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$\frac{92}{100}$

**STT 6310/4310** **Exam 1** **Start Date: Oct. 16, 2018**
**Instructor: Gengxin Li** **(Take home exam – 100 pts.)** **Due Date: Oct 23, 2018**

1. What are phases of clinical trials? Please compare these phases.

Clinical trials which are the experimentation with human classified into 4 phases.

Phase I: To explain possible toxic effect of drugs and determine a tolerated dose for future experimentation

Phase II: Screening and feasibility by initial assessment for the therapeutic effect further assessment of toxicities.

Phase III: Comparison of new intervention (drug and theraphy) to the current standard of treatment both with respect to efficacy and toxicity.

Phase IV: Observational study of morbidity adverse effects after a drug is on the market.

2. Which issues do we need to design a clinical trial?

In order to know whether there is enough evidence of efficacy to make it worth further study in larger and more costly clinical trial. There are two kinds of issues we need to design a clinical trial

(1) Surrogate markers: used to evaluate the treatment efficacy

(2) Surrogate endpoint: to determine whether the proposed treatment should be further studied.

3. In phase II study, X denotes the number of patients who completely respond, and it follows the binomial distribution with the total number of patient (n) and the probability of getting complete response (p). What's the point estimator of p, and the distribution of this estimator? Please compute 99% confidence interval for true p when the estimator of response rate is 0.25 and total number of patients is 25.

① $\hat{P} = \pi = \frac{x}{n}$

$\hat{p} \sim N(\pi, \frac{\pi(1-\pi)}{n})$ $-1$

② Since $X \sim Bin(n,p)$ then $\begin{cases} E(x) = np \\ Var(x) = np(1-p) \end{cases}$

$\pi \overset{iid}{\sim}$ Beta distribution with $\begin{cases} E(\pi) = E(\frac{x}{n}) = \frac{1}{n} E(x) = P \\ Var(\pi) = Var(\frac{x}{n}) = \frac{1}{n^2} Var X = \frac{P(1-P)}{n} \end{cases}$

③ 99% C.I for $P$ is $\pi \pm Z_{\frac{\alpha}{2}} \sqrt{\frac{\frac{x}{n}(1-\frac{x}{n})}{n}}$

$\begin{cases} \frac{x}{n} = 0.25 \\ n = 25 \\ \alpha = 0.01 \\ Z_{\frac{\alpha}{2}} = 2.575 \end{cases}$

$0.25 \pm 2.575 \times \sqrt{\frac{0.25 \times 0.75}{25}} = 0.25 \pm 2.575 \times 0.087 = 0.25 \pm 0.223$

$C.I = [0.027, 0.473]$

$-1$

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4. In a phase II trial, 4 of 20 patients respond to a new drug for lung cancer. ① Please find the exact confidence 95% interval for the response rate (p) for X=k, k=4, and n=20. ② What about 95% confidence interval of the response rate (p)? ③ Compare the exact confidence 95% interval with 95% confidence interval.

Solution: ① $\begin{cases} A: P_{P_L(4)}(X \geq 4) = \frac{\alpha}{2} = 0.025 \\ B: P_{P_U(4)}(X \leq 4) = \frac{\alpha}{2} = 0.025 \end{cases} \Rightarrow \begin{cases} P_{P_L}(X \leq 3) = 0.975 \\ P_{P_U}(X \leq 4) = 0.025 \end{cases}$ Check the tables of the Binomial Cumulative dist.

From $\begin{cases} \text{equation } A \Rightarrow P_L = 0.06 \\ \text{equation } B \Rightarrow P_U = 0.41 \end{cases}$ hence the exact 95% C.I for P is $[0.06, 0.44]$

② $\hat{P} = \frac{4}{20} = 0.2$ ; $\alpha = 0.05 \Rightarrow Z_{\frac{\alpha}{2}} = Z_{0.025} = 1.96$ 95% C.I of P: $0.2 \pm 1.96 \times \sqrt{\frac{0.2 \times 0.8}{20}}$

95% C.I of P. $0.2 \pm 0.1753 \Rightarrow [0.0247, 0.3753]$

③ From the results in the above calculation, we get:
Both the upper and Lower confidence limit of exact 95% C.I is greater than normal approximation 95% C.I.

