

**Statistics 641, Fall 2012**  
**Homework #4**  
**Answers**

1. The data file “data1.csv” (in csv format, comma delimited, same dataset as in homework 1) contains columns

- **x0**: baseline value of response variable
- **x1**: value of response variable at first follow-up time
- **x2**: value of response variable at second follow-up time
- **z**: treatment variable (0,1)

Assume that the responses are normally distributed.

- (a) For the first follow-up response (**x1**) test the null hypothesis that there is no difference by treatment by

- i. ignoring baseline

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Fit model for **x1** with just **z**:

```
> summary(lm(x1~z, data=D))
```

[snip]

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	60.914	1.809	33.677	<2e-16 ***
z	3.886	2.515	1.545	0.128

[snip]

The mean difference is 3.886 with SE 2.515, and *t*-statistic 1.545.

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- ii. using change from baseline (**x1-x0**)

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```
> summary(lm(x1-x0~z, data=D))
```

[snip]

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	-0.2679	0.9919	-0.270	0.7881
z	3.5745	1.3792	2.592	0.0122 *

[snip]

The mean difference is 3.5745 with SE 1.3892 and *t*-statistic 2.592.

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- iii. fitting regression model  $x_1 = \alpha_0 + \alpha_1 x_0 + \beta z + \epsilon$ .

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```
> summary(lm(x1~z+x0, data=D))
```

[snip]

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	13.7465	3.6149	3.803	0.000361 ***

z	3.6458	1.2252	2.976	0.004337	**
x0	0.7709	0.0573	13.454	< 2e-16	***

[snip]

The mean difference is 3.6458 with SE 1.2252 and *t*-statistic 2.976.

Why do the conclusions differ from these three analysis?

In (iii) the coefficient for x0 is .771, suggesting (assuming equal variances for x0 and x1) that the correlation is greater than .5, so the change from baseline should have smaller variance than the follow-up value alone. This is borne out in the differences between (i) and (ii). Since this coefficient is not too close to one, we expect that the regression model in (iii) should have smaller variance than either (i) or (ii), and again this is borne out in the results.

- (b) Repeat each of (i), (ii), and (iii) above for the response at the second follow-up time (x2).

```
> summary(lm(x2~z, data=D))
```

[snip]

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	61.618	2.063	29.868	<2e-16 ***
z	6.872	2.868	2.396	0.0200 *

[snip]

```
> summary(lm(x2-x0~z, data=D))
```

[snip]

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	0.4357	2.6931	0.162	0.8721
z	6.5610	3.7446	1.752	0.0852 .

[snip]

```
> summary(lm(x2~z+x0, data=D))
```

[snip]

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	52.7430	8.4511	6.241	6.55e-08 ***
z	6.8270	2.8644	2.383	0.0206 *
x0	0.1451	0.1340	1.083	0.2836

[snip]

In the third analysis, the coefficient for x0 is small, suggesting that there is much less correlation between x2 and x0 than between x1 and x0. Therefore, we expect that the change from baseline will be much less efficient than ignoring baseline altogether. Again this is borne out in the results. In this case the third analysis gives essentially the same result as the first.

- (c) Comment on the differences between (a) and (b).

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Change from baseline beats observed follow-up value alone when correlation between baseline and follow-up is high, and loses when correlation is low. In either case, the regression model is at least as good as the others and should always be preferred.

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2. Suppose that we have a phase II, single arm trial using a two stage design. The hypotheses of interest are  $H_0: \pi \leq 0.15$  versus  $H_1: \pi \geq 0.4$  where  $\pi$  is the true success rate. Let  $y_k$  be the total number of successes through stage  $k$ ,  $k = 1, 2$ . Note: you can use the functions `dbinom` and `pbinom` in R to calculate binomial probabilities.

- (a) We enroll 16 subjects in stage 1 and stop and accept  $H_0$  if we observe  $a_1 = 3$  or fewer responses ( $y_1 \leq 3$ ), otherwise we continue to stage 2. Find the stopping probabilities under both  $H_0$  and  $H_1$ .

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Under  $H_0$ , the stopping probability is  $\Pr\{y_1 \leq 3\} = .7899$ , and under  $H_1$  it is .0651.

In R:

```
> pbinom(3, 16, .15)
[1] 0.7898907
> pbinom(3, 16, .40)
[1] 0.06514674
```

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- (b) At stage 2 we enroll an additional 16 subjects and reject  $H_0$  if  $y_2 > 8$ . Compute the overall probabilities of rejection under both  $H_0$  and  $H_1$  for the two-stage trial.

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We accept  $H_0$  if  $y_1 \leq 3$  and  $y_2 \leq 8$ . Under  $H_0$  this probability is

$$\Pr\{y_1 \leq 3\} + \sum_{i=4}^8 \Pr\{y_1 = i\} \Pr\{x_2 \leq 8 - i\} = .9659$$

In R:

```
> pbinom(3, 16, .15) + sum(dbinom(4:8,16,.15)*pbinom(4:0, 16, .15))
[1] 0.9658661
```

Under  $H_1$ , this probability is 0.0969.

```
> pbinom(3, 16, .40) + sum(dbinom(4:8,16,.40)*pbinom(4:0, 16, .40))
[1] 0.09691022
```

Therefore, the rejection probabilities are  $1-0.9659=0.0341$  and  $1-0.0969=0.9031$  under  $H_0$  and  $H_1$  respectively.

