BIOS 7400 Clinical Trials Assignment 2

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library("gvlma")  
library("epitools")  
library("tidyr")

# Assignment I

**Write out the following formula for a control group labeled as Y. Discuss how randomization in treatment allocation can help cancel out the bias of the effect of regression to the mean.**

By using the randomization in treatment allocation to reduce the effects of regress to mean (RTM) at the design stage, we assume the subjects are randomly assigned to treatment or control groups, the responses from two groups should be equally affected by RTM. Here, we can estimate the magnitude of the effect of RTM for treatment and control groups as below.

The formula (1) and formula (2) represent the estimation of the effect of RTM for treatment and control group, respectively. The mean change in the control group includes both effects of RTM and the placebo, so the difference between the mean change of treatment group and the mean change of control group, such as (1)-(2), could cancel out the effect of the RTM. Hence, the estimate of the treatment effect could be more accuracy after adjusting for RTM.

Reference: Adrian G Barnett, Jolieke C van der Pols, Annette J Dobson; Regression to the mean: what it is and how to deal with it, International Journal of Epidemiology, Volume 34, Issue 1, 1 February 2005, Pages 215–220, <https://doi.org/10.1093/ije/dyh299>

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# Assignment II

**Use the data (data\_surrogate.txt) to perform surrogate validation analysis.**

* **Use outcome1 as surrogate outcome and outcome2 as the true clinical outcome**
* **Provide the calculation of PE, RE and .**
* **Based on the calculation results, can you support outcome1 as a good surrogate for outcome2?**

In order to check Prentice's criteria, the linear models was conducted as below.

where Z: treatment group. Assume "-1": Case group and "1": Control group. We also assume j indexes subjects, and and are normal with mean 0.

Prentice1<-lm(formula = Outcome2~Outcome1,data = DT2)  
Prentice2<-lm(formula = Outcome2~Outcome1+Treatment,data = DT2)

For the criterion one:

summary(Prentice1)

##   
## Call:  
## lm(formula = Outcome2 ~ Outcome1, data = DT2)  
##   
## Residuals:  
## Min 1Q Median 3Q Max   
## -43.922 -4.699 1.730 6.376 30.004   
##   
## Coefficients:  
## Estimate Std. Error t value Pr(>|t|)   
## (Intercept) -6.74763 0.89136 -7.57 1.9e-12 \*\*\*  
## Outcome1 0.92561 0.06168 15.01 < 2e-16 \*\*\*  
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
##   
## Residual standard error: 10.56 on 179 degrees of freedom  
## Multiple R-squared: 0.5571, Adjusted R-squared: 0.5547   
## F-statistic: 225.2 on 1 and 179 DF, p-value: < 2.2e-16

Based on the result from the linear model test, we found the null hypothesis is rejected with the p value less than 2e-16.

For second criterion:

summary(Prentice2)

##   
## Call:  
## lm(formula = Outcome2 ~ Outcome1 + Treatment, data = DT2)  
##   
## Residuals:  
## Min 1Q Median 3Q Max   
## -44.520 -4.014 1.441 6.310 29.402   
##   
## Coefficients:  
## Estimate Std. Error t value Pr(>|t|)   
## (Intercept) -6.18097 1.13595 -5.441 1.73e-07 \*\*\*  
## Outcome1 0.92213 0.06189 14.899 < 2e-16 \*\*\*  
## Treatment1 -1.27240 1.57873 -0.806 0.421   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1  
##   
## Residual standard error: 10.57 on 178 degrees of freedom  
## Multiple R-squared: 0.5587, Adjusted R-squared: 0.5538   
## F-statistic: 112.7 on 2 and 178 DF, p-value: < 2.2e-16

From the result of the linear model test, we found the coefficient of the treatment is not significant with p value 0.421. Hence, we accept the null hypothesis. Based on these two test, we can conclude that our candidate still as a valid surrogate.

## Proportion explained by surrogate outcome(PE)

Assume the assumptions are acceptable. The calculation of PE, RE, and are presented below.

