Longitudinal Data Modeling

Dr. Marietta Kirchner Dr. Alexandra Lauer

September 24, 2024

Table of contents

Preface

1 Introduction

1.1 Workshop Structure

This class focuses on the longitudinal modeling of data from Patient Reported Outcomes (PROs). It is meant to be hands-on class with applications in R.

Content and structure follow the book by (Mallinckrodt and Lipkovich 2016). We would like to extend our warmest gratitude towards Dr. Mallinckrodt for providing the example data for the workshop.

The following topics will be covered:

- Welcome and Introduction (WS session 1)
- Exploration and visualization of longitudinal data (WS session 1/2)
- Inferences from longitudinal data (WS session 3 + 4)
- Assessment of missingness patterns (WS session 5)
- Sensitivity analyses to assess the impact of missingness (WS session 6)
- Annex: Inferences from longitudinal binary data (WS session 7)

1.2 Longitudinal Data

This workshop focuses on the analysis of data observed in randomized clinical trials (RCTs). Here, patients have assessments taken at the start of their treatment and then subsequently throughout the course of the trial based on a pre-specified schedule of assessments. The measurement at the start of the treatment is usually referred to as the baseline.

Researchers can be interested in

1. the occurrence of a certain event during the course of the trial, e.g. death or a cardiac event, or the time to the occurrence of such an event, or
2. the longitudinal profile from multiple repeated measurements taken, with a focus on either estimates at a landmark visit or across several time points.

The outcomes under point 1. can be handled via a comparison of the percentages of patients with events between treatment arms, or a time-to-event analysis. Both are out of scope of this workshop.

1.3 Basics about RStudio (pre-read)

If you are not used to working with R and RStudio so far, we recommend for you to familiarize yourself with the following useful content:

- RStudio User Guide
- RStudio Cheatsheet
- The following two cheatsheets for dplyr (data wrangling) and ggplot2 (plotting and visualizations)
- This video about Quarto

2 Longitudinal Data Exploration and Visualization

2.1 Introduction

- Data on individuals followed over time with information collected at several time points.
- Clusters are the individuals who are followed over time.
- Repeated observations may or may not be taken at regular times (balanced, fixed occasions, do not differ between subjects).
- Our interest is in the change from baseline.

Datasets used in this course:

- Example data is taken from (Mallinckrodt and Lipkovich 2016). The authors generated data sets based on two nearly identically designed antidepressant clinical trials by randomly selecting subjects from the original data.
- Contain data on the continuous variable HAMD17 (Hamilton 17-item rating scale for depression).
- Two treatement arms are included: placebo (arm 1) vs. drug (arm 2).
- Assessments were taken at baseline and weeks 1, 2, 4, 6, and 8.

There are 3 data sets created from the original data:

- Data *all2* = Subsample of the large dataset with n=50, visits: weeks 2, 4, 8.
- Data *high2* = Large dataset with n=100, high dropout = 70% (drug), 60% (placebo).
- Data *low2* = Large dataset with n=100, low dropout = 18%.

We are mainly working with the *all2* data set in the following. There is one application on the *high2* data set. We are not considering the *low2* data set.

2.2 Data set all2

- Small data set with n=50 subjects.
- 1st version: complete data where all subjects adhered to the originally assigend study medication, variable *change*

- 2nd version = missing data: identical to the first except some data were missing (drop-out), variable *chgdrop*

Looking at the variables in the data set

```
head(all2)
```

```
# A tibble: 6 x 14
  subject  time chgdrop trt   basval change pgiimp gender chgrescue dropout_grp
  <fct>   <dbl>   <dbl> <chr>  <dbl>  <dbl>  <dbl> <chr>      <dbl> <chr>
1 1           1     -11 2         24    -11      3 F            -11 Week 2 Drop~
2 1           2      NA 2         24    -16      2 F            -26 Week 2 Drop~
3 1           3      NA 2         24    -24      2 F            -34 Week 2 Drop~
4 2           1      -6 1         20     -6      4 F             -6 Week 2 Drop~
5 2           2      NA 1         20     -8      4 F            -18 Week 2 Drop~
6 2           3      NA 1         20     -5      5 F            -15 Week 2 Drop~
# i 4 more variables: aval <dbl>, avisit <fct>, week <dbl>, group <fct>
```

2.2.1 Task 1 - Exploration of data set all2 - 15 minutes working time

Only consider the complete data, variable *change*

- Are the data balanced and equally spaced?
- Number of observations by week? - Summary statistics for HAMD17 (change from baseline) by week.
- Plot trajectories for each individual, different colors for each treatment group (or panels).
- Add mean to your plot or generate new plot with mean change from baseline by treatment group.
- Plot mean change from baseline for each treatment group stratified by sex. Comment on the plot.

2.2.2 Task 1 - Discussion, possible solution

Table: Summary statistics mean (SD) for HAMD17 by treatment and week in the all2 data set

```
all2 %>%
  select(change, group, avisit) %>%
  tbl_strata(strata=group,
             ~.x %>%
               tbl_summary(by = avisit,
```

```
                          statistic = list(
      all_continuous() ~ "{mean} ({sd})"),
      digits = all_continuous() ~ 2 ) %>%
      modify_header(label = "**Variable**")
)
```

Variable	**Week 2**, N = 25	**Week 4**, N = 25	**Week 8**, N = 25	**Week 2**, N = 25	**Week 4**, N = 25	**Week 8**, N = 25
change	-4.20 (3.66)	-6.80 (4.25)	-9.88 (4.85)	-5.24 (5.49)	-8.60 (5.39)	-13.24 (5.54)

Figure: individual trajectories stratified by treatment group

```
ggplot(data = all2, aes(x = week, y = change, group=subject)) +
  geom_point() + geom_line() + facet_grid(.~group) + ylab("Change from baseline HAMD17") +
  scale_x_continuous(name="Visit [week]", breaks=c(2,4,8))
```

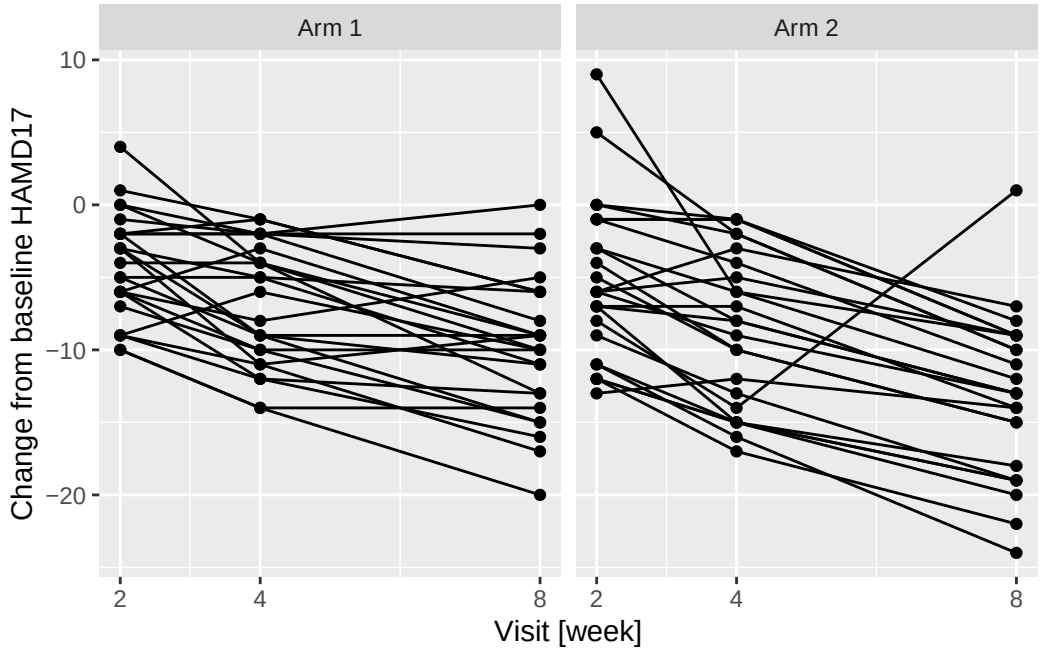


Figure 2.1: Individual trajectories of HAMD17 by treatment group

Figure: Mean change from baseline for each treatment group

```
ggplot(data = all2, aes(x = week, y = change)) +
  geom_point(aes(colour=factor(group))) + ylab("Change from baseline HAMD17") +
  scale_x_continuous(name="Visit [week]", breaks=c(2,4,8)) +
  stat_summary(aes(group = group, colour=factor(group)), geom = "line", fun.y = mean,
               size = 1) +
  stat_summary(aes(group = group, colour=factor(group)), geom = "point", fun.y = mean,
               shape=17,size = 2)
```

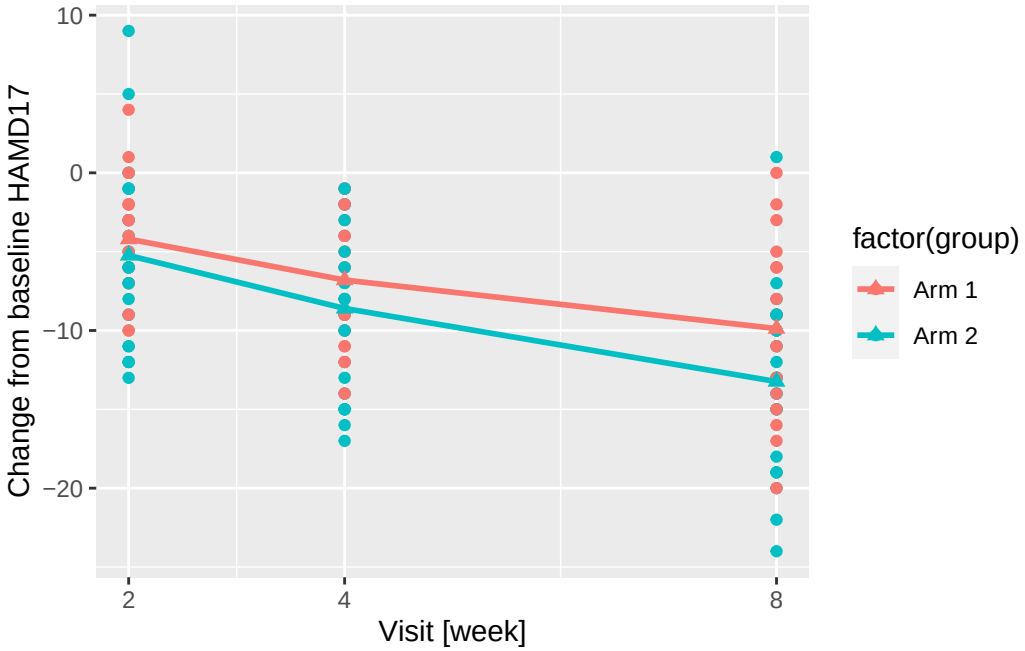


Figure 2.2: Mean HAMD17 change from baseline by treatment group

Frequency for sex per treatment group

```
all2 %>% filter(time==1) %>%
  tbl_summary(
    include = c(gender),
    by = group
  )
```

Characteristic	**Arm 1**, N = 25	**Arm 2**, N = 25
PATIENT SEX		
F	10 (40%)	19 (76%)

Characteristic	Arm 1, N = 25	Arm 2, N = 25
M	15 (60%)	6 (24%)

Figure: Mean change from baseline stratified by sex

```
ggplot(data = all2, aes(x = week, y = change)) +  facet_grid(.~gender) +
  geom_point(aes(colour=factor(group))) + ylab("Change from baseline HAMD17") +
  scale_x_continuous(name="Visit [week]", breaks=c(2,4,8)) +
  stat_summary(aes(group = group, colour=factor(group)), geom = "line", fun.y = mean,
               size = 1) +
  stat_summary(aes(group = group, colour=factor(group)), geom = "point", fun.y = mean,
               shape=17,size = 2)
```

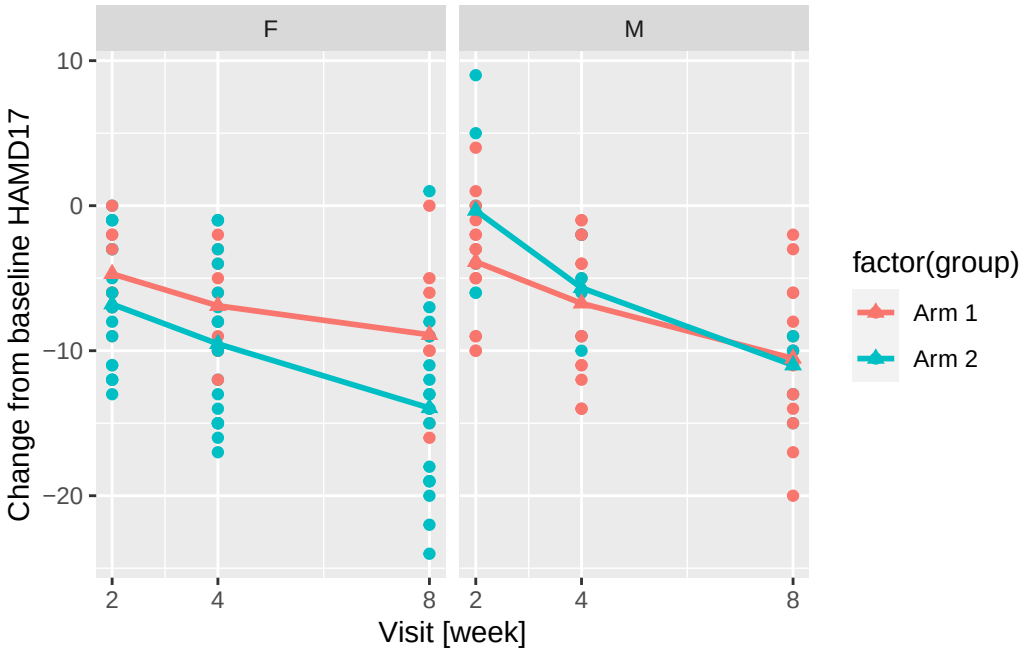


Figure 2.3: Mean HAMD17 change from baseline by treatment group stratified by sex

2.2.3 Data set all2 with drop-out

- 2nd version = missing data: identical to the first except some data were missing (drop-out), variable *chgdrop*
- This version is later relevant when considering missing data. Thus, have a short look at the data.

