

P9185_project1

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```
library(tidyverse)
```

```
## Warning: package 'ggplot2' was built under R version 4.3.2
```

```
## Warning: package 'purrr' was built under R version 4.3.2
```

```
## Warning: package 'stringr' was built under R version 4.3.2
```

```
## -- Attaching core tidyverse packages ----- tidyverse 2.0.0 --
```

```
## v dplyr      1.1.2      v readr      2.1.4
```

```
## v forcats   1.0.0      v stringr   1.5.1
```

```
## v ggplot2    3.4.4      v tibble    3.2.1
```

```
## v lubridate  1.9.2      v tidyr     1.3.0
```

```
## v purrr      1.0.2
```

```
## -- Conflicts ----- tidyverse_conflicts() --
```

```
## x dplyr::filter() masks stats::filter()
```

```
## x dplyr::lag()     masks stats::lag()
```

```
## i Use the conflicted package (<http://conflicted.r-lib.org/>) to force all conflicts to become errors
```

```
library(lme4)
```

```
## Loading required package: Matrix
```

```
##
```

```
## Attaching package: 'Matrix'
```

```
##
```

```
## The following objects are masked from 'package:tidyr':
```

```
##
```

```
##      expand, pack, unpack
```

```
library(nlme)
```

```
##
```

```
## Attaching package: 'nlme'
```

```
##
```

```
## The following object is masked from 'package:lme4':
```

```
##
```

```
##      lmList
```

```
##
```

```
## The following object is masked from 'package:dplyr':
```

```
##
```

```
##      collapse
```

```
library(lattice)
library(gtsummary)
library(DHARMA)
```

```
## Warning: package 'DHARMA' was built under R version 4.3.2
```

```
## This is DHARMA 0.4.6. For overview type '?DHARMA'. For recent changes, type news(package = 'DHARMA')
```

```
library(knitr)
library(kableExtra)
```

```
##
## Attaching package: 'kableExtra'
##
## The following object is masked from 'package:dplyr':
##
##     group_rows
```

```
library(webshot)
```

```
baseline.dat <- read.csv("baseline.csv")
endpoints.dat <- read.csv("endpoints.csv")
```

Data cleaning and EDA

```
endpoints.AE <-
  endpoints.dat %>%
  select(ptid, AE_pillA_week1:AE_gelC_week4) %>%
  pivot_longer(
    cols = starts_with("AE_"),
    names_to = c("drug", "week"),
    names_pattern = "AE_(.*)_(week\\d+)",
    values_to = "AE"
  ) %>%
  mutate(drug = case_when(
    str_detect(drug, "pillA") ~ "Pill A",
    str_detect(drug, "gelB") ~ "Gel B",
    str_detect(drug, "gelC") ~ "Gel C"
  ),
  week = parse_number(week))

endpoints.Adhere <-
  endpoints.dat %>%
  select(ptid, Adhere_pillA_week1:Adhere_gelC_week4) %>%
  pivot_longer(
    cols = starts_with("Adhere_"),
    names_to = c("drug", "week"),
    names_pattern = "Adhere_(.*)_(week\\d+)",
    values_to = "Adhere"
```

```

) %>%
mutate(drug = case_when(
  str_detect(drug, "pillA") ~ "Pill A",
  str_detect(drug, "gelB") ~ "Gel B",
  str_detect(drug, "gelC") ~ "Gel C"
),
week = parse_number(week)) %>%
mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C")))

endpoints.period <-
endpoints.dat %>%
select(ptid, period1:period3) %>%
mutate(sequence = case_when(
  period1 == "Pill A" & period2 == "Gel B" & period3 == "Gel C" ~ "ABC",
  period1 == "Pill A" & period2 == "Gel C" & period3 == "Gel B" ~ "ACB",
  period1 == "Gel B" & period2 == "Gel C" & period3 == "Pill A" ~ "BCA",
  period1 == "Gel B" & period2 == "Pill A" & period3 == "Gel C" ~ "BAC",
  period1 == "Gel C" & period2 == "Pill A" & period3 == "Gel B" ~ "CAB",
  period1 == "Gel C" & period2 == "Gel B" & period3 == "Pill A" ~ "CBA",
  TRUE ~ "Other" # This is the default case
)) %>%
mutate(
  seq1 = case_when(
    sequence == "ABC" ~ 1,
    sequence == "CAB" ~ 2,
    sequence == "BCA" ~ 3,
    sequence == "BAC" ~ 4,
    sequence == "ACB" ~ 5,
    sequence == "CBA" ~ 6,
  ),
  seq2 = case_when(
    sequence == "ABC" | sequence == "BAC" ~ 0,
    sequence == "CAB" | sequence == "ACB" ~ 1,
    sequence == "BCA" | sequence == "CBA" ~ 2
  )
) %>%
pivot_longer(
  cols = starts_with("period"),
  names_prefix = "period",
  names_to = "period",
  values_to = "drug"
) %>%
mutate(period = as.numeric(period)) %>%
mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C"))) %>%
mutate(seq2 = factor(seq2, levels = c(0,1,2), labels = c("AB", "AC", "BC")))

endpoints.lag <-
endpoints.period %>%
select(ptid, period, drug) %>%
group_by(ptid) %>%
mutate(drug_lag = lag(as.character(drug))) %>%
ungroup() %>%
replace_na(list(drug_lag = "None")) %>%
mutate(

```