P1\_1<-lm(formula = Outcome2~Treatment+Outcome1,data = DT2)  
P1\_2<-lm(formula = Outcome2~Treatment,data = DT2)

The and were generated from the linear model, and the values were applied to the formula below.

PE= = = 0.5631

In the code below, we used bootstrapping method to estimate the 95% bootstrapped confidence interval of PE which is based on 10,000 replications.

library(boot)  
set.seed(30949)  
BootPE<-function(formulaA,formulaB,data,indices) {  
 d<-data[indices,]  
 P1<-lm(formulaA ,data = d)  
 P2<-lm(formulaB ,data = d)  
 PE<-(P2$coefficients[[2]]-P1$coefficients[[2]])/P2$coefficients[[2]]  
 return(PE)  
}  
PEresults<-boot(data = DT2,statistic = BootPE,R = 10000,formulaA= Outcome2~Treatment+Outcome1,formulaB= Outcome2~Treatment)  
boot.ci(PEresults,type = "basic")

BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS

Based on 10000 bootstrap replicates

Intervals : Lower Upper

95% (-2.0936, 3.5506 ) Calculations and Intervals on Original Scale

## Relative effect(RE)

P2\_1<-lm(formula = Outcome2~Treatment,data = DT2)  
P2\_2<-lm(formula = Outcome1~Treatment,data = DT2)

RE= = = 1.6375

## Adjusted association

varMatrix<-as.data.frame(var(x = DT2[,c(3,4)]))  
kable(varMatrix)

|  |  |  |
| --- | --- | --- |
| Variance and cocariace matrix | Outcome1 | Outcome2 |
| Outcome1 | 162.7126 | 150.6080 |
| Outcome2 | 150.6080 | 250.2189 |

The adjusted = = =0.7464

The adjusted correlation between the clinical outcome and the surrogate outcome is 0.7464.

# Summary

From the statistical surrogate validation process, our candidate passed the two criteria directly, which reject the null hypothesis and also retain the null hypothesis for the linear models respectively. We can assume the candidate is possible to be the good surrogate as the true clinical outcome. Although the lower bound of 95% bootstrapped confidence of PE (-2.09) on 10,000 replication is not larger than 0.5, there are still some reasons that show the outcome one as a good surrogate for the outcome two. First, the observed proportion explained by the surrogate outcome is 0.5631 which is larger than 0.5. Second, the adjusted correlation between the clinical outcome and the surrogate outcome is 0.74, which shown higher correlated with the clinical outcome. Last, the relative effect of the treatment on outcome two versus outcome one usually be expected as a value of 1 that represent the treatment effect on both measurements are similar. However, our relative effect is 1.6375, which shows the treatment effect on both outcomes is not perfectly matched but acceptable.

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# Assignment III

**Use the DBP dataset.**

* **Please use t test and Wilcoxon rank‐sum test to test the difference of the treatment on blood pressure change (the difference between the blood pressure measured on time 4, DBP4, and measured on time 1, DBP1).**
* **Present the results and write the report on your findings.**

## t test

Before doing t test, we used the F test to compare two variances, and the result of the F test will be used in the following t test.

(FvarTest<-var.test(diff~TRT,data = DT3))

##   
## F test to compare two variances  
##   
## data: diff by TRT  
## F = 2.3863, num df = 19, denom df = 19, p-value = 0.06534  
## alternative hypothesis: true ratio of variances is not equal to 1  
## 95 percent confidence interval:  
## 0.9445351 6.0289245  
## sample estimates:  
## ratio of variances   
## 2.386322

From the result above, we found the p-value of F test is 0.0653 which implies that the variances between two groups are the same. Hence, two sample t test with equal variances will be used in this study.

