Supplement 3

```
## Analysis of Larach MH data
## Written by Steve Shafer, March - June, 2014

remove(list=ls())
require("PF")
require ("DescTools")

SCREENONLY <- TRUE

setwd("c:/projects/larach/Revision 4")
DATA <- read.csv("Larach.Processed.June 2014.csv",as.is=TRUE)

SPREAD <- .07 # Used to spread points on graph so they can be seen
OFFSET <- SPREAD*3/2

CEX.POINTS <- 1
DEAD.POINTS <- CEX.POINTS * 1.2
DATA$COLOR <- c("red","blue","green3","orange")[DATA$Probe+1]
DATA$PCH <- c(16,10)[DATA$Died+1]
DATA$CEX <- c(CEX.POINTS,DEAD.POINTS)[DATA$Died+1]
DATA$DIC.PCH <- c(16,10)[DATA$DIC+1]
DATA$DIC.CEX <- c(CEX.POINTS,DEAD.POINTS)[DATA$DIC+1]

TIMESTAMP <- format(Sys.time(), "%y%m%d.%H%M%S")
PDFNAME <- paste0("Larach MH Analysis for ",TIMESTAMP,".pdf")

if (SCREENONLY)
  {
  par(omi=c(0,0,0.0,0),mfcol=c(1,1))
  con <- stdout()
  } else {
  pdf(file=PDFNAME,height=7.5, width = 10)
  par(omi=c(1,1,1.5,1),mfcol=c(1,1))
  con <- file("Larach Results.txt", "w")
  }

LEGEND <- function(X,Y,DX, DY,TEXT)
{
  points(X, Y,      col="orange",pch=16,cex=CEX.POINTS)
  points(X, Y+DY,   col="green3",pch=16,cex=CEX.POINTS)
  points(X, Y+DY*2, col="blue",  pch=16,cex=CEX.POINTS)
  points(X, Y+DY*3, col="red",   pch=16,cex=CEX.POINTS)
  points(X, Y-DY, col="black",pch=10,cex=DEAD.POINTS)

  text(X+DX, Y,      "Other Probe",col="orange",adj=c(0,0.5))
  text(X+DX, Y+DY,   "Core Probe", col="green3",adj=c(0,0.5))
  text(X+DX, Y+DY*2, "Skin Probe", col="blue",adj=c(0,0.5))
  text(X+DX, Y+DY*3, "No Probe",   col="red",adj=c(0,0.5))
```

```
  text(X+DX, Y-DY  , TEXT,     col="black",adj=c(0,0.5))
}

#### Figure 2, Temperature drives death ####
# Include Other Probe information
DATA1 <- DATA[!is.na(DATA$Peak.Temp),]
ORDER <- order(DATA1$Peak.Temp)
DATA1 <- DATA1[ORDER,]

X <- DATA1$Peak.Temp
Y <- cumsum(DATA1$Died)
plot(X, Y, type="b",
     xlab="Maximum Temperature",ylab="Cumulative Deaths",bty="l",
     pch=46,col="grey", xaxs="r", yaxs="r", cex=0.8,
cex.axis=1.2,las=1,
     cex.lab=1.3,lwd=.8)
points(X,Y-OFFSET+DATA1$Probe*SPREAD,col=DATA1$COLOR,pch=DATA1$PCH,
cex=DATA1$CEX)
LEGEND(43,1.5,.2,.75,"Died")

## Primary Variable: Death, Core Probe vs skin or none ####
TABLE <- table(DATA$Probe,DATA$Died)
colnames(TABLE) <- c("Alive","Dead")
rownames(TABLE) <- c("None","Skin","Core","Other")
print(TABLE)

# Remove line 4, "Other"
TABLE <- TABLE[-4,]

CochranArmitageTest(TABLE,alternative="decreasing")
RRsc(c(TABLE[1,2],sum(TABLE[1,]),TABLE[3,2],sum(TABLE[3,])),rnd = 6,
pf=FALSE,alpha=0.05)
RRsc(c(TABLE[2,2],sum(TABLE[2,]),TABLE[3,2],sum(TABLE[3,])),rnd = 6,
pf=FALSE,alpha=0.05)