```

A_lag = ifelse(drug_lag == "Pill A", 1, 0),
B_lag = ifelse(drug_lag == "Gel B", 1, 0),
C_lag = ifelse(drug_lag == "Gel C", 1, 0)
)%>%
mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C")))

endpoints.period <- left_join(endpoints.period, endpoints.lag)

```

```
## Joining with 'by = join_by(ptid, period, drug)'
```

```
endpoints.AE <- left_join(endpoints.AE, endpoints.period)
```

```
## Joining with 'by = join_by(ptid, drug)'
```

```
endpoints.Adhere <- left_join(endpoints.Adhere, endpoints.period)
```

```
## Joining with 'by = join_by(ptid, drug)'
```

```

endpoints.AE.weeksum <-
  endpoints.AE %>%
  select(-week) %>%
  group_by(ptid, drug, period) %>%
  mutate(AE_sum = sum(AE)) %>%
  ungroup() %>%
  mutate(AE_ind = as.factor(ifelse(AE_sum > 0, 1, 0))) %>%
  select(-AE) %>%
  distinct() %>%
  mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C")))

endpoints.Adhere <-
  endpoints.Adhere %>%
  mutate(total_week = period*week,
         nonAdhere = 7-Adhere)

```

```

# 0- baseline; 1- 1st treatment; 2- 1st wash out; 3- 2nd treatment;
# 4- 2nd wash out; 5- third treatment; 6- third wash out

```

```

endpoints.PK <-
  baseline.dat %>%
  select(ptid, bviral0:sviral6) %>%
  mutate(
    dbvial1 = -bviral1 - bviral0,
    dsvial1 = -sviral1 - sviral0,
    dbvial2 = -bviral3 - bviral2,
    dsvial2 = -sviral3 - sviral2,
    dbvial3 = -bviral5 - bviral4,
    dsvial3 = -sviral5 - sviral4
  ) %>%
  pivot_longer(
    cols = starts_with("d"),
    names_to = c("measure", "period"),
    names_pattern = "d(.*vial)(\\d+)",

```

```

    values_to = "dvalue"
  ) %>%
  select(ptid, measure, period, dvalue) %>%
  mutate(period = as.numeric(period),
         dvalue = -dvalue)

```

```

endpoints.Adhere.sum <-
  endpoints.Adhere %>%
  select(ptid, period, week, Adhere) %>%
  group_by(ptid, period) %>%
  summarize(Adhere_sum = sum(Adhere)) %>%
  mutate(Adhere_rate = Adhere_sum/28)

```

'summarise()' has grouped output by 'ptid'. You can override using the
'.groups' argument.

```

endpoints.PK <- left_join(endpoints.PK, endpoints.Adhere.sum)

```

Joining with 'by = join_by(ptid, period)'

```

endpoints.PK <-
  left_join(endpoints.PK, endpoints.AE.weeksum) %>%
  mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C"))) %>%
  mutate(measure = factor(measure, labels = c("Skin", "Blood"), levels = c("svial", "bvial"))) %>%
  mutate(AE_ind = factor(ifelse(AE_ind == 1, "Yes", "No")))

```

Joining with 'by = join_by(ptid, period)'

```

#endpoints.PK.bvial <- endpoints.PK %>% filter(measure == "bvial")
#endpoints.PK.svial <- endpoints.PK %>% filter(measure == "svial")

```

```

Adhere.demo <-
  baseline.dat %>%
  select(ptid, age, gender, race) %>%
  mutate(
    gender = factor(gender, labels = c("male", "female"), levels = c(0,1)),
    race = factor(race, levels = c("white", "black", "others"))
  )

```

```

endpoints.Adhere.total <-
  endpoints.Adhere.sum %>%
  select(ptid, Adhere_sum) %>%
  group_by(ptid) %>%
  summarize(Adhere_total = sum(Adhere_sum))

```

```

Adhere.demo <- left_join(Adhere.demo, endpoints.Adhere.total) %>%
  mutate(non_Adhere_total = 84 - Adhere_total)

```

Joining with 'by = join_by(ptid)'

```
# AE response
traj.AE <-
  endpoints.AE.weeksum %>%
  ggplot(aes(x = period, y = AE_ind)) +
  geom_line(alpha = 0.2, aes(group = factor(ptid))) +
  geom_point(alpha = 0.1, size = 0.8)

traj.AE
```

```
# AE response
traj.Adhere <-
  endpoints.Adhere %>%
  ggplot(aes(x = total_week, y = Adhere)) +
  geom_line(alpha = 0.2, aes(group = factor(ptid))) +
  geom_point(alpha = 0.1, size = 0.8)

traj.Adhere

xyplot(Adhere ~ period, endpoints.Adhere, type=c('g','p','l'))
```

Primary Objective

Safety

