Study Protocol and Statistical Analysis Plan for the Isotonic Solutions and Major Adverse Renal Events Trial (SMART)

Li Wang and Daniel Byrne
Department of Biostatistics
Vanderbilt University School of Medicine

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A All R Code

```
# Load R packages
require(rms)
require(lme4)
require(knitr)

knitrSet(echo=TRUE,cache=FALSE)
ltx <- function(x, ...) {
  if('caption' %in% names(list(...))) latex(x, ..., file='')
  else latex(x, table.env=FALSE, ..., file='')
}

# Set working directory
setwd("")
# Read data into R
load("SMART.fulldata.R")
# Load R functions
source("LoessWithCI.R")
source("reshape.R")
source("SummaryTable.R")

# Table 1 - Comparisons of baseline characteristics between study groups
options(digits=3)
ltx(summaryM(unit + patient.age + patient.gender + patient.race.v2 + patient.weight + patient.bmi +
             source.of.admission + primary.diagnosis + Sepsis + TBI + ventilator.flag + inotropic.flag +
             uhc.expected.mort + hemodialysis.pre.icu + lowestcreatpriortoenc + mostrecentcreatpriortoenc +
             lowestcreatdurencpriorto.icu + lowestcreatdurencpriorto.icu.imp + make30.baselinecrsource +
             make30.baselinecr + make30.baselinecr.calculate + make30.baselinecr.DurEncPriorToICU +
             make30.baselinecr.PriorToEnc + present.AKI + present.CKD +  present.CKD.calculate +
             present.CKD.DurEncPriorToICU + present.CKD.PriorToEnc ~ group, data = fulldata, test=TRUE),
    where="htbp", caption="Patient characteristics at baseline", exclude1 = FALSE, prN=TRUE, prn=FALSE,
    long = TRUE, prmsd = TRUE, npct = 'both', prtest='P', size="footnotesize", digits=2, longtable=TRUE,
    landscape=FALSE, cener="centering", label = 'table:basedesc', what = '%', pctdig=3,
    colheads = c('NS','BL','Test statistics'), lines.page=62, rowlabel.just = "p{0.25\\linewidth}")

# Table 2 - Comparison of patients' outcomes between groups
ltx(summaryM(make30.final + make30.criteriamet + make30.death + new.rrt.verified + make30.crrt +
             make30.renaldysfunction.persistent +  make30.renaldysfunction.persistent.survivor +
             make30.renaldysfunction.persistent.survivor.woRRT + make30.renaldysfunction.kdigo +
             died.in.ICU + died.30day + died.60day + icufreeday + ventfreeday + inotropicfreeday +
             rrtfreeday + rrtday + ventilator.flag + unit.ventilator.days + inotropic.flag +
             unit.inotropic.days + make30.maxcr + make30.baselinecr + make30.finalcreatbeforedischarge +
             make30.finalstudycreat + make30.finalstudycreat.survivor + highestdailycreat.max +
             change.creat + deathinicu + incidentAKI ~ group, data = fulldata, test=TRUE, continuous=3),
    where="htbp", caption="Patient outcomes", exclude1 = FALSE, prN=TRUE,prn=FALSE,
    long = TRUE, prmsd = TRUE, npct = 'both', prtest='P', size="footnotesize", digits=2, longtable=TRUE,
    landscape=FALSE, cener="centering", label = 'table:outcome', what = '%', pctdig=3,
    colheads = c('NS','BL','Test statistics'), lines.page=62, rowlabel.just = "p{0.25\\linewidth}")

## We will present the unadjusted effect and the effect adjusted for cluster and period for all these
## secondary outcomes

# Comparison of IV fluids received between groups - supplemental table
temp <- expand.grid(c('ns.base','lr','plasmalyte','balanced','isotonic.crystalloid',
                      'nonisotonic.crystalloid','albumins','bloodproduct','total.fluid'),
                    c('b',0:7,'cum3','cum7','cum14','cum30','unit','unitbeforecross','unitaftercross','hosp'))
varList <- apply(temp[order(temp[,1]),], 1, paste, collapse=".")
```

```
ltx(summaryM(as.formula(paste(paste(varList, collapse=" + "), "group", sep=" ~ ")),
             data = fulldata, test=TRUE, continuous=4),
    where="htbp", caption="Fluids", exclude1 = FALSE, prN=TRUE, prn=FALSE, vnames="name",
    long = TRUE, prmsd = TRUE, npct = 'both', prtest='P', size="footnotesize", digits=2,
    longtable=TRUE, landscape=FALSE, cener="centering", label = 'table:fluid', what = '%', pctdig=3,
    colheads = c('NS','BL','Test statistics'), lines.page=66, rowlabel.just = "p{0.2\\linewidth}")

# Comparison of IV fluids received between groups - supplemental table
temp <- expand.grid(c('ns.base','lr','plasmalyte','balanced','isotonic.crystalloid',
                      'nonisotonic.crystalloid','albumins','bloodproduct','total.fluid'),
                    paste0(c('b',0:7,'cum3','cum7','cum14','cum30','unit','unitbeforecross',
                             'unitaftercross','hosp'),'_binary'))
varList <- apply(temp[order(temp[,1]),], 1, paste, collapse=".")