(TtestResult<-t.test(diff~TRT,data = DT3,var.equal=TRUE))  
## Two Sample t-test  
##   
## data: diff by TRT  
## t = -6.1103, df = 38, p-value = 4.018e-07  
## alternative hypothesis: true difference in means is not equal to 0  
## 95 percent confidence interval:  
## -7.987838 -4.012162  
## sample estimates:  
## mean in group A mean in group B   
## -10.3 -4.3

The two sample t-test showed that the difference of effect between baseline and time 4 is significantly different with a p-value less than 0.0001. The 95% confidence interval of the difference between Group A and Group B is between -7.9878 and -4.0122.

## Wilcoxon rank-sum test

(Wil\_result<-wilcox.test(diff~TRT,data = DT3, conf.int = TRUE))

##   
## Wilcoxon rank sum test with continuity correction  
##   
## data: diff by TRT  
## W = 31.5, p-value = 4.832e-06  
## alternative hypothesis: true location shift is not equal to 0  
## 95 percent confidence interval:  
## -7.999960 -3.999987  
## sample estimates:  
## difference in location   
## -5.999929

A Wilcoxon rank-sum test can be used to determine whether two dependent samples were followed from populations having the same distribution. From the result above, we found it is significant to reject the null hypothesis with a statistic W =31.5 and p-value =4.83e-06. We can conclude the distribution of the difference of effect between two different groups is significantly different.

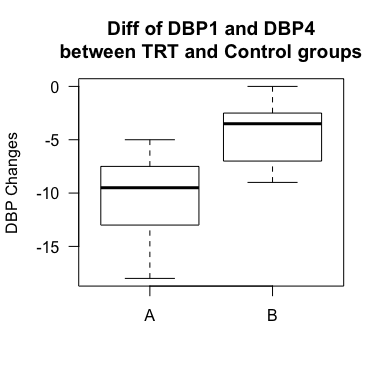
## Summary

In this analysis, we can easily find the averages of the blood pressure that measured at the baseline and time 4, and the blood pressure changes between the two-time points are not the same between the treatment group and the control group. Within the treatment group (A), we could found the average blood pressure at the time 4 is 106.25 which is reduced from 116.55 at the baseline. The mean of blood pressure change between these two time-points is -10.3 (SD=3.69) for group A and -4.3 (SD=2.39) for group B, respectively.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| TRT | mean\_DBP1 | mean\_DBP4 | mean\_Diff | SD\_diff |
| A | 116.55 | 106.25 | -10.3 | 3.69 |
| B | 116.75 | 112.45 | -4.3 | 2.39 |

From the boxplot, we found it seems to have a significant change between baseline and time 4.

boxplot(diff~TRT,data = DT3,ylab="DBP Changes", las=1,main="Diff of DBP1 and DBP4\nbetween TRT and Control groups")



By using the formal statistical test to identify the significant difference of the treatment on blood pressure change from the baseline to the time 4, we can found both of the parametric (t test) and non-parametric (Wilcoxon) methods are significant to reject the null hypothesis with the p-value less than 0.0001. The 95% confidence interval of blood pressure changes from both statistical methods also indicated a consistency range in the table below. Hence, we can conclude the there is significantly different from the treatment on blood pressure change from the baseline (time 1) to time 4.

|  |  |  |  |
| --- | --- | --- | --- |
| Test | Statistic | p-value | 95% confidence interval (Lower,Upper) |
| T test | -6.11 | 4.018e-07 | -7.988, -4.012 |
| Wilcoxon test | 31.5 | 4.832e-06 | -8, -4 |

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# Assignment IV

**Use the CRASH trial (Corticosteroid Randomization After Significant Head Injury) data to compare the odds for “death” over “survival” between corticosteroid and placebo treatments.**

* **Use the prop.test in R to perform the statistical analysis**
* **The comparison should be made for “best prognosis”, “intermediate prognosis” and “worst prognosis” groups as well as all the subjects pooled together.**
* **Calculate the risk difference, risk ratio and odds ratio for the comparisons**
* **Present the results and write a report on your findings.**

