Statistics 641, Fall 2014
Homework #4
Solutions

1. A randomized, two-arm trial is conducted comparing a control treatment (A) to a experimental treatment (B). The primary outcome is all-cause mortality.

   (a) After completion of the trial (between 1.5 and 3 years follow-up), we observe the following table:

	Subjects	Deaths	Person-years follow-up
A	500	241	835
B	500	219	876

   Assume exponential survival and compute the hazard ratio, the Wald test statistic for the log-hazard ratio and a 95% confidence interval for the hazard ratio.

The hazard ratio is

$$\frac{\widehat{\lambda}_B}{\widehat{\lambda}_A} = \frac{219/876}{241/835} = 0.866$$

From page 15 of the notes from September 25 (lecture 8), the variance of $\widehat{\beta} = \log \widehat{\lambda}_B/\widehat{\lambda}_A$ is

$$\mathrm{Var}\left(\widehat{\beta}\right) = \frac{1}{241} + \frac{1}{219} = 0.008715$$

and the Wald statistic is

$$\frac{\widehat{\beta}^2}{\mathrm{Var}\left(\widehat{\beta}\right)} = \frac{(\log 0.866)^2}{0.00875} 2.37$$

or

$$\frac{\widehat{\beta}}{\sqrt{\mathrm{Var}\left(\widehat{\beta}\right)}} = 1.54 \sim N(0,1)$$

(This corresponds to a p-value of 0.12, so it does not reach conventional levels of statistical significance.)

You could also calculate a Wald test on the hazard ratio scale, rather than the log-hazard ratio scale. By the delta-method

$$\mathrm{Var}\left(e^{\widehat{\beta}}\right) = e^{2\widehat{\beta}}\mathrm{Var}\left(\widehat{\beta}\right) = 0.866^2 \times 0.00875 = 0.00656$$

and the test is

$$\frac{(1-0.866)^2}{0.00656} = 2.73$$

or

$$\frac{1-0.866}{\sqrt{0.00656}} = 1.65$$

The 95% CI for β is $\log 0.866 \pm 1.961\sqrt{0.008715} = (-0.327, 0.039)$, and the 95% CI for $\lambda_B/\lambda_A = (0.721, 1.040)$

(b) It is noted that many subjects do not adhere to their assigned treatment and when subjects are classified by their level of adherence, we observe the following table:

	Adherence	Subjects	Deaths	Person-years follow-up
A	$> 80\%$	110	52	180
	50%–80%	240	153	352
	$\leq 50\%$	150	36	303
B	$> 80\%$	145	51	262
	50%–80%	280	148	463
	$\leq 50\%$	75	20	151

Compute hazard ratios for subjects within each stratum based on adherence ($> 80\%$, 50%–80%, $\leq 50\%$), and note the differences with the overall comparison in part (a). Which result is more credible as an assessment of the effect of treatment and why?

The within-stratum hazard ratios are

$$> 80\%: \quad \frac{51/262}{52/180} = 0.674$$

$$50\%\text{-}80\%: \quad \frac{148/463}{153/352} = 0.735$$

$$\leq 50\%: \quad \frac{20/151}{36/303} = 1.115$$

The hazard ratios for the "better compliers" ($> 80\%$ and 50%-80% strata) are much smaller than the overall comparison (the *intention-to-treat (ITT) analysis*). It might be tempting to conclude that this analysis provides evidence of treatment benefit that is not evident in the intention-to-treat analysis, however, the within-stratum analysis is not credible for several reasons.

- The randomization ensures that the treatment assignments are independent of outcomes, and therefore, the ITT analysis is a valid test of the null hypothesis that there is no net causal effect of treatment assignment on outcomes.
- Adherence to assigned treatment clearly depends on both treatment and outcome.
  - 110 out of 500 (22%) of group A subjects and 145 out of 500 (29%) of group B subjects were in the $> 80\%$ groups, so these are almost certainly non-comparable subsets. Similarly, the group A and group B subjects within the other two strata are not comparable.
  - The event rates clearly differ by adherence:

    52/180=0.289, 153/352 =0.435, 36/303=0.119 in group A
    51/262 = 0.195, 148/463 = 0.320, 20/151= 0.132 in group B

    so adherence and outcomes are certainly related.

  The apparent benefit of B relative to A in the stratified analysis does not represent a valid causal effect of treatment.

  Note that even had we not been able to identify differences in adherence between groups, we cannot verify the assumptions necessary for this to be valid causal inference.