ltx(summaryM(as.formula(paste(paste(varList, collapse=" + "), "group", sep=" ~ ")),
             data = fulldata, test=TRUE, continuous=4),
    where="htbp", caption="Fluids", exclude1 = FALSE, prN=TRUE, prn=FALSE, vnames="name",
    long = TRUE, prmsd = TRUE, npct = 'both', prtest='P', size="footnotesize", digits=2, longtable=TRUE,
    landscape=FALSE, cener="centering", label = 'table:fluidbinary', what = '%', pctdig=3,
    colheads = c('NS','BL','Test statistics'), lines.page=66, rowlabel.just = "p{0.2\\linewidth}")

# Comparison of serum laboratory values between groups - supplemental table
temp <- expand.grid(c('firstdaily','lowestdaily','highestdaily'),
                    c('.na.','.k.','.cl.','.co2.','.bun.','creat.'),0:7)
varList <- c(apply(temp[order(temp[,2],temp[,1]),], 1, paste, collapse=""),
             c("lowestdaily.na.min","highestdaily.na.max","na.145","na.135",
               "lowestdaily.k.min","highestdaily.k.max","k.5","k.3",
               "lowestdaily.cl.min","highestdaily.cl.max","cl.110","cl.90" ,
               "lowestdaily.co2.min","highestdaily.co2.max","co2.30","co2.20",
               "lowestdaily.bun.min","highestdaily.bun.max",
               "lowestdailycreat.min","highestdailycreat.max"))
ltx(summaryM(as.formula(paste(paste(varList, collapse=" + "), "group", sep=" ~ ")),
             data = fulldata, test=TRUE,continuous=4),
    where="htbp", caption="Electrolytes", exclude1 = FALSE, prN=TRUE, prn=FALSE,
    long = TRUE, prmsd = TRUE, npct = 'both', prtest='P', size="footnotesize", digits=2, longtable=TRUE,
    landscape=FALSE, cener="centering", label = 'table:elec', what = '%', pctdig=3,
    colheads = c('NS','BL','Test statistics'), lines.page=65, rowlabel.just = "p{0.2\\linewidth}")

# Comprison of indications for new RRT between groups - supplemental table
ltx(summaryM(oliguria + k.6.5 + ph.7.20 + bun.70 + cr.3.39 + organ.edema + other.renal + other.nonrenal +
               rrtuse.postdischarge + text ~ group, data = subset(fulldata, new.rrt.verified==1),
             test=TRUE, continuous=3), where="htbp", caption="Indications for RRT", exclude1 = FALSE,
    prN=TRUE,prn=FALSE, long = TRUE, prmsd = TRUE, npct = 'both', prtest='P', size="small", digits=2,
    longtable=TRUE, landscape=FALSE, cener="centering", label = 'table:indi', what = '%', pctdig=3,
    colheads = c('NS','BL','Test statistics'), lines.page=58, rowlabel.just = "p{0.4\\linewidth}")

# Comparison of baseline comorbidities between groups - supplemental table
ltx(summaryM(cpd + chf + bla + fed + mtc + cvd + cag + dbu + vld + car + peb + aid + lvd + lym +
             pcd + ond + pvo + rnf + obs + wgt + hyu + par + st. + psy + dep + hyc + alc + drg +
             dfa + dbc + thy ~ group, data = fulldata, test=TRUE, continuous=3),
    where="htbp", caption="Elixhauser", exclude1 = FALSE, prN=TRUE,prn=FALSE,
    long = TRUE, prmsd = TRUE, npct = 'both', prtest='P', size="small", digits=2, longtable=TRUE,
    landscape=FALSE, cener="centering", label = 'table:eli', what = '%', pctdig=3,
    colheads = c('NS','BL','Test statistics'), lines.page=57, rowlabel.just = "p{0.2\\linewidth}")
```

```r
# Comparison of volume of each study crystaloid received between groups - figure
fig1 <- fulldata[,c('encounternumber','group','ns.base.b','balanced.b',
                    paste0('ns.base.',0:7),paste0('balanced.',0:7))]

fig11<-data.frame(t(with(fig1,apply(fig1[,paste0('ns.base.',0:7)],1,function(x)cumsum(c(x))))))
fig12<-data.frame(t(with(fig1,apply(fig1[,paste0('balanced.',0:7)],1,function(x)cumsum(c(x))))))

names(fig11) <- paste0('ns.base.0.',0:7)
names(fig12) <- paste0('balanced.0.',0:7)

fig1 <- cbind(fig1, fig11, fig12)

fig1.out <- data.frame(day=rep(1:9,4),
                       group=rep(c('salinearm.saline','salinearm.balance',
                                   'balancearm.balance','balancearm.saline'),each=9),
                       mean=rep(NA,36), lower=rep(NA,36), upper=rep(NA,36))

nsL <- c('ns.base.b',paste0('ns.base.0.',0:7))
bL <- c('balanced.b',paste0('balanced.0.',0:7))


for (i in 1:length(nsL)) {
  temp1 <- smean.cl.boot(fig1[[nsL[i]]][fig1$group=='NS'], B=1000, reps=TRUE)
  fig1.out[i,3:5] <- temp1[1:3]
  temp2 <- smean.cl.boot(fig1[[bL[i]]][fig1$group=='NS'], B=1000, reps=TRUE)
  fig1.out[i+9,3:5] <- temp2[1:3]
  temp3 <- smean.cl.boot(fig1[[bL[i]]][fig1$group=='BL'], B=1000, reps=TRUE)
  fig1.out[i+18,3:5] <- temp3[1:3]
  temp4 <- smean.cl.boot(fig1[[nsL[i]]][fig1$group=='BL'], B=1000, reps=TRUE)
  fig1.out[i+27,3:5] <- temp4[1:3]
}

pdf('fig1.pdf', width=8, height=5)
par(mfrow=c(1,2), mar=c(3.5,4,2,1))
plot(1, type="n", axes=F, xlab="", ylab="Cumulative volume (mL)", ylim=c(0,3000),xlim=c(0,9))