```
endpoints.AE.weeksum <- left_join(endpoints.AE.weeksum, Adhere.demo)
```

Testing crossover effects

```
## Joining with 'by = join_by(ptid)'
```

```
# centered age for better interpretation
endpoints.AE.weeksum$age <- endpoints.AE.weeksum$age - mean(endpoints.AE.weeksum$age)
AE.crossover.model <- glmer(AE_ind ~ period + seq2 + (1|ptid), data = endpoints.AE.weeksum, family = binomial)
summary(AE.crossover.model)
```

```
## Generalized linear mixed model fit by maximum likelihood (Laplace
## Approximation) [glmerMod]
## Family: binomial ( logit )
## Formula: AE_ind ~ period + seq2 + (1 | ptid)
## Data: endpoints.AE.weeksum
##
##      AIC      BIC    logLik deviance df.resid
##    296.3    317.8   -143.2    286.3     535
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.11505 -0.07043 -0.06691 -0.05449  1.91167
##
## Random effects:
```

```
## Groups Name      Variance Std.Dev.
## ptid (Intercept) 13.76    3.71
## Number of obs: 540, groups: ptid, 180
##
## Fixed effects:
##           Estimate Std. Error z value Pr(>|z|)
## (Intercept) -5.34481    1.63489  -3.269  0.00108 **
## period      0.06021    0.24570   0.245  0.80642
## seq2AC      -0.47270    0.84401  -0.560  0.57544
## seq2BC       0.12225    0.80708   0.151  0.87961
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##      (Intr) period seq2AC
## period -0.345
## seq2AC -0.316  0.003
## seq2BC -0.319  0.004  0.489

AE.crossover.model.null <- glmer(AE_ind ~ period + (1|ptid), data = endpoints.AE.weeksum, family = binom)
anova(AE.crossover.model, AE.crossover.model.null)
```

```
## Data: endpoints.AE.weeksum
## Models:
## AE.crossover.model.null: AE_ind ~ period + (1 | ptid)
## AE.crossover.model: AE_ind ~ period + seq2 + (1 | ptid)
##           npar      AIC      BIC logLik deviance Chisq Df
## AE.crossover.model.null      3 292.88 305.76 -143.44  286.88
## AE.crossover.model          5 296.34 317.79 -143.17  286.34 0.5451  2
##           Pr(>Chisq)
## AE.crossover.model.null
## AE.crossover.model          0.7614
```

No significant crossover effect found.

Modeling

```
#model.AE.1 <- glmer(AE_ind ~ drug + period + seq2 + (1|ptid), data = endpoints.AE.weeksum, family = binom)
#summary(model.AE.1)

#model.AE.lag <- glmer(AE_ind ~ drug + period + A_lag + B_lag + C_lag + (1|ptid), data = endpoints.AE.weeksum, family = binom)
#summary(model.AE.lag)

model.AE <- glmer(AE_ind ~ drug + period + age + gender + race + (1|ptid), data = endpoints.AE.weeksum, family = binom)
summary(model.AE)
```

```
## Generalized linear mixed model fit by maximum likelihood (Adaptive
## Gauss-Hermite Quadrature, nAGQ = 6) [glmerMod]
## Family: binomial ( logit )
## Formula: AE_ind ~ drug + period + age + gender + race + (1 | ptid)
```

```
## Data: endpoints.AE.weeksum
##
##      AIC      BIC    logLik deviance df.resid
##    273.8    312.5   -127.9    255.8     531
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -1.0318 -0.2694 -0.1421 -0.0678  4.9077
##
## Random effects:
## Groups Name          Variance Std.Dev.
## ptid    (Intercept) 1.233     1.11
## Number of obs: 540, groups: ptid, 180
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept) -3.566136   0.777541  -4.586 4.51e-06 ***
## drugGel B    0.182680   0.421212   0.434  0.665
## drugGel C   -0.198414   0.443484  -0.447  0.655
## period       0.060845   0.216327   0.281  0.779
## age          0.196494   0.040420   4.861 1.17e-06 ***
## genderfemale 0.106236   0.426127   0.249  0.803
## raceblack   -0.519507   0.551649  -0.942  0.346
## raceothers  -0.003037   0.497646  -0.006  0.995
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) drgGlB drgGlC period age    gndrfm rcbclk
## drugGel B    -0.335
## drugGel C    -0.234  0.492
## period       -0.594  0.056 -0.026
## age          -0.408  0.027 -0.025  0.028
## genderfemal -0.301  0.001  0.001 -0.001 -0.048
## raceblack   -0.311 -0.007  0.002  0.004 -0.044  0.143
## raceothers  -0.394  0.003 -0.001  0.009  0.026  0.120  0.495
```