Table: Summary statistics for HAMD17 by treatment and week in the all2 data set with drop-outs

```
all2 %>%
  select(chgdrop, group, avisit) %>%
  tbl_strata(strata=group,
             ~.x %>%
               tbl_summary(by = avisit,
                           statistic = list(
      all_continuous() ~ "{mean} ({sd})"),
      digits = all_continuous() ~ 2 ) %>%
      modify_header(label = "**Variable**")
)
```

Variable	**Week 2**, N = 25	**Week 4**, N = 25	**Week 8**, N = 25	**Week 2**, N = 25	**Week 4**, N = 25	**Week 8**, N = 25
chgdrop	-4.20 (3.66)	-6.80 (4.63)	-10.17 (4.88)	-5.24 (5.49)	-8.14 (5.27)	-13.11 (5.44)
Unknown	0	5	7	0	3	6

Figure: Mean change from baseline for each treatment group in the all2 data set with drop-outs

```
ggplot(data = all2, aes(x = week, y = chgdrop)) +
  geom_point(aes(colour=factor(group))) + ylab("Change from baseline HAMD17") +
  scale_x_continuous(name="Visit [week]", breaks=c(2,4,8)) +
  stat_summary(aes(group = group, colour=factor(group)), geom = "line", fun.y = mean,
               size = 1) +
  stat_summary(aes(group = group, colour=factor(group)), geom = "point", fun.y = mean,
               shape=17,size = 2)
```

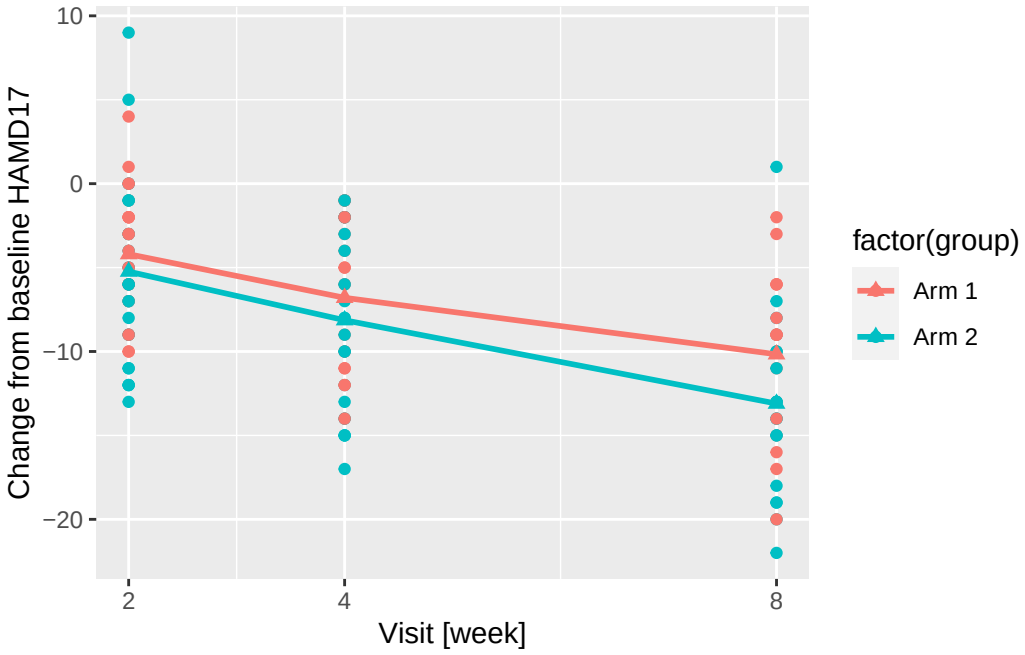


Figure 2.4: Mean HAMD17 change from baseline by treatment group

2.3 Data set high2

- Large data set with n=100 subjects.
- Note that we have no intermittent missing values but drop-outs.

Looking at the variables in the data set.

```
head(high2)
```

```
# A tibble: 6 x 16
# Groups:   patient [2]
  patient trt   poolinv basval  week change pgiimp   age gender  drop .groups
    <dbl> <chr> <chr>    <dbl> <dbl>  <dbl>  <dbl> <dbl> <chr>  <dbl> <chr>
1    1401 1     005         19     1     -7      3  44.5 F          2 drop
2    1401 1     005         19     2     -4      3  44.5 F          2 drop
3    1411 2     005         17     1      0      3  35.7 F          8 drop
4    1411 2     005         17     2     -2      3  35.7 F          8 drop
5    1411 2     005         17     4      2      3  35.7 F          8 drop
6    1411 2     005         17     6     -3      2  35.7 F          8 drop
```

```
# i 5 more variables: aval <dbl>, group <fct>, avisit <fct>, dropout_grp <fct>,
#   subject <fct>
```

2.3.1 Task 2 - Exploration of data set high2 - 15 minutes working time

- Explore the drop-outs e.g. number of observations by week.
- Summary statistics for HAMD17 change.
- Generate and interpret the group-wise boxplots of the change from baseline.
- Mean change from baseline for different drop-out groups (by treatment). Comment on the plot.

2.3.2 Task 2 Discussion, possible solution

Table: Summary statistics for HAMD17 by treatment and week in the high2 data set

```
high2 %>% ungroup() %>%
  select(change, group, avisit) %>%
  tbl_strata(strata=group,
             ~.x %>%
               tbl_summary(by = avisit,
                           statistic = list(
                             all_continuous() ~ "{mean} ({sd})"),
                           digits = all_continuous() ~ 2 ) %>%
              modify_header(label = "**Variable**")
  )
```

Variable	**Week 1**, N = 100	**Week 2**, N = 92	**Week 4**, N = 85	**Week 6**, N = 73	**Week 8**, N = 60	**Week 1**, N = 100	**Week 2**, N = 90	**Week 4**, N = 85	**Week 6**, N = 75	**Week 8**, N = 70
change	-1.49 (3.91)	-3.16 (5.69)	-4.51 (6.23)	-5.51 (6.16)	-6.58 (5.99)	-1.84 (5.58)	-4.30 (6.82)	-6.47 (6.84)	-8.29 (6.96)	-8.99 (7.04)

Figure: Distribution of HAMD17 change from baseline

```
ggplot(data = high2, aes(x = avisit, y = change, fill=group)) +
  geom_boxplot() + ylab("Change from baseline HAMD17") + xlab("Visit")
```

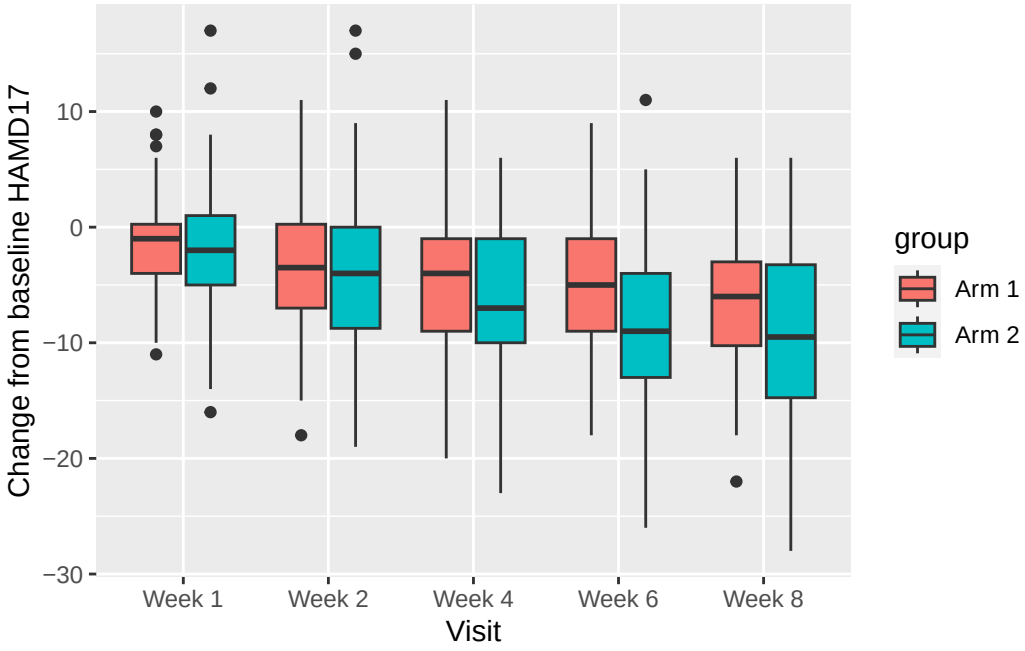


Figure 2.5: Distribution of HAMD17 change from baseline by treatment group at each visit

Figure: Mean HAMD17 changes by drop-out group

```
ggplot(data = high2, aes(x = week, y = change, group=patient)) +
  geom_point(col="lightgray") + geom_line(col="lightgray") + facet_grid(.~group) +
  ylab("Change from baseline HAMD17") + scale_x_continuous(name="Visit [week]", breaks=c(1
  stat_summary(aes(group = dropout_grp, colour=factor(dropout_grp)), geom = "line", fun.y
               size = 1) +
  stat_summary(aes(group = dropout_grp, colour=factor(dropout_grp)), geom = "point", fun.y
               shape=17,size = 2)
```

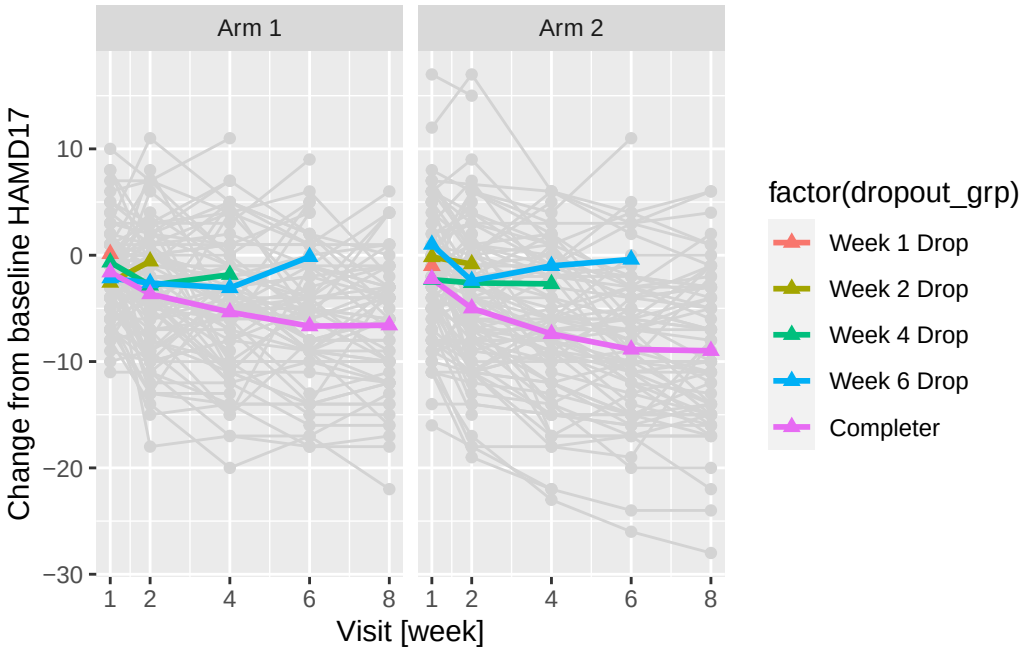


Figure 2.6: Visit-wise mean HAMD17 changes from baseline by treatment group and drop-out

3 Correlation structure, covariance matrices

- Longitudinal data allows to exploit the correlation between outcomes within subjects regardless of whether or not focus is on a single landmark time point.
- Model within-subject error correlation
- Different residual covariance structures can be implemented

3.1 Overview - different covariance matrices

- Variance components (VC) independence structure
- Compound symmetry (CS) also known as exchangeable
- Toeplitz (TOEP)
- First order auto regressive (AR(1))
- Unstructured (UN)

Selected covariance structures for data with three assessment times (t=3) are shown below. Note that with three assessment times, the number of parameters estimated for the various structures did not differ as much as would be the case with more assessment times. Thus, results from different covariance structures are more similar than would be the case with more assessment times.

3.1.1 Independence structure (VC)

Constant variance. It is assumed to be no correlation between assessments (residuals are independent across time).

$$R = \begin{bmatrix} \sigma^2 & 0 & 0 \\ 0 & \sigma^2 & 0 \\ 0 & 0 & \sigma^2 \end{bmatrix}$$

3.1.2 Compound symmetry (CS)

Constant variance and constant covariance across all assessments. Also known as exchangeable. It requires two parameter estimates. Most simplest repeated measures (i.e., correlated errors) structure.

$$R = \begin{bmatrix} \sigma^2 + \sigma_1 & \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma^2 + \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma_1 & \sigma^2 + \sigma_1 \end{bmatrix}$$

3.1.3 Unstructured (UN)

This is the most general (saturated) model. It has t + [t(t-1)/2] parameters to be estimated. Here it is 3 + 3 = 6 parameters.

$$R = \begin{bmatrix} \sigma_1^2 & \sigma_{21} & \sigma_{31} \\ \sigma_{21} & \sigma_2^2 & \sigma_{32} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 \end{bmatrix}$$

3.1.4 Toeplitz structure (TOEP)

Homogenous variances and heterogenous correlations. Same correlation value is used whenever the degree of adjacency is the same e.g. correlation between times 1 and 2 = correlation between times 2 and 3. Repeated measurements are assumed to be equally spaced. TOEP requries t parameter estimates so here we have t=3 parameter.

$$R = \begin{bmatrix} \sigma^2 & \sigma_1^2 & \sigma_2^2 \\ \sigma_1^2 & \sigma^2 & \sigma_1^2 \\ \sigma_2^2 & \sigma_1^2 & \sigma^2 \end{bmatrix}$$

3.1.5 Autoregressive structure (AR(1))

Correlation decreases as time between observations increases. Assumtpion of equal spacing between each repeated measurement must be reasonably applicable. This structure requires the estimation of two parameters.

$$R = \begin{bmatrix} \sigma^2 & \sigma^2\rho & \sigma^2\rho^2 \\ \sigma^2\rho & \sigma^2 & \sigma^2\rho \\ \sigma^2\rho^2 & \sigma^2\rho & \sigma^2 \end{bmatrix}$$

3.1.6 Spatial Power (SP)

Spatial covariance structures does not require equal spacing between measurements. Instead, as long as the distance between visits can be quantified in terms of time and/or other coordinates, the spatial covariance structure can be applied. Covariances are mathematical functions of Euclidean distances between observed measurements. Again, two parameters need to be estimated.