with(subset(fig1.out, group=='salinearm.saline'),
     errbar(c(0.7, 2:9), mean, upper, lower, pch=5,cex=1.1,add=TRUE))
with(subset(fig1.out, group=='salinearm.saline' & day > 1), lines(day, mean, lty=2))
with(subset(fig1.out, group=='salinearm.balance'),
     errbar(c(0.3, 2:9), mean, upper, lower, pch=16, cex=1.2, add=TRUE))
with(subset(fig1.out, group=='salinearm.balance' & day > 1), lines(day, mean, lty=1))
legend(0,3100, pch=c(16,5),cex=c(1.2,1.1), c('Balanced fluid','0.9% Saline'), lty=c(1,2), bty='n')
axis(side=1,at=2:9,labels=c('0','1','2','3','4','5','6','7'))
axis(side=2,at=seq(0,3000,by=500), labels=seq(0,3000,by=500))
text(0.6,500, 'Before\nenrollment\non day 0', cex=0.7)
mtext('Saline Arm', side=3, line=0.5, cex=1.3)
mtext('Days after enrollment', side=1, line=2, at=5.5)
lines(c(1.5,1.5), c(0,1500), col = "gray60")
box()

plot(1, type="n", axes=F, xlab="", ylab="Cumulative volume (mL)", ylim=c(0,3000),xlim=c(0,9))
with(subset(fig1.out, group=='balancearm.balance'),
     errbar(c(0.3, 2:9), mean, upper, lower, pch=16, cex=1.2, add=TRUE))
with(subset(fig1.out, group=='balancearm.balance' & day > 1), lines(day, mean, lty=1))
with(subset(fig1.out, group=='balancearm.saline'),
     errbar(c(0.7, 2:9),mean, upper, lower, pch=5,cex=1.1,add=TRUE))
with(subset(fig1.out, group=='balancearm.saline' & day > 1), lines(day, mean, lty=2))
legend(0,3100, pch=c(16,5),cex=c(1.2,1.1), c('Balanced fluid','0.9% Saline'), lty=c(1,2), bty='n')
axis(side=1,at=2:9,labels=c('0','1','2','3','4','5','6','7'))
```

```
axis(side=2,at=seq(0,3000,by=500), labels=seq(0,3000,by=500))
text(0.6, 500, 'Before\nenrollment\non day 0',cex=0.7)
mtext('Balanced Arm', side=3, line=0.5, cex=1.3)
mtext('Days after enrollment', side=1, line=2, at=5.5)
lines(c(1.5,1.5), c(0,1500), col = "gray60")
box()
dev.off()


# Heterogeny of treatment effect - figure
dd <- datadist(fulldata[,c('make30.final','make30.death','new.rrt.verified',
                           'isotonic.crystalloid.cum3','isotonic.crystalloid.cum30',
                           'patient.age','source.of.admission.v2','source.of.admission',
                           'ventilator.flag','inotropic.flag','group','Sepsis','TBI',
                           'hemodialysis.pre.icu','receive.nonassign.crys','uhc.expected.mort',
                           'cat','time','unit')]); options(datadist = 'dd')

NS <- subset(fulldata, group=='NS')
BL <- subset(fulldata, group=='BL')

oout <- vector('list',2)
vvar <- c('unit','source.of.admission.v2','ventilator.flag','inotropic.flag','Sepsis','TBI','cat')
grp <- c('NS','BL')


for (j in 1:2){
  for (i in 1:length(vvar)){
    oout[[j]]  <- c(oout[[j]],paste0(table(fulldata[[vvar[i]]][fulldata$group==grp[j]],
                                           fulldata$make30.final[fulldata$group==grp[j]])[,2],'/',
         table(fulldata[[vvar[i]]][fulldata$group==grp[j]]),'(',
         round(100*prop.table(table(fulldata[[vvar[i]]][fulldata$group==grp[j]],
                                    fulldata$make30.final[fulldata$group==grp[j]]),1)[,2],1),')'))
  }
  oout[[j]] <- c(oout[[j]],
                 paste(
                   paste0(table(fulldata$make30.final[fulldata$group==grp[j]])[2],'/',
                          nrow(subset(fulldata, group==grp[j])),'(',
                          round(100*prop.table(table(fulldata$make30.final[fulldata$group==grp[j]]))[2],
                                1),')')))
}

freq <- paste(oout[[1]], oout[[2]], sep=" ")


vvar <- c('unit','source.of.admission.v2','ventilator.flag','inotropic.flag','Sepsis','TBI','cat')

p.int <- rep(NA, length(vvar))
out <- NA

p.int[1] <- anova(lrm(as.formula(paste("make30.final", paste(c("group",'unit'), collapse="*"),
                                       sep=" ~ ")), data=fulldata, x=TRUE, y=TRUE))[2,3]
for (j in 1:length(levels(fulldata$unit))){
    m.sub <- lrm(make30.final ~ group, data=subset(fulldata,unit==levels(fulldata$unit)[j]), x=TRUE, y=TRUE)
    out <- rbind(out,c(summary(m.sub,group='NS')[2,c(4,6,7)], anova(m.sub)[1,3]))
}
out <- out[-1,]
```

```
for (i in 2:length(vvar)){
  m.int <- glmer(as.formula(paste("make30.final",
                                  paste(paste(c("group",vvar[i]), collapse="*"),"(1 | unit)",sep=" + "),
                                  sep=" ~ ")), data=fulldata, family=binomial)
  m.int0 <- glmer(as.formula(paste("make30.final", paste("group",vvar[i], "(1 | unit)",sep=" + "),
                                   sep=" ~ ")), data=fulldata, family=binomial)
  p.int[i] <- anova(m.int, m.int0)$Pr[2]
  for (j in 1:length(levels(fulldata[[vvar[i]]]))){
    m.sub <- glmer(make30.final ~ group + (1 | unit),
                   data=subset(fulldata,fulldata[[vvar[i]]]==levels(fulldata[[vvar[i]]])[j]),