```
tbl.AE <-
  model.AE %>%
  tbl_regression(
    estimate_fun = function(x) style_number(x, digits = 3),
    exponentiate = T,
    label = list(
      drug ~ "Treatment",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race"
    ),
    include = everything()

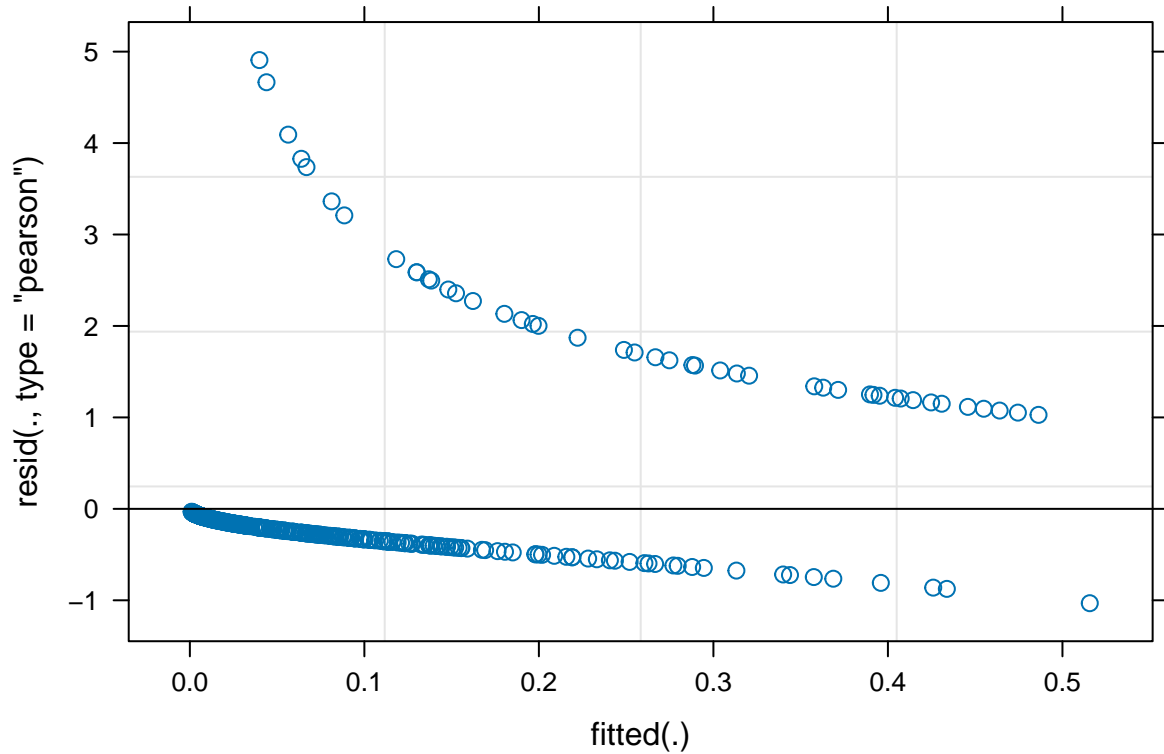
# Convert tbl_regression to gt for more flexible handling
gt.AE <- tbl.AE %>% as_gt()
gt::gtsave(gt.AE, file = "./image/tbl_AE.png")
```



```
## Registered S3 method overwritten by 'webshot2':
##   method      from
##   print.webshot webshot
```

```
# Model diagnostic
```

```
plot(model.AE)
```



```
# Model comparison
```

```
#model.AE.nolag <- glmer(AE_ind ~ drug + period + (1|ptid), data = endpoints.AE.weeksum, family = binom
```

```
#summary(model.AE.nolag)
```

```
#anova(model.AE.lag, model.AE.nolag)
```

Adherence

```
endpoints.Adhere <- left_join(endpoints.Adhere, Adhere.demo)
```

Testing crossover effects

```
## Joining with 'by = join_by(ptid)'
```

```

endpoints.Adhere$age <- endpoints.Adhere$age - mean(endpoints.Adhere$age)
Adhere.crossover.model <- glmer(cbind(Adhere, nonAdhere) ~ period + week + seq2 + (1|ptid), data = endpoints.Adhere,
summary(Adhere.crossover.model)

```

```

## Generalized linear mixed model fit by maximum likelihood (Laplace
##   Approximation) [glmerMod]
##   Family: binomial ( logit )
## Formula: cbind(Adhere, nonAdhere) ~ period + week + seq2 + (1 | ptid)
##   Data: endpoints.Adhere
##
##           AIC          BIC    logLik deviance df.resid
##    4740.2    4774.3   -2364.1   4728.2     2154
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -4.9259 -0.4753  0.2952  0.5532  3.1181
##
## Random effects:
##   Groups Name            Variance Std.Dev.
##   ptid    (Intercept)  3.026      1.74
## Number of obs: 2160, groups:  ptid, 180
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)   3.427453   0.256862  13.344  <2e-16 ***
## period        -0.004359   0.032537  -0.134    0.893
## week          -0.293577   0.024193 -12.135  <2e-16 ***
## seq2AC        -0.069610   0.334614  -0.208    0.835
## seq2BC         0.091676   0.335935   0.273    0.785
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##          (Intr) period week   seq2AC
## period -0.254
## week   -0.261  0.000
## seq2AC -0.660  0.000  0.000
## seq2BC -0.656  0.000  0.000  0.503

```

No significant crossover effect found.