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# Compare the proportion of dead between Corticosteroid and Placebo groups for the whole subjects together

where C: Corticosteroid group and P: Placebo group

AllTable<-table(DT4$Trt,DT4$Status)  
(AllResult<-prop.test(AllTable))

##   
## 2-sample test for equality of proportions with continuity  
## correction  
##   
## data: AllTable  
## X-squared = 14.71, df = 1, p-value = 0.0001254  
## alternative hypothesis: two.sided  
## 95 percent confidence interval:  
## 0.01647864 0.05127062  
## sample estimates:  
## prop 1 prop 2   
## 0.2600000 0.2261254

kable(AllTable)

|  |  |  |
| --- | --- | --- |
| For overall subjects | Dead | Survival |
| Corticosteroid | 1248 | 3552 |
| Placebo | 1075 | 3679 |

To test the equality of proportion in the two groups of the whole subjects, we found the result of the proportion test shown the there is significant difference proportion of dead between Corticosteroid group and Placebo group with p value Next, we stratified the subjects into three groups and compared their proportions separately.

prop.test.revised<-function(data=DT4,cat){  
 BestPro<-data%>%filter(Prognosis==cat)  
 proportion\_test<-prop.test(table(BestPro$Trt,BestPro$Status))  
 result\_table<-data.frame("Prognosis"=cat,"X-square"=proportion\_test$statistic,  
 "p-value"=proportion\_test$p.value,  
 "P\_Corticosteroid"=proportion\_test$estimate[[1]],  
 "P\_Placebo"=proportion\_test$estimate[[2]])  
 return(result\_table)}  
Result\_prop\_test<-rbind(prop.test.revised(cat = "Best"),prop.test.revised(cat = "Intermediate"),prop.test.revised(cat = "Worst"))  
row.names(Result\_prop\_test)<-c("Best","Intermediate","Worst")  
kable(format(Result\_prop\_test[,-1],digits=3))

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Stratified groups | Chi square | p.value | PCorticosteroid | PPlacebo |
| Best | 0.447 | 0.5037 | 0.0422 | 0.0369 |
| Intermediate | 5.854 | 0.0155 | 0.1752 | 0.1431 |
| Worst | 12.102 | 0.0005 | 0.5615 | 0.4994 |

We found the proportion of dead between two groups for the best prognosis is not statistically different. Regarding the intermediate group and worst group, we reject the null hypothesis and accept the alternative hypothesis with p value 0.0155 and , respectively.

## Risk Difference, Risk Ratio, and Odds Ratio

epiValue<-function(dt=DT4,cat=NA){  
 if (is.na(cat)){  
 Risk\_result<-epitab(x = dt$Trt,y = dt$Status,rev="both", method = c("riskratio"))$tab  
 Odds\_result<-epitab(x = dt$Trt,y = dt$Status,rev="both", method = c("oddsratio"))$tab  
 whole\_result<-cbind(Risk\_result,Odds\_result[,c(5:8)])  
 return(data.frame(whole\_result))  
 } else {  
 dt<-dt%>%filter(Prognosis==cat)  
 Risk\_result<-epitab(x = dt$Trt,y = dt$Status,rev="both", method = c("riskratio"))$tab  
 Odds\_result<-epitab(x = dt$Trt,y = dt$Status,rev="both", method = c("oddsratio"))$tab  
 whole\_result<-cbind(Risk\_result,Odds\_result[,c(5:8)])  
 return(data.frame(whole\_result))  
 }  
}  
Overall\_result<-epiValue()  
Best\_result<-epiValue(cat="Best")  
Inter\_result<-epiValue(cat="Intermediate")  
Worst\_result<-epiValue(cat="Worst")

Here list the estimates we used in previous analysis.