                   family=binomial)
    cc <- confint(m.sub,parm="beta_")
    out <- rbind(out,c(exp(cbind(est=fixef(m.sub),cc)[2,]),
                       summary(m.sub)$coefficients[2,4]))
  }
}

mm <- glmer(make30.final ~ group + (1 | unit), data = fulldata, family = binomial(link=logit))
cc <- confint(mm,parm="beta_")

out <- rbind(out,
             c(exp(cbind(est=fixef(mm),cc)[2,]),
                       summary(mm)$coefficients[2,4]))



# Main secondary analysis: group assignment by crystalloid volume interaction
mo <- lrm(make30.final ~ group * rcs(isotonic.crystalloid.cum30,3), data = fulldata, x = TRUE, y = TRUE)
# Secondary analysis: group assignment by severity of illness interaction
mp <- lrm(make30.final ~ group * uhc.expected.mort, data = fulldata, x = TRUE, y = TRUE)
# Sensitivity analysis: group assignment by crystalloid volume interaction
mq <- lrm(make30.final ~ group * rcs(isotonic.crystalloid.cum3,3), data = fulldata, x = TRUE, y = TRUE)


pdf('fig2.pdf', width=8, height=8)
layout(matrix(c(1,2,3,3,3,3), 3, 2, byrow = TRUE))
fulldata$group2 <- fulldata$group
levels(fulldata$group2) <- c('Saline','Balanced fluid')

par(mar=c(3,4,1,1))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum30,make30.final,group=group, col=c('red','blue'),
                           side=c(3,1), xlim=c(0,10000), ylim=c(0,1), xlab='', ylab='', hists=TRUE,
                           cex.axis=1, textsize=1))
mtext('Total isotonic crystalloid through day 30 (mL)', side=1, line=2.5,cex=1)
mtext('Incidence of MAKE30', side=2, line=2.5,cex=1)
text(10000,0.9,paste0('P-value for interaction = ',sprintf("%4.3f",anova(mo)[2,3])), adj=1)
text(9000,0.33,'Saline',col='red')
text(9000,0.2,'Balanced',col='blue')


par(mar=c(3,4,1,1))
with(fulldata, LoessWithCI(uhc.expected.mort,make30.final,group=group, col=c('red','blue'),
                           side=c(3,1), xlim=c(0,1), ylim=c(0,1), xlab='', ylab='', hists=TRUE,
                           cex.axis=1, textsize=1))
mtext('Predicted in-hospital mortality', side=1, line=2.5,cex=1)
mtext('Incidence of MAKE30', side=2, line=2.5,cex=1)
text(0.65,0.1,paste0('P-value for interaction = ',sprintf("%4.3f",anova(mp)[2,3])))
text(0.85,0.65,'Saline',col='red')
text(0.8,0.9,'Balanced',col='blue')
```

```r
par(mar=c(4,28,2,15))
yval <- c(29,28,27,26,25,23,22,21,20,19,17,16,14,13,11,10,8,7,5,4,3,2,1)
hh <- 30:1
yval1 <- hh[-which(30:1 %in% yval)]
OR <- out[,1]
LCI <- out[,2]
UCI <- out[,3]
DIFF <- log(UCI) - log(LCI)
XLAB=''
MAIN=''
L <- length(OR)
AXIS=c(0.1,0.3,1,5,10)
XLIM=c(0.3,2)
PCH=c(rep(16,nrow(out)-1),18)
CEX=c(rep(0.8,nrow(out)-1),2)

plot(OR, yval, xlim = XLIM, pch = PCH, cex = CEX, log = "x", axes = FALSE, xlab = XLAB, ylab = "",
     ylim = c(1, 30), main = MAIN)
points(OR, yval, pch=PCH, cex=CEX)
  for (ii in 1:L){
    if (!is.na(UCI[ii]) & UCI[ii] > XLIM[2]){
      UCI[ii] <- XLIM[2]
    }
  }
  for (ii in 1:L){
    if (!is.na(LCI[ii]) & LCI[ii] < XLIM[1]){
      LCI[ii] <- XLIM[1]
    }
  }
  segments(LCI, yval,UCI, yval, lwd=1)
  arrows(LCI[LCI==XLIM[1]]+0.1, yval[LCI==XLIM[1]], LCI[LCI==XLIM[1]], yval[LCI==XLIM[1]],length=0.06)
  arrows(UCI[UCI==XLIM[2]]-0.1, yval[UCI==XLIM[2]], UCI[UCI==XLIM[2]], yval[UCI==XLIM[2]], length=0.06)
  axis(1, at=AXIS, labels = AXIS, cex=0.5)
  segments(1,0,1,30)

mtext('Favors Balanced',side=1,at=0.6,line=3,cex=0.8)
mtext('Favors Saline',side=1,at=1.7,line=3,cex=0.8)

mtext(c('MICU','CVICU','NEICU','TICU','SICU',
        'Emergency Department','Operating room','Transfer from another hospital','Hospital ward','Other',
        'No','Yes', 'No','Yes', 'No','Yes', 'No','Yes', 'Normal','AKI','CKD','RRT','Overall'),
      side=2, at=yval, line=c(rep(25,length(yval)-1),27),adj=0, cex=c(rep(0.7,length(yval)-1),1),las=2)

mtext(c('Unit','Source of admission','Receipt of mechanical ventilation','Receipt of vasopressors',
        'Sepsis','TBI','Categories of kidney function'), side=2, at=yval1, line=27,adj=0, cex=0.7,las=2)
mtext(oout[[1]], at=yval, side=2, line=7, adj=1, las=2, cex=0.7)
mtext(oout[[2]], at=yval, side=2, line=0, adj=1, las=2, cex=0.7)
mtext('Saline',at=31, side=2, line=7, adj=1, las=2, cex=1)
mtext('Balanced',at=31, side=2, line=0, adj=1, las=2, cex=1)
arrows(0.8, -1.5, 0.5, -1.5, length=0.1, xpd = TRUE)
arrows(1.3, -1.5, 2, -1.5, length=0.1, xpd = TRUE)
mtext(paste0(sprintf("%3.2f",out[,1]),'(',sprintf("%3.2f",out[,2]),'-',sprintf("%3.2f",out[,3]),')'),
      at=yval, side=4, line=0,adj=0,las=2,cex=0.7)
mtext(sprintf("%4.3f",out[,4]),at=yval, side=4, line=7, adj=0, las=2, cex=0.7)
mtext(sprintf("%4.3f",p.int),at=yval1, side=4, line=12, adj=0, las=2, cex=0.7)
mtext('P Value', at=31, side=4, line=6, adj=0, las=2, cex=0.7)