5. ① Please briefly describe the Gehan's two stage design. Suppose the minimal response rate (p0) is 0.3. ② How large must n be so that if there are 0 responses among n patients we are relatively confident that the response rate is not 30% or better for X~Bin(n, p) and α=0.025. ③ We want the 99% confidence interval for the response rate to be within +-16% when a new drug is considered minimally effective at p0=30%, what about the sample size necessary for this degree of precision is? ④ Please use these values to interpret the Gehan's two stage design.

①: If the minimal acceptable response rate is given as $\lambda_0$, then choose $n_0$ patients in the 1st stage, such that $n_0 = \frac{\ln\alpha}{\ln(1-\lambda_0)}$. if there are 0 response among 1st $n_0$ patients. then stop and declare the treatment a failure. if there was at least 1 patients response, another $n_0$ patients would be treated likewise.

② $n = \frac{\ln\alpha}{\ln(1-\lambda)} = \frac{\ln 0.025}{\ln 0.7} = \frac{-3.689}{-0.3567} \approx 11$. ③ $\frac{\alpha}{2} = 0.005$ $Z_{\frac{\alpha}{2}} = 2.575$ $\lambda_0 = 0.3$

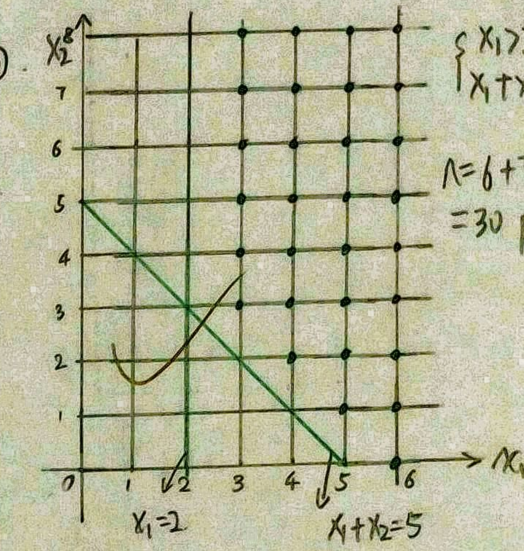
$Z_{\frac{\alpha}{2}} \cdot \sqrt{\frac{\lambda_0(1-\lambda_0)}{n}} = 0.16$

$2.575 \times \sqrt{\frac{0.3 \times 0.7}{n}} = 0.16$ $\Rightarrow n = 54.5 \approx 55.$

④ In this example, Gehan's design would treat 11 patients in the first stage. If none responded, the treatment would be declared a failure. and study stop. If at least 1 response, another 11 patients would be treated. and a 99% C.I for P would be computed using 55 patients.

6. ① Please briefly describe the Simon's two stage design. Suppose X1 is the number of patients who respond in the first stage and X2 is the number of patients who respond in the second stage where n1 = 6, n=14. X1>2 and X1+X2>5. ② Please draw the figure to show the combinations that satisfy the two conditions. How many pairs (combinations) satisfy these conditions?

① Let $r_1$ and $r$ denote some given number related to the clinical trial design, if $X_1 \le r_1$ in the 1st stage, declacl̶are the treatment a failure. if $X_1 > r_1$ in the 1st stage and after two stages $X_1 + X_2 > r$, the treatment is declared a success. if $X_1 > r$ in the 1st stage, declare the treatment success and there is no need to proceed to 2nd stage.

② 


$\begin{cases} X_1 > 2 \\ X_1 + X_2 > 5 \end{cases}$

$n = 6+7+8+9$
$= 30$ pairs.

There are 30 pairs satisfy these conditions

7. For a Hierarchical Model, $X_i|n_i,\pi_i \sim Bin(n_i,\pi_i),\ i = 1,\dots,N$ and $\pi_1,\dots,\pi_N$ *are iid* $(\mu_\pi, \delta_\pi^2)$. Let $p_i = \frac{X_i}{n_i}$ denote the sample proportion that respond from the ith study. ① What about conditional expectation and conditional variance of $p_i$ given $n_i, \pi_i$ (i.e., $E(p_i|n_i,\pi_i)$ *and* $Var(p_i|n_i,\pi_i)$)? ② What about the expectation and variance of of $p_i$ (i.e., $E(p_i)$*and* $Var(p_i)$)? ③ What's the estimate for $\delta_\pi^2$?

