Statistics 641, Fall 2012
Homework #5
Answers

1. Heart patients have a greater risk of a second heart attack (MI) immediately following the first MI, then they do 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:

   (a) 1.5 year recruitment, 4 year followup

   (b) 2 year recruitment, 3.5 year followup

   Compute the required sample sizes for each of these two designs assuming equal numbers of patients in each treatment group. *Hint: You need to compute the probability that a subject will experience an event during the trial. The hazard function will be piecewise linear.*

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

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

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 $e^{-\Lambda(t)}$.

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

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

For the two scenarios we have

(a) $E[\delta] = 0.1305$

(b) $E[\delta] = 0.1073$

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

(a) $507.4/.1305 = 3887$

(b) $507.4/.1073 = 4727$

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2. Suppose that we have a binary outcome, and wish to show non-inferiority of treatment B relative to treatment A. In designing the trial we assumed that the failure rate in each treatment groups is $\pi_A = \pi_B = 0.30$. Given these rates, we consider that an increase in failure rate to 0.36 to constitute non-inferiority and enroll 1300 subjects in each treatment group.

   We can parameterize this margin of interest in (at least) two ways:

   - $\delta = 0.36 - 0.30 = 0.06$
   - $\delta = \log \dfrac{\pi_B(1-\pi_A)}{(1-\pi_B)\pi_A} = \log(0.36/0.64) - \log(0.30/0.70) = .272$

   Suppose at the trial's end we observe the following:

	failures	successes
A	273	1027
B	299	1001

   (a) Construct a 95% confidence interval for $\pi_B - \pi_A$. Does this interval contain $\delta = 0.06$?

   We have $\hat{\pi}_A = 273/1300 = .21$ and $\hat{\pi}_B = 299/1300 = .23$. Variances are $0.21 \times 0.79/1300 = 0.0001276$ and $0.23 \times 0.77/1300 = 0.0001362$ for groups A and B respectively. The 95% CI is $.23 - .21 \pm \sqrt{0.0001276 + 0.0001362} \times 1.96 = (-0.0119, 0.0519)$. This interval does not include 0.06, so we can conclude that B is not-inferior to A at the 95% confidence level.

   (b) Construct a 95% confidence interval for $\log(OR)$. Does this interval contain $\delta = 0.272$.

   If $\beta = \log(OR)$, then $\hat{\beta} = \log(299/1001) - \log(273/1027) = 0.1166$. The variance of $\hat{\beta}$ is $1/273 + 1/1027 + 1/299 + 1/1001 = 0.008980$ (delta method), so the 95% CI is $.1166 \pm \sqrt{0.008980} \times 1.96 = (-0.0691, 0.3023)$ This interval does include 0.272, so we cannot conclude that B is non-inferior to A at the 95% confidence level.

   (c) Why do the results of (a) and (b) differ? Comment on the sensitivity of the non-inferiority hypothesis to the choice of scale (parameterization).

   Unlike a null hypothesis of equality, the hypothesis of inferiority (true treatment difference larger than $\delta > 0$) depends on the parameterization. In the case of equality $\pi_B - \pi_A = 0$, $\log(\pi_B/\pi_A) = 0$ and $\log[\pi_B(1-\pi_A)/\pi_A(1-\pi_B)] = 0$ are all equivalent. In the non-inferiority case, we replace the "=0" with $\geq \delta$ (for properly defined δs), and they are no longer equivalent.

In this example, the observed rates $\hat{\pi}_A$ and $\hat{\pi}_B$ are much lower than expected, so the difference, $\hat{\pi}_B - \hat{\pi}_A$ is proportionally larger than expected and as the underlying rates decrease the variance (proportional to $\pi(1-\pi)$) decreases, shrinking the length of the confidence interval, making it easier to exclude δ for a fixed difference, $\pi_B - \pi_A$.