mtext('P Value for', at=31.5, side=4, line=10, adj=0, las=2, cex=0.7)
mtext('Interaction', at=31, side=4, line=10, adj=0, las=2, cex=0.7)
```

```
mtext('Odds Ratio (95% CI)', side=3, line=-0.5, cex=1)
dev.off()


# Comparison of first, lowest, and highest serum laboratory value each day between groups - figure
elec.long=table.to.long(fulldata,
                            list(firstdaily.na=paste0("firstdaily.na.",0:7),
                                 lowestdaily.na=paste0("lowestdaily.na.",0:7),
                                 highestdaily.na=paste0("highestdaily.na.",0:7),

                                 firstdaily.k=paste0("firstdaily.k.",0:7),
                                 lowestdaily.k=paste0("lowestdaily.k.",0:7),
                                 highestdaily.k=paste0("highestdaily.k.",0:7),

                                 firstdaily.cl=paste0("firstdaily.cl.",0:7),
                                 lowestdaily.cl=paste0("lowestdaily.cl.",0:7),
                                 highestdaily.cl=paste0("highestdaily.cl.",0:7),

                                 firstdaily.co2=paste0("firstdaily.co2.",0:7),
                                 lowestdaily.co2=paste0("lowestdaily.co2.",0:7),
                                 highestdaily.co2=paste0("highestdaily.co2.",0:7),

                                 firstdaily.bun=paste0("firstdaily.bun.",0:7),
                                 lowestdaily.bun=paste0("lowestdaily.bun.",0:7),
                                 highestdaily.bun=paste0("highestdaily.bun.",0:7),

                                 firstdaily.creat=paste0("firstdailycreat.",0:7),
                                 lowestdaily.creat=paste0("lowestdailycreat.",0:7),
                                 highestdaily.creat=paste0("highestdailycreat.",0:7)))
elec.long <- elec.long[,c("encounternumber","group","firstdaily.na.score","lowestdaily.na.score",
                          "highestdaily.na.score","firstdaily.k.score","lowestdaily.k.score",
                          "highestdaily.k.score","firstdaily.cl.score","lowestdaily.cl.score",
                          "highestdaily.cl.score","firstdaily.co2.score","lowestdaily.co2.score",
                          "highestdaily.co2.score","firstdaily.bun.score","lowestdaily.bun.score",
                          "highestdaily.bun.score","firstdaily.creat.score","lowestdaily.creat.score",
                          "highestdaily.creat.score")]
elec.long$day=rep(0:7,nrow(fulldata))

dd.eleclong <- datadist(elec.long); options(datadist = 'dd.eleclong')


elec.model.list1 <- c('first','lowest','highest')
elec.model.list2 <- c('na','k','cl','co2','bun','creat')
ylablist <- c('Sodium (mmol/L)','Potassium (mmol/L)','Chloride (mmol/L)',
              'Bicarbonate (mmol/L)','Blood urea nitrogen (mg/dL)','Creatinine (mg/dL)')
pval <- matrix(rep(NA,3*6*2), ncol=12)

for (i in 1:length(elec.model.list1)){
  for (j in 1:length(elec.model.list2)){
    form <- as.formula(paste(paste0(elec.model.list1[i],'daily.',elec.model.list2[j],'.score'),
                             'group*rcs(day,3)', sep=' ~ '))
    tempmod <- robcov(lrm(form, data=elec.long, x = TRUE, y = TRUE), cluster = elec.long$encounternumber)
    pval[i,(j-1)*2+1] <- sprintf("%4.3f", anova(tempmod)[1,3])
    pval[i,(j-1)*2+2] <- sprintf("%4.3f", anova(tempmod)[2,3])
  }
}
pval0 <- pval
pval <- matrix(ifelse(as.numeric(pval0)<0.001,'<.001',pval0),ncol=12)
```

```r
for (i in 1:3){
  pdf(paste0('fig',i+2,'.pdf'), width=8, height=6)
  layout(matrix(c(1,2,3,4,5,6), ncol=3))
  par(mar=c(3.5,4,1,1))
  outcomelist <- paste0(elec.model.list1[i],'daily.',elec.model.list2,'.score')
  for (j in 1:6){
    LoessWithCI(elec.long$day, elec.long[[outcomelist[j]]], group=elec.long$group,
              col=c('red','blue'), side=c(3,1), pprint=TRUE,
              pval1=pval[i,(j-1)*2+1], pval2=pval[i,(j-1)*2+2],
              xlab='Day', ylab=ylablist[j],
              cex.axis=1.5, textsize=1.5, curvelabprint=TRUE,
              labellab=c('Saline','Balanced'), labelcol=c('red','blue'))
  }
  dev.off()
}


# Sensitivity analysis of interaction between study groups and crystalloid received through day 3
# supplemental figure
pdf("fig6.pdf")
par(mfrow=c(1,1),mar=c(4,4,1,2))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum3,make30.final,group=group, col=c('red','blue'),
                           side=c(3,1), xlim=c(0,10000), ylim=c(0,1), xlab='', ylab='', hists=TRUE,
                           cex.axis=1.5, textsize=1.5, curvelabprint=TRUE,
                           labellab=c('Saline','Balanced'), labelcol=c('red','blue')))
mtext('Total isotonic crystalloid through day 3', side=1, line=2.5,cex=1)
