Randomized Control Trial - BotB Example

```
library(ggplot2)
library(Hmisc)
library(lme4)
library(lmerTest)
library(dplyr)
```

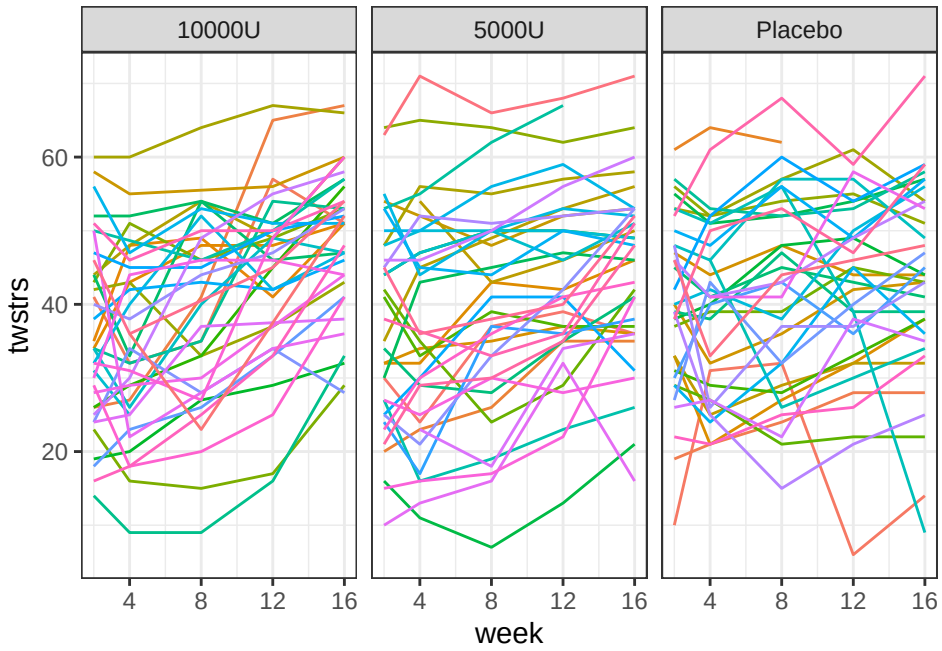
The data are from a multicenter, randomized control trial of botulinum toxin type B (BotB) in patients with cervical dystonia from nine U.S. sites. $N = 36$ individuals were randomized to placebo, $N = 36$ were randomized to 5000 units of BotB, and $N = 37$ were randomized to 10,000 units of BotB.

The response variable is the total score on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), which measures severity, pain, and disability of cervical dystonia (high scores mean more impairment). TWSTRS was measured at baseline (week 0) and at weeks 2, 4, 8, 12, and 16 after treatment began.

```
getHdata(cdystonia)
head(cdystonia)
```

```
##     week site id treat age sex twstrs
## 1 1    0    1  1 5000U  65   F     32
## 1 2    2    1  1 5000U  65   F     30
## 1 3    4    1  1 5000U  65   F     24
## 1 4    8    1  1 5000U  65   F     37
## 1 5   12    1  1 5000U  65   F     39
## 1 6   16    1  1 5000U  65   F     36
```

```
## Warning: Combining variables of class <labelled> and <factor> was deprecated in ggplot2
## 3.4.0.
## i Please ensure your variables are compatible before plotting (location:
##   `join_keys()`)
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.
```




```
forICC <- lmer(twstrs ~ 1 + (1|uid), data=both)
summary(forICC)
```

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: twstrs ~ 1 + (1 | uid)
##    Data: both
##
## REML criterion at convergence: 3821.7
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -4.4452 -0.5564  0.0276  0.5366  3.0305
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  uid      (Intercept) 119.19   10.917
##  Residual              53.53    7.317
## Number of obs: 522, groups:  uid, 108
##
## Fixed effects:
##             Estimate Std. Error      df t value Pr(>|t|)
## (Intercept)   40.672      1.099 106.887   37.01   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The ICC is $119.19/(119.19 + 53.53) = 0.69$. Thus, 69% of the variability in the TWSTRS score is due to the individual.