# Figure 3: What best predicts Death?
NormPlot <- function(VAR,X,TEXT)
{
  DATA1 <- DATA[!is.na(DATA[,VAR]),]
  TTEST <- t.test(DATA1[DATA1$Died==0,VAR],DATA1[DATA1$Died==1,VAR])
  MEAN.0 <- mean(DATA1[DATA1$Died==0,VAR])
  MEAN.1 <- mean(DATA1[DATA1$Died==1,VAR])
  MEAN <- (MEAN.0+MEAN.1)/2
  CI <- TTEST$conf.int[2]-TTEST$conf.int[1]
  DIFF <- (DATA1[,VAR]-MEAN)/CI
  MEAN.0 <- (MEAN.0-MEAN)/CI
  MEAN.1 <- (MEAN.1-MEAN)/CI
  points(DATA1$Probe*SPREAD - OFFSET +
X,DIFF,col=DATA1$COLOR,pch=DATA1$PCH, cex=DATA1$CEX)
  lines(c(X-.3,X+.3),c(MEAN.0,MEAN.0),col="black",lty=1,lwd=2)
```

```
  lines(c(X-.3,X+.3),c(MEAN.1,MEAN.1),col="darkgrey",lty=1,lwd=2)
  text(X, -2,paste0(TEXT," (",signif(TTEST$p.value,
2),")"),srt=-45,adj=0,col="black",font=2,cex=.8,xpd=NA)
  cat(TTEST$p.value)
}

plot(1, 1, type="n", ylim=c(-2,2),xlim=c(0,7),
     xlab="",ylab="Normalized Value",bty="n",
     xaxs="r", yaxs="r", cex=0.8, cex.axis=1.2,las=1,
     cex.lab=1.3,lwd=.8,xaxt="n")

NormPlot("Peak.Temp",1,"Peak Temp")
NormPlot("Peak.K",2,"Peak K")
NormPlot("pH",3,"pH")
NormPlot("Base.Deficit",4,"Base Deficit")
NormPlot("aCO2",5,"Arterial CO2")
NormPlot("ETCO2",6, "ET CO2")

##############################################
# Figure 4: Time to Dantrolene vs. Peak Temp
# Look at Time to Dantrolene vs. Peak Temp
X <- DATA1$Induction.to.Dantrolene
Y <- DATA1$Peak.Temp
plot(X, Y, type="n",
     xlab="Induction to Dantrolene (min)",ylab="Peak
Temperature",bty="l",
     pch=20,col="black", xaxs="r", yaxs="r", cex=0.8,
cex.axis=1.2,las=1,
     cex.lab=1.3,lwd=2)
points(X,Y,col=DATA1$COLOR,pch=DATA1$PCH,cex=DATA$CEX)
LEGEND(460,42.5,20,.75,"Died")

GLM <- glm(Y ~ X)
lines(GLM$model[,"X"],GLM$fitted.values,col="black",lwd=2)
summary(GLM)
P <- summary(GLM)$coefficients[2,4]
text(450,40,paste0("P = ",round(P*4,5)),adj=0)

###Secondary Analsyses: Fluid, DIC ####
TABLE <- xtabs(formula=~Died+Fluid,data=DATA, exclude = c(NA, NaN))
FLUID.FISHER <- fisher.test(TABLE)
FLUID.RR <-
RRsc(c(TABLE[2,2],TABLE[1,2]+TABLE[2,2],TABLE[2,1],TABLE[1,1]+TABLE[2,
1]), rnd = 6, pf=FALSE)
cat("Relative Risk:", FLUID.RR$estimate["MN method","RR"],
    " LL:",FLUID.RR$estimate["MN method","LL"],
    " UL:",FLUID.RR$estimate["MN method","UL"],
    "P = ",FLUID.FISHER$p.value)

print(TABLE)
```

```
#### Temperature drives DIC ####
DATA1 <- DATA[!is.na(DATA$Peak.Temp),]
ORDER <- order(DATA1$Peak.Temp)
DATA1 <- DATA1[ORDER,]

X <- DATA1$Peak.Temp
Y <- cumsum(DATA1$DIC)
plot(X, Y, type="b",
     xlab="Maximum Temperature",ylab="Cumulative DIC",bty="l",
     pch=46,col="grey", xaxs="r", yaxs="r", cex=0.8,
cex.axis=1.2,las=1,
     cex.lab=1.3,lwd=.8)
points(X,Y-OFFSET
+DATA1$Probe*SPREAD,col=DATA1$COLOR,pch=DATA1$DIC.PCH,
cex=DATA1$DIC.CEX)
LEGEND(43,1.5,.2,.75,"DIC")

##########################################
# Peak Temp to Dantrolene vs. Peak Temp
X <- DATA1$Induction.to.Dantrolene - DATA1$Induction.to.Peak.Temp