mtext('Incidence of MAKE30', side=2, line=2.5,cex=1)
text(10000,0.9,paste0('P-value for interaction = ',sprintf("%4.3f",anova(mq)[2,3])), adj=1)
dev.off()


# Interaction between study groups and volume crystalloid received with regard to chloride concentration
# supplemental figure
pdf('fig7.pdf')
par(mar=c(4,4,1,1))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum30,highestdaily.cl.max,group=group,
                           col=c('red','blue'), side=c(3,1), xlim=c(0,10000), ylim=c(105,120), xlab='',
                           ylab='', hists=TRUE, cex.axis=1.5, textsize=1.5,
                           curvelabprint=TRUE, labellab=c('Saline','Balanced'),
                           labelcol=c('red','blue')))
mtext('Total isotonic crystalloid through day 30 (mL)', side=1, line=2.5,cex=1)
mtext('Highest chloride (mmol/L)', side=2, line=2.5,cex=1)
text(10000,119,paste0('P-value for interaction = ',sprintf("%4.3f",
            anova(lrm(highestdaily.cl.max ~ group * rcs(isotonic.crystalloid.cum30,3),
                      data = fulldata, x = TRUE, y = TRUE))[2,3])), adj=1)
dev.off()

# Compliance with assigned fluid by volume of fluid received - supplemental figure
pdf('fig8.pdf')
par(mfrow=c(1,1),mar=c(4,4,1,1))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum30,saline.prop,group=group, col=c('red','blue'),
                           side=c(3,1), xlim=c(0,10000), ylim=c(0,1), xlab='', ylab='', hists=TRUE,
                           cex.axis=1.5, textsize=1.5, curvelabprint=TRUE,
                           labellab=c('Saline','Balanced'), labelcol=c('red','blue')))
mtext('Total isotonic crystalloid through day 30 (mL)', side=1, line=2.5,cex=1)
mtext('Proportion of saline among total isotonic crystalloid received', side=2, line=2.5,cex=1)
dev.off()
```

```
# Interaction between study groups and volume crystalloid received with regard to bicarbonate
# concentration - supplemental figure
pdf('fig9.pdf')
par(mar=c(4,4,1,1))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum30,lowestdaily.co2.min,group=group,
                           col=c('red','blue'), side=c(3,1), xlim=c(0,10000), ylim=c(12,22), xlab='',
                           ylab='', hists=TRUE, cex.axis=1.5, textsize=1.5, curvelabprint=TRUE,
                           labellab=c('Saline','Balanced'), labelcol=c('red','blue')))
mtext('Total isotonic crystalloid through day 30 (mL)', side=1, line=2.5,cex=1)
mtext('Lowest bicarbonate concentration', side=2, line=2.5,cex=1)
p<-anova(lrm(lowestdaily.co2.min ~ group * rcs(isotonic.crystalloid.cum30,3),
             data = fulldata, x = TRUE, y = TRUE))[2,3]
text(10000,21,ifelse(p<0.001, 'P-value for interaction <.001',
                     paste0('P-value for interaction = ',sprintf("%4.3f",p))), adj=1)
dev.off()


# Interaction between study groups and volume crystalloid received with regard to highest daily
# creatinine - supplemental figure
pdf('fig10.pdf')
par(mar=c(4,4,1,1))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum30,highestdailycreat.max,group=group,
                           col=c('red','blue'), side=c(3,1), xlim=c(0,10000), ylim=c(1,5), xlab='',
                           ylab='', hists=TRUE, cex.axis=1.5, textsize=1.5, curvelabprint=TRUE,
                           labellab=c('Saline','Balanced'), labelcol=c('red','blue')))
mtext('Total isotonic crystalloid through day 30 (mL)', side=1, line=2.5,cex=1)
mtext('Highest creatinine concentration (mg/dL)', side=2, line=2.5,cex=1)
p<-anova(lrm(highestdailycreat.max ~ group * rcs(isotonic.crystalloid.cum30,3),
             data = fulldata, x = TRUE, y = TRUE))[2,3]
text(10000,4.8,ifelse(p<0.001, 'P-value for interaction <.001',
                      paste0('P-value for interaction = ',sprintf("%4.3f",p))), adj=1)
dev.off()



# Interaction between study groups and volume crystalloid received with regard to AKI -
# supplemental figure
pdf('fig11.pdf')
par(mar=c(4,4,1,1))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum30,incidentAKI,group=group, col=c('red','blue'),
                           side=c(3,1), xlim=c(0,10000), ylim=c(0,1), xlab='', ylab='', hists=TRUE,
                           cex.axis=1.5, textsize=1.5, curvelabprint=TRUE,
                           labellab=c('Saline','Balanced'), labelcol=c('red','blue')))
p<-anova(lrm(incidentAKI ~ group * rcs(isotonic.crystalloid.cum30,3),
             data = fulldata, x = TRUE, y = TRUE))[2,3]
mtext('Total isotonic crystalloid through day 30 (mL)', side=1, line=2.5,cex=1)
mtext('Rate of incident AKI', side=2, line=2.5,cex=1)
text(10000,0.95,ifelse(p<0.001, 'P-value for interaction <.001',
                       paste0('P-value for interaction = ',sprintf("%4.3f",p))), adj=1)