```

model.Adhere <- glmer(cbind(Adhere, nonAdhere) ~ period + week + drug + age + gender + race + (1|ptid),
summary(model.Adhere)

```

Modelling

```

## Generalized linear mixed model fit by maximum likelihood (Adaptive
##   Gauss-Hermite Quadrature, nAGQ = 4) [glmerMod]
##   Family: binomial ( logit )

```

```
## Formula: cbind(Adhere, nonAdhere) ~ period + week + drug + age + gender +
##      race + (1 | ptid)
##      Data: endpoints.Adhere
##
##      AIC      BIC    logLik deviance df.resid
##  1946.5    2003.3   -963.3   1926.5     2150
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -7.4654 -0.2438  0.2480  0.4875  2.5294
##
## Random effects:
##      Groups Name      Variance Std.Dev.
##      ptid   (Intercept) 0.9557   0.9776
## Number of obs: 2160, groups:  ptid, 180
##
## Fixed effects:
##              Estimate Std. Error z value Pr(>|z|)
## (Intercept)   4.68581    0.21817  21.478  <2e-16 ***
## period         0.02055    0.03543   0.580    0.562
## week          -0.32010    0.02570 -12.455  <2e-16 ***
## drugGel B     -1.92216    0.08246 -23.311  <2e-16 ***
## drugGel C     -1.57422    0.08292 -18.984  <2e-16 ***
## age           0.20123    0.01210  16.627  <2e-16 ***
## genderfemale  0.25215    0.17110   1.474    0.141
## raceblack     0.10728    0.21381   0.502    0.616
## raceothers   -0.00788    0.21320  -0.037    0.971
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##              (Intr) period week   drgG1B drgG1C age   gndrfm rcb1ck
## period      -0.324
## week         -0.349 -0.002
## drugGel B    -0.306 -0.033  0.074
## drugGel C    -0.295 -0.021  0.059  0.717
## age          0.091  0.005 -0.041 -0.061 -0.045
## genderfemal -0.382  0.011 -0.003 -0.005 -0.003 -0.042
## raceblack   -0.558  0.005 -0.001 -0.004 -0.004  0.126  0.074
## raceothers  -0.544  0.017  0.000  0.000  0.001  0.043  0.009  0.556
```

```
tbl.Adhere <-
  model.Adhere %>%
  tbl_regression(
    estimate_fun = function(x) style_number(x, digits = 3),
    exponentiate = T,
    label = list(
      week ~ "Week",
      drug ~ "Treatment",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race"
    )
  )
```

```

# Convert tbl_regression to gt for more flexible handling
gt.Adhere <- tbl.Adhere %>% as_gt()
gt::gtsave(gt.Adhere, file = "./image/tbl_Adhere.png")

# model comparison
#model.Adhere.nolag <- glmer(cbind(Adhere, nonAdhere) ~ period + week + drug + (1|ptid), data = endpoints.PK)

#anova(model.Adhere.1, model.Adhere.nolag)

```

Secondary Objective

Effects of AE and Adhere on PK

```

traj.PK <-
  endpoints.PK %>%
    ggplot(aes(x = period, y = dvalue, group = measure)) +
    geom_smooth(method = "lm", se = FALSE, show.legend = FALSE) +
    geom_line(alpha = 0.2, aes(group = factor(ptid))) +
    geom_point(alpha = 0.1, size = 0.8) +
    facet_wrap(vars(measure), scales = "free_y")

traj.PK

```

```

endpoints.PK <- left_join(endpoints.PK, Adhere.demo)

```

Testing crossover effects

```

## Joining with 'by = join_by(ptid)'

```

```

PK.crossover.model.bviral <- lmer(dvalue ~ period + seq2 + (1|ptid) , data = endpoints.PK %>% filter(measure == "Blood"))
summary(PK.crossover.model.bviral)

```

```

## Linear mixed model fit by REML ['lmerMod']
## Formula: dvalue ~ period + seq2 + (1 | ptid)
## Data: endpoints.PK %>% filter(measure == "Blood")
##
## REML criterion at convergence: 5063.3
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -2.6292 -0.5857 -0.1232  0.4413  3.8575
##
## Random effects:
##  Groups   Name                Variance Std.Dev.
##  ptid     (Intercept)         119.6     10.94
##  Residual                        611.6     24.73

```