① $\begin{cases} E(p_i|n_i,\pi_i) = E(\frac{X_i}{n_i}) = \frac{E(X_i)}{n_i} = \frac{n_i\pi_i}{n_i} = \pi_i \\ Var(p_i|n_i,\pi_i) = Var(\frac{X_i}{n_i}) = \frac{1}{n_i^2} Var X_i = \frac{1}{n_i^2}\cdot n_i\pi_i(1-\pi_i) = \frac{\pi_i(1-\pi_i)}{n_i} \end{cases}$

② $Var(p_i|n_i,\pi_i) = E(p_i^2|n_i,\pi_i) - E^2(p_i|n_i,\pi_i) = E(p_i^2 - p_i|n_i,\pi_i) + E(p_i|n_i,\pi_i) - E^2(p_i|n_i,\pi_i)$

$E(p_i^2-p_i|n_i,\pi_i) = Var(p_i|n_i,\pi_i) + E^2(p_i|n_i,\pi_i) - E(p_i|n_i,\pi_i) = \frac{\pi_i(1-\pi_i)}{n_i} + \pi_i^2 - \pi_i$

$E(p_i^2-p_i|n_i,\pi_i) = \frac{n_i-1}{n_i}\pi_i(\pi_i-1) \Rightarrow E(\frac{p_i(1-p_i)}{n_i-1}|n_i,\pi_i) = \frac{\pi_i(1-\pi_i)}{n_i}$ ……equation Ⓐ

$\begin{cases} E(p_i) = E\{E(p_i|n_i,\pi_i)\} = E(\pi_i) = \mu_\pi \\ Var(p_i) = E\{Var(p_i|n_i,\pi_i)\} + Var\{E(p_i|n_i,\pi_i)\} = E\{\frac{\pi_i(1-\pi_i)}{n_i}\} + Var\pi_i \end{cases}$

Applying Ⓐ $= E\{E(\frac{p_i(1-p_i)}{n_i-1}|n_i,\pi_i)\} + Var\pi_i = E(\frac{p_i(1-p_i)}{n_i-1}) + \delta_\pi^2$

$= \frac{\sum_{i=1}^{N}\frac{p_i(1-p_i)}{n_i-1}}{N} + \delta_\pi^2$

③ $\delta_\pi^2 = Var(p_i) - E\{\frac{\pi_i(1-\pi_i)}{n_i}\} = Var(p_i) - \frac{\sum_{i=1}^{N}\frac{p_i(1-p_i)}{n_i-1}}{N}$

$\hat{\delta}_\pi^2 = E(Var p_i) - \frac{\sum_{i=1}^{N}\frac{p_i(1-p_i)}{n_i-1}}{N} = S_p^2 - \frac{\sum_{i=1}^{N}\frac{p_i(1-p_i)}{n_i-1}}{N} = \frac{\sum_{i=1}^{N}(p_i-\bar{p})^2}{N-1} - \frac{\sum_{i=1}^{N}\frac{p_i(1-p_i)}{n_i-1}}{N}$

8. Example for results of one particular treatment for lung cancer.

| Study | # of patients $(n_i)$ | % response rate | $(p_i-\bar{p})^2$ | $p_i(1-p_i)/(n_i-1)$ |
|---|---|---|---|---|
| 1. A study | 12 | 65 | 0.136 | 0.0207 |
| 2. B study | 52 | 12 | 0.026 | 0.0021 |
| 3. C study | 26 | 5 | 0.054 | 0.0019 |
| 4. D study | 39 | 42 | 0.019 | 0.0064 |
| 5. E study | 148 | 35 | 0.005 | 0.0015 |
| 6. F study | 10 | 17 | 0.0124 | 0.0157 |
| 7. G study | 47 | 21 | 0.0051 | 0.0036 |
| | | | $\Sigma=0.251$ | $\Sigma=0.0519$ |

Using this example to estimate $\delta_\pi^2$.

$$\hat{\delta}_\pi^2 = S_p^2 - \frac{\sum_{i=1}^{N}\frac{p_i(1-p_i)}{n_i-1}}{N} = \frac{\sum_{i=1}^{N}(p_i-\bar{p})^2}{N-1} - \frac{\sum^{N}\frac{p_i(1-p_i)}{n_i-1}}{N} = \frac{0.257}{7-1} - \frac{0.0519}{7}$$

$$= 0.0428 - 0.0074 = 0.0354$$

From the result, we conclude that the data is not good because the major part is from $\delta_\pi^2$

9-10. There is a clinical trial regarding the Hypertension disease: two treatments are involved in this study (Treatment A and Treatment B), and the DBP values of 30 subjects are recorded at time point 1 and time point 5 for two treatments.