For spatial exponential, the covariance structure is defined as follows:

$$R = \begin{bmatrix} \sigma^2 & \sigma^2\rho_{12} & \sigma^2\rho_{13} \\ \sigma^2\rho_{21} & \sigma^2 & \sigma^2\rho_{23} \\ \sigma^2\rho_{31} & \sigma^2\rho_{32} & \sigma^2 \end{bmatrix}$$

with

$$\rho_{ij} = \rho^{d_{ij}}$$

where

$$d_{ij}$$

is the distance between time point i and time point j e.g. distance in weeks.

3.2 Selecting the covariance structure

There are a variety of considerations when selecting the covariance structure:

- number of parameters
- interpretation of the structure
- model fit

UN is the most flexible (complex) structure and can fail to run especially if one has many repeated measures. Choose a reasonable covaraiance structure which is the best compromise between model fit and complexity. E.g. use AIC as it penalises more complex models.

3.3 Task 3 - Exploration of correlation in the data

- Compute the empirical correlations between measurement timepoints in the all2 data set (e.g. correlation between baseline and post-baseline changes, variable *change*).
- Looking at these correlations + using your knowledge of the experiment (e.g., spacing of measurements), comment on the suitability of the correlation structures VC, CS, UN, AR(1).

3.4 Task 3 - Discussion and possible solution

Table: Correlation and covariance matrix

```
all2.w <- all2 %>%
  pivot_wider(id_cols=subject,names_from = time, values_from = c(basval,change)) %>%
  select(-c(basval_2,basval_3))

cor(all2.w[-1])
```

```
           basval_1   change_1   change_2    change_3
basval_1  1.00000000 -0.2636447 -0.3165711 -0.02915138
change_1 -0.26364471  1.0000000  0.7557078  0.51502724
change_2 -0.31657106  0.7557078  1.0000000  0.71298768
change_3 -0.02915138  0.5150272  0.7129877  1.00000000
```

```
cov(all2.w[-1])
```

```
          basval_1  change_1  change_2   change_3
basval_1 16.3330612 -4.955918 -6.253061 -0.6391837
change_1 -4.9559184 21.634286 17.179592 12.9967347
change_2 -6.2530612 17.179592 23.887755 18.9061224
change_3 -0.6391837 12.996735 18.906122 29.4351020
```

3.5 Taking a step back: Consequences of Ignoring Correlation among Longitudinal Data

This technical detour is motivated by (Fitzmaurice 2011). Let us assume we are only interested in the first two responses in a clinical study, say Visit 1 (Baseline) and Visit 2. Our interest lies in an assessment of mean changes over time (for the sake of simplicity in a single treatment group only), i.e. we wish to estimate

$$\hat{\delta} := \hat{\mu}_2 - \hat{\mu}_1 = \frac{1}{N}\sum_{i=1}^{N}(Y_{i2} - Y_{i1}),$$

where Y_{i1} and Y_{i2} are observations from subject i at Visit 1 and Visit 2, respectively. To obtain the standard error (SE) and get a notion of variability, we compute the variance of $\hat{\delta}$ and see that

$$\text{Var}(\hat{\delta}) = \text{Var}\left(\frac{1}{N}\sum_{i=1}^{N}(Y_{i2} - Y_{i1})\right) = \frac{1}{N}(\sigma_1^2 + \sigma_2^2 - 2\sigma_{12})\,.$$

The inclusion of the term $-2\sigma_{12}$ accounts for the correlation between responses at Visit 1 and Visit 2. As data from adjacent visits is usually positively correlated, the omission of the correlation term leads to an overestimation of the variance and thus the SE associated with the treatment effect.

4 Inference from Longitudinal Data

This section will focus on the application of Mixed Model with Repeated Measures (MMRMs). Our main focus will be the modeling of the means of the data. MMRMs are generalizations of standard linear models in the way that data is allowed to be correlated between subsequent measurements from the same subject and exhibit non-constant variability. A nice summary can be found in the user manual for the MIXED Procedure SAS, or the vignette for the `mmrm` package (Sabanes Bove et al. 2024).

The primary assumptions for MMRMs are:

- The data are normally distributed
- The means (expected values) of the data are linear in terms of a certain set of parameters.
- The variances and covariances of the data are in terms of a different set of parameters, and they exhibit a structure matching one of those outlined in the former chapter.

The mixed linear model can be described via the following formula

$$y_i = X_i\beta + Z_i\gamma_i + \varepsilon_i\,,\; i = 1, \ldots, N$$

where y is the vector of responses (observed data, dependent variable), β is an unknown vector of fixed effects with known design matrix X, γ is an unknown vector of random effects with known design matrix Z, and ε is an unknown random error vector. Furthermore N denotes the total number of subjects in our analysis. For the sake of readability, we will omit the subject index and simplify the above formula to

$$y = X\beta + Z\gamma + \varepsilon\,.$$

We will further assume that γ and ε are uncorrelated Gaussian random variables with expectation 0 and variances G and R, respectively. Then the variance-covariance matrix of y is given by

$$\mathrm{Var}(y) := V = ZGZ' + R\,.$$

In this case ZGZ' comprises the random effects component, and R is the within-subject component.

In this workshop we will focus on the case where only the within-subject component is accounted for, via modeling of the R matrix. The random effects component $Z\gamma$ will be omitted. In this case we will have $\text{Var}(y) = V = R$, resulting in a model given by

$$y = X\beta + \varepsilon\,.$$

4.1 Categorical Time

In the following sections we will use the package `mmrm` (Sabanes Bove et al. 2024). You can start and familiarise yourself with the main function `mmrm()` using the command

```
library(mmrm)
?mmrm
```

Two inputs are strictly required to get `mmrm()` to work:

- A model formula
- The dataset, containing the response, as well as all fixed effects and variables in the covariance matrix.

Exercise: Fit a model `fit_cat_time` using the dataset `all2`, with change as dependent variable, baseline value, visit, baseline by visit interaction and treatment by visit interaction as fixed effects and an unstructured covariance matrix for visits within each subject.

- How do different choices for covariance matrices change the results? What is the difference on the estimation procedure?
- You can obtain a summary of the fit results via `summary(fit_cat_time)`. How do you interpret the fit summary?
- Look at the structure of the fit summary and try to extract the estimate of the R matrix.
- How do other choices of covariance structures influence the estimation?

4.1.1 Unstructured (US)

Unstructured corresponds to a saturated variance-covariance matrix and involves the estimation of $m\,(m+1)/2$ variance components, where m is the number of follow-up visits. In our case, we can see that a total of 6 variance parameters were estimated.

```r
fit_cat_time <- mmrm::mmrm(
  formula = change ~ basval*avisit + trt*avisit + us(avisit | subject),
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

summary(fit_cat_time)
```

```
mmrm fit

Formula:     change ~ basval * avisit + trt * avisit + us(avisit | subject)
Data:        all2 (used 150 observations from 50 subjects with maximum 3
timepoints)
Covariance:  unstructured (6 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
   822.4    833.9   -405.2    810.4

Coefficients:
                     Estimate Std. Error        df t value Pr(>|t|)
(Intercept)           1.98452    3.27479  47.00000   0.606  0.54743
basval               -0.31235    0.15905  47.00000  -1.964  0.05548 .
avisitWeek 4         -0.90862    2.39866  47.00000  -0.379  0.70654
avisitWeek 8        -10.58630    3.45922  47.00000  -3.060  0.00365 **
trt2                 -1.18993    1.27265  47.00000  -0.935  0.35457
basval:avisitWeek 4  -0.08542    0.11650  47.00000  -0.733  0.46704
basval:avisitWeek 8   0.24779    0.16801  47.00000   1.475  0.14691
avisitWeek 4:trt2    -0.80100    0.93217  47.00000  -0.859  0.39454
avisitWeek 8:trt2    -2.20106    1.34432  47.00000  -1.637  0.10825
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 2  Week 4  Week 8
Week 2 20.6112 15.3034 12.2766
Week 4 15.3034 21.3565 17.6648
Week 8 12.2766 17.6648 27.6127
```

We can assess the structure of the fit summary via

```
str(summary(fit_cat_time))
```

```
List of 15
 $ cov_type        : chr "us"
 $ reml            : logi TRUE
 $ n_groups        : int 1
 $ n_theta         : int 6
 $ n_subjects      : int 50
 $ n_timepoints    : int 3
 $ n_obs           : int 150
 $ beta_vcov       : num [1:9, 1:9] 10.724 -0.501 -2.675 -4.267 -1.047 ...
  ..- attr(*, "dimnames")=List of 2
  .. ..$ : chr [1:9] "(Intercept)" "basval" "avisitWeek 4" "avisitWeek 8" ...
  .. ..$ : chr [1:9] "(Intercept)" "basval" "avisitWeek 4" "avisitWeek 8" ...
 $ varcor          : num [1:3, 1:3] 20.6 15.3 12.3 15.3 21.4 ...
  ..- attr(*, "dimnames")=List of 2
  .. ..$ : chr [1:3] "Week 2" "Week 4" "Week 8"
  .. ..$ : chr [1:3] "Week 2" "Week 4" "Week 8"
 $ method          : chr "Kenward-Roger"
 $ vcov            : chr "Kenward-Roger"
 $ coefficients    : num [1:9, 1:5] 1.985 -0.312 -0.909 -10.586 -1.19 ...
  ..- attr(*, "dimnames")=List of 2
  .. ..$ : chr [1:9] "(Intercept)" "basval" "avisitWeek 4" "avisitWeek 8" ...
  .. ..$ : chr [1:5] "Estimate" "Std. Error" "df" "t value" ...
 $ n_singular_coefs: int 0
 $ aic_list        :List of 4
  ..$ AIC     : num 822
  ..$ BIC     : num 834
  ..$ logLik  : num -405
  ..$ deviance: num 810
 $ call            : language mmrm::mmrm(formula = change ~ basval * avisit + trt * avisit +
 - attr(*, "class")= chr "summary.mmrm"
```

and then extract the covariance matrix

```
summary(fit_cat_time)$varcor
```

```
         Week 2   Week 4   Week 8
Week 2 20.61117 15.30339 12.27661
```

```
Week 4 15.30339 21.35648 17.66478
Week 8 12.27661 17.66478 27.61271
```

4.1.2 Compound Symmetry (CS)

We can choose different types of covariance structures by modification of the model formula.

The compound symmetry structure assumes equal variances (diagonal elements are all equal) and equal covariances (off-diagonal elements are all equal). From the model summary we can see that two variance-covariance parameters are estimated.

This model is the most simple choice of repeated measures variance-covariance modeling. In most cases, it is overly simplistic, but can be a good fallback option in case of model non-convergence (especially when prespecification of analysis methods is required).

```r
fit_cat_time_cs <- mmrm::mmrm(
  formula = change ~ basval*avisit + trt*avisit + cs(avisit | subject),
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

summary(fit_cat_time_cs)
```

```
mmrm fit

Formula:     change ~ basval * avisit + trt * avisit + cs(avisit | subject)
Data:        all2 (used 150 observations from 50 subjects with maximum 3
timepoints)
Covariance:  compound symmetry (2 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
   827.2    831.0   -411.6    823.2

Coefficients:
                    Estimate Std. Error        df t value Pr(>|t|)
(Intercept)          1.98452    3.48848  76.39000   0.569 0.571107
basval              -0.31235    0.16943  76.39000  -1.844 0.069126 .
avisitWeek 4        -0.90862    2.91606  94.00000  -0.312 0.756042
```

```
avisitWeek 8        -10.58630    2.91606  94.00000  -3.630 0.000461 ***
trt2                 -1.18993    1.35569  76.39000  -0.878 0.382845
basval:avisitWeek 4  -0.08542    0.14163  94.00000  -0.603 0.547856
basval:avisitWeek 8   0.24779    0.14163  94.00000   1.750 0.083448 .
avisitWeek 4:trt2    -0.80100    1.13324  94.00000  -0.707 0.481424
avisitWeek 8:trt2    -2.20106    1.13324  94.00000  -1.942 0.055098 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 2  Week 4  Week 8
Week 2 23.1948 15.0832 15.0832
Week 4 15.0832 23.1948 15.0832
Week 8 15.0832 15.0832 23.1948
```

4.1.3 Toeplitz (TOEP)

Use of the Toeplitz structure is not a very sensible choice here, as visits are not equally spaced, i.e. the difference between baseline and time1, and time1 and time2 is 2 weeks, respectively, while the difference between time2 and time3 is 4 weeks. Toeplitz thus ignores the differences in time spacing.

We can see that the covariance estimates for responses at Week 2 (time1) and Week 4 (time2) are the same as the ones for responses at Week 4 (time2) and Week 8 (time3), although their time difference doubles.