* Risk = proportion in group with condition present[Dead]
  + For overall: = 0.26 and = 0.23.
  + For best prognosis: = 0.04 and = 0.04.
  + For intermediate prognosis: = 0.18 and = 0.14.
  + For worst prognosis: = 0.56 and = 0.5.
* Risk Difference = Risk[Corticosteroid]-Risk[Placebo]
  + For overall: = 0.03.
  + For best prognosis: = 0.
  + For intermediate prognosis: = 0.04.
  + For worst prognosis: = 0.06.
* Risk Ratio = Risk[Corticosteroid]/Risk[Placebo]
  + For overall: = 1.15.
  + For best prognosis: = 1.14.
  + For intermediate prognosis: = 1.22.
  + For worst prognosis: = 1.12.
* Odds[Placebo] = Dead[group1]/Survival[group1]
  + For overall: = 0.29.
  + For best prognosis: = 0.04.
  + For intermediate prognosis: = 0.17.
  + For worst prognosis: = 1.
* Odds[Corticosteroid] = Dead[group2]/Survival[group2]
  + For overall: = 0.35.
  + For best prognosis: = 0.04.
  + For intermediate prognosis: = 0.21.
  + For worst prognosis: = 1.28.
* Odds Ratio = Odds[Corticosteroid]/Odds[Placebo]
  + For overall: = 1.2.
  + For best prognosis: = 1.15.
  + For intermediate prognosis: = 1.27.
  + For worst prognosis: = 1.28.

## Summary

For the proportion test, we compared the percentage of dead between corticosteroid group and placebo group, and we found it is significantly different with the p value less than 0.05. After comparing the different stratifications, "Best prognosis," Intermediate prognosis," and "Worst prognosis," we only accept the null hypothesis of equal proportion for two groups within the Best prognosis subjects (p value<0.001). Both results of "Intermediate prognosis" and "Worst prognosis" are shown the significant differences in the percentage of dead between corticosteroid and placebo groups. If we only consider the proportion of death for pooled subjects, we found the proportion of death is 26% in the Corticosteroid group and 22% in the placebo group. After stratifying the subject base on their prognosis situation, we found the highest proportion of dead is 56% that belongs to the subjects who are "Worst prognosis" and received corticosteroid treatment. The minimum percentage of death is 3% that is the subject who is with "Best prognosis" and received the only placebo.

TotalTable<-data.frame(rbind(Overall\_result,Best\_result,Inter\_result,Worst\_result))  
TotalTable$category<-rep(c("Overall","Best","Intermediate","Worst"),c(2,2,2,2))  
format(TotalTable,digits=4)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Prognosis | Treatment | Survival |  | Dead |  | Risk Ratio | Odds Ratio |
| Overall | Placebo | 3679 | 0.7739 | 1075 | 0.2261 | 1.0000 | 1.0000 |
| Corticosteroid | 3552 | 0.7400 | 1248 | 0.2600 | 1.1500 | 1.2020 |
| Best | Placebo1 | 1539 | 0.9631 | 59 | 0.0369 | 1.0000 | 1.0000 |
| Corticosteroid1 | 1522 | 0.9578 | 67 | 0.0422 | 1.1420 | 1.1480 |
| Intermediate | Placebo2 | 1347 | 0.8569 | 225 | 0.1431 | 1.0000 | 1.0000 |
| Corticosteroid2 | 1328 | 0.8248 | 282 | 0.1752 | 1.2240 | 1.2710 |
| Worst | Placebo3 | 793 | 0.5006 | 791 | 0.4994 | 1.0000 | 1.0000 |
| Corticosteroid3 | 702 | 0.4385 | 899 | 0.5615 | 1.1240 | 1.2840 |

Comparing the odds ratio and risk ratio between corticosteroid and placebo groups, we also found the results are also compatible with previous proportion test, which also reported the subjects receiving corticosteroid in the worst prognosis had 1.124 times the risk of death compared to subjects who received the only placebo. Also, for the subject receiving corticosteroid treatment, the odds of being dead are 1.284 times larger than the odds for a subject receiving the only placebo under the worst prognosis. For the subjects receiving corticosteroid under intermediate prognosis had 1.224 times the risk of death compares to the placebo group, and the odds ratio is 1.271 which is also similar to the worst prognosis.