```
## Number of obs: 540, groups:  ptid, 180
##
## Fixed effects:
##           Estimate Std. Error t value
## (Intercept) 130.7500     3.4910  37.453
## period      0.7444     1.3034   0.571
## seq2AC      0.3222     3.2838   0.098
## seq2BC      0.4556     3.2838   0.139
##
## Correlation of Fixed Effects:
##      (Intr) period seq2AC
## period -0.747
## seq2AC -0.470  0.000
## seq2BC -0.470  0.000  0.500
```

```
PK.crossover.model.sviral <- lmer(dvalue ~ period + seq2 + (1|ptid) , data = endpoints.PK %>% filter(measure == "Skin")
summary(PK.crossover.model.sviral)
```

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: dvalue ~ period + seq2 + (1 | ptid)
## Data: endpoints.PK %>% filter(measure == "Skin")
##
## REML criterion at convergence: 5683.6
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -2.2467 -0.6327 -0.1555  0.5250  3.7762
##
## Random effects:
## Groups Name Variance Std.Dev.
## ptid (Intercept) 656 25.61
## Residual 1771 42.08
## Number of obs: 540, groups:  ptid, 180
##
## Fixed effects:
##           Estimate Std. Error t value
## (Intercept) 237.4333     6.3593  37.336
## period      0.7528     2.2177   0.339
## seq2AC     -2.9333     6.4450  -0.455
## seq2BC     -4.5056     6.4450  -0.699
##
## Correlation of Fixed Effects:
##      (Intr) period seq2AC
## period -0.697
## seq2AC -0.507  0.000
## seq2BC -0.507  0.000  0.500
```

No significant crossover effect found for both type of measurements.

```
endpoints.PK <-
  endpoints.PK %>%
```

```

mutate(age = age - mean(age)) %>%
group_by(period) %>%
mutate(Adhere_mean = mean(Adhere_sum), .keep = "all") %>%
ungroup() %>%
mutate(Adhere_sum_centered = Adhere_sum - Adhere_mean)
# Combining two measures into one model
model.PK.bviral <- lmer(dvalue ~ drug + period + Adhere_sum_centered + AE_ind + age + gender + race + (

```

Modelling

```
## boundary (singular) fit: see help('isSingular')
```

```
summary(model.PK.bviral)
```

```

## Linear mixed model fit by REML ['lmerMod']
## Formula: dvalue ~ drug + period + Adhere_sum_centered + AE_ind + age +
##         gender + race + (1 | ptid)
## Data: endpoints.PK %>% filter(measure == "Blood")
##
## REML criterion at convergence: 4829.5
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -3.4144 -0.6349 -0.0091  0.5867  4.2875
##
## Random effects:
##  Groups   Name                Variance Std.Dev.
##  ptid     (Intercept)          0.0      0.0
##  Residual                    475.3    21.8
## Number of obs: 540, groups:  ptid, 180
##
## Fixed effects:
##              Estimate Std. Error t value
## (Intercept)    123.1878   3.3772  36.476
## drugGel B         3.3371   2.5012   1.334
## drugGel C         8.5553   2.4147   3.543
## period           0.6657   1.1490   0.579
## Adhere_sum_centered -1.2813   0.2427 -5.279
## AE_indYes        28.3384   3.5420   8.001
## age             -1.3065   0.1717 -7.609
## genderfemale       7.2093   1.9078   3.779
## raceblack        -2.9727   2.3766 -1.251
## raceothers       -1.5018   2.3562 -0.637
##
## Correlation of Fixed Effects:
##              (Intr) drgGlB drgGlC period Adhr__ AE_ndY age      gndrfm rcblk
## drugGel B    -0.371
## drugGel C    -0.371  0.558
## period       -0.680  0.000  0.000
## Adhr_sm_cnt -0.151  0.394  0.307  0.000
## AE_indYes    -0.082 -0.026  0.008 -0.009 -0.026
## age          0.099 -0.253 -0.202  0.002 -0.649 -0.190
## genderfemal -0.272 -0.040 -0.032  0.000 -0.103 -0.018  0.043

```

```
## raceblack    -0.414 -0.003 -0.001  0.000 -0.006  0.035  0.072  0.098
## raceothers   -0.405  0.016  0.012  0.000  0.040  0.002 -0.005  0.048  0.552
## optimizer (nloptwrap) convergence code: 0 (OK)
## boundary (singular) fit: see help('isSingular')
```

```
# refactor (A as reference)
```

```
model.PK.sviral <- lmer(dvalue ~ drug + period + Adhere_sum_centered + AE_ind + age + gender + race + (1 | ptid))
summary(model.PK.sviral)
```