Y <- DATA1$Peak.Temp
plot(X, Y, type="n",
     xlab="Peak Temp to Dantrolene (min)",ylab="Peak
Temperature",bty="l",
     pch=20,col="black", xaxs="r", yaxs="r", cex=0.8,
cex.axis=1.2,las=1,
     cex.lab=1.3,lwd=2)
points(X,Y,col=DATA1$COLOR,pch=DATA1$PCH,cex=DATA$CEX)
LEGEND(460,42.5,20,.75,"Died")

GLM <- glm(Y ~ X)
lines(GLM$model[,"X"],GLM$fitted.values,col="black",lwd=2)
summary(GLM)
P <- summary(GLM)$coefficients[2,4]
text(450,40,paste0("P = ",round(P*4,5)),adj=0)

##########################################
# First AE to Dantrolene vs. Peak Temp
X <- DATA1$Induction.to.Dantrolene - DATA1$Induction.to.AE
Y <- DATA1$Peak.Temp
plot(X, Y, type="n",
     xlab="First AE to Dantrolene (min)",ylab="Peak
Temperature",bty="l",
     pch=20,col="black", xaxs="r", yaxs="r", cex=0.8,
cex.axis=1.2,las=1,
     cex.lab=1.3,lwd=2)
points(X,Y,col=DATA1$COLOR,pch=DATA1$PCH,cex=DATA$CEX)
LEGEND(460,42.5,20,.75,"Died")
```

```
GLM <- glm(Y ~ X)
lines(GLM$model[,"X"],GLM$fitted.values,col="black",lwd=2)
summary(GLM)
P <- summary(GLM)$coefficients[2,4]
text(200,40,paste0("P = ",round(P,5)),adj=0)


#######################################################################
###############
# Supplementary analyses
# Look at Time to Dantrolene vs. Peak Temp: are there statistical
differences?

GLM <- glm(Peak.Temp ~
Induction.to.Dantrolene,data=DATA1[DATA1$Probe==2,])
B <- summary(GLM)$coefficients[1,1]
M <- summary(GLM)$coefficients[2,1]
DATA1$Peak.Adjusted <- DATA1$Peak.Temp - B -
DATA1$Induction.to.Dantrolene*M

X <- DATA1$Induction.to.Dantrolene
Y <- DATA1$Peak.Adjusted
plot(X, Y, type="n",
     xlab="Induction to Dantrolene (min)",ylab="Adjusted Peak
Temperature",bty="l",
     pch=20,col="black", xaxs="r", yaxs="r", cex=0.8,
cex.axis=1.2,las=1,
     cex.lab=1.3,lwd=2)
points(X,Y,col=DATA1$COLOR,pch=DATA1$PCH,cex=DATA$CEX)
LEGEND(460,3,20,.75,"Died")

GLM <- glm(Peak.Adjusted ~
Induction.to.Dantrolene,data=DATA1[DATA1$Probe==2,])
lines(GLM$model[,"Induction.to.Dantrolene"],GLM
$fitted.values,col="green3",lwd=2)

GLM <- glm(Peak.Adjusted ~
Induction.to.Dantrolene,data=DATA1[DATA1$Probe==0,])
lines(GLM$model[,"Induction.to.Dantrolene"],GLM
$fitted.values,col="red",lwd=2)
P <- summary(GLM)$coefficients[2,4]
TAU <-
KendallTauB(DATA1$Peak.Adjusted[DATA1$Probe==0],DATA1$Induction.to.Dan
trolene[DATA1$Probe==0],conf.level=0.95)
text(290,3.5,paste0("P = ",round(P,2)),adj=1, col="red",cex=.9,font=2)

GLM <- glm(Peak.Adjusted ~
Induction.to.Dantrolene,data=DATA1[DATA1$Probe==1,])
lines(GLM$model[,"Induction.to.Dantrolene"],GLM
```

```
$fitted.values,col="blue",lwd=2)
P <- summary(GLM)$coefficients[2,4]
TAU <-
KendallTauB(DATA1$Peak.Adjusted[DATA1$Probe==1],DATA1$Induction.to.Dan
trolene[DATA1$Probe==1],conf.level=0.95)
text(330,1.6,paste0("P = ",round(P,2)),adj=1, col="blue",cex=.