The same line of reasoning for the lack of sensibility of the Toeplitz structure can be applied to the autoregressive structure (AR(1)). The example is not shown here.

```r
fit_cat_time_toep <- mmrm::mmrm(
  formula = change ~ basval*avisit + trt*avisit + toep(avisit | subject),
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

summary(fit_cat_time_toep)
```

```
mmrm fit

Formula:     change ~ basval * avisit + trt * avisit + toep(avisit | subject)
Data:        all2 (used 150 observations from 50 subjects with maximum 3
timepoints)
```

```
Covariance:  Toeplitz (3 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
   818.6    824.3   -406.3    812.6

Coefficients:
                     Estimate Std. Error        df t value Pr(>|t|)
(Intercept)           1.98452    3.52061  74.67000   0.564  0.57466
basval               -0.31235    0.17099  74.67000  -1.827  0.07174 .
avisitWeek 4         -0.90862    2.56351  92.39000  -0.354  0.72381
avisitWeek 8        -10.58630    3.43000  56.08000  -3.086  0.00315 **
trt2                 -1.18993    1.36818  74.67000  -0.870  0.38724
basval:avisitWeek 4  -0.08542    0.12450  92.39000  -0.686  0.49436
basval:avisitWeek 8   0.24779    0.16659  56.08000   1.487  0.14249
avisitWeek 4:trt2    -0.80100    0.99623  92.39000  -0.804  0.42344
avisitWeek 8:trt2    -2.20106    1.33297  56.08000  -1.651  0.10428
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 2  Week 4  Week 8
Week 2 23.6312 17.3491 12.3576
Week 4 17.3491 23.6312 17.3491
Week 8 12.3576 17.3491 23.6312
```

4.1.4 Spatial Power (SP_EXP)

The choice of the spatial power variance-covariance structure makes sense here, as the visits are not equally spaced. In this case, two parameters are estimated. The first parameter is the variance (diagonal elements) and second one is the time difference between subsequent visits.

Note that in this example, we need to use the numeric `week` variable, as spatial power requires the information about the distance of subsequent visits in the estimation of the variance-covariance matrix.

We can see from the fit summary, that the covariance displayed is a 2 * 2 square matrix. As the distance will be used to derive the corresponding element in that matrix, unit distance is used here.

```r
fit_cat_time_sp <- mmrm::mmrm(
  formula = change ~ basval*avisit + trt*avisit + sp_exp(week | subject),
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

summary(fit_cat_time_sp)
```

```
mmrm fit

Formula:     change ~ basval * avisit + trt * avisit + sp_exp(week | subject)
Data:        all2 (used 150 observations from 50 subjects with maximum 3
timepoints)
Covariance:  spatial exponential (2 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
   818.5    822.4   -407.3    814.5

Coefficients:
                     Estimate Std. Error        df t value Pr(>|t|)
(Intercept)           1.98452    3.54179  76.71000   0.560  0.57690
basval               -0.31235    0.17202  76.71000  -1.816  0.07331 .
avisitWeek 4         -0.90862    2.24976  84.19000  -0.404  0.68733
avisitWeek 8        -10.58630    3.52591 117.26000  -3.002  0.00327 **
trt2                 -1.18993    1.37641  76.71000  -0.865  0.39000
basval:avisitWeek 4  -0.08542    0.10927  84.19000  -0.782  0.43653
basval:avisitWeek 8   0.24779    0.17125 117.26000   1.447  0.15057
avisitWeek 4:trt2    -0.80100    0.87430  84.19000  -0.916  0.36220
avisitWeek 8:trt2    -2.20106    1.37024 117.26000  -1.606  0.11089
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        0       1
0 23.9079 21.3749
1 21.3749 23.9079
```

4.1.5 Conclusion

While the unstructured variance-covariance matrix provides the highest degree of flexibility, we can see from the AIC and BIC estimates that spatial power in our example provides and even better fit in comparison to the model complexity. Note that this is also true for the Toeplitz structure, but we rejected this approach as the unequal spacing of visits renders this approach nonsensible.

4.2 Continuous Time

Time as continuous effect -> single df for time and trt-by-time interaction

Modeling: - Need avisit for structure of covariance matrix - Implicit assumption is for the covariance between values for two timepoints to be equal, regardless of the specific timing

```
fit_cont_time <- mmrm::mmrm(
  formula = change ~ basval*week + trt*week + us(avisit | subject),
  weights = all2$week,
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

summary (fit_cont_time)
```

```
mmrm fit

Formula:     change ~ basval * week + trt * week + us(avisit | subject)
Data:        all2 (used 150 observations from 50 subjects with maximum 3
timepoints)
Weights:     all2$week
Covariance:  unstructured (6 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
   838.0    849.5   -413.0    826.0

Coefficients:
            Estimate Std. Error       df t value Pr(>|t|)
```

```
(Intercept)  6.83666    3.82960 47.00000   1.785  0.08068 .
basval      -0.47981    0.18600 47.00000  -2.580  0.01308 *
week        -1.94296    0.57420 47.00000  -3.384  0.00145 **
trt2        -0.49024    1.48826 47.00000  -0.329  0.74331
basval:week  0.05275    0.02789 47.00000   1.892  0.06472 .
week:trt2   -0.36226    0.22315 47.00000  -1.623  0.11119
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 2   Week 4   Week 8
Week 2 41.3658  42.8600  49.0752
Week 4 42.8600  86.6690 100.0141
Week 8 49.0752 100.0141 220.9000
```

Can also apply non-linear transformations of time variable, in case the anticipated effect is not necessarily linear in time:

```r
all2$timesq <- all2$week^2

fit_cont_timesq <- mmrm::mmrm(
  formula = change ~ basval*timesq + trt*timesq + us(avisit | subject),
  weights = all2$week,
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

summary(fit_cont_timesq)
```

```
mmrm fit

Formula:     change ~ basval * timesq + trt * timesq + us(avisit | subject)
Data:        all2 (used 150 observations from 50 subjects with maximum 3
timepoints)
Weights:     all2$week
Covariance:  unstructured (6 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
```

```
   861.8    873.3   -424.9    849.8

Coefficients:
               Estimate Std. Error        df t value Pr(>|t|)
(Intercept)    3.298095   3.300323 47.000000   0.999  0.32275
basval        -0.396751   0.160290 47.000000  -2.475  0.01698 *
timesq        -0.191395   0.053074 47.000000  -3.606  0.00075 ***
trt2          -1.224631   1.282574 47.000000  -0.955  0.34455
basval:timesq  0.005800   0.002578 47.000000   2.250  0.02916 *
timesq:trt2   -0.032220   0.020626 47.000000  -1.562  0.12497
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 2   Week 4   Week 8
Week 2 42.2220  41.1223  47.8394
Week 4 41.1223  90.1270 102.6988
Week 8 47.8394 102.6988 222.5403
```

4.3 (Adjusted) LS Means from MMRMs

LS Means are means of the dependent variable adjusted for covariates in the statistical model. We can obtain LS Means estimates and contrasts allowing for a treatment comparison using the `emmeans` package.

Example: Calculate the observed (raw) means of changes along with number of patients by treatment group from the dataset `all2` overall and by visit. Then take the model `fit_cat_time` and derive the respective LS Means from the model. What do you observe?

```r
# Raw means

all2 %>%
  dplyr::group_by(group) %>%
  dplyr::summarise(
    N = dplyr::n(),
    Mean = mean(change),
    .groups = "drop"
  )
```

```
# A tibble: 2 x 3
  group     N  Mean
```

```
  <fct> <int> <dbl>
1 Arm 1    75 -6.96
2 Arm 2    75 -9.03
```

```r
all2 %>%
  dplyr::group_by(group, avisit) %>%
  dplyr::summarise(
    N = dplyr::n(),
    Mean = mean(change),
    .groups = "drop"
  )
```

```
# A tibble: 6 x 4
  group avisit     N   Mean
  <fct> <fct>  <int>  <dbl>
1 Arm 1 Week 2    25  -4.2
2 Arm 1 Week 4    25  -6.8
3 Arm 1 Week 8    25  -9.88
4 Arm 2 Week 2    25  -5.24
5 Arm 2 Week 4    25  -8.6
6 Arm 2 Week 8    25 -13.2
```

The respective LS Means from the model with time as a fixed factor yields the following estimates:

```r
library(emmeans)

emmeans::ref_grid(fit_cat_time)
```

```
'emmGrid' object with variables:
    basval = 19.56
    avisit = Week 2, Week 4, Week 8
    trt = 1, 2
```

```r
emmeans(fit_cat_time, ~trt)
```

```
NOTE: Results may be misleading due to involvement in interactions
```

```
 trt emmean    SE df lower.CL upper.CL
 1    -6.90 0.836 47    -8.58    -5.22
 2    -9.09 0.836 47   -10.77    -7.41

Results are averaged over the levels of: avisit
Confidence level used: 0.95
```

```
emmeans(fit_cat_time, ~trt*avisit)
```

```
 trt avisit emmean    SE df lower.CL upper.CL
 1   Week 2  -4.13 0.899 47    -5.93    -2.32
 2   Week 2  -5.31 0.899 47    -7.12    -3.51
 1   Week 4  -6.70 0.916 47    -8.55    -4.86
 2   Week 4  -8.70 0.916 47   -10.54    -6.85
 1   Week 8  -9.86 1.033 47   -11.94    -7.79
 2   Week 8 -13.26 1.033 47   -15.33   -11.18

Confidence level used: 0.95
```

4.3.1 Observed vs. balanced margins

In the example above we have used the standard option for the weights in the calculation of LS Means. We will delve deeper into the following two options and will try to understand the difference:

- `weights = "equal"`: Each stratum induced by covariate levels is assigned the same weight in the calculation of the LS Means. This is the default option.
- `weights = "proportional"`: Each stratum induced by covariate levels is assigned a weight according to their observed proportion in the calculation of the LS Mean. This option gives each stratum a weight corresponding to its size. Estimates using this option are reflective of the balance of covariates in the data.

Exercise: Based on the `fit_cat_time` model, compare the LS Means for the change in the response variable by treatment overall and treatment by visit interaction using the different options for `weight`. Compare the results for the two LS Means options to the observed means and to one another.

Discuss the following points:

- Why is there no difference between LS Means estimates for the overall treatment effect and the treatment by visit interaction? (Hint: Create a frequency table)

Now update the `fit_cat_time` model to `fit_cat_time2`, and include the covariate `gender`. Estimate the same LS Means for the change in the response variable by treatment (overall) and treatment by visit interaction.

- Why is there a difference now between results from the different LS Means options? (Hint: another frequency table can help)
- What effect could missing data have on the estimation, even in the case of `fit_cat_time`? I.e. what would happen if this data was not complete but subject to missingness, with the degree of missing data increasing over time and being disproportionate between treatment arms?

Solution:

We first calculate the LS Means, using the different `weights` options and find they are indeed identical.

```
# These will yield the same results:
emmeans(fit_cat_time, ~trt, weights = "equal")
```

```
NOTE: Results may be misleading due to involvement in interactions

 trt emmean    SE df lower.CL upper.CL
 1    -6.90 0.836 47    -8.58    -5.22
 2    -9.09 0.836 47   -10.77    -7.41

Results are averaged over the levels of: avisit
Confidence level used: 0.95
```

```
emmeans(fit_cat_time, ~trt, weights = "proportional")
```

```
NOTE: Results may be misleading due to involvement in interactions

 trt emmean    SE df lower.CL upper.CL
 1    -6.90 0.836 47    -8.58    -5.22
 2    -9.09 0.836 47   -10.77    -7.41

Results are averaged over the levels of: avisit
Confidence level used: 0.95
```

```
emmeans(fit_cat_time, ~trt*avisit, weights = "equal")
```

```
 trt avisit emmean    SE df lower.CL upper.CL
 1   Week 2  -4.13 0.899 47    -5.93    -2.32
 2   Week 2  -5.31 0.899 47    -7.12    -3.51
 1   Week 4  -6.70 0.916 47    -8.55    -4.86
 2   Week 4  -8.70 0.916 47   -10.54    -6.85
 1   Week 8  -9.86 1.033 47   -11.94    -7.79
 2   Week 8 -13.26 1.033 47   -15.33   -11.18

Confidence level used: 0.95
```

```
emmeans(fit_cat_time, ~trt*avisit, weights = "proportional")
```

```
 trt avisit emmean    SE df lower.CL upper.CL
 1   Week 2  -4.13 0.899 47    -5.93    -2.32
 2   Week 2  -5.31 0.899 47    -7.12    -3.51
 1   Week 4  -6.70 0.916 47    -8.55    -4.86
 2   Week 4  -8.70 0.916 47   -10.54    -6.85
 1   Week 8  -9.86 1.033 47   -11.94    -7.79
 2   Week 8 -13.26 1.033 47   -15.33   -11.18

Confidence level used: 0.95
```

Now we can update the model to include the covariate `gender`. We can specify this a new model using the `mmrm()` function again, or simply use `update()` to add the new covariate to the model. Either way is fine, and a look into the model formula from the fit summary shows the two approaches work interchangeably.

```
fit_cat_time2 <- update(fit_cat_time, . ~ . + gender)
summary(fit_cat_time2)
```

```
mmrm fit

Formula:
change ~ basval + avisit + trt + (us(avisit | subject)) + gender +
    basval:avisit + avisit:trt
Data:        all2 (used 150 observations from 50 subjects with maximum 3
timepoints)
Covariance:  unstructured (6 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
```

```
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
   817.0    828.5   -402.5    805.0

Coefficients:
                     Estimate Std. Error        df t value Pr(>|t|)
(Intercept)           0.47589    3.23944  46.14000   0.147  0.88385
basval               -0.30674    0.15200  45.44000  -2.018  0.04951 *
avisitWeek 4         -0.90862    2.39786  47.00000  -0.379  0.70645
avisitWeek 8        -10.58630    3.45626  47.00000  -3.063  0.00362 **
trt2                 -0.34868    1.30287  46.74000  -0.268  0.79016
genderM               2.32931    1.29556  45.99000   1.798  0.07876 .
basval:avisitWeek 4  -0.08542    0.11646  47.00000  -0.734  0.46689
basval:avisitWeek 8   0.24779    0.16786  47.00000   1.476  0.14657
avisitWeek 4:trt2    -0.80100    0.93186  47.00000  -0.860  0.39439
avisitWeek 8:trt2    -2.20106    1.34318  47.00000  -1.639  0.10795
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 2  Week 4  Week 8
Week 2 18.8295 14.3160 12.0002
Week 4 14.3160 21.1623 18.1813
Week 8 12.0002 18.1813 28.8384
```

