8, 9.8	6.717
3.4, 3.9, 6.7, 7.5, 8.8, 9.8	6.683

Therefore, there are 7 allocations yielding a mean difference at least as extreme as the one observed. There are a total of

$$\binom{12}{6} = 924$$

possible allocations, so the one-sided p-value is $7/924 = .0076$.

t-test and Wilcoxon rank-sum test:

```
> u <- c(3.9, 6.7, 7.5, 3.4, 8.8, 9.8) ; v <- c(3.0, 1.7, 4.6, 3.6, 1.2, 3.1)
> t.test(u,v)
Welch Two Sample t-test
data:  u and v
t = 3.2591, df = 7.203, p-value = 0.01334
...
> wilcox.test(u,v)
Wilcoxon rank sum test
```

```
data:  u and v
W = 33, p-value = 0.01515
alternative hypothesis: true location shift is not equal to 0
```

One-sided p-values are $0.01334/2 = 0.0067$ (t-test) and 0.01515/2=0.0076, and these are comparable to that above. In fact, by default, `wilcox.test` uses the randomization distribution in small samples, and this p-value is identical to that above. This suggests that the number of sequences with rank-sum at least as large as that in the original sample is the same as the number with mean difference at least as large. Interestingly, these are *not* the same sequences. For the actual allocation, the rank sum for group B is 54, but the rank sum using the starred (*) allocation in the table above is 53 (less extreme), whereas the rank sum allocating 3.6, 3.9, 4.6, 7.5, 8.8, 9.8 to B has rank-sum 54 (at least as extreme), but group mean $6.367 < 6.683$.

4. Suppose that we have two treatments with a 1:1 permuted block randomization with blocks of size 6 (i.e., within each block of 6 we randomly allocate 3 to each treatment). We enroll 12 subjects and in the two blocks we observe the following summary tables:

Group	D	A	Total
1	3	0	3
2	0	3	3
	3	3	6

Group	D	A	Total
1	2	1	3
2	0	3	3
	2	4	6

(a) Calculate the size of the reference set (all possible allocations of treatments to subjects).

We have two blocks of size 6. Within each block we allocate 3 to group 1 and the remaining 3 to group 2. There are $\binom{6}{3} = 20$ ways of doing this within each block. Thus the reference set has $20 \times 20 = 400$ allocations.

(b) If x_j is the number of deaths in group 1 for block j, find the sample space for $U(0) = \sum_j x_j - E[x_j]$ and corresponding sampling probabilities under the randomization distribution. (*Hint: x_j has a hypergeometric distribution*).

In x_j be the entry in the upper left corner of block j, $j = 1, 2$.

x_1 takes 4 possible values: 0,1,2,3. $\quad E[x_1] = 3 \times 3/6 = 1.5$
x_2 takes 3 possible values: 0,1,2. $\quad E[x_1] = 2 \times 3/6 = 1$

$U(0)$ takes values according to the following table:

$x_2 \backslash x_1$:	0	1	2	3
0	-2.5	-1.5	-0.5	0.5
1	-1.5	-0.5	0.5	1.5
2	-0.5	0.5	1.5	2.5

Each x_j has a hypergeometric distribution, so if m_j is the total number of deaths in block j (3 or 2), then the x_j has probability

$$\Pr\{x_j = x\} = \frac{\binom{3}{x}\binom{3}{m_j - x}}{\binom{6}{m_j}}$$

$$\Pr\{x_1 = 0\} = \Pr\{x_1 = 3\} = \frac{\binom{3}{0}\binom{3}{3}}{\binom{6}{3}} = \tfrac{1}{20},$$

$$\Pr\{x_1 = 1\} = \Pr\{x_1 = 2\} = \frac{\binom{3}{1}\binom{3}{2}}{\binom{6}{3}} = \tfrac{9}{20}$$

Similarly,

$$\Pr\{x_2 = 0\} = \Pr\{x_2 = 2\} = \frac{\binom{3}{0}\binom{3}{2}}{\binom{6}{2}} = \tfrac{1}{5}, \qquad \Pr\{x_1 = 1\} = \frac{\binom{3}{1}\binom{3}{1}}{\binom{6}{2}} = \tfrac{3}{5}$$

Thus,

$$\begin{aligned}
\Pr\{U(0) = -2.5\} &= \Pr\{x_1 = x_2 = 0\} = \frac{1}{20} \times \frac{1}{5} = \frac{1}{100} \\
\Pr\{U(0) = -1.5\} &= \Pr\{x_1 = 1, x_2 = 0\} + \Pr\{x_1 = 0, x_2 = 1\} = \frac{9}{20} \times \frac{1}{5} + \frac{1}{20} \times \frac{3}{5} = \frac{12}{100} \\
\Pr\{U(0) = -0.5\} &= \Pr\{x_1 = 2, x_2 = 0\} + \Pr\{x_1 = 1, x_2 = 1\} + \Pr\{x_1 = 2, x_2 = 0\} \\
&= \frac{9}{20} \times \frac{1}{5} + \frac{9}{20} \times \frac{3}{5} + \frac{1}{20} \times \frac{1}{5} = \frac{37}{100}
\end{aligned}$$

By symmetry,

$$\Pr\{U(0) = 2.5\} = \frac{1}{100} \qquad \Pr\{U(0) = 1.5\} = \frac{12}{100} \qquad \Pr\{U(0) = 0.5\} = \frac{37}{100}$$

Hence $U(0)$ takes values $\{-2.5, -1.5, -0.5, 0.5, 1.5, 2.5\}$ with probabilities $\{1/100, 12/100, 37/100, 37/100, 12/100, 1/100\}$.

(c) Calculate the one-sided randomization p-value for the observed data.

The observed value of $U(0)$ is $(3 - 1.5) + (2 - 1) = 2.5$. The one-sided randomization p-value is $\Pr\{U(0) \geq 2.5\} = 0.01$ from the distribution in part (b).

(Note that the stratified chi-square statistic (Mantel-Haenszel) is $2.5^2/.708 = 8.824$ *which corresponds to a large-sample p-value of 0.003.)*