| Subject | TRT | DBP1 | DBP5 | Age | Sex |
|---|---|---|---|---|---|
| 1 | A | 114 | 105 | 43 | F |
| 2 | A | 116 | 101 | 51 | M |
| 3 | A | 119 | 98 | 48 | F |
| 4 | A | 115 | 101 | 42 | F |
| 5 | A | 116 | 105 | 49 | M |
| 6 | A | 117 | 102 | 47 | M |
| 7 | A | 118 | 99 | 50 | F |
| 8 | A | 120 | 102 | 61 | M |
| 9 | A | 114 | 103 | 43 | F |
| 10 | A | 115 | 97 | 51 | M |
| 11 | A | 117 | 101 | 47 | F |
| 12 | A | 116 | 102 | 45 | M |
| 13 | A | 119 | 104 | 54 | F |
| 14 | A | 118 | 99 | 52 | M |
| 15 | A | 115 | 102 | 42 | F |
| 16 | B | 114 | 113 | 39 | M |
| 17 | B | 116 | 110 | 40 | F |
| 18 | B | 114 | 109 | 39 | F |
| 19 | B | 114 | 115 | 38 | M |
| 20 | B | 116 | 109 | 39 | F |

| | | | | | |
|---|---|---|---|---|---|
| 21 | B | 114 | 110 | 41 | M |
| 22 | B | 119 | 115 | 56 | F |
| 23 | B | 118 | 112 | 56 | M |
| 24 | B | 114 | 108 | 38 | F |
| 25 | B | 120 | 113 | 57 | M |
| 26 | B | 117 | 115 | 47 | F |
| 27 | B | 118 | 110 | 48 | M |
| 28 | B | 121 | 115 | 61 | F |
| 29 | B | 116 | 111 | 49 | M |
| 30 | B | 118 | 112 | 52 | M |

9. Please design the hypothesis and test the mean difference of DBP5 between treatment A and treatment B, and write down the formula, results and your codes? (Please write down all equations and statistics)

Test: $\begin{cases} H_0: \mu_1 = \mu_2 \\ H_a: \mu_1 \neq \mu_2 \end{cases}$

Formula:

$$\begin{cases} SD_1 = \sqrt{\dfrac{\sum_{j=1}^{n} (y_{1j} - \bar{y}_{1\cdot})^2}{n_1 - 1}} \\ SD_2 = \sqrt{\dfrac{\sum_{j=1}^{n} (y_{2j} - \bar{y}_{2\cdot})^2}{n_2 - 1}} \end{cases}$$

$$F^* = \frac{SS_{between} / (2-1)}{SS_{within} / (n_1 + n_2 - 2)}$$

should be verified the assumption of ANOVA

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$$\begin{cases} SS_{between} = \sum_{i=1}^{2} n_i (\bar{y}_{i\cdot} - \bar{y})^2 \\ SS_{within} = \sum_{i=1}^{2} (n_i - 1) SD_i^2 \end{cases}$$

From the R output:

$\begin{cases} \bar{y}_{1\cdot} = 101.4 \\ \bar{y}_{2\cdot} = 111.8 \end{cases}$ $\begin{cases} SD_1^2 = 5.686 \\ SD_2^2 = 6.0286 \end{cases}$ $\begin{cases} \bar{y} = 106.6 \\ SS_{between} = 811.2 \\ SS_{within} = 164 \end{cases}$ $\begin{cases} F^* = 138.5 \\ F_{(0.95, 1, 28)} = 4.2 \end{cases}$ $\Rightarrow F^* > F_{(0.95, 1, 28)}$

In this case, we conclude Ha.

10. For each treatment, DBP1 and DBP5 will be paired data, please use three methods we have learned in the class to test the difference between DBP1 and DBP5 for treatment A?

Please see the attachment.