Next, let's fit a model using week, treatment, and the interaction between them to predict TWSTRS. We will also include a random intercept for individuals.

```
rInt <- lmer(twstrs ~ week*treat + (1|uid), data=both)
summary(rInt)
```

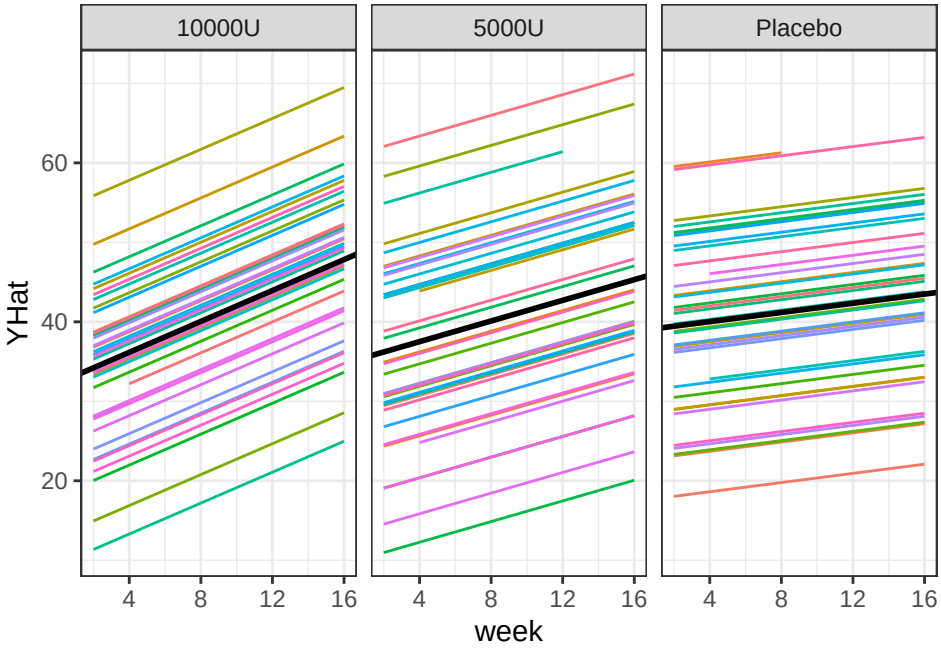
```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: twstrs ~ week * treat + (1 | uid)
##    Data: both
##
## REML criterion at convergence: 3674.8
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -5.6638 -0.5663 -0.0284  0.5561  3.5597
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  uid      (Intercept) 124.69   11.167
##  Residual              37.71    6.141
## Number of obs: 522, groups:  uid, 108
##
## Fixed effects:
##                    Estimate Std. Error        df t value Pr(>|t|)
## (Intercept)        32.26685    2.03738 139.91978  15.837  < 2e-16 ***
## week                0.97280    0.09018 412.39743  10.787  < 2e-16 ***
## treat5000U          2.63704    2.90322 140.28252   0.908   0.3653
## treatPlacebo        6.60054    2.92256 139.99176   2.258   0.0255 *
## week:treat5000U    -0.32257    0.12831 411.94912  -2.514   0.0123 *
## week:treatPlacebo  -0.68373    0.12937 412.18166  -5.285 2.04e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##             (Intr) week   t5000U trtPlc w:5000
## week        -0.367
## treat5000U  -0.702  0.258
## treatPlaceb -0.697  0.256  0.489
## wk:trt5000U  0.258 -0.703 -0.371 -0.180
## wek:trtPlcb  0.256 -0.697 -0.180 -0.369  0.490

## Warning: Using `size` aesthetic for lines was deprecated in ggplot2 3.4.0.
## i Please use `linewidth` instead.
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.

## Warning: Combining variables of class <vctrs:::common_class_fallback> and <factor> was
## deprecated in ggplot2 3.4.0.
## i Please ensure your variables are compatible before plotting (location:
##   `combine_vars()`)
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.

## Warning: Combining variables of class <labelled> and <factor> was deprecated in ggplot2
## 3.4.0.
## i Please ensure your variables are compatible before plotting (location:
##   `combine_vars()`)
## This warning is displayed once every 8 hours.
```

```
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.
```



