Reanalysis of 03-Zecca

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Reference

Zecca, E., Brunelli, C., Centurioni, F., Manzoni, A., Pigni, A., & Caraceni, A. (2017). Fentanyl Sublingual Tablets Versus Subcutaneous Morphine for the Management of Severe Cancer Pain Episodes in Patients Receiving Opioid Treatment: A Double-Blind, Randomized, Noninferiority Trial. *Journal of Clinical Oncology*, 35(7), 759–765. https://doi.org/10.1200/JCO.2016.69.9504

Notes from reading methods section

- Dependant variable: Pain intensity (PI) (average across follow-ups, AVP_30)
- Independant variable: treatment group
  - Fentanyl sublingual tablets FST (n=57, 1 from 58 was excluded)
  - Subcutaneous morphine SCM (n=56)
- Covariate: basline PI
- Design: 1-way ANCOVA with group as IV and baselie PI as covariate

Reading data

Data is loaded, reshaped if necessary, and factors are specified.

```
PATH = file.path(path.expand("~"), "Data", "ancova") # ancova project folder
data = read_excel(file.path(PATH, "dataPrimaryStudies", "03-Zecca", "03-Zecca.xls"))
data = as.data.frame(data)
data$tratt = as.factor(data$tratt)
```

Descriptives

Dependant variable

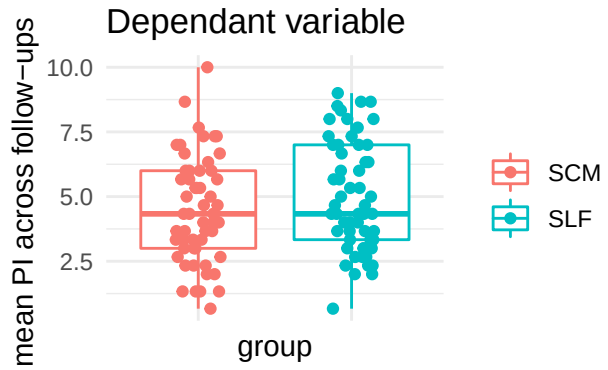
Number of samples and mean (SD) in levels of the independant variables.

```
tab.dv = array(NA, dim=c(2,3))
tab.dv[,1] = levels(data$tratt)
tab.dv[,2] = summary(data$tratt)
tab.dv[,3] = tapply(data$pain_mea_30, data$tratt,
                    function (x) sprintf("%0.2f (%0.2f)", mean(x), sd(x)))
```

```r
colnames(tab.dv) = c("group", "n", "mean (SD)")
print(tab.dv)
```

```
##      group n    mean (SD)
## [1,] "SCM" "56" "4.48 (2.03)"
## [2,] "SLF" "57" "4.97 (2.12)"
```

```r
ggplot(data, aes(y=pain_mea_30, x=tratt, color=tratt)) +
  geom_boxplot() +
  geom_point(position = position_jitter(width = 0.15, height = 0)) +
  theme_minimal() +
  theme(axis.text.x = element_blank(), legend.title = element_blank()) +
  xlab("group") + ylab("mean PI across follow-ups ") + ggtitle("Dependant variable")
```

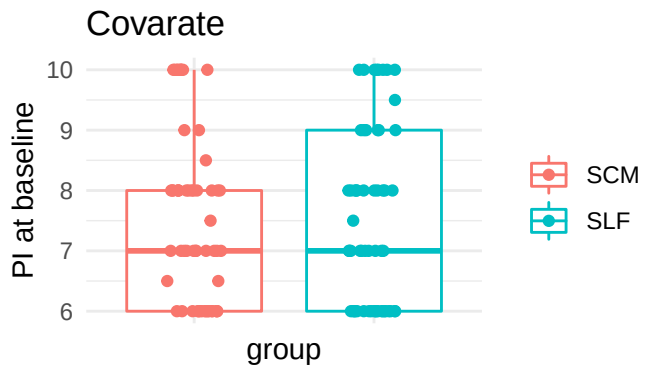


Covariate(s)

```r
tab.cv = array(NA, dim=c(2,3))
tab.cv[,1] = levels(data$tratt)
tab.cv[,2] = summary(data$tratt)
tab.cv[,3] = tapply(data$pain_mea_bas, data$tratt,
                    function (x) sprintf("%0.2f (%0.2f)", mean(x), sd(x)))
colnames(tab.cv) = c("group", "n", "mean (SD)")
print(tab.cv)
```

```
##      group n    mean (SD)
## [1,] "SCM" "56" "7.54 (1.39)"
## [2,] "SLF" "57" "7.53 (1.45)"
```

```r
ggplot(data, aes(y=pain_mea_bas, x=tratt, color=tratt)) +
  geom_boxplot() +
  geom_point(position = position_jitter(width = 0.15, height = 0)) +
  theme_minimal() +
  theme(axis.text.x = element_blank(), legend.title = element_blank()) +
  xlab("group") + ylab("PI at baseline") + ggtitle("Covarate")
```



Main analysis ANCOVA

```
# Orthogonal contrasts
contrasts(data$tratt) = contr.helmert(2)

fit.ancova = aov(pain_mea_30 ~ pain_mea_bas + tratt, data = data)
result = Anova(fit.ancova, type=3) # Type III
print(result)
```

```
## Anova Table (Type III tests)
##
## Response: pain_mea_30
##               Sum Sq  Df F value    Pr(>F)
## (Intercept)   24.426   1  9.9081  0.002118 **
## pain_mea_bas 207.658   1 84.2329 2.989e-15 ***
## tratt          6.914   1  2.8047  0.096830 .
## Residuals    271.182 110
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The paper used ANCOVA to to a non-inferiority analysis. We calculate ANCOVA adjusted means and 95%-CI.