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2. (a) Suppose that we have a population composed of four sub-populations A, B, C and D (note that in general we can't observe A, B, C, D so we don't know which groups individuals are in, or even that there are such groups). For a sample of 100 people from this population, we have the following table (assume for the sake of this problem that there is no sampling variability so observed proportions represent population proportions exactly).

Stratum	Dead	Alive	Total
A	12	48	60
B	8	12	20
C	6	4	10
D	6	4	10
Total	32	68	100

Let $Y_t(u)$ and $Y_c(u)$ be the potential outcomes (1=dead, 0=alive) for subject u, and assume that we have two treatments, t (experimental) and c (control) but that neither has any effect on mortality (i.e., the null hypothesis of no treatment effect is true). Also let $T(u)$ be the treatment *received* by subject u.

i. Calculate $E[Y_c(u)], E[Y_t(u)]$ and $E[Y_t(u)] - E[Y_c(u)]$.

Both $E[Y_c(u)]$ and $E[Y_t(u)]$ are the overall mortality rate, 32/100=0.32. Since these expectations are equal, $E[Y_t(u)] - E[Y_c(u)] = 0$.

ii. Suppose that all 100 subjects are assigned c, however, those in groups A and B receive c but subjects in groups C and D do not. Calculate $E[Y_c(u)|T(u) = c]$.

$E[Y_c(u)|T(u) = c]$ is the mortality rate among subjects in strata A and B:

$$\frac{12 + 8}{60 + 20} = 0.25$$

iii. Suppose that all 100 subjects are assigned t, however, those in group A actually receive t but subjects in groups B, C and D receive c instead. Calculate $E[Y_t(u)|T(u) = t]$ and $E[Y_t(u)|T(u) = t] - E[Y_c(u)|T(u) = c]$.

$E[Y_t(u)|T(u) = t]$ is the mortality rate among subjects in stratum A:

$$\frac{12}{60} = 0.20$$

(Note that I intended $E[Y_c(u)|T(u) = c]$ to be calculated from the previous part, but that wasn't stated clearly. No deduction if you used the setup from this part.) $E[Y_t(u)|T(u) = t] - E[Y_c(u)|T(u) = c] = 0.2 - 0.25 = -0.05$

iv. Compare the results of 2(a)ii and 2(a)iii. What does this tell you about a *Per-Protocol* analysis when the null hypothesis is true? Is 2(a)iii a valid *causal* analysis?

The *Per-Protocol* analysis shows that there is a difference in mortality rates between subjects assigned t who adhere to their assigned treatment and subjects assigned c who adhere to their assigned treatment. While this is in fact *true*, it is does *not* represent a causal effect of treatment, but rather a bias due to the selection of subjects that receive their respective treatments (there is *no* effect of treatment on probability of death).

Specifically, treatment received is *not* independent of outcomes. Note that for subjects assigned c the probability of having received c given that a subject is dead is

$$\Pr\{T(u) = c|\text{Dead}\} = \frac{12+8}{32} = 0.625$$

whereas the probability of having received c given that a subject is alive is

$$\Pr\{T(u) = c|\text{Alive}\} = \frac{48+12}{68} = 0.8824$$

Similarly, for subjects assigned t

$$\Pr\{T(u) = t|\text{Dead}\} = 0.375$$

and

$$\Pr\{T(u) = t|\text{Alive}\} = 0.7059.$$

Clearly treatment *received* is not independent of outcomes.

(b) Suppose that we randomize 200 subjects to either t or c with equal probability, so that we will have 100 subjects per group (i.e., we will have a table like the one above for each treatment group). Using the conditions of part (a), except that subjects in group D *always* receive treatment t, and subjects in group B *always* receive treatment c regardless of assigned treatment ("crossovers"). Note that subjects in group C receive *neither* treatment.

i. Calculate $E[Y_c(u)|T(u) = c]$, $E[Y_t(u)|T(u) = t]$ and $E[Y_t(u)|T(u) = t] - E[Y_c(u)|T(u) = c]$.

We have the following table of outcomes and treatment received by assigned treatment. $E[Y_c(u)|T(u) = c]$ and $E[Y_t(u)|T(u) = t]$ can be obtained by counting deaths and the total number of subjects *receiving* c and t respectively.