Let's fit a model with random intercepts and a random slope for week to compare with the previous model that includes only random intercepts.

```
rIntSlp <- lmer(twstrs ~ week*treat + (week|uid), data=both)
anova(rIntSlp, rInt, refit=FALSE)
```

```
## Data: both
## Models:
## rInt: twstrs ~ week * treat + (1 | uid)
## rIntSlp: twstrs ~ week * treat + (week | uid)
##         npar    AIC    BIC  logLik deviance Chisq Df Pr(>Chisq)
## rInt       8 3690.8 3724.9 -1837.4   3674.8
## rIntSlp   10 3658.7 3701.3 -1819.3   3638.7 36.14  2   1.42e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The model with random intercepts and random slope for week fits statistically signficantly better than the model with only random intercepts, $\chi^2(2) = 36.14, p < .001$.

In looking at the plot of the actual data it seems highly unlikely that a random slope only model would fit better than a random intercept and random slope model but let's check anyway.

```
rSlp <- lmer(twstrs ~ week*treat + (-1 + week|uid), data=both)
anova(rIntSlp, rSlp, refit=FALSE)
```

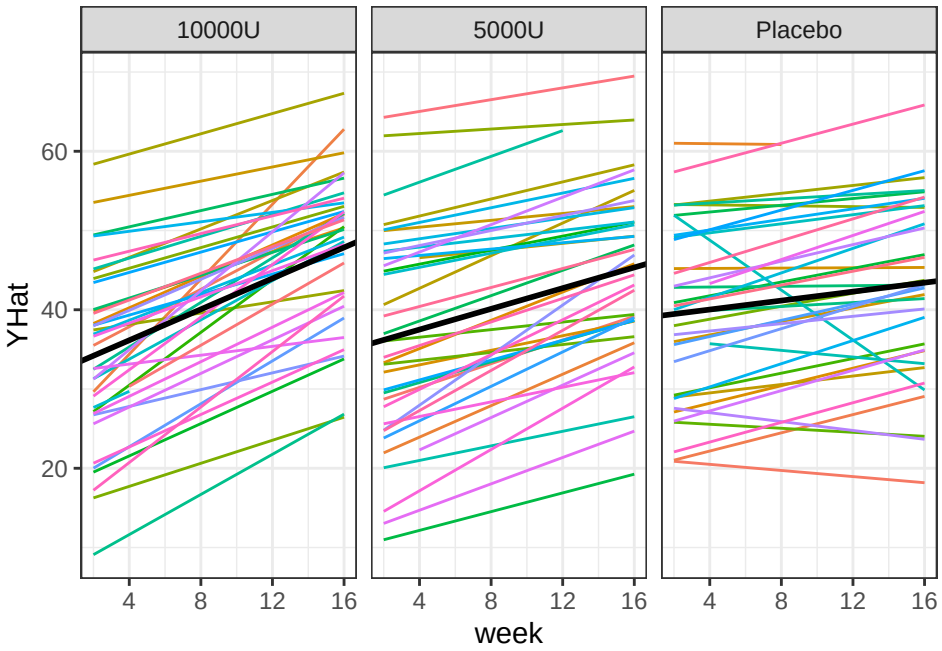
```
## Data: both
## Models:
## rSlp: twstrs ~ week * treat + (-1 + week | uid)
## rIntSlp: twstrs ~ week * treat + (week | uid)
##         npar    AIC    BIC  logLik deviance  Chisq Df Pr(>Chisq)
## rSlp       8 3983.1 4017.2 -1983.6   3967.1
## rIntSlp   10 3658.7 3701.3 -1819.3   3638.7 328.44  2  < 2.2e-16 ***
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Indeed, the model with random intercepts and random slope for week fits statistically significantly better than the model with only a random slope for week, $\chi^2(2) = 328.44, P < .001$. So we will go with the random intercept and random slope model.

```
summary(rIntSlp)
```