A look into the reference grid shows us the new factor levels for `gender`. Note that `gender` itself will not be included in the `emmeans()` statement, but the output indicates the averaging over its levels (same for the levels of `avisit`)

```
# Reference grid shows us the new levels
emmeans::ref_grid(fit_cat_time2)
```

```
'emmGrid' object with variables:
    basval = 19.56
    avisit = Week 2, Week 4, Week 8
    trt = 1, 2
    gender = F, M
```

```r
# These two won't yield the same results
emmeans(fit_cat_time2, ~trt*avisit, weights = "equal")
```

```
 trt avisit emmean    SE   df lower.CL upper.CL
 1   Week 2  -4.36 0.869 45.7    -6.11    -2.61
 2   Week 2  -4.71 0.923 46.8    -6.57    -2.85
 1   Week 4  -6.94 0.920 46.4    -8.79    -5.09
 2   Week 4  -8.09 0.972 48.1   -10.04    -6.13
 1   Week 8 -10.10 1.063 45.5   -12.24    -7.96
 2   Week 8 -12.65 1.108 48.2   -14.88   -10.42

Results are averaged over the levels of: gender
Confidence level used: 0.95
```

```r
emmeans(fit_cat_time2, ~trt*avisit, weights = "proportional")
```

```
 trt avisit emmean    SE   df lower.CL upper.CL
 1   Week 2  -4.55 0.890 46.2    -6.34    -2.75
 2   Week 2  -4.89 0.890 46.2    -6.69    -3.10
 1   Week 4  -7.13 0.941 47.1    -9.02    -5.23
 2   Week 4  -8.27 0.941 47.1   -10.17    -6.38
 1   Week 8 -10.29 1.081 46.6   -12.46    -8.11
 2   Week 8 -12.83 1.081 46.6   -15.01   -10.66

Results are averaged over the levels of: gender
Confidence level used: 0.95
```

The following frequency table shows the imbalance in the distribution of the `gender` variable. We can see that Treatment 1 has more men than women, whereas Treatment 2 has more women than men.

```r
table(all2$trt, all2$gender)
```

```
    F  M
  1 30 45
  2 57 18
```

The data is no longer balanced across the covariates in the model. The `weights = "equal"` option is agnostic to this imbalance and assigns all levels equal weights, whereas the `weights = "proportional"` assigns a weight reflecting the proportional size of the stratum over which the average is taken.

4.3.2 Contrasts

Most of the times, the quantity we are truly interested in when reading out a study, is the contrast between treatment arms. This contrast can be built either based on LS Means at some landmark time point, or as a longitudinal (linear) combination of LS Means from multiple time points.

We can use the `pairs()` or the `contrast()` functions, where the latter provides more flexibility for the calculation of linear combinations from multiple timepoints.

```
lsmns <- emmeans::emmeans(fit_cat_time, ~trt*avisit, weights = "proportional")
pairs(lsmns, reverse = TRUE, adjust = NULL)
```

```
contrast                  estimate    SE   df t.ratio p.value
trt2 Week 2 - trt1 Week 2    -1.19 1.273 47.0  -0.935  0.3546
trt1 Week 4 - trt1 Week 2    -2.58 0.659 47.0  -3.917  0.0003
trt1 Week 4 - trt2 Week 2    -1.39 1.284 61.3  -1.082  0.2835
trt2 Week 4 - trt1 Week 2    -4.57 1.284 61.3  -3.559  0.0007
trt2 Week 4 - trt2 Week 2    -3.38 0.659 47.0  -5.133  <.0001
trt2 Week 4 - trt1 Week 4    -1.99 1.296 47.0  -1.536  0.1313
trt1 Week 8 - trt1 Week 2    -5.74 0.950 47.0  -6.043  <.0001
trt1 Week 8 - trt2 Week 2    -4.55 1.370 73.3  -3.321  0.0014
trt1 Week 8 - trt1 Week 4    -3.16 0.716 47.0  -4.416  0.0001
trt1 Week 8 - trt2 Week 4    -1.17 1.381 61.1  -0.846  0.4007
trt2 Week 8 - trt1 Week 2    -9.13 1.370 73.3  -6.664  <.0001
trt2 Week 8 - trt2 Week 2    -7.94 0.950 47.0  -8.361  <.0001
trt2 Week 8 - trt1 Week 4    -6.55 1.381 61.1  -4.742  <.0001
trt2 Week 8 - trt2 Week 4    -4.56 0.716 47.0  -6.373  <.0001
trt2 Week 8 - trt1 Week 8    -3.39 1.462 47.0  -2.319  0.0248
```

```
### This is the same as the following
prs <- contrast(lsmns, method = "revpairwise", adjust = NULL)
```

Note that both `pairs()` and `contrast()` provide multiple options for fine-tuning. We chose `adjust = NULL` in order to not perform any multiplicity adjustment (default method would

have been the Tukey method). We also chose `reverse = TRUE` to reverse the order of comparisons performed by `pairs()`, as the default would have given us the contrast for Treatment 1 - Treatment 2. Consequently, we applied `method = "revpairwise"` in the `contrast()` function.

We can obtain the coefficients in the calculation of the contrasts via `coef()`:

```
coef(prs)
```

```
           trt avisit c.1 c.2 c.3 c.4 c.5 c.6 c.7 c.8 c.9 c.10 c.11 c.12 c.13
trt1 Week 2   1 Week 2  -1  -1   0  -1   0   0  -1   0   0    0   -1    0    0
trt2 Week 2   2 Week 2   1   0  -1   0  -1   0   0  -1   0    0    0   -1    0
trt1 Week 4   1 Week 4   0   1   1   0   0  -1   0   0  -1    0    0    0   -1
trt2 Week 4   2 Week 4   0   0   0   1   1   1   0   0   0   -1    0    0    0
trt1 Week 8   1 Week 8   0   0   0   0   0   0   1   1   1    1    0    0    0
trt2 Week 8   2 Week 8   0   0   0   0   0   0   0   0   0    0    1    1    1
           c.14 c.15
trt1 Week 2    0    0
trt2 Week 2    0    0
trt1 Week 4    0    0
trt2 Week 4   -1    0
trt1 Week 8    0   -1
trt2 Week 8    1    1
```

The output above is probably more than we wanted. We are only interested in contrasts between Treatments 1 and 2 at the same time points. Here `contrast()` provides more flexibility. Instead of parsing a string with the name of a method to the `method` argument, we provide a named list of coefficients. These coefficients are identical with the onces we can see in the coefficient matrix above. We can use it as a guide.

```
contrast(
  lsmns,
  method = list(
    "Difference Trt 2 - Trt 1 at Week 4" = c(0, 0, -1, 1, 0, 0),
    "Difference Trt 2 - Trt 1 at Week 8" = c(0, 0, 0, 0, -1, 1)
  ),
  adjust = NULL)
```

```
contrast                            estimate   SE df t.ratio p.value
Difference Trt 2 - Trt 1 at Week 4    -1.99 1.30 47  -1.536  0.1313
Difference Trt 2 - Trt 1 at Week 8    -3.39 1.46 47  -2.319  0.0248
```

This way of computing LS Means from our MMRM allows us to calculate all kinds of linear combinations of LS Means. Assume we were interested in the **longitudinal** mean of changes from baseline averaged over Weeks 2, 4 and 8. This would look like this:

```
contrast(
  lsmns,
  method = list(
    "Difference Trt 2 - Trt 1 Averaged over Weeks 2, 4 and 8" = c(-1, 1, -1, 1, -1, 1)/3
  ),
  adjust = NULL)
```

```
contrast                                                  estimate   SE df
Difference Trt 2 - Trt 1 Averaged over Weeks 2, 4 and 8    -2.19 1.18 47
t.ratio p.value
 -1.850  0.0705
```

4.4 Fit diagnostics

The following section closely follows the content in Chapter 10 in (Fitzmaurice 2011).

Our analysis should be concluded with a look into the fit diagnostics, more specifically, the residuals. Residuals are defined by the difference between the true responses and the fitted values from the model:

$$r := y - X\hat{\beta}\,,$$

where $\hat{\beta}$ are the estimated coefficients from our model. Residuals provide an estimate of the true vector of random errors

$$\varepsilon = y - X\beta\,.$$

As per our modeling assumptions, ε should follow a normal distribution with mean zero. The mean of the residuals is zero and therefore identical with the mean of the error term. For the covariance of the residuals however, the variance-covariance matrix of ε only serves us as an approximation (as suggested by (Fitzmaurice 2011) for all 'practical applications'):

$$Cov(r) \approx Cov(\varepsilon) = R\,.$$

This assumption has several implications on the residual diagnostics:

- The variance is not necessarily constant. Plotting the fitted values versus the residuals might therefore lead to a non-constant range. An examination of the residual variance or autocorrelation among residuals is therefore not very meaningful.
- Residuals from analyses of longitudinal data can exhibit correlation with the covariates. Scatterplots of residuals versus selected covariates can therefore reveal systematic trends (which normally should not be the case).

A transformation of residuals to achieve constant variance and zero correlation is therefore often useful. This transformation uses the so-called *Cholesky decomposition* of the variance-covariance matrix R. Let L be a lower triangular matrix, such that

$$R = L\,L'\,,$$

then the transformed residuals are given by

$$r^* = L^{-1}(y - X\beta)\,.$$

In the `mmrm` package, transformed residuals can be derived using the `type = "normalized"` option.

Exercise: Which visualisations can you think of that make sense to assess the goodness of fit here? Create a new `tibble` (or `data.frame`) containing the variables of importance and try plotting them in a meaningful way. Discuss the results within your group.

Solution:

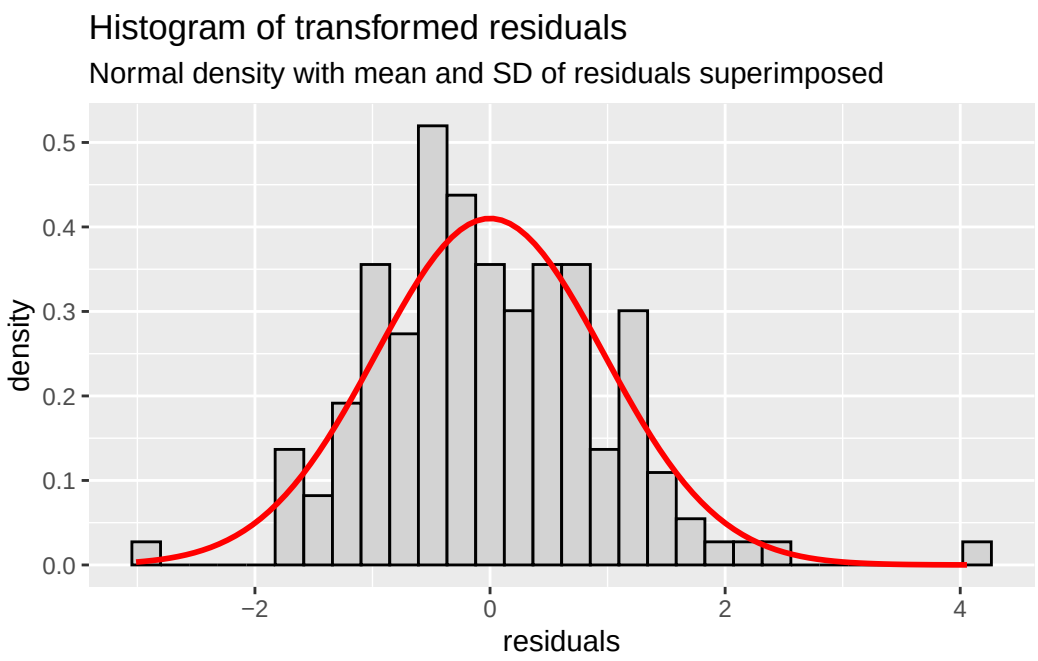
To avoid repetition, let us first save the important variables to perform fit diagnostics in a `tibble`.

```
df_residuals <- dplyr::tibble(
  residuals = residuals(fit_cat_time, type = "normalized"),
  predictions = fitted(fit_cat_time),
  all2
)
```

We can firstly look into a histogram of transformed residuals. The shape should resemble the density function of normal distribution with mean zero and positive variance. Superimposing the density function with mean and SD derived from the model residuals, let's us see that this is indeed the case. We can also detect a slight skewness to the right.