	Assigned c			Assigned t		
Stratum	$T(u)$	Dead	Total	$T(u)$	Dead	Total
A	c	12	60	t	12	60
B	c	8	20	c	8	20
C	–	6	10	–	6	10
D	t	6	10	t	6	10

Subjects who *receive* c are either those in group A and assigned c, or those in group B.

$$E[Y_c(u)|T(u) = c] = \frac{12+8+8}{60+20+20} = \frac{28}{100} = 0.28$$

Subjects who *receive* t are either those in group A and assigned t, or those in group D.

$$\begin{aligned} & E[Y_t(u)|T(u)=t] \\ = & \frac{12+6+6}{60+10+10} \\ = & \frac{24}{80} \\ = & 0.30 \end{aligned}$$

ii. . What do the results in 2(b)i tell you about an *As-Treated* analysis when the null hypothesis is true? Is 2(b)i a valid *causal* analysis?

Similar to (a), the *As-Treated* analysis indicates that there is a difference in mortality rates between subjects *receiving* t and subjects *receiving* c. Again, however, it does *not* due represent a causal effect of treatment, but rather a bias in the selection of subjects receiving their respective treatments. Again, treatment received is *not* independent of outcomes.

(c) Now suppose that treatment t is effective and that if t is received, we would observed the following table:

Stratum	Dead	Alive	Total
A	9	51	60
B	6	14	20
C	4	6	10
D	5	5	10
Total	24	76	100

Also assume that treatment c has no effect (same as no treatment).

i. Calculate $E[Y_t(u)]$ and $E[Y_t(u)] - E[Y_c(u)]$.

$$E[Y_t(u)] = \frac{24}{100} = 0.24$$

Since $E[Y_c(u)]$ is the same as in (a), we have

$$E[Y_t(u)] - E[Y_c(u)] = 0.24 - 0.32 = -0.08$$

ii. Now suppose 200 subjects are randomized 1:1 to t or c. As in 2(a)ii, when assigned treatment c, subjects in groups A and B receive it, while those in C and D receive no treatment. As in 2(a)iii, when assigned t, subjects in group A receive t, while those in groups B, C and D receive no treatment.

Let $\tilde{Y}_\tau(u)$ be the potential outcome for subject u if *assigned* treatment $\tilde{T}(u) = \tau$. and calculate $E[\tilde{Y}_t(u)|\tilde{T}(u)=t]$ and $E[\tilde{Y}_t(u)|\tilde{T}(u)=t] - E[\tilde{Y}_c(u)|\tilde{T}(u)=c]$.

Because adherence makes no difference to subjects assigned c, $E[\tilde{Y}_c(u)|\tilde{T}(u) = c] = 0.32$ as in part (a).

For subjects assigned t, those in group A receive t and therefore $\tilde{Y}_t(u) = Y_t(u)$ and while those in groups B, C and D receive no treatment and therefore $\tilde{Y}_t(u) = Y_c(u)$ (because no treatment and c yield the same response).

$$E[\tilde{Y}_c(u)|\tilde{T}(u) = t] = \frac{9+8+6+6}{100} = 0.29.$$

Therefore $E[\tilde{Y}_t(u)|\tilde{T}(u) = t] - E[\tilde{Y}_c(u)|\tilde{T}(u) = c] = 0.29 - 0.32 = -0.03$, which is smaller in absolute value than $|-0.08|$ (which imposes full-adherence). In this setting, the effect of non-adherence is to shrink the observed difference between groups.

iii. Assuming the conditions of 2(c)ii, calculate $E[Y_t(u)|T(u) = t]$ and $E[Y_t(u)|T(u) = t] - E[Y_c(u)|T(u) = c]$.

Similar to 2(a)ii, $E[Y_c(u)|T(u) = c] = 0.25$ and similar to 2(a)iii, $E[Y_t(u)|T(u) = t] = 0.15$. Therefore $E[Y_t(u)|T(u) = t] - E[Y_c(u)|T(u) = c] = 0.15 - 0.25 = -0.10$.

iv. Compare the results in 2(c)i, 2(c)ii and 2(c)iii. What does this tell you about the *Intention to Treat Analysis* and the *Per-Protocol* analysis when the null hypothesis is false?

The ITT analysis provides a valid causal analysis of *assignment to treatment*. The *per-protocol* analysis is not a valid causal analysis, because as above, adherence is not independent of outcome.

The ITT estimand is -0.03, and while smaller in absolute value than the full-adherence estimand of -0.08, it is impossible to recover the full adherence estimand from observed data with incomplete adherence. I.e., since subjects in groups B, C and D were never observed having received t, it is impossible to know their outcomes. The *per-protocol* analysis does *not* recover the full-adherence estimand as it ignores subjects in groups C and D entirely, and includes group B subjects only for treatment c. It can't possibly yield a valid causal answer.