On the other hand, as the rates decrease, the expected cell counts (x) in the failure column decrease, increasing their contribution to the variance ($1/x$), whereas since the counts in the success column are already much larger, the corresponding decrease in the contribution to the variance due to increases in these cell counts do not offset the increases from the first column (i.e., $1/273 + 1/1027 > 1/390 + 1/910$). Hence, the variance of the observed log(OR) increases as the rates decrease, increasing the width of the confidence interval. Hence, it is more difficult to conclude non-inferiority on the log(OR) scale if the observed rates are lower than expected.

3. 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 $1 - \beta$.

$$Z_{1-\beta} = \frac{\sqrt{2580}(\pi_A - \pi_B)}{2\sqrt{\bar{\pi}(1-\bar{\pi})}} - Z_{1-\alpha/2}$$

so

$$1 - \beta = \Phi\left[\frac{\sqrt{2580}(\pi_A - \pi_B)}{2\sqrt{\bar{\pi}(1-\bar{\pi})}} - Z_{1-\alpha/2}\right]$$

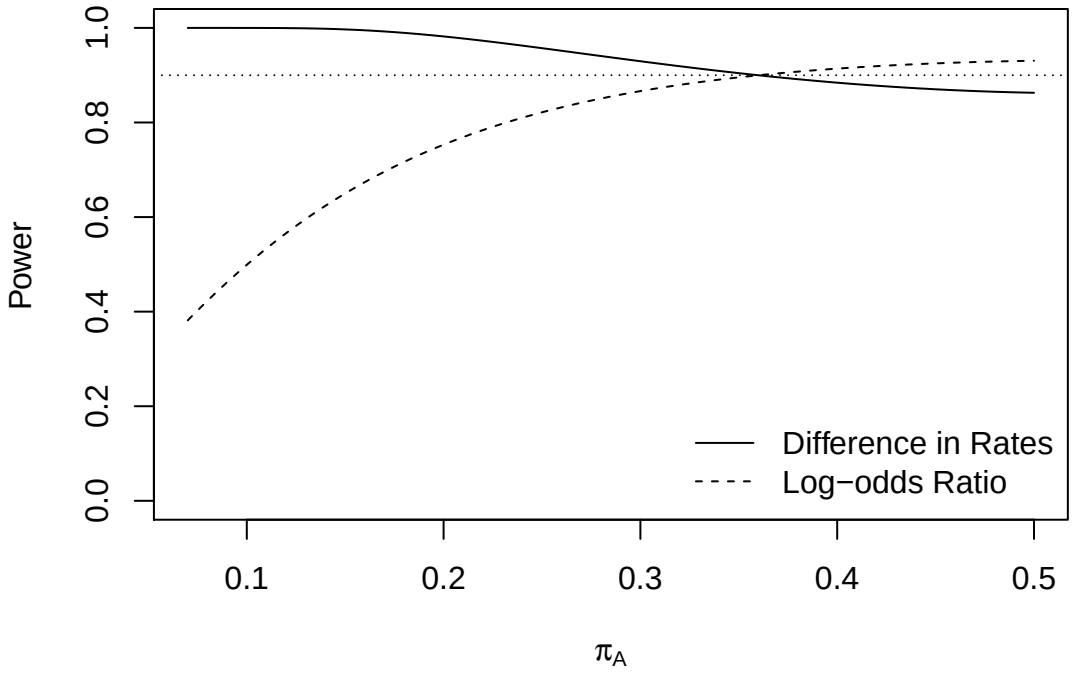
where Φ is the standard normal CDF.

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

$$1 - \beta = \Phi\left[\frac{\sqrt{2580} \times 0.06}{2\sqrt{(\pi_A - .03)(1.03 - \pi_A)}} - Z_{1-\alpha/2}\right]$$

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

$$\pi_B = \frac{0.7619\pi_A}{1 - .2381\pi_A}$$



As in the previous problem, for fixed risk difference, the variability in $\bar{\pi}_A - \bar{\pi}_B$ decreases as π_A decreases, so the standardized difference, $|\pi_A - \pi_B|/\sqrt{\bar{\pi}(1-\bar{\pi})}$ 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.