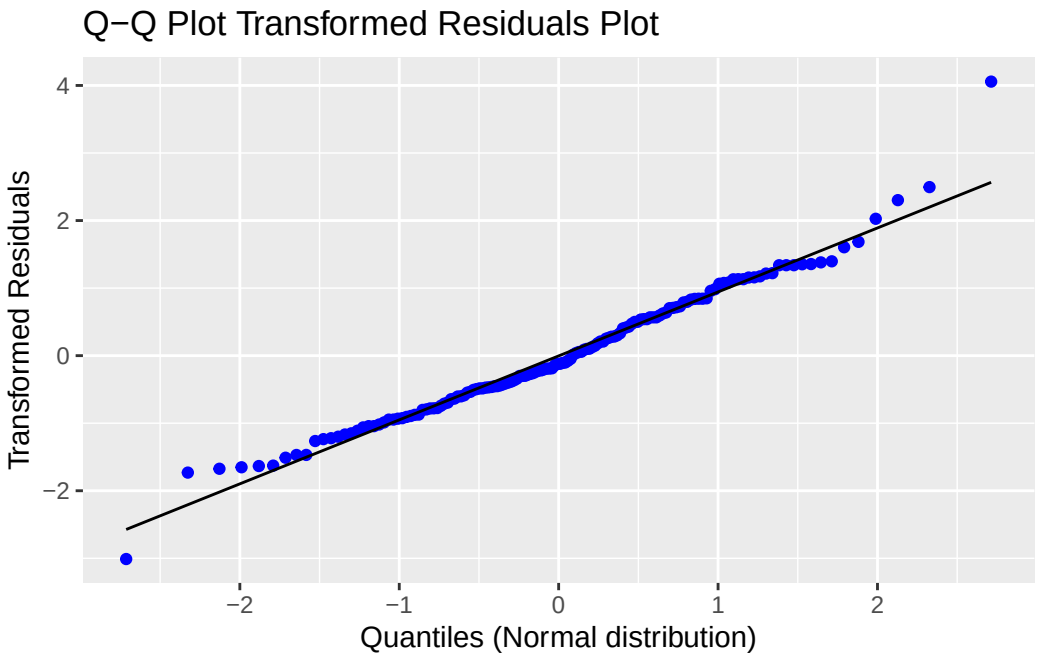
```
library(ggplot2)

df_residuals %>%
  ggplot(aes(x = residuals)) +
  geom_histogram(aes(y = after_stat(density)), fill='lightgray', col='black') +
```

```
  stat_function(fun = dnorm, args = list(mean=mean(df_residuals$residuals), sd=sd(df_resid
  ggtitle(
    label = "Histogram of transformed residuals",
    subtitle = "Normal density with mean and SD of residuals superimposed"
  )
```



Alternatively, we can create a Q-Q-Plot.

```
df_residuals %>%
  ggplot(aes(sample = residuals)) +
  stat_qq(color = "blue") +
  stat_qq_line() +
  labs(
    x = "Quantiles (Normal distribution)",
    y = "Transformed Residuals"
  ) +
  ggtitle(
    label = "Q-Q Plot Transformed Residuals Plot"
  )
```



How to interprete the Q-Q plot:

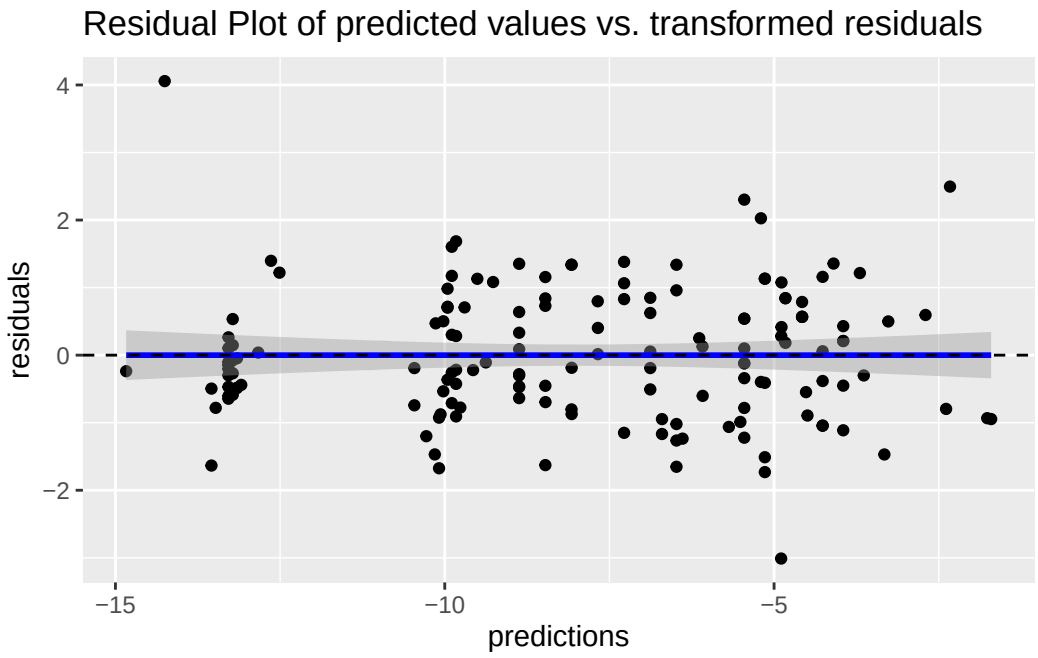
We can use the following fourfold table to assess the shape characteristics derivable from this plot, depending on where the data on which end of the plot is bend compared to the linear trend line:

		Upper right corner	
		Above	Below
Lower left corner	Above	Skewed to the right	Light-tailed
Lower left corner	Below	Heavy-tailed	Skewed to the left

We can see that our data is skewed to the right, as the data in the upper right corner and data in the lower left corner of the plot bend above the linear trend line. This is also a trend we can observe from the histogram.

```
df_residuals %>%
  ggplot(aes(x = predictions, y = residuals)) +
  geom_point() +
  geom_smooth(method = lm, color = "blue") +
  geom_hline(yintercept = 0, show.legend = FALSE, linetype = 2) +
  ggtitle(
```

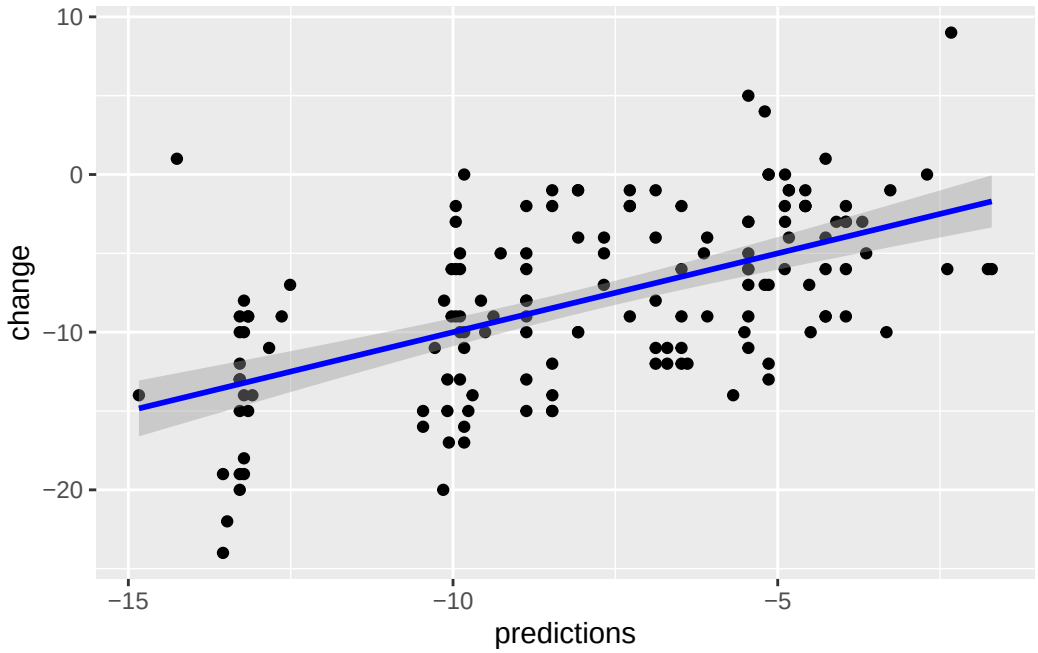
```
    label = "Residual Plot of predicted values vs. transformed residuals"
  )
```



What do we see?

- The points in the plot look well dispersed and symmetric around zero. The fitted line shows no departure from zero.
- There is no systematic trend, but a rather random scatter.
- We can spot a couple of outliers.

```
df_residuals %>%
  ggplot(aes(x = predictions, y = change)) +
  geom_point() +
  geom_smooth(method = lm, color = "blue")
```



4.5 Baseline as a Response (cLDA + LDA)

In the former examples we used baseline severity as a continuous covariate, which is the most common approach. In this case we treat `baseval` as a *fixed effect* and used changes from baseline as response variable in our model formula. This approach comes with a couple of caveats:

- Only subjects with a non-missing baseline and at least one non-missing follow-up response contribute to the analysis (i.e. at least one non-missing change from baseline value).
- Only subjects with complete covariate data contribute to the analysis.

Hence, if `baseval` is missing for a subject, this subject will not be included in our model. (Liang and Zeger 2000) introduced the so-called LDA (longitudinal data analysis) and cLDA (constrained longitudinal data analysis) models. The basic idea behind these models is that baseline can be regarded as a response at Time 0, and can therefore be included in the vector of responses.

In order to fit the model, we need to apply some data wrangling upfront and add baseline to the response column (`aval`). Note that this step is usually not required when dealing with CDISC compliant datasets, such as ADaM or SDTM.

```r
base <- dplyr::distinct(all2, subject, trt, basval, group, gender) %>%
  dplyr::mutate(
    time = 0,
    aval = basval,
    avisit = "Baseline"
  )

all2_lda <- dplyr::bind_rows(all2, base) %>%
  dplyr::mutate(
    avisit = forcats::fct_reorder(avisit, time)
  )

### Check Order of avisit levels:
levels(all2_lda$avisit)
```

```
[1] "Baseline" "Week 2"   "Week 4"   "Week 8"
```

We can now fit a model, including `aval` as a response variable, treatment (`group`), visit (`avisit`) and a treatment-by-time interaction term:

```r
lda <- mmrm(
  formula = aval ~ group*avisit + us(avisit | subject),
  data = all2_lda,
  control = mmrm_control(method = "Kenward-Roger")
)
```

The LS Mean estimates per treatment arm for mean changes to Week 8 (Time 3) are now obtained via contrasts between Week 3 and Baseline:

```r
lsmns <- emmeans(lda, ~group*avisit, weights = "proportional")
contrast(
  lsmns,
  method = list(
    "LS Means for Change from Baseline to Week 8 Treatment 1" = c(-1, 0, 0, 0, 0, 0, 1, 0)
    "LS Means for Change from Baseline to Week 8 Treatment 2" = c(0, -1, 0, 0, 0, 0, 0, 1)
    "LS Means for Difference in Changes to Week 8 btw. Treatment 2 and Treatment 1" = c(1,
  ),
  adjust = NULL
)
```

```
contrast
```

```
LS Means for Change from Baseline to Week 8 Treatment 1
LS Means for Change from Baseline to Week 8 Treatment 2
LS Means for Difference in Changes to Week 8 btw. Treatment 2 and Treatment 1
estimate   SE df t.ratio p.value
   -9.88 1.01 48  -9.768  <.0001
  -13.24 1.01 48 -13.089  <.0001
   -3.36 1.43 48  -2.349  0.0230
```

A note on caveats associated with LDA models:

- In cases where the treatment effect has a rapid onset, the linearity assumption underlying the model is violated.
- Use of baseline as a response, as opposed to a covariate, ignores the predictive nature of baseline severity as an explanatory factor in the residual error.

Generally, LDA models can be very useful in trials with only very few visits per patient due to the additional response value being included. In longer trials however, it is recommended to refrain from their use for the disadvantages stated above. In this case, a decent data quality is key to avoid missing baseline data (if possible completely) and reduce the degree of missingness with regards to follow-up data as much as possible.

4.6 Addendum on Linear Mixed Effect Models

In this chapter we have dealt with models where the response is modeled as a linear combination of *fixed effect* parameters β and a random error ε

$$y = X\beta + \varepsilon\,.$$

The fixed effects in this model represent the population effects and we used the random error to model the subject-specific influences. Although we used the term mixed model for repeated measures (MMRM), this nomenclature is misleading in the way that our model does not truly deserve the term *mixed*. A true mixed model would require the involvement of *fixed* and *random* effects. The latter have previously been omitted.

While we will not cover random coefficient models (also known as random slope and intercept models or RS&I models) in depth in this class, we would like to point to couple of useful features. For further reading, one can refer to Chapter 8 in (Fitzmaurice 2011).

The distinction between *fixed* and *random* effects in linear mixed effect models allows for modeling of both between-subject and within-subject variations. In random coefficient models (i.e. MMRMs with a non-trivial random effect) each subject is assumed to have their own (linear) rate of response over time, expressed as random slopes and intercepts.

"*In addition it is not only possible to estimate parameters that describe how the mean response changes in the population of interest, it is also possible to predict how individual response trajectories change over time. For example, linear mixed effects models can be used to obtain predictions of individual growth trajectories over time.*" (Fitzmaurice 2011)

Linear mixed effects models therefore allow for inferences on the individual (subject) basis rather than the entirety of individuals (population).

Another advantage of linear mixed models is their flexibility with respect to imbalances in longitudinal data. We are no longer bound by the restriction to have (approximately) the same number of observations per subject, i.e. the approximately the same length of follow-up, or even for the visits to be taken at the same times. This feature is especially useful whenever we are dealing with parallel design studies, involving the comparison of interventions with different dosing/ assessment frequencies.

Note that the `mmrm` package so far does not allow for fitting of linear mixed effect models, in the sense that an actual *random effects* term is included in the model formula. For these kind of models, we point to the package `lme4` (Bates et al. 2015).

5 Missing Data

So far, we conducted all our analyses on the basis of complete data. This is a blissful, yet highly unusual setting.

We use the following definition for missing data, borrowed from (Roderick JA Little 2019):

"*Missing data are unobserved values that would be meaningful for analysis if observed; in other words, a missing value hides a meaningful value.*"

We distinguish the following patterns of missingness:

- **Monotonic missingness/ dropout**: All values by a subject after a certain time are missing. More specifically, if responses are missing at visit $n \in \mathbb{N}$, then responses are also missing for every subsequent visit $n+m$, for all $m \in \mathbb{N}$. *Example:* Subject drop-out from the clinical study.
- **Intermittend missingness**: Subjects miss one or several visits, but return for later visits. *Example:* A subject with data collected at baseline and Time 1 (Week 2), a missing value at Time 2 (Week 4) and a non-missing value at Time 3 (Week 8).

