

Statistics 641, Spring 2018
Homework #6
Solutions

- 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 group is $p_A = p_B = 0.30$. Given these rates, we consider that an increase in failure rate to at most $p_B = 0.36$ to constitute non-inferiority and we enrolled 1300 subjects in each treatment group.

We can parameterize the non-inferiority margin in (at least) two ways:

- $\delta = 0.36 - 0.30 = 0.06$
- $\delta = \log OR = \log(0.36/0.64) - \log(0.30/0.70) = .272$

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

	failures	successes
A	273	1027
B	299	1001

- Construct a 95% confidence interval for $p_B - p_A$. Does this interval contain $\delta = 0.06$?

We have $\hat{p}_A = 273/1300 = .21$ and $\hat{p}_B = 299/1300 = .23$. 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.

- 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.

- 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 $p_B - p_A = 0$, $\log(p_B/p_A) = 0$ and $\log[p_B(1 - p_A)/p_A(1 - p_B)] = 0$ are all equivalent. In the non-inferiority case, we replace the “=0” with $\geq \delta$ (for properly defined δ s), and they are no longer equivalent.

In this example, the observed rates \hat{p}_A and \hat{p}_B are much lower than expected, so the difference, $\hat{p}_B - \hat{p}_A$ is proportionally larger than expected and as the underlying rates decrease the variance (proportional to $p(1 - p)$) decreases, shrinking the length of the

confidence interval, making it easier to exclude δ for a fixed difference, $p_B - p_A$.

On the other hand, the variance of the estimated log-OR is $1/n_A \hat{p}_A(1 - \hat{p}_A) + 1/n_B \hat{p}_B(1 - \hat{p}_B)$ which is larger for the observed rates than for the assumed rates. Hence, the confidence is wider than expected and it is more difficult to conclude non-inferiority on this scale.

2. Suppose that we have a binary outcome, and wish to show superiority of treatment B relative to treatment A. In designing the trial we assumed that the failure rates are $p_A = 0.36$ and $p_B = 0.30$ 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 $\alpha = .05$.

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

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

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

- (b) Suppose that the true control rate, p_A is different than expected. For the sample size found in (a),
- plot power as a function of true p_A for $.07 \leq p_A \leq 0.5$ under the assumption of constant risk difference $p_A - p_B = 0.06$ and
 - on the same figure, plot power as a function of true p_A under the assumption of constant log-odds ratio $\log(p_A/(1 - p_A)) - \log(p_B/(1 - p_B)) = 0.272$.

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 $1 - \beta$.

$$Z_{1-\beta} = \frac{\sqrt{2580}(p_A - p_B)}{2\sqrt{\bar{p}(1 - \bar{p})}} - Z_{1-\alpha/2}$$

so

$$1 - \beta = \Phi \left[\frac{\sqrt{2580}(p_A - p_B)}{2\sqrt{\bar{p}(1 - \bar{p})}} - Z_{1-\alpha/2} \right]$$

where Φ is the standard normal CDF.

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

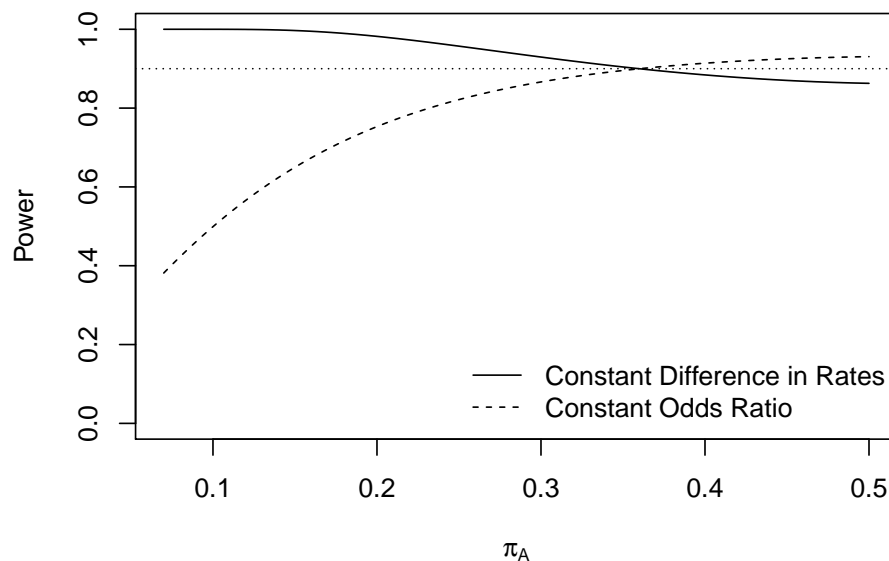
$$1 - \beta = \Phi \left[\frac{\sqrt{2580} \times 0.06}{2\sqrt{(p_A - .03)(1.03 - p_A)}} - Z_{1-\alpha/2} \right]$$

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

$$\frac{p_B}{1 - p_B} = \frac{0.7619 p_A}{1 - p_A} \quad \text{and solving for } p_B, \quad p_B = \frac{0.7619 p_A}{1 - .2381 p_A}$$

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))*0.272/2-1.96),
+      lty=2)
> abline(h=.9,lty=3)
> legend("bottomright", bty="n", lty=1:2, c("Constant Difference in Rates",
+      "Constant Odds Ratio"))
```



For fixed risk difference, the variability in $\hat{p}_A - \hat{p}_B$ decreases as \hat{p}_A decreases, so the standardized difference, $|p_A - p_B|/\sqrt{\text{Var}(\hat{p}_A - \hat{p}_B)}$ 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 p_A , with a corresponding decrease in power.

3. 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% (hazard ratio = 0.75). We wish to perform a study of patients enrolled immediately following an MI with (uniform) recruitment and study length of either:
- (i) 1.5 year recruitment, 4 year overall study length
 - (ii) 2 year recruitment, 3.5 year overall study length
- (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.
Hints: You will need to compute the probability that a random subject will experience an event during the trial. The cumulative hazard function is 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. $507.4/0.1073 = 4727$