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Q9-R code

```
> data=matrix(0,15,3)
> data=matrix(0,30,3)
> data[,1]=c(114,116,119,115,116,117,118,120,114,115,117,116,119,118,115,114,
116,114,114,116,114,119,118,114,120,117,118,121,116,118)
> data[,2]=c(105,101,98,101,105,102,99,102,103,97,101,102,104,99,102,113,110,
109,115,109,110,115,112,108,113,115,110,115,111,112)
> data[,3]=c('A','A','A','A','A','A','A','A','A','A','A','A','A','A','A','B',
'B','B','B','B','B','B','B','B','B','B','B','B','B','B')
> write.table(data,'data.midterm.txt',quote = F)
> data=read.table('data.midterm.txt')
> data
    V1  V2 V3
1  114 105  A
2  116 101  A
3  119  98  A
4  115 101  A
5  116 105  A
6  117 102  A
7  118  99  A
8  120 102  A
9  114 103  A
10 115  97  A
11 117 101  A
12 116 102  A
13 119 104  A
14 118  99  A
15 115 102  A
16 114 113  B
17 116 110  B
18 114 109  B
19 114 115  B
20 116 109  B
21 114 110  B
22 119 115  B
23 118 112  B
24 114 108  B
25 120 113  B
26 117 115  B
27 118 110  B
28 121 115  B
29 116 111  B
30 118 112  B
> id.a=which(data[,3]=='A')
> id.b=which(data[,3]=='B')
> id.a
 [1]  1  2  3  4  5  6  7  8  9 10 11 12 13 14 15
> id.b
 [1] 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
> data.a=data[id.a,]
> data.b=data[id.b,]
> data.a;data.b
    V1  V2 V3
1  114 105  A
2  116 101  A
3  119  98  A
4  115 101  A
```

```
5  116 105  A
6  117 102  A
7  118  99  A
8  120 102  A
9  114 103  A
10 115  97  A
11 117 101  A
12 116 102  A
13 119 104  A
14 118  99  A
15 115 102  A
    V1  V2 V3
16 114 113  B
17 116 110  B
18 114 109  B
19 114 115  B
20 116 109  B
21 114 110  B
22 119 115  B
23 118 112  B
24 114 108  B
25 120 113  B
26 117 115  B
27 118 110  B
28 121 115  B
29 116 111  B
30 118 112  B
> mean.a=mean(data.a[,2])
> mean.b=mean(data.b[,2])
> mean.a
[1] 101.4
> mean.b
[1] 111.8
> var.a=var(data.a[,2])
> var.b=var(data.b[,2])
> var.a
[1] 5.685714
> var.b
[1] 6.028571
> na=nrow(data.a)
> nb=nrow(data.b)
> ss.in=(na-1)*var.a+(nb-1)*var.b
> mean=mean(data[,2])
> mean
[1] 106.6
> ss.bt=na*(mean.a-mean)*(mean.a-mean)+nb*(mean.b-mean)*(mean.b-mean)
> ss.bt
[1] 811.2
> F=(ss.bt/(2-1))/(ss.in/(na+nb-2))
> F
[1] 138.4976
> ss.in
[1] 164
> F.critical=qf(.95, df1=1, df2=na+nb-2)
> F.critical
[1] 4.195972
```

Q10-Method I:

```
> data.aa=cbind(data.a[,1:2],data.a[,1]-data.a[,2])
> data.aa
    V1  V2 data.a[, 1] - data.a[, 2]
1  114 105                         9
2  116 101                        15
3  119  98                        21
4  115 101                        14
5  116 105                        11
6  117 102                        15
7  118  99                        19
8  120 102                        18
9  114 103                        11
10 115  97                        18
11 117 101                        16
12 116 102                        14
13 119 104                        15
14 118  99                        19
15 115 102                        13
> n=nrow(data.aa)
> n
[1] 15
> mean.a.d=mean(data.aa[,3])
> mean.a.d
[1] 15.2
> var.a.d=var(data.aa[,3])
> var.a.d
[1] 11.45714
> sem.d=sqrt(var.a.d/n)
> sem.d
[1] 0.873962
> T.d=mean.a.d/sem.d
> T.d
[1] 17.39206
> alpha=0.05
> t.critical=qt(1-alpha/2,n-1)
> t.critical
[1] 2.144787
```

Test: $\begin{cases} H_0: d=0 \\ H_a: d\neq 0 \end{cases}$ $d=\mu_1-\mu_2$

Formula: $SEM=\dfrac{SD_d}{\sqrt{n}}$

$t_{obs}=\dfrac{\bar{d}}{SEM}$

From the output: $SD_d^2=11.457$

$\bar{d}=15.2$

$SEM=0.874$

$t_{obs}=17.4$

$t_{0.975,14}=2.201$ × $2.145$ −1

RR: $t_{obs}>t_{0.975,14}$

In this case.

Since $t_{obs}=17.4>t_{0.975,14}=2.145$

We conclude $H_a$.

