Statistics 641, Fall 2012
Homework #3
Answers

1. (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), with probability of death varying according to the following table:

	A	B	C	D
Proportion of population:	0.6	0.2	0.1	0.1
Probability of Death:	0.2	0.4	0.6	0.6

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 $\mu = E[Y_t(u)] - E[Y_c(u)]$.

$$\begin{aligned} E[Y_c(u)] = E[Y_t(u)] &= \sum_{g=A}^{D} \Pr\{Y_c(u) = 1 | u \in g\} \Pr\{u \in g\} \\ &= 0.2 \times 0.6 + 0.4 \times 0.2 + 0.6 \times 0.1 + 0.6 \times 0.1 = 0.32. \end{aligned}$$

Since these expectations are equal, $\mu = 0$.

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

We have the following table

Stratum	$T(u)$	proportion	$E[Y(u)]$
A	c	0.6	0.2
B	c	0.2	0.4
C	–	0.1	0.6
D	–	0.1	0.6

$$\begin{aligned} E[Y_c(u)|T(u) = c] &= \frac{\Pr\{Y_c(u) = 1 | u \in A\} \Pr\{u \in A\} + \Pr\{Y_c(u) = 1 | u \in B\} \Pr\{u \in B\}}{\Pr\{u \in A\} + \Pr\{u \in B\}} \\ &= \frac{0.2 \times 0.6 + 0.4 \times 0.2}{0.6 + 0.2} \\ &= 0.25 \end{aligned}$$

iii. Suppose that all subjects are assigned t, however, those in group A actually receive t but subjects in groups B, C and D do not. Calculate $E[Y_t(u)|T(u) = t]$.

We have the following table

Stratum	$T(u)$	proportion	$E[Y(u)]$
A	t	0.6	0.2
B	–	0.2	0.4
C	–	0.1	0.6
D	–	0.1	0.6

$$\begin{aligned} E[Y_t(u)|T(u) = t] &= \Pr\{Y_t(u) = 1|u \in A\} \\ &= 0.2 \end{aligned}$$

iv. Compare the results of 1(a)ii and 1(a)iii. What does this tell you about a *Per-Protocol* analysis when the null hypothesis is true?

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 *not* due to an effect of treatment, but rather a bias due to the selection of subjects that receive their respective treatments.

(b) Using the conditions of part 1a, 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. Suppose further that subjects are randomly *assigned* either t or c with equal probability.

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

In the following table "proportion" refers to the proportion of the study population in a given stratum (A,B,C,D) *and* an assigned treatment group (one half of the proportions in the table in 1(a))

	Assigned c			Assigned t		
Stratum	$T(u)$	proportion	$E[Y(u)]$	$T(u)$	proportion	$E[Y(u)]$
A	c	0.3	0.2	t	0.3	0.2
B	c	0.1	0.4	c	0.1	0.4
C	–	0.05	0.6	–	0.05	0.6
D	t	0.05	0.6	t	0.05	0.6

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

$$\begin{aligned} &E[Y_c(u)|T(u) = c] \\ &= \frac{\Pr\{Y_c(u) = 1|u \in A, \text{assigned } c\}\Pr\{u \in A, \text{assigned } c\} + \Pr\{Y_c(u) = 1|u \in B\}\Pr\{u \in B\}}{\Pr\{u \in A, \text{assigned } c\} + \Pr\{u \in B\}} \\ &= \frac{0.2 \times 0.3 + 0.4 \times 0.2}{0.3 + 0.2} \\ &= 0.28 \end{aligned}$$

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

$$\begin{aligned} & E[Y_t(u)|T(u)=t] \\ &= \frac{\Pr\{Y_t(u)=1|u\in A, \text{assigned } t\}\Pr\{u\in A, \text{assigned } t\} + \Pr\{Y_t(u)=1|u\in D\}\Pr\{u\in D\}}{\Pr\{u\in D, \text{assigned } t\} + \Pr\{u\in D\}} \\ &= \frac{0.2\times 0.3 + 0.6\times 0.1}{0.3+0.1} \\ &= 0.30 \end{aligned}$$

ii. Compare the results in 1(b)i. What does this tell you about an *As-Treated* analysis when the null hypothesis is true?

Similar to 1(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 is *not* due to an effect of treatment, but rather a bias in the selection of subjects receiving their respective treatments.

(c) Now suppose that treatment t is effective and that if t is received, the probabilities of death in groups A, B and C are

	A	B	C	D
Probability of Death:	0.15	0.3	0.4	0.5

i. Calculate $E[Y_t(u)]$ and μ.

$$E[Y_t(u)] = 0.15\times 0.6 + 0.3\times 0.2 + 0.4\times 0.1 + 0.5\times 0.1 = 0.24$$

Since $E[Y_c(u)]$ is the same as in 1(a), we have

$$\mu = 0.24 - 0.32 = -0.08$$

The remaining parts of this problem weren't stated as clearly as they should have been, so I'm ignoring them.

ii. Let $\tilde{Y}_\tau(u)$ be the potential outcome for subject u if *assigned* treatment $\tilde{T}(u)=\tau$. Assume the conditions of 1(a)ii and 1(a)iii and calculate $E[\tilde{Y}_t(u)|\tilde{T}(u)=t]$ and $\tilde{\mu} = E[\tilde{Y}_t(u)|\tilde{T}(u)=t] - E[\tilde{Y}_c(u)|\tilde{T}(u)=c]$.

iii. Assuming the conditions of 1(a)ii and 1(a)iii calculate $E[Y_t(u)|T(u)=t]$ and $\mu_A = E[Y_t(u)|T(u)=t] - E[Y_c(u)|T(u)=c]$.

iv. Compare the results in 1(c)i, 1(c)ii and 1(c)iii. What does this tell you about the *Intention to Treat Analysis* and the *Per-Protocol* analysis when the null hypothesis is false?