Note that, following the nomenclature introduced by (Roderick JA Little 2019), we use the term missing data *pattern*, to describe which data are missing in the data matrix of subject responses, and the term missing data *mechanism*, which describes the relationship between missing and observed values in the subject responses.

Our dataset contains a second variable `chgdrop`, which is subject to missingness. Let's rerun our initial MMRM with `chgdrop` as dependent variable, baseline value, visit, baseline by visit interaction and treatment by visit interaction as fixed effects and an unstructured covariance matrix for visits within each subject.

This formulation is very similar to the one at the beginning of the former chapter. How do the results differ in terms of LS Means of change from baseline by treatment arm over time?

```
fit_cat_time <- mmrm::mmrm(
  formula = chgdrop ~ basval*avisit + trt*avisit + us(avisit | subject),
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)
```

```r
# summary(fit_cat_time)

model_lsmeans <- emmeans::emmeans(fit_cat_time, ~trt*avisit, weights = "proportional")
model_lsmeans
```

```
 trt avisit emmean    SE   df lower.CL upper.CL
 1   Week 2  -4.10 0.900 47.0    -5.91    -2.29
 2   Week 2  -5.29 0.899 47.0    -7.10    -3.48
 1   Week 4  -6.42 0.974 46.5    -8.38    -4.46
 2   Week 4  -8.52 0.951 44.8   -10.43    -6.60
 1   Week 8  -9.73 1.142 40.4   -12.03    -7.42
 2   Week 8 -12.62 1.114 40.1   -14.88   -10.37

Confidence level used: 0.95
```

```r
emmeans::emmeans(fit_cat_time, ~trt*avisit, weights = "proportional") %>%
  contrast(
    list(
      "Difference in LS Means at Week 8" = c(0, 0, 0, 0, -1, 1),
      "Difference in longitudinal LS Means to Week 8" = c(-1, 1, -1, 1, -1, 1)/3
    )
  )
```

```
 contrast                                          estimate   SE   df t.ratio
 Difference in LS Means at Week 8                     -2.90 1.60 40.3  -1.814
 Difference in longitudinal LS Means to Week 8        -2.06 1.23 46.8  -1.671
 p.value
  0.0772
  0.1014
```

To understand the nature of the differences between the model using `change` as a response variable and the one with `chgdrop`, we need to look closer into the extent of missing data and understand its nature.

5.1 Missing Data Mechanisms

To understand the nature of missing data in our clinical trial, we consider the following taxonomy, introduced by (Roderick JA Little 2019). We differentiate between the following three types of missing data:

- **Missing Completely at Random (MCAR)**: Conditional on all covariates in our analysis, the probability of missingness does not depend on either observed or unobserved values of the response variable.
- **Missing at Random (MAR)**: Conditional on all covariates and observed response values in our analysis, the probability of missingness does not depend on the unobserved values of the response variable.
- **Missing not at Random (MNAR)**: Conditional on all covariates and observed response values in our analysis, the probability of missingness does depend on the unobserved values of the response variable.

(Mallinckrodt and Lipkovich 2016) give the following interpretation around the three types of missingness:

"*With MCAR, the outcome variable is not related to the probability of dropout (after taking into account covariates). In MAR, the observed values of the outcome variable are related to the probability of dropout, but the unobserved outcomes are not (after taking into account covariates and observed outcomes). In MNAR the unobserved outcomes are related to the probability of dropout even after the observed outcomes and covariates have been taken into account.*"

The following two sections outline handling strategies for missing data. However, the best approach to handle missing data is to minimise its extent. While the occurence of missing data can rarely be avoided at all (think about the collection of questionnaire data in oncology studies and the missing data after subjects die), it is important to pursue an "as complete as can be" data collection.

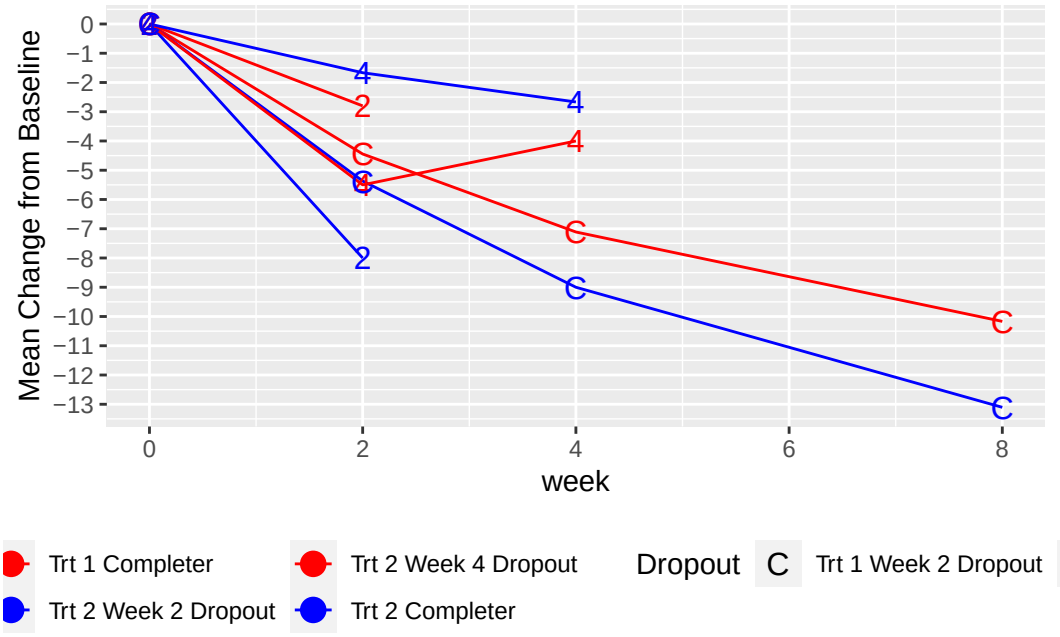
Baseline and screening data are of utmost importance in a pursuit of data completeness. If a screening value is missing, but was meant to be used as a covariate, this subjects' whole data will be dropped from the analysis even if all responses were observed. If the baseline response variable was missing we are unable to compute a change from baseline, which also leads to the loss of this subjects' data in the model (although LDA models are still able to provide an estimate) even if all post-baseline values were observed.

5.2 Missing data handling I (descriptive stats + visualisations)

To gain an understanding of the impact of missingness on the average response trajectories, we can plot the mean changes from baseline by visit for each drop-out group. The three drop-out groups (variable `dropout_grp`) are:

- Drop-outs at Week 2: Subjects who completed baseline and Week 2, but discontinued from the study prior to Week 4.

- Drop-outs at Week 4: Subjects who completed baseline, Week 2 and Week 4, but discontinued from the study prior to Week 8.
- Completers: Subjects who completed all visits in the study.



Exercise: Try to interpret the plot above and discuss the following topics around missingness:

- Look into the data. Which missing data pattern is present in this dataset?
- What can be seen in the plot? How does the drop-out time affect the observed mean response trajectories?
- What other aspects, apart from response, could influence a subjects' likelihood to drop-out from the study?
- Which other summaries/ visualizations can be useful to characterize and monitor the degree of missingness in clinical study data?

Solution: A look into the data shows that all missing values stem from a monotinic missingness pattern.

The figure above shows a notable difference between mean response trajectories per drop-out group. The completers in both treatment arms show a steady decrease of HAMD17 scores over time, which is equivalent to an increase in depression symptoms.

Week 4 drop-outs under treatment 2 only showed a moderate change from baseline, while the treatment 1 subjects experienced an increase in HAMD17 scores. A possible explanation could be that changes under treatment 2 were not regarded meaningful by patients, while the increase in scores under treatment 1 made subjects drop out of the study.

Week 2 drop-outs under treatment 2 showed notable improvements of HAMD17 scores compared to treatment 1, yet the drop-out could potentially be linked to the occurrence of adverse events.

Although the extent of missing data should be reduced to the bare minimum, it can never be avoided completely, especially with Patient-Reported Outcomes (PRO) data. In the reporting of PRO clinical trial data, it is therefore important to transparently summarize the extent of missingness. This is usually done via so-called *compliance tables*.

Compliance tables summarize three key components to characterize missingness in our data:

- The number of subjects initially randomized in the trial.
- The number of subjects for whom data is expected. This is the number of patients who are still ongoing in the study (alive and not discontinued) and for whom an assessment is scheduled following the schedule of assessments in the clinical trial protocol.
- The number of subjects by whom the assessment has been completed.

From these numbers, we can derive the *available data rate* and the *compliance* for visit i as follows:

$$\text{Available Data Rate}_i := 100\,\frac{\#\{\text{Subj. with assessment i completed}\}}{\#\{\text{Subj. randomized}\}}\,,$$
$$\text{Compliance Rate}_i := 100\,\frac{\#\{\text{Subj. with assessment i completed}\}}{\#\{\text{Subj. assessment i expected}\}}\,.$$

The available data rate indicates the degree of missingness due to drop-outs or deaths from the study. It shows how many of the initially randomized patients are still ongoing at a certain visit.

The compliance rate indicates the degree of missingness due to skipped assessments by patients, who are still ongoing in the study and expected to provide their measurement.

One can summarize compliance and available data rate by means of a table or stacked bar charts with study visits on the x-axis and percentage of patients with measurements at the respective visit, drop-out, skipped assessments, death etc. on the y-axis.

5.3 Missing data handling II (naive analytic approaches)

This section provides an overview of simple and most of the times overly naive methods to deal with missing data. Although we will introduce more suitable methods in the next chapter, the approaches introduced in this section have gained questionable popularity in the past, which is why we introduce them here. The following methods to compute or completely ignore missing data exist:

- Complete Case Analysis: Discard all subjects with missing observations and only conduct the analysis on subjects with complete follow-up data.
- Last observation carried forward (LOCF): Handling of monotonic missing data. The missing visits are imputed with the last non-missing value. This approach assumes a constant trend of observations after drop-out from the study, i.e. the response level remains the same as the last response under the study drug.
- Baseline observation carried forward (BOCF): Handling of monotonic missing data. The missing visits are imputed with the baseline value. This approach assumes that subjects' symptom severity or functioning (whichever was measured in the study) *bounce back* to the baseline state, prior to the intiation of the study drug.

5.3.1 Complete Case Analyses

Let us run a complete case analysis on the `all2` dataset.

Exercise: Fit an MMRM with response variable `chgdrop`, with baseline severity, treatment and visit as fixed effects, as well as baseline-by-visit and treatment-by-visit interaction, using an unstructured variance-covariance matrix on the `all2` completers.

- How do the results differ from the results obtained in the former chapter (response variable `change`, no missing data)?
- How do the results differ from the results obtained at the beginning of this chapter (response variable `chgdrop` with missing data)?
- Discuss the limitations of the complete case analysis. Which sources of bias can you identify?

Solution:

We firstly select our completers dataset. As this is a filtering exercise based on post-baseline characteristics, we first look into the distribution of subjects per treatment arm (note that we lost our randomization effect):

```r
### Completers only
all2_comp <- dplyr::filter(all2, dropout_grp == "Completer")

all2_comp %>%
  dplyr::group_by(group) %>%
  dplyr::summarise(
    N = dplyr::n_distinct(subject),
    .groups = "drop"
  )
```

```
# A tibble: 2 x 2
  group     N
  <fct> <int>
1 Arm 1    18
2 Arm 2    19
```

In this case, we are left with 18 and 19 subjects per arm, which reduced our sample size notably, but at least left us with close to equal sizes of our treatment groups. This is not normal. Usually the stratification of data based on post-baseline assessments can lead to imbalances (it might still have, as we only checked the distribution of the treatment arms).

```r
### Complete Case Analysis
fit_cat_time_compl <- mmrm::mmrm(
  formula = chgdrop ~ basval*avisit + trt*avisit + us(avisit | subject),
  data = all2_comp,
  control = mmrm_control(method = "Kenward-Roger")
)

summary(fit_cat_time_compl)
```

```
mmrm fit

Formula:     chgdrop ~ basval * avisit + trt * avisit + us(avisit | subject)
Data:        all2_comp (used 111 observations from 37 subjects with maximum 3
timepoints)
Covariance:  unstructured (6 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
```

```
     AIC      BIC   logLik deviance
   608.8    618.5   -298.4    596.8

Coefficients:
                      Estimate Std. Error        df t value Pr(>|t|)
(Intercept)            1.89223    3.60558  33.99000   0.525 0.603124
basval                -0.31950    0.17281  33.99000  -1.849 0.073201 .
avisitWeek 4          -1.63943    2.46046  34.00000  -0.666 0.509708
avisitWeek 8         -12.36928    3.39084  34.00000  -3.648 0.000877 ***
trt2                  -1.13978    1.56623  33.99000  -0.728 0.471768
basval:avisitWeek 4   -0.05179    0.11793  34.00000  -0.439 0.663301
basval:avisitWeek 8    0.33515    0.16252  34.00000   2.062 0.046899 *
avisitWeek 4:trt2     -0.99990    1.06880  34.00000  -0.936 0.356113
avisitWeek 8:trt2     -1.78825    1.47295  34.00000  -1.214 0.233089
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 2  Week 4  Week 8
Week 2 23.2319 16.8721 14.6422
Week 4 16.8721 21.7589 17.9166
Week 8 14.6422 17.9166 27.5347
```

```r
model_lsmeans <- emmeans::emmeans(fit_cat_time_compl, ~trt*avisit, weights = "proportional
model_lsmeans
```

```
 trt avisit emmean   SE df lower.CL upper.CL
 1   Week 2  -4.33 1.12 34    -6.61    -2.06
 2   Week 2  -5.47 1.09 34    -7.69    -3.26
 1   Week 4  -6.98 1.09 34    -9.19    -4.77
 2   Week 4  -9.12 1.06 34   -11.27    -6.97
 1   Week 8 -10.17 1.21 34   -12.63    -7.71
 2   Week 8 -13.10 1.18 34   -15.49   -10.71

Confidence level used: 0.95
```

```r
emmeans::emmeans(fit_cat_time_compl, ~trt*avisit, weights = "proportional") %>%
  contrast(
    list(
      "Difference in LS Means at Week 8" = c(0, 0, 0, 0, -1, 1),
      "Difference in longitudinal LS Means to Week 8" = c(-1, 1, -1, 1, -1, 1)/3
```

```
    )
  )
```

```
contrast                                          estimate   SE df t.ratio p.value
Difference in LS Means at Week 8                     -2.93 1.69 34  -1.733  0.0922
Difference in longitudinal LS Means to Week 8        -2.07 1.42 34  -1.455  0.1548
```