dev.off()



# Interaction between study groups and volume crystalloid received with regard to new RRT -
# supplemental figure
pdf('fig12.pdf')
par(mar=c(4,4,1,1))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum30,new.rrt.verified,group=group, col=c('red','blue'),
                           side=c(3,1), xlim=c(0,10000), ylim=c(0,0.3), xlab='', ylab='', hists=TRUE,
```

```
                          cex.axis=1.5, textsize=1.5, curvelabprint=TRUE,
                          labellab=c('Saline','Balanced'), labelcol=c('red','blue')))
mtext('Total isotonic crystalloid through day 30 (mL)', side=1, line=2.5,cex=1)
mtext('Receipt of RRT', side=2, line=2.5,cex=1)
p<-anova(lrm(new.rrt.verified ~ group * rcs(isotonic.crystalloid.cum30,3),
             data = fulldata, x = TRUE, y = TRUE))[2,3]
text(10000,0.28,ifelse(p<0.001, 'P-value for interaction <.001',
                       paste0('P-value for interaction = ',sprintf("%4.3f",p))), adj=1)
dev.off()



# Interaction between study groups and volume crystalloid received with regard to death
# Supplemental figure
pdf('fig13.pdf')
par(mar=c(4,4,1,1))
with(fulldata, LoessWithCI(isotonic.crystalloid.cum30,make30.death,group=group, col=c('red','blue'),
                          side=c(3,1), xlim=c(0,10000), ylim=c(0,0.45), xlab='', ylab='', hists=TRUE,
                          cex.axis=1.5, textsize=1.5, curvelabprint=TRUE,
                          labellab=c('Saline','Balanced'), labelcol=c('red','blue')))
p<-anova(lrm(make30.death ~ group * rcs(isotonic.crystalloid.cum30,3),
             data = fulldata, x = TRUE, y = TRUE))[2,3]
mtext('Total isotonic crystalloid through day 30 (mL)', side=1, line=2.5,cex=1)
mtext('Mortality', side=2, line=2.5,cex=1)
text(10000,0.4,ifelse(p<0.001, 'P-value for interaction <.001',paste0('P-value for interaction = ',
                                                                      sprintf("%4.3f",p))), adj=1)
dev.off()




## Primary Analysis
m1 <- glmer(make30.final ~ group + patient.age + patient.gender + patient.race.v2 +
              source.of.admission.v2 + ventilator.flag + inotropic.flag + Sepsis + TBI + (1 | unit),
            data = fulldata, family = binomial(link=logit))
# compute confidence interval
cc <- confint(m1,parm="beta_")
ctab <- cbind(est=fixef(m1),cc)
latex(ctab, file='', where='!h')



## Sensitivity Analysis - Missing Creatinine Measures
labs <- csv.get('LabsByDay.csv', lowernames=TRUE, header = TRUE, sep = ",", na.strings = c("","NA","NULL"))
labs <- subset(labs, encounter.number %in% fulldata$encounternumber)
names(labs)[2] <- 'encounternumber'

creat.all <- labs[,c('encounternumber', paste0('firstdailycreat.',0:30), paste0('lowestdailycreat.',0:30),
                     paste0('highestdailycreat.',0:30))]

creat.all$max.creat <- ifelse(apply(creat.all[,2:94], 1, function(x)sum(is.na(x)))==93, NA,
                              apply(creat.all[,2:94], 1, function(x)max(x, na.rm=TRUE)))
creat.all$min.creat <- ifelse(apply(creat.all[,2:94], 1, function(x)sum(is.na(x)))==93, NA,
                              apply(creat.all[,2:94], 1, function(x)min(x, na.rm=TRUE)))

creat.first=reshape(labs[,c('encounternumber',paste0('firstdailycreat.',0:30))],
                    varying=list(2:32), idvar='encounternumber', times=0:30, direction='long')
creat.first <- subset(creat.first, !is.na(firstdailycreat.0))
```

```r
creat.first <- creat.first[order(creat.first$encounter, creat.first$time),]
ff = tapply(creat.first[["firstdailycreat.0"]], creat.first$encounternumber, head, n=1)
creat.first[["first.creat"]] = ff[as.character(creat.first$encounternumber)]
creat.first <- unique(creat.first[,c('encounternumber','first.creat')])

fulldata <- merge(fulldata, creat.all[,c('encounternumber','min.creat','max.creat')],
                  by='encounternumber', all.x=TRUE)
fulldata <- merge(fulldata, creat.first, by='encounternumber', all.x=TRUE)
fulldata <- upData(fulldata,
                   make30.firstcreat = ifelse(make30.death == 1 |
                                        new.rrt.verified ==1 |
                                        make30.finalstudycreat/first.creat>=2, 1, 0),
                   make30.mincreat = ifelse(make30.death == 1 |
                                       new.rrt.verified ==1 |
                                       make30.finalstudycreat/min.creat>=2, 1, 0),
                   make30.maxcreat = ifelse(make30.death == 1 |
                                       new.rrt.verified ==1 |
                                       make30.finalstudycreat/max.creat>=2, 1, 0),
                   make30.creat1.5=ifelse(make30.death == 1 |
                                      new.rrt.verified ==1 |