2. Suppose that we have 8 subjects in each of two groups. We observe the following responses:
   Control: 0.2 0.8 1.9 2.2 2.6 3.9 8.2 21.8
   Experimental: 2.8 5.1 7.1 7.7 12.3 18.8 27.1 39.7

   (a) Calculate by hand the Wilcoxon rank sum test statistic for the comparison of the two groups.

Use "C" and "E" to denote the two groups. The observations are ordered as follows:

	0.2	0.8	1.9	2.2	2.6	2.8	3.9	5.1	7.1	7.7	8.2	12.3	18.8	21.8	27.1	39.7
group:	C	C	C	C	C	E	C	E	E	E	C	E	E	C	E	E
rank:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

The sum of the ranks in group "E" is $T = 6+8+9+10+12+13+15+16 = 89$. The expected rank in group E is $8 \times 17/2 = 68$, so the $T - E[T] = 89 - 68 = 21$.

Because there are no ties, the variance is $8 \times 8 \times 17/12 = 90.667$. The chi-square test statistic is

$$\frac{21^2}{90.667} = 4.86$$

This statistic has (asymptotically) a chi-square distribution with 1 df. The p-value is 0.0274. (Note that by default the `wilcox.test` function in R uses the exact distribution, so the p-value is slightly different. Will discuss exact p-value later.)

   (b) Calculate by hand the Mann-Whitney U-statistic for the comparison of the two groups.

First, there are no ties, so there will be no 1/2's. Second, in this table, for each observation in group "E", M_j is the number of "C" subjects that are smaller:

Experimental:	2.8	5.1	7.1	7.7	12.3	18.8	27.1	39.7
M_j	5	6	6	6	7	7	8	8

The sum of the values in the second row is $5+6+6+6+7+7+8+8 = 53$. The expected value is $8 \times 8/2 = 32$. Hence $U = 53 - 32 = 21$, the same as the Wilcoxon rank sum. The variance is the same as above so the rest of the computation is identical.

   (c) Using your software of choice (or by hand if you wish), perform the t-test for the comparisons between the two groups.

Using the `t.test` function in *R*,

```
> t.test(c(0.2,0.8,1.9,2.2,2.6,3.9,8.2,21.8),
+  c(2.8,5.1,7.1,7.7,12.3,18.8,27.1,39.7))

Welch Two Sample t-test

data:  c(0.2, 0.8, 1.9, 2.2, 2.6, 3.9, 8.2, 21.8) and
      c(2.8, 5.1, 7.1, 7.7, 12.3, 18.8, 27.1, 39.7)
t = -1.9093, df = 10.993, p-value = 0.08265
alternative hypothesis: true difference in means is not equal to 0
```

The p-value from the t-test is 0.0827.

Note

- the data do not appear to be close to normal: there are many small values (less than, say, 5 or 10) but several relatively large values (greater than 20). The data are skewed significantly to the right.
- The p-value using the Wilcoxon/Mann-Whitney test is much smaller than the p-value from the t-test.
- For non-normal data, the Wilcoxon/Mann-Whitney test can have greater power than the t-test, which is sensitive to large values. Because the Wilcoxon/Mann-Whitney test is based on ranks, it is insensitive to major deviations from normality.

Note: by "by hand" I mean that you should show all the steps involved in the calculation. You are free (encouraged) to use a computer to do the arithmetic. You can also use the appropriate `R` *functions to check your answers.*

3. Suppose all subjects in a trial are followed for 1 year, and at the end of that time they either survive disease free (DFS), survive but experience a recurrence of disease, or die. Note that these responses are naturally ordered: DFS is good, death is bad, and recurrence is in between. Subjects are randomly assigned either treatment 1 (control) or treatment 2 (experimental). We observe the following:

	DFS	Recurrence	Dead
Treatment 1	33	17	41
Treatment 2	44	18	25

(a) Compute (by hand) the test statistic for the Wilcoxon rank-sum test assuming that responses are ordered as shown.

The ranks for the DFS subjects range from 1 to 77, for Recurrence from 78 to 112, and the Dead subjects from 113 to 178. Thus the mean ranks in the three groups are (1+77)/2=39, (78+112)/2=95, and (113+178)/2=145.5. The rank sum for Treatment 2 is $T_2 = 44 \times 39 + 18 \times 95 + 25 \times 145.5 = 7063.5$. The expected value of T_2 is $87 \times (178 + 1)/2 = 7785.5$, so $U = 7063.5 - 7785.5 = -723$. The variance is

$$\frac{87 \times 91}{178 - 1}\left(\frac{1}{178}(77 \times 39^2 + 35 * 975^2 + 66 \times 145.5^2 - \frac{(1 + 178)^2}{4}\right) = 101620.8$$

The test statistic is $723^2/101620.8 = 5.14$.

(b) What do these results suggest regarding the effect of treatment.

Lower average rank in group 2 suggests that treatment group 2 has better outcomes than treatment group 1.