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: dvalue ~ drug + period + Adhere_sum_centered + AE_ind + age +
##         gender + race + (1 | ptid)
## Data: endpoints.PK %>% filter(measure == "Skin")
##
## REML criterion at convergence: 5307.2
##
## Scaled residuals:
##      Min       1Q   Median       3Q      Max
## -3.4537 -0.5850 -0.0498  0.5570  4.2058
##
## Random effects:
##   Groups   Name      Variance Std.Dev.
##   ptid     (Intercept) 146.8    12.12
##   Residual                1042.7   32.29
## Number of obs: 540, groups:  ptid, 180
##
## Fixed effects:
##              Estimate Std. Error t value
## (Intercept)    203.0237     5.3793  37.742
## drugGel B       20.0856     3.7827   5.310
## drugGel C       31.8145     3.6226   8.782
## period           0.5979     1.7019   0.351
## Adhere_sum_centered -2.7580     0.4058 -6.797
## AE_indYes       55.7538     5.6078   9.942
## age            -2.3541     0.2955 -7.967
## genderfemale    24.7575     3.3682   7.350
## raceblack        0.2649     4.1977   0.063
## raceothers     -2.6481     4.1618 -0.636
##
## Correlation of Fixed Effects:
##              (Intr) drgGlB drgGlC period Adhr__ AE_ndY age      gndrfm rcbldk
## drugGel B    -0.352
## drugGel C    -0.353  0.571
## period       -0.632  0.000  0.000
## Adhr_sm_cnt -0.159  0.436  0.342  0.000
## AE_indYes    -0.082 -0.026  0.010 -0.009 -0.022
## age          0.097 -0.272 -0.219  0.002 -0.632 -0.177
## genderfemal -0.303 -0.042 -0.034  0.000 -0.097 -0.016  0.036
## raceblack    -0.459 -0.003 -0.001  0.000 -0.005  0.032  0.075  0.098
## raceothers   -0.449  0.017  0.013  0.000  0.038  0.002 -0.002  0.048  0.553
```

```
tbl.PK.bviral <-
  model.PK.bviral %>%
  tbl_regression(
    estimate_fun = function(x) style_number(x, digits = 3),
    exponentiate = F,
    label = list(
      Adhere_sum_centered ~ "Days of adherece (within a period, centered)",
      drug ~ "Treatment",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race",
      AE_ind ~ "Occurence of adverse effects"
    )
  )

gt.PK.bviral <- tbl.PK.bviral %>% as_gt()
gt::gtsave(gt.PK.bviral, file = "./image/tbl_PK_bviral.png")

tbl.PK.sviral <-
  model.PK.sviral %>%
  tbl_regression(
    estimate_fun = function(x) style_number(x, digits = 3),
    exponentiate = F,
    label = list(
      Adhere_sum_centered ~ "Days of adherece (within a period, centered)",
      drug ~ "Treatment",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race",
      AE_ind ~ "Occurence of adverse effects"
    )
  )

gt.PK.sviral <- tbl.PK.sviral %>% as_gt()
gt::gtsave(gt.PK.sviral, file = "./image/tbl_PK_sviral.png")
#model.PK %>% tbl_regression()
```

Demographic difference

Redundant model? Already did the analysis when doing adherence analysis.

```
# gender change to factors
model.demo <- glm(cbind(Adhere_total, non_Adhere_total) ~ age + gender + race, data = Adhere.demo, family = binomial)

summary(model.demo)
```

```
##
## Call:
## glm(formula = cbind(Adhere_total, non_Adhere_total) ~ age + gender +
##      race, family = binomial, data = Adhere.demo)
```



```
##
## Coefficients:
##           Estimate Std. Error z value Pr(>|z|)
## (Intercept) -3.297199   0.133821 -24.639 < 2e-16 ***
## age         0.172885   0.004457  38.786 < 2e-16 ***
## genderfemale 0.347049   0.052047   6.668 2.59e-11 ***
## raceblack    0.067662   0.065187   1.038  0.2993
## raceothers   -0.124692   0.065759  -1.896  0.0579 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
## Null deviance: 3380.2 on 179 degrees of freedom
## Residual deviance: 1178.3 on 175 degrees of freedom
## AIC: 1752.6
##
## Number of Fisher Scoring iterations: 5
```

```
tbl_regression(model.demo, exponentiate = T)
```

```
## Table printed with 'knitr::kable()', not {gt}. Learn why at
## https://www.danielsjoberg.com/gtsummary/articles/rmarkdown.html
## To suppress this message, include 'message = FALSE' in code chunk header.
```

Characteristic	**OR**	**95% CI**	**p-value**
age	1.19	1.18, 1.20	<0.001
gender			
male	—	—	
female	1.41	1.28, 1.57	<0.001
race			
white	—	—	
black	1.07	0.94, 1.22	0.3
others	0.88	0.78, 1.00	0.058

```
tbl.demo <-
  model.demo %>%
  tbl_regression(
    estimate_fun = function(x) style_number(x, digits = 3),
    exponentiate = T,
    label = list(
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race"
    )
  )

gt.demo <- tbl.demo %>% as_gt()
gt::gtsave(gt.demo, file = "./image/tbl_demo.png")
```

```
endpoints.Adhere.regimen <-
  endpoints.Adhere %>%
  mutate(product = factor(ifelse(drug == "Pill A", "Pill", "Gel"), levels = c("Pill", "Gel")),
```

