**Homework 3, CPH 675 Clinical Trials Spring 2015, Dominic LaRoche**

**Due: 10 April 2015**

**Include only relevant code and output. Please do not show data manipulation code.**

2. [8pts] Use the renal cancer dataset to investigate the whether the treatment effect (over time) on quality of life (as measured by the trial outcome index) depends on the baseline risk score (riskgrp; higher scores indicate greater risk). Use a mixed model, assuming a means model, random intercept and including the baseline TOI as an outcome. State your methods and your conclusion. You do *not* have to give an effect size and CI here.

m1<-lmer(toi~ftime\*treat\*friskgrp + (1|id), data=renal)

m1b<-lm(toi~ftime\*treat\*friskgrp, data=renal)#need this to generate the contrast skeleton

#compare treatment by risk group interactions

cc2<-contrast::contrast(m1b,a=list(friskgrp="1",treat=1,ftime="1"),b=list(friskgrp="0",treat=0, ftime="1"))

cc2$X[1:24]<-c(rep(0,4),1,rep(0,11),1,0,rep(1/3,3),rep(0,3))# group 1 vs 0

trt.grp1v0<-summary(glht(m1,linfct=cc2$X))

trt.grp1v0

Linear Hypotheses:

Estimate Std. Error z value Pr(>|z|)

1 == 0 -0.8246 4.4745 -0.184 0.854

(Adjusted p values reported -- single-step method)

cc2$X[1:24]<-c(rep(0,4),1,rep(0,11),0,1,rep(0,3),rep(1/3,3))# group 2 vs 0

trt.grp2v0<-summary(glht(m1,linfct=cc2$X))

trt.grp2v0

Linear Hypotheses:

Estimate Std. Error z value Pr(>|z|)

1 == 0 -1.379 6.049 -0.228 0.82

(Adjusted p values reported -- single-step method)

cc2$X[1:24]<-c(rep(0,4),1,rep(0,11),1,-1,rep(1/3,3),rep(-1/3,3))# group 2 vs 1

trt.grp2v1<-summary(glht(m1,linfct=cc2$X))

trt.grp2v1

Linear Hypotheses:

Estimate Std. Error z value Pr(>|z|)

1 == 0 1.616 7.260 0.223 0.824

(Adjusted p values reported -- single-step method)

I fit a general linear mixed model with patient id included as a random variable. I included a 3-way interaction between measurement time, treatment arm, and risk group to determine if the treatment effect over time differed among treatment groups. I did not find a statistically significant difference in treatment effect among the risk groups at the alpha=0.05 level.

3. [10pts] Use the renal dataset and appropriate contrasts to estimate the unadjusted treatment effect and 95% CI as measured by

a) the third time point. Compare to last homework’s estimates. Show the code for your model and contrast statement (estimate/lincom).

m2<-lmer(toi~ftime\*treat+(1|id),data=renal)

m2b<-lm(toi~ftime\*treat,data=renal)#needed to get the contrast matrix since the lmer method is a bit funky

ccA<-contrast::contrast(m2b,a=list(ftime="3",treat=1), b=list(ftime="3",treat=0))

estA<-summary(glht(m2, linfct=ccA$X))

resultsA<-matrix(c(estA$test$coef,estA$test$sigma,estA$test$coef-(qt(.975,563)\*estA$test$sigma),estA$test$coef+(qt(.975,563)\*estA$test$sigma)),1,4)

colnames(resultsA)<-c("Estimate","SE","Lower 95% CI","Upper 95% CI")

resultsA

Estimate SE Lower 95% CI Upper 95% CI

[1,] -9.726763 2.506918 -14.65082 -4.802708

This result is larger (in magnitude) than the result from the last homework and, most importantly, has a smaller standard error.

b) the average of the 3 post-baseline TOI assessments. SAS users may need to use the divisor option in the estimate statement.

ccB$X<-ccA$X

ccB$X[6:8]<-c(1/3,1/3,1/3)

estB<-summary(glht(m2, linfct=ccB$X))

resultsB<-matrix(c(estB$test$coef,estB$test$sigma,estB$test$coef-(qt(.975,563)\*estB$test$sigma),estB$test$coef+(qt(.975,563)\*estB$test$sigma)),1,4)

colnames(resultsB)<-colnames(resultsA)

resultsB

Estimate SE Lower 95% CI Upper 95% CI

[1,] -6.81506 2.121011 -10.98112 -2.648998

4. [10pts] Use the renal cancer data to perform survival analysis. Note that the data is in long form, but for survival analysis it needs to be in wide form. Create a Kaplan-Meier survival graph and test whether the survival profiles are the same. Use months as your survival time unit and good graphing habits.

renalw$survmnths<-renalw$survtime/30 #convert to months

sv1<-Surv(renalw$survmnths, event=renalw$dead)

sf1<-survfit(sv1~treat,data=renalw)

ggSurvival(sf1, spot.cens=T, CI=T, xlab="Survival Months", stratName="Arm", groupNames=c("Control","Treatment"),groupNameLevels=c("Control","Treatment"))#this is a home-built plotting function

svtest<-survdiff(sv1~treat,data=renalw, rho=0) #rho=0 corresponds to log-rank test

svtest

N Observed Expected (O-E)^2/E (O-E)^2/V

treat=0 97 70 75.9 0.465 0.981

treat=1 100 81 75.1 0.470 0.981

Chisq= 1 on 1 degrees of freedom, p= 0.322

C:\Classes\ClinicalTrials\HW3_plot.emf

5. [4pts] Estimate the median survival time and 95% CI for each of the treatment groups.

sf1 #print method gives median survival times and 95% CIs

The control group had a median survival time of 17.4 months (95% CI 13.9, 22) whereas the treatment group had a median survival time of 13 months (95% CI 8.3, 6.2).

6. [8pts] Use the Cox proportional hazards model to compare arms, while adjusting for risk group. Report results briefly, including an effect size for treatment and CI.

renalw$friskgrp<-factor(renalw$riskgrp)

d<-datadist(renalw)

options(datadist="d")

mcph<-cph(sv1~treat+friskgrp,data=renalw)

mcph

summary(mcph)

Effects Response : sv1

Factor Low High Diff. Effect S.E. Lower 0.95 Upper 0.95

treat 0 1 1 0.070158 0.17423 -0.27133 0.41165

Hazard Ratio 0 1 1 1.072700 NA 0.76236 1.50930

friskgrp - 0:1 2 1 NA -0.254440 0.20061 -0.64763 0.13875

Hazard Ratio 2 1 NA 0.775350 NA 0.52328 1.14880

friskgrp - 2:1 2 3 NA 0.931260 0.21069 0.51832 1.34420

Hazard Ratio 2 3 NA 2.537700 NA 1.67920 3.83510

I found that treatment, after controlling for risk group, was associated with a slightly higher risk of death (HR = 1.07, 95% CI= 0.76, 1.51) although this effect was not statistically significant.

7. [10pts] Is there evidence of a difference in treatment on the survival effect based on risk group? Report the HRs and 95% CIs for treatment by risk group (based on one model).

m2cph<-cph(sv1~treat\*friskgrp,data=renalw)

m2cph

summary(m2cph)

I did not find any evidence for a treatment by risk-group interaction.

|  |  |  |  |
| --- | --- | --- | --- |
|  | HR | Lower 95% CI | Upper 95% CI |
| Treat\*Risk Group=1 | 0.54 | 0.25 | 1.18 |
| Treat\*Risk Group=2 | 0.79 | 0.31 | 1.99 |