Statistics 641, Fall 2013
Homework #5
Solutions

1. 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 π 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.

   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
```

   (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.

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

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

   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
### or, equivalently, (note that pbinom(x,...) is zero if x < 0)
> sum(dbinom(4:16,16,.15)*pbinom(8-4:16, 16, .15,lower=F))
```

```
[1] 0.03413386
> sum(dbinom(4:16,16,.40)*pbinom(8-4:16, 16, .40,lower=F))
[1] 0.9030898
```

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

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,
$E[N] = 16 \times 0.0651 + 32 \times (1 - 0.0651) = 30.96$.

(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?

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.

2. The dataset `data4.csv` contains data collected from a crossover study with 40 subjects per sequence. The variables in the dataset are:

`seq`	Assigned treatment sequence
`y`	Response
`id`	Subject id
`period`	Period
`z`	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.

```
> 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
```

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

```
> 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
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
...
```

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
...
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
```

(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
---
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.