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: twstrs ~ week * treat + (week | uid)
##    Data: both
##
## REML criterion at convergence: 3638.7
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.9626 -0.4428 -0.0134  0.4814  3.3040
##
## Random effects:
##  Groups   Name        Variance Std.Dev. Corr
##  uid      (Intercept) 165.6931 12.8722
##           week          0.3098  0.5566  -0.51
##  Residual              27.7688  5.2696
## Number of obs: 522, groups:  uid, 108
##
## Fixed effects:
##                   Estimate Std. Error       df t value Pr(>|t|)
## (Intercept)        32.2493     2.2490 104.9367  14.339  < 2e-16 ***
## week                0.9759     0.1206 103.6228   8.089  1.2e-12 ***
## treat5000U          2.6384     3.2043 105.1425   0.823 0.412149
## treatPlacebo        6.6472     3.2265 105.0207   2.060 0.041852 *
## week:treat5000U    -0.3226     0.1714 104.1206  -1.882 0.062624 .
## week:treatPlacebo  -0.6932     0.1730 103.9894  -4.008 0.000115 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##             (Intr) week   t5000U trtPlc w:5000
## week        -0.547
## treat5000U  -0.702  0.384
## treatPlaceb -0.697  0.381  0.489
## wk:trt5000U  0.385 -0.704 -0.550 -0.268
## wek:trtPlcb  0.382 -0.698 -0.268 -0.549  0.491
```



There is the categorical predictor, `treat`, and a significant interaction, so the easiest way to go about interpreting this model is to write out the equations for each treatment group.

For 10000U, the reference group:

$$\widehat{Y} = 32.249 + 0.976 * week$$

Thus, the expected baseline score on TWSTRS for those in the 10,000U treatment group is 32.249. This value is significantly different from 0, $t(104.93) = 14.339, p < .001$, using the Satterthwaite approximation. However, there is quite a bit of variability among individuals around this value, specifically, the standard deviation is 12.87. For each one week increase, the TWSTRS score is expected to increase by 0.976 points in the 10,000U group, which is statistically significant, $t(103.61) = 8.088, p < .001$ using the Satterthwaite approximation. In addition, there is quite a bit of variability among individuals in this effect, specifically, the standard deviation for the effect of week is 0.557.

For the 5000U group:

$$\widehat{Y} = 32.249 + 2.638 + 0.976 * week - 0.323 * week = 34.887 + 0.653 * week$$

Thus, the expected baseline score on TWSTRS for those in the 5000U treatment group is 34.887. This value is not significantly different from that for the 10,000U group, $t(105.135) = 0.823, p = .412$ using the Satterthwaite approximation. However, there is quite a bit of variability among individuals around this value, specifically, the standard deviation is 12.87. Note that this estimate of the variability is the same for all treatment groups. For each one week increase, the TWSTRS score is expected to increase by 0.653 points in the 5000U group, although this effect is not significantly different from the effect for the 10,000U group, $t(104.11) = -1.882, p = .063$ using the Satterthwaite approximation. Again, there is quite a bit of variability among individuals in this effect, specifically, the standard deviation for the effect of week is 0.557. Note again that this estimate is not permitted to vary across treatment groups due to the way that we specified the model.

For the placebo group:

$$\widehat{Y} = 32.249 + 6.647 + 0.976 * week - 0.693 * week = 38.896 + 0.283 * week$$

Thus, the expected baseline score on TWSTRS for those in the placebo group is 38.896. This value is significantly different than that of the 10,000U group, $t(105.014) = 2.06, p = .042$ using the Satterthwaite approximation. Again, there is quite a bit of variability among individuals around this value, specifically, the standard deviation is 12.87. Note that this estimate of the variability is the same for all treatment groups. For each one week increase, the TWSTRS score is expected to increase by 0.283 points in the placebo group, and this effect is significantly different from the 10,000U group, $t(104.11) = -4.008, p < .001$ using the Satterthwaite approximation. Again, there is quite a bit of variability among individuals in this effect, specifically, the standard deviation for the effect of week is 0.557. Note again that this estimate is not permitted to vary across treatment groups due to the way that we specified the model.

Finally, the correlation between random intercepts and random slopes is -0.51 which indicates that the lower an individual starts out, the steeper their slope is over the course of the study.

```
anova(rIntSlp, ddf = "Kenward-Roger")
```

```
## Type III Analysis of Variance Table with Kenward-Roger's method
##            Sum Sq Mean Sq NumDF  DenDF F value    Pr(>F)
## week       2267.5 2267.46     1 103.61 81.6548 9.794e-15 ***
## treat       119.1   59.55     2 104.95  2.1444 0.1222384
## week:treat  446.1  223.05     2 103.60  8.0324 0.0005715 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```