```

    freq = factor(case_when(
      drug == "Pill A" ~ "once",
      drug == "Gel B" ~ "three times",
      drug == "Gel C" ~ "once"
    ), levels = c("once", "three times"))

model.Adhere.product.1 <- glmtoolbox::glmgee(cbind(Adhere, nonAdhere) ~ period + week + age*product + g
model.Adhere.product.2 <- glmtoolbox::glmgee(cbind(Adhere, nonAdhere) ~ period + week + age*product + g
model.Adhere.product.3 <- glmtoolbox::glmgee(cbind(Adhere, nonAdhere) ~ period + week + age*product + g

AIC(model.Adhere.product.1)

## [1] 6236.017

AIC(model.Adhere.product.2)

## [1] 6134.663

AIC(model.Adhere.product.3)

## [1] 6488.798

#summary(model.Adhere.product.1)
#summary(model.Adhere.product.2)
#summary(model.Adhere.product.3)

model.Adhere.freq.1 <- glmtoolbox::glmgee(cbind(Adhere, nonAdhere) ~ period + week + age*freq + gender*
model.Adhere.freq.2 <- glmtoolbox::glmgee(cbind(Adhere, nonAdhere) ~ period + week + age*freq + gender*
model.Adhere.freq.3 <- glmtoolbox::glmgee(cbind(Adhere, nonAdhere) ~ period + week + age*freq + gender*

AIC(model.Adhere.freq.1)

## [1] 5782.133

AIC(model.Adhere.freq.2)

## [1] 5885.311

AIC(model.Adhere.freq.3)

## [1] 5878.866

#summary(model.Adhere.freq.1)
#summary(model.Adhere.product.2)
#summary(model.Adhere.product.3)

```

Demographic difference

Table one

```
baseline.demo <-
  left_join(Adhere.demo, baseline.dat %>% select(ptid, bviral0, sviral0)) %>%
  left_join(
    ,
    endpoints.period %>% select(ptid, sequence) %>% distinct()
  )
```

```
## Joining with 'by = join_by(ptid)'
## Joining with 'by = join_by(ptid)'
```

```
library(table1)
```

```
##
## Attaching package: 'table1'
##
## The following objects are masked from 'package:base':
##
##      units, units<-
```

```
baseline.demo$gender <- factor(baseline.demo$gender, levels = c("male", "female"), labels = c("Male", "Female"))
baseline.demo$race <- factor(baseline.demo$race, levels = c("white", "black", "others"), labels = c("White", "Black", "Others"))
```

```
label(baseline.demo$gender) = "Gender"
label(baseline.demo$race) = "Race"
label(baseline.demo$age) = "Age"
label(baseline.demo$bviral0) = "Baseline blood viral load"
label(baseline.demo$sviral0) = "Baseline skin viral load"
label(baseline.demo$sequence) = "Treatment sequence"
library(gt)
demo.tab <-
  table1(~ age + gender + race + bviral0 + sviral0 | sequence,
    data=baseline.demo, caption="" ) %>% as.data.frame() %>% gt()
demo.tab
```

	ABC	ACB	BAC	BCA	CAB	CB
	(N=30)	(N=30)	(N=30)	(N=30)	(N=30)	(N=30)
Age						
Mean (SD)	33.4 (8.29)	31.0 (7.14)	30.9 (7.23)	32.9 (8.44)	32.3 (6.82)	31.0 (7.14)
Median [Min, Max]	34.0 [19.0, 44.0]	29.0 [18.0, 42.0]	31.5 [20.0, 44.0]	32.0 [19.0, 45.0]	33.0 [21.0, 44.0]	31.0 [19.0, 44.0]
Gender						
Male	17 (56.7%)	19 (63.3%)	14 (46.7%)	16 (53.3%)	18 (60.0%)	15 (50.0%)
Female	13 (43.3%)	11 (36.7%)	16 (53.3%)	14 (46.7%)	12 (40.0%)	15 (50.0%)
Race						
White	8 (26.7%)	9 (30.0%)	7 (23.3%)	7 (23.3%)	12 (40.0%)	9 (30.0%)
Black	12 (40.0%)	13 (43.3%)	12 (40.0%)	10 (33.3%)	8 (26.7%)	9 (30.0%)

Others	10 (33.3%)	8 (26.7%)	11 (36.7%)	13 (43.3%)	10 (33.3%)	12
Baseline blood viral load						
Mean (SD)	120 (18.3)	123 (22.5)	119 (21.0)	123 (17.0)	128 (14.3)	127
Median [Min, Max]	122 [78.0, 152]	121 [73.0, 165]	114 [81.0, 181]	124 [79.0, 162]	125 [105, 163]	124
Baseline skin viral load						
Mean (SD)	207 (29.0)	203 (24.3)	212 (30.1)	205 (23.3)	207 (23.6)	209
Median [Min, Max]	202 [161, 282]	203 [161, 282]	205 [154, 275]	199 [167, 277]	207 [160, 245]	204

```
gtsave(demo.tab, filename = "table1.png")
```