Alternatively,

```
> 1-pbinom(8,16,.15) + sum(dbinom(4:8,16,.15)*(1-pbinom(4:0, 16, .15)))
[1] 0.03413386
> 1-pbinom(8,16,.40) + sum(dbinom(4:8,16,.40)*(1-pbinom(4:0, 16, .40)))
[1] 0.9030898
```

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- (c) Compute the expected sample sizes for  $\pi = 0.15$  and  $\pi = 0.4$ .

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$N$  is either 16 or 32, depending on whether we stop at stage 1. Under  $H_0$ ,  
 $E[N] = 16 \times 0.7899 + 32 \times (1 - 0.7899) = 19.36$  and under  $H_1$ ,  
 $E[N] = 16 \times 0.0651 + 32 \times (1 - 0.0651) = 30.96$ .

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- (d) Suppose, instead, we perform a single stage trial with  $N = 32$  subjects and we reject  $H_0$  if we observe more than 8 successes. Find the type I and type II error rates. What is the advantage of the two-stage trial?

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Under  $H_0$ , probability of rejection (type I error) is  $\Pr\{y > 8\} = 1 - 0.9587 = .0413$ , and under  $H_1$  the acceptance probability (type II error) is  $\Pr\{y \leq 8\} = 0.0575$ . The type I error rate is slightly smaller for the two-stage trial, but the type II error rate is larger. The advantage of the 2 stage trial is that we can have the potential to stop earlier and discard ineffective treatments sooner.

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3. The dataset `data2.csv` contains data collected from a crossover study with 40 subjects per sequence. The variables in the dataset are:

<code>seq</code>	Assigned treatment sequence
<code>y</code>	Response
<code>id</code>	Subject id
<code>period</code>	Period
<code>z</code>	Treatment ("A" or "B")

- (a) Calculate the means within each treatment group separately for periods 1 and 2. Using these means, calculate the estimate of the treatment difference assuming no carryover.

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```
> m <- with(data, tapply(y, list(z, period), mean))
> m
      1      2
A  9.6625 22.7025
B 10.1000 22.9200
# difference in "AB" group:
> m[2,2]-m[1,1]
[1] 13.2575
# difference in "BA" group:
> m[2,1]-m[1,2]
[1] -12.6025
# mean difference:
> (m[2,2]-m[1,1] + m[2,1]-m[1,2])/2
[1] 0.3275
```

Note that the estimate of period effect is:

```
> (m[2,2]-m[1,1] - (m[2,1]-m[1,2]))/2
[1] 12.93
```

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(b) Fit a regression model that estimates the treatment difference and its standard error.

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```
> summary(lm(y ~ z + period + id, data=data))
```

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	-3.409e+00	6.695e-01	-5.091	2.41e-06 ***
zB	3.275e-01	1.412e-01	2.320	0.022947 *
period	1.293e+01	1.412e-01	91.602	< 2e-16 ***
ids02	1.750e+00	8.927e-01	1.960	0.053535 .
...				
ids80	-1.400e+00	8.927e-01	-1.568	0.120878

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...

The estimate of treatment effect is 0.3275 with SE 0.1412. The *p*-value is 0.0229.

Alternative using mixed-effects model from package lme4:

```
> lmer(y ~ z + period + (1|id), data=data)
```

Linear mixed model fit by REML

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Random effects:

Groups	Name	Variance	Std.Dev.
id	(Intercept)	9.2589}	3.04284
Residual		0.79697	0.89273

Number of obs: 160, groups: id, 80

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	-3.2125	0.4129	-7.78
zB	0.3275	0.1412	2.32
period	12.9300	0.1412	91.60

Correlation of Fixed Effects:

	(Intr) zB
zB	-0.171
period	-0.513 0.000

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- (c) Fit a regression model to estimate the effect of treatment using only period 1. (This is equivalent to a parallel group trial in which subjects are assigned only one of “A” or “B.”)

```
> summary(lm(y ~ z, data=data, subset=period==1))
```

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	9.6625	0.4734	20.412	<2e-16 ***
zB	0.4375	0.6695	0.654	0.515

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Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

- (d) Comment on the differences between the analyses in parts (b) and (c).

The standard errors of the two estimates are quite different

- Cross-over analysis: SE = 0.1412
- Parallel group (period 1 only): SE = 0.6695

This suggests that there is high correlation between the period 1 and period 2 observations from each subject. Because the cross-over model is based on within-subject differences, the subject-level effects are accounted for and the variability is significantly reduced providing greater power.

Even though the point estimate of the difference is larger in period 1 analysis, the increased variance results in a statistically in-significant difference.