9,font=2)

GLM <- glm(Peak.Adjusted ~
Induction.to.Dantrolene,data=DATA1[DATA1$Probe==3,])
lines(GLM$model[,"Induction.to.Dantrolene"],GLM
$fitted.values,col="orange",lwd=2)
P <- summary(GLM)$coefficients[2,4]
TAU <-
KendallTauB(DATA1$Peak.Adjusted[DATA1$Probe==3],DATA1$Induction.to.Dan
trolene[DATA1$Probe==3],conf.level=0.95)
text(410,-0.8,paste0("P = ",round(P,2)),adj=1, col="orange",cex=.
9,font=2)

# The independent variable is Temp Monitoring. All of the other
variables
# are outcome variables. For binary outcomes, Fisher Exact can be used
to
# calculate P values. Relative Risk and RR confidence intervals will
be
# calculated with RRsc, which exactly matches SatXact calculation.


par(mfcol=c(1,2))
# Create graphs of continuous variables
GRAPH_CONTINUOUS <- function(VAR,TEXT)
{
#  VAR <- "Peak.Temp"
#  TEXT <- "Peak Temperature"
  DATA1 <- DATA[!is.na(DATA[,VAR]),]
  DATA1$Y <- DATA1[,VAR]
  ORDER <- order(DATA1$Y)
  DATA1 <- DATA1[ORDER,]
  N1 <- nrow(DATA1)
  DATA1$X <- (seq(1,N1)-.5)/N1
  DATA1$X <- qnorm(DATA1$X)

  plot(DATA1$X,DATA1$Y,col=DATA1$COLOR,type="p", pch=DATA1$PCH,
       ylab = TEXT,
       xlab="Z Score",
       bty="l")

  # Normalize Y axis
  MEAN <- mean(DATA1$Y)
  SD <- sd(DATA1$Y)
```

```
  DATA1$Y<- (DATA1$Y-MEAN)/SD

  plot(DATA1$X,DATA1$Y,col=DATA1$COLOR,type="p", pch=DATA1$PCH,
       ylab = "Normalized",
       xlab="Z Score",
       bty="l")
  # Identify Line

lines(c(min(DATA1$X),max(DATA1$X)),c(min(DATA1$X),max(DATA1$X)),col="b
lack",lty=1,lwd=1)

  LEGEND (-2,max(DATA1$Y)*.4,.1,max(DATA1$Y)*.1,"Died")
}

GRAPH_CONTINUOUS("Peak.Temp","Peak Temperature")
GRAPH_CONTINUOUS("ETCO2","End Tidal CO2")
GRAPH_CONTINUOUS("pH","Arterial pH")
GRAPH_CONTINUOUS("aCO2","Arterial CO2")
GRAPH_CONTINUOUS("Base.Deficit","Base Deficit")
GRAPH_CONTINUOUS("Peak.K","Potassium")
GRAPH_CONTINUOUS("Dantrolene.Dose","Dantrolene Dose")

par(mfcol=c(1,1))

if (!SCREENONLY)
  {
  dev.off()
  close(con)
  }

# Is percentage statistically higher than prior cohort?

M <- matrix(c(8,84-8,4,291-4),nrow=2)
M.TEST <- fisher.test(M)
M.TEST$p.value * 5
M.RR <- RRsc(c(M[1,1],M[1,1]+M[2,1],M[1,2],M[1,2]+M[2,2]), rnd = 6,
             alpha=0.05/5, pf=FALSE)
M.RR
```