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Q10-Method II:

```
> data.a
    V1  V2 V3
1  114 105  A
2  116 101  A
3  119  98  A
4  115 101  A
5  116 105  A
6  117 102  A
7  118  99  A
8  120 102  A
9  114 103  A
10 115  97  A
11 117 101  A
12 116 102  A
13 119 104  A
14 118  99  A
15 115 102  A
> mean.x=mean(data.a[,1])
> mean.y=mean(data.a[,2])
> mean.x
[1] 116.6
> mean.y
[1] 101.4
> var.x=var(data.a[,1])
> var.y=var(data.a[,2])
> var.x
[1] 3.542857
> var.y
[1] 5.685714
> sd.x=sd(data.a[,1])
> sd.y=sd(data.a[,2])
> sd.x
[1] 1.882248
> sd.y
[1] 2.384474
> corr.a=cor(data.a[,1],data.a[,2])
> corr.a
[1] -0.2482717
> n=nrow(data.a)
> n
[1] 15
> sem=sqrt((var.x+var.y-2*corr.a*sd.x*sd.y)/n)
> sem
[1] 0.873962
> T.2=(mean.x-mean.y)/sem
> T.2
[1] 17.39206
> t.critical
[1] 2.144787
```

Test: $\begin{cases} H_0: d=0 \\ H_a: d\neq 0 \end{cases}$

Formula: $r = \dfrac{\sum_{i=1}^{n}(x_i-\bar{x})(y_i-\bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i-\bar{x})^2\sum_{i=1}^{n}(y_i-\bar{y})^2}}$

$SEM = \sqrt{\dfrac{SD_x^2+SD_y^2-2r\,SD_x SD_y}{n}}$

$t_{obs} = \dfrac{\bar{x}-\bar{y}}{SEM}$

From the output

$\bar{x} = 116.6$

$\bar{y} = 101.4$

$r = -0.248$

$SD_x^2 = 3.54$

$SD_y^2 = 5.686$

$SD_x = 1.88$

$SD_y = 2.38$

$SEM = 0.874$

$t_{obs} = 17.392$

$t_{0.975,14} = 2.145$

RR: $t_{obs} > t_{0.975,14}$

In this case, since $t_{obs} > t_{0.975,14}$ we conclude $H_a$.

Q10-Method III

```
> mean.within=apply(data.a[,1:2],1,mean)
> mean.within
    1     2     3     4     5     6     7     8     9    10    11    12 
109.5 108.5 108.5 108.0 110.5 109.5 108.5 111.0 108.5 106.0 109.0 109.0 
   13    14    15 
111.5 108.5 108.5 
> mean.group=apply(data.a[,1:2],2,mean)
> mean.group
   V1    V2 
116.6 101.4 
> ss.within=sum((data.a[,1:2]-mean.within)^2)
> ss.within
[1] 1813
> mean.all=mean(mean.within)
> mean.all
[1] 109
> n=nrow(data.a)
> n
[1] 15
> ss.trt=sum(n*(mean.group-mean.all)^2)
> ss.trt
1732.8
> ss.res=ss.within-ss.trt
> ss.res
[1] 80.2
> F.obs=(ss.trt/1)/(ss.res/(n-1))
> F.obs
[1] 302.4838
> F.critical=qf(0.95,1,n-1)
> F.critical
[1] 4.60011
```

Test $\begin{cases} H_0: d=0 \\ H_a: d\neq 0. \end{cases}$

Formula:

$SS_{within}$ subject $i = (x_i - \overline{xy_i})^2 + (y_i - \overline{xy_i})^2$

$SS_{within} = \sum_{i=1}^{n} SS_{within}$ subject $i$

$SS_{treatment} = n(\bar{x} - \bar{\bar{T}})^2 + n(\bar{y} - \bar{\bar{T}})^2.$

where $\bar{\bar{T}}$ denotes the overall mean.

$SS_{residual} = SS_{within} - SS_{treatment}.$

$F_{obs} = \dfrac{SS_{treatment} / df_{treatment}}{SS_{residual} / df_{residual}}$

where $\begin{cases} df_{treatment} = 1 \\ df_{residual} = n-1 \end{cases}$

$n$ is # of pairs

From the R output

$SS_{within} = 1813.$

$SS_{treatment} = 1732.8$

$SS_{residual} = 80.2.$

$F_{obs} = 302.48$

RR: $F_{obs} > F_{0.95,1,14}$

In this case. Since $F_{obs} = 302.48 > F_{0.95,1,14} = 4.6$

we conclude $H_a$.