                                      make30.finalstudycreat/make30.baselinecr>=1.5, 1, 0))


############### Imputation

temp <- fulldata
temp$basecreat1 <- ifelse(temp$make30.baselinecrsource=='Calculated', NA, temp$make30.baselinecr)
temp$basecreat2 <- ifelse(temp$make30.baselinecrsource %in%
                          c('Calculated','LowestCreatDurEncPriorTo_ICU'), NA, temp$make30.baselinecr)
temp$race2 <- temp$patient.race
levels(temp$race2) <- list('WHITE'='WHITE', 'BLACK'='BLACK',
                           'OTHER'=c('ALASKAN/INDIAN','ASIAN', 'DECLINED', 'PACIFIC ISLAND','UNKNOWN/TBD'))

creat.impute <- aregImpute( ~ patient.age + patient.gender + race2 + group + source.of.admission.v2 +
                            Sepsis + TBI + ventilator.flag + inotropic.flag + hemodialysis.pre.icu +
                            isotonic.crystalloid.cum30 + uhc.expected.mort + make30.death +
                            new.rrt.verified + min.creat + max.creat + make30.finalstudycreat +
                            basecreat1, x=TRUE, data=temp, burnin=2, n.impute=5)
creat.imputed <- as.data.frame(creat.impute$x)

creat.impute2 <- aregImpute( ~ patient.age + patient.gender + race2 + group + source.of.admission.v2 +
                             Sepsis + TBI + ventilator.flag + inotropic.flag + hemodialysis.pre.icu +
                             isotonic.crystalloid.cum30 + uhc.expected.mort + make30.death +
                             new.rrt.verified + min.creat + max.creat + make30.finalstudycreat +
                             basecreat2, x=TRUE, data=temp, burnin=2, n.impute=5)
creat.imputed2 <- as.data.frame(creat.impute2$x)

fulldata=cbind(fulldata,creat.imputed[,18],creat.imputed2[,18])

fulldata <- upData(fulldata,
                   make30.imp.cal = ifelse(make30.death == 1 |
                                       new.rrt.verified ==1 |
                                       make30.finalstudycreat/creat.imputed[, 17]>=2, 1, 0),
                   make30.imp2 = ifelse(make30.death == 1 | new.rrt.verified ==1 |
                                      make30.finalstudycreat/creat.imputed2[, 17]>=2, 1, 0))


tt <- datadist(fulldata[,c('make30.final','group')]); options(datadist = 'tt')
```

```
ImpVar <- c('make30.final','make30.imp.cal','make30.imp2','make30.firstcreat','make30.maxcreat',
            'make30.mincreat','make30.creat1.5')

SenAnalysis <- NA
for (i in 1:length(ImpVar)){

   mmod <- glmer(as.formula(paste(ImpVar[i], "group + patient.age + patient.gender +
                                  patient.race.v2 + source.of.admission.v2 + ventilator.flag +
                                  inotropic.flag + Sepsis + TBI + (1 | unit)", sep=" ~ ")),
                 data = fulldata, family = binomial)

    cc <- confint(mmod,parm="beta_")
    SenAnalysis <- rbind(SenAnalysis,c(exp(cbind(est=fixef(mmod),cc)[2,]),
                                       summary(mmod)$coefficients[2,4]))
}

mtemp <- glmer(make30.final ~ group + patient.age + patient.gender +
                                  patient.race.v2 + source.of.admission.v2 + ventilator.flag +
                                  inotropic.flag + Sepsis + TBI + (1 | unit),
                                  data = subset(fulldata,!make30.baselinecrsource=='Calculated'),
                                  family = binomial)
cc <- confint(mtemp,parm="beta_")
SenAnalysis <- rbind(SenAnalysis[-1,],
                  c(exp(cbind(est=fixef(mtemp),cc)[2,]),
                                       summary(mtemp)$coefficients[2,4]))

rownames(SenAnalysis) <- c('ITT','Single imputation on missing baseline creatinine',
                           'Single imputation treating LowestCreatDurEncPriorToICU missing',
                           'Use first creatinine','Use highest creatinine','Use lowest creatinine',
                           'Use ratio 1.5 instead of 2','Complete cases')
kable(outtemp, digits=2, caption='Sensitivity Analysis Using Different Renal Dysfunction Calculation',
      align=rep('c',4), escape=FALSE, format='latex')




# All other sensitivity analysis
# 1. Modified intention-to-treat population: patients who received at least 500 mL of isotonic
#    crystalloid in the 72 hours after enrollment
AnalysisSet <- subset(fulldata, mod.itt=='Yes')

# 2. Washout: excluding pateints admitted within the 7 days prior to a cross-over in ICU fluid group
#             assignment
AnalysisSet <- subset(fulldata, crossover7=='No')

# 3. Per protocol: excluding patients who remained in the ICU through a cross-over or were transferred
#                  between study ICUs
fulldata <- subset(fulldata, crossover=='No')

# 4. Repeat same analysis including only the first admission per patient
```