```
n = summary(data$tratt)
means.adj = effect("tratt", fit.ancova, se=T)
MD = means.adj$fit[1] - means.adj$fit[2]
# variance assumed unequal
SE = sqrt(means.adj$se[1]^2 + means.adj$se[2]^2)
#ci95 = c(MD - 1.96*SE, MD + 1.96*SE)
# SE based on t-distribution because n1 and n2 < 60
myt = qt(.975, df= n[1] + n[2] - 2)
ci95 = c(MD - myt*SE, MD + myt*SE)

sprintf("%.2f (%.2f, %.2f)", MD, ci95[1], ci95[2])
```

```
## [1] "-0.49 (-1.08, 0.09)"
```

Comparing ANCOVA in original study with reanalysis

Independant variable

```
tab.IV = rbind(stats.orig.IV, stats.rep.IV)
rownames(tab.IV) = c("original Study", "reanalysis")
print(t(tab.IV))
```

```
##         original Study reanalysis
## Fvalue  NA             "2.80"
## df1     NA             " 1"
## df2     NA             "110"
## pvalue  NA             "0.097"
## MD      "-0.49"        "-0.49"
## lowerCI "-1.1"         "-1.08"
## upperCI "0.09"         "0.09"
```

Covariate

```
tab.CV = rbind(stats.orig.CV, stats.rep.CV)
rownames(tab.CV) = c("original Study", "reanalysis")
print(t(tab.CV))
```

```
##         original Study reanalysis
## Fvalue  NA             "84.23"
## df1     NA             " 1"
## df2     NA             "110"
## pvalue  NA             "< 0.0001"
## MD      NA             NA
## lowerCI NA             NA
## upperCI NA             NA
```

Assumptions

1. Homogeneity of variance

- ANOVA/ANCOVA is fairly robust in terms of the error rate when sample sizes are equal.
- When groups with larger sample sizes have larger variances than the groups with smaller sample sizes, the resulting F-ratio tends to be conservative. That is, it's more likely to produce a non-significant result when a genuine difference does exist in the population.
- Conversely, when the groups with larger sample sizes have smaller variances than the groups with smaller samples sizes, the resulting F-ratio tends to be liberal and can inflate the false positive rate.

```
tapply(data$pain_mea_30, data$tratt, sd)
```

```
##      SCM      SLF
## 2.030992 2.121189
```

```
leveneTest(pain_mea_30 ~ tratt, data = data)
```

```
## Levene's Test for Homogeneity of Variance (center = median)
##        Df F value Pr(>F)
```

```
## group   1  0.3764 0.5408
##       111
```

2. Independence between covariate and IV

When the covariate and the experimental effect (independent variable) are not independent the treatment effect is obscured, spurious treatment effects can arise and the interpretation of the ANCOVA is seriously compromised.

We test whether our groups differ on the CV. If the groups do not significantly differ then is appropriate to use the covariate.

```
fit.cv = aov(pain_mea_bas ~ tratt, data = data)
Anova(fit.cv, type=3)
```

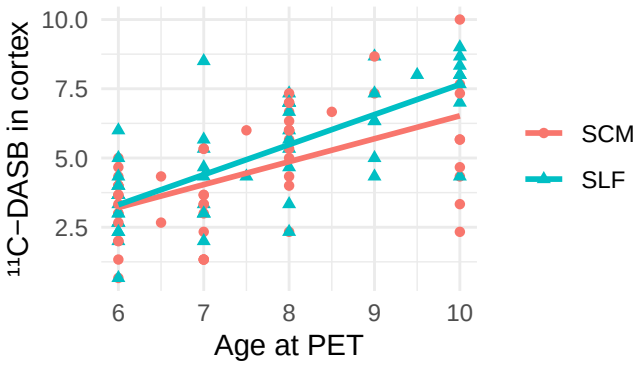
```
## Anova Table (Type III tests)
##
## Response: pain_mea_bas
##             Sum Sq  Df   F value Pr(>F)
## (Intercept) 6408.4   1 3180.7293 <2e-16 ***
## tratt          0.0   1    0.0012  0.972
## Residuals    223.6 111
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

3. Homogeneity of regression slopes

```
fit.hrs = aov(pain_mea_30 ~ pain_mea_bas*tratt, data = data)
Anova(fit.hrs, type=3)
```

```
## Anova Table (Type III tests)
##
## Response: pain_mea_30
##                     Sum Sq  Df F value    Pr(>F)
## (Intercept)         23.374   1  9.5251   0.00257 **
## pain_mea_bas       204.174   1 83.2032 4.304e-15 ***
## tratt                1.988   1  0.8100   0.37011
## pain_mea_bas:tratt   3.704   1  1.5096   0.22185
## Residuals          267.477 109
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
ggplot(data, aes(y=pain_mea_30, x=pain_mea_bas, color=tratt, shape=tratt)) +
  geom_point() +
  geom_smooth(formula = y ~ x,method=lm, se=FALSE, fullrange=TRUE) +
  theme_minimal() +
  theme(legend.title = element_blank()) +
  xlab("Age at PET") + ylab("[11]C-DASB in cortex")
```



Data was analyzed according to recommendations by Field, Miles, & Field (2012).