A comparison to the results using the full response trajectories for all randomized subjects (response variable `change`) yields:

```
### complete response trajectory on all randomized subjects

fit_cat_time <- mmrm::mmrm(
  formula = change ~ basval*avisit + trt*avisit + us(avisit | subject),
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

model_lsmeans <- emmeans::emmeans(fit_cat_time, ~trt*avisit, weights = "proportional")
model_lsmeans
```

```
trt avisit emmean    SE df lower.CL upper.CL
1   Week 2  -4.13 0.899 47    -5.93    -2.32
2   Week 2  -5.31 0.899 47    -7.12    -3.51
1   Week 4  -6.70 0.916 47    -8.55    -4.86
2   Week 4  -8.70 0.916 47   -10.54    -6.85
1   Week 8  -9.86 1.033 47   -11.94    -7.79
2   Week 8 -13.26 1.033 47   -15.33   -11.18

Confidence level used: 0.95
```

```
emmeans::emmeans(fit_cat_time, ~trt*avisit, weights = "proportional") %>%
  contrast(
    list(
      "Difference in LS Means at Week 8" = c(0, 0, 0, 0, -1, 1),
      "Difference in longitudinal LS Means to Week 8" = c(-1, 1, -1, 1, -1, 1)/3
    )
  )
```

```
contrast                                          estimate   SE df t.ratio p.value
Difference in LS Means at Week 8                     -3.39 1.46 47  -2.319  0.0248
Difference in longitudinal LS Means to Week 8        -2.19 1.18 47  -1.850  0.0705
```

We can see that the mean change from baseline to Week 8 using the complete response trajectory is actually lower (i.e. better) under Treatment 2 than the ones from the complete case analysis. For Treatment 1 the mean change from baseline to Week 8 is a little higher (i.e. worse) for the complete response trajectory on all randomized subjects as compared to the complete case analysis. A possible explanation could be that the favorable treatment effect of Treatment 2 came at the cost of adverse events, which made subjects drop out from the study, while the lack of early efficacy under Treatment 1 made subjects drop out, which lead them to not experience the favorable effects in the longer term.

A comparison to the analysis results based on the incomplete response trajectory (data as is), yields:

```r
### Response data as is (including missings)

fit_cat_time <- mmrm::mmrm(
  formula = chgdrop ~ basval*avisit + trt*avisit + us(avisit | subject),
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

emmeans::emmeans(fit_cat_time, ~trt*avisit, weights = "proportional")
```

```
trt avisit emmean    SE   df lower.CL upper.CL
1   Week 2  -4.10 0.900 47.0    -5.91    -2.29
2   Week 2  -5.29 0.899 47.0    -7.10    -3.48
1   Week 4  -6.42 0.974 46.5    -8.38    -4.46
2   Week 4  -8.52 0.951 44.8   -10.43    -6.60
1   Week 8  -9.73 1.142 40.4   -12.03    -7.42
2   Week 8 -12.62 1.114 40.1   -14.88   -10.37

Confidence level used: 0.95
```

```r
emmeans::emmeans(fit_cat_time, ~trt*avisit, weights = "proportional") %>%
  contrast(
    list(
      "Difference in LS Means at Week 8" = c(0, 0, 0, 0, -1, 1),
      "Difference in longitudinal LS Means to Week 8" = c(-1, 1, -1, 1, -1, 1)/3
```

```
    )
  )
```

```
contrast                                          estimate   SE   df t.ratio
Difference in LS Means at Week 8                     -2.90 1.60 40.3  -1.814
Difference in longitudinal LS Means to Week 8        -2.06 1.23 46.8  -1.671
p.value
 0.0772
 0.1014
```

We can see that mean changes from baseline to Week 8 are higher (i.e. worse) under both treatment arms using the data as is, as compared to the complete case analysis. In this case, the complete case analysis overestimates the treatment effect in both arms. This effect is often observed with complete case analyses, due to the inherent selection bias that arises from the inclusion of completers only.

5.3.2 Discussion

Complete Case Analysis is subject to selection bias, as the analysis is only conducted on subjects who complete the study and therefore did not drop out due to the experience of adverse events of the lack of efficacy. Selection of subjects based on post-baseline events can lead to notable imbalances between our treatment arms and the distribution of covariates. Results from the Complete Case Analysis can therefore be hard to interpret (due to the loss of randomization), and are frequently overestimating the true treatment effect.

In principle, this method should be avoided.

6 Sensitivity Analyses

Purpose: talk about sensitivity analyses with respect to missing data

- MMRM is an appropriate choice for the primary analysis in many longitudinal clinical trials under the missing at random (MAR) assumption.
- MMRM can handle missing values. BUT: need of baseline and at least one post-baseline value.
- No imputation for individual missing values but missing data is implicitly imputed.
- Exploit the correlation between outcomes within subjects.
- MAR: future outcomes for subjects who discontinued are assumed be similar to the future outcomes of subjects who continued if they had the same values of past (observed) outcomes, covariates,...

6.1 Purpose of sensitivity analyses

- Consider sensivitiy analyses to check model assumptions e.g. assumption of MAR.
- Comparing results from sensitivity analyses: how much inference rely on the assumptions.
- Here, inference with regard to the treatment effect. Thus, investigate how treatment effects vary depending on assumptions (about missing data).
- Uncertainty from incompleteness cannot be objectively evaluated from observed data so there is a need for missing data sensitivity analyses.

6.2 MMRM vs. MI

- Flexibility in modeling treatment effects over time and the within-patient error correlation structure makes MMRM a widely useful analysis.
- MMRM, MI: two major approaches to missing data with good statistical properties. Both rely on MAR assumption (for MI: standard implementation).
- MMRM: missing values implicitly imputed, MI: missing values explicitly imputed.
- MMRM vs. MI: approximately equivalent provided the variables used in the imputation model are the same as those included in the analysis model (level of equivalence will depend on the number of imputations)

- MI: imputation model with at least those variables from the primary model, additional auxiliary variables can be used in the imputation model to improve the accuracy of the missing data prediction.
- Handling missing not at random (MNAR) possible for MI (e.g. reference-based imputation) but not within MMRM.
- MMRM does not work if missing baseline values are present. Missing baseline values can be imputed first. Additionally, at least one post-baseline value has to be observed. Alternative: LDA where baseline is part of the response vector.

Note that, when implemented in similar manners, MI and MMRM have similar assumptions and yield similar results. Thus, MI implemented similarly to MMRM is not a sensitivity analysis!

6.3 Missing covariates (baseline data) only

- Missing baseline value of the outcome (and other covariates) is a common situation
- MMRM not efficient or potential biased estimates as subjects with missing covariates are excluded from the analysis
- (Kayembe and Breukelen 2022) compared different methods e.g. unadjusted analysis, complete case, mean imputation, MI: mean imputation seems to be appropriate as long as the covariates are measured before randomization (produces unbiased treatment effect estimates with good coverage, easy to implement)

Now, we consider the situation as in our data sets: baseline observed, no intermittent missing values, drop-outs = monotone missing pattern

6.4 Sensitivity analyses - Simple approaches

In general, these simple approaches are not recommended for use. Methods are of historic interest and provide a useful starting point. Here, we consider two simple approaches. We will apply these two methods in the practical part to compare results.

6.4.1 Last observation carried forward (LOCF)

For each subject, LOCF imputes missing values using the last observed value for that subject. Typically, under LOCF the repeated masures nature of the data is ignored and a single outcome for each subject is analyzed.

LOCF was used in the past, justified as it was thought that it provides conservative estimates. However, conditions under which LOCF yield conservative estimates and maintain control of

Type I error rates are not straightforward and cannot be assured at the beginning of the trial. For example, LOCF is likely to overestimate treatment benefit if dop-out in the control gorup is more frequent.

6.4.2 Complete case (CC)

Other names: observed case/ completers analysis

Reduce the data set selecting only those subjects with observed outcome value(s).

Completers analysis may create selection bias, may cause overestimation of within group effects particularly at the last scheduled visit.

6.5 Sensitivity analyses - Handling nonignorable missingness (MNAR)

- Assumption of MAR is often reasonable, but possibility of data missing not at random (MNAR) is difficult to rule out.
- Thus, analysis under MNAR needed.
- Analysis under MNAR: these methods are heavily assumption driven and the assumptions are not testable as we do not have the missing data.
- Consider a sensitivity analysis framework allowing assessment of robustness of results to the various assumptions.
- MNAR methods: different possibilities e.g. class of pattern-mixture models. The pattern-mixture model allows missing outcomes to be imputed under a chosen scenario and in this way can be used to complete the data set and apply the primary analysis to this completed data set.
- MI can be used to explore departures from MAR (for analysis under a MNAR assumption). This is referred to as controlled MI and includes delta-based MI and reference-based MI (belong to the class of pattern mixture models). Data is imputed under an alternative MNAR distribution that reflects a relevant scenario for the unobserved data. The imputed data sets are then analysed as with standard MI.

6.5.1 Reference-based multiple imputation

- Has received increasing attention in clinical trials as it provides an attractive approach for a sensitivity analysis because missing data assumptions are framed in an intuitive way. The departure from MAR is captured in a qualitative way, making the formulation of the problem intuitive.

- For example, a plausible MNAR mechanism in a placebo-controlled trial is to assume that subjects in the experimental arm who dropped out stop taking their treatment and have similar outcomes to those in the placebo arm.
- Remember: MI under MAR assumes that the outcome distribution of patients with missing data is the same as the outcome distribution of patients with complete data, conditional on relevant covariates. However, if most patients withdraw from the study after treatment discontinuation, then this is not plausible, as patients who withdraw from the study treatment are expected to have a worse otucome than patients who stay on study treatment. Thus, addressing missing data under a MAR assumption estimates a hypothetical estimand and not a treatment policy estimand.
- Different options to handle missing outcome data for reference-based imputation were described (Carpenter and Kenward 2013): e.g. jump to reference (J2R), copy reference (CR), copy increments in reference (CIR)

Jump to reference J2R assumes that after treatment discontinuation, the patient's mean outcome distribution is that of a reference group, usually the control group. This is a very extreme assumption, as this implies that any efficacy of the drug vanishes immediately after discontinuation - may be plausible for symptomatic treatments.

Copy reference CR assumes that the patient's outcome distribution both before and after treatment discontinuation is the same as the distribution of the reference group. This has a milder effect than J2R: If a treatment-group patient has an outcome that is better than the reference group mean before treatment discontinuation, their imputed values after treatment discontinuation will also be better than the reference group mean.

Copy increments in reference CIR assumes that after treatment discontinuation, the increments are the same as those from the reference group. This is much milder than J2R and CR and implies that benefit gained from the treatment before discontinuation is not lost.

The conventional approach to analyse data using these reference based approaches is MI, following the same steps as MI under MAR.

Software, R: e.g. the rbmi package supports reference-based strategies (Gower-Page and Wolbers 2022)

6.5.2 Delta-based multiple imputation

- Impute data assuming all unobserved subjects having a poorer or better response than those observed, by adding or subtracting a delta parameter δ to the expected value of the e.g. MAR imputed values.
- Delta can be implemented in all treatment groups, or in only one group, or may vary by treatment group or an alternative specified factor.
- Choice of values for the sensitivity parameter δ: e.g. selection by content experts.

- Steps: 1. missing values are imputed using standard MI procedure e.g. under MAR (but can also be under MNAR e.g. combinded with copy reference approach), 2. imputed values are shifted by adding some fixed value δ to reflect the MNAR mechanism, 3. analysis with standard statistical methods including Rubin's rule to combine results

6.6 Practical part

- Take the (*all2*) *high2* data set
- Look at the MMRM and at the complete case (CC) analysis (refer to section Missing Data for the *all2* data set).
- Apply additionally LOCF and compare results.
- Try MNAR method reference-based MI with J2R and CIR by using the rbmi package. Compare with the other results.

6.6.1 Set-up to use rbmi

Have a short look at the `rbmi()` package first.

```
library(rbmi)
?rbmi

vignette(topic = "quickstart", package = "rbmi")
```

```
starting httpd help server ... done
```

The workflow is based on 4 core functions:

- draws() - fits the imputation models, different methods possible, we will use method_bayes() for MI based on Bayesian posterior parameter draws from MCMC sampling
- impute() - creates multiple imputed data sets
- analyse() - analyses each of the multiple imputed data sets, default = ancova, other options possible
- pool() - combines the results across imputed data sets, for method_bayes (see above) pooling and inference is based on Rubin's rule

Implemented imputation strategies in rbmi:

- Missing at Random (MAR)
- Jump to Reference (JR)

- Copy Reference (CR)
- Copy Increments in Reference (CIR)

I will show how it looks like for the *all2* data set and you will then explore the methods using the *high2* data set.

6.6.2 Plenum - Solution for all2 data set

1. Complete case

Table: Adjusted means for the complete case data set (all2 data with drop-out, select completer)

```
model_lsmeans_cc
```

```
 trt avisit emmean   SE df lower.CL upper.CL
 1   Week 2  -4.33 1.12 34    -6.61    -2.06
 2   Week 2  -5.47 1.09 34    -7.69    -3.26
 1   Week 4  -6.98 1.09 34    -9.19    -4.77
 2   Week 4  -9.12 1.06 34   -11.27    -6.97
 1   Week 8 -10.17 1.21 34   -12.63    -7.71
 2   Week 8 -13.10 1.18 34   -15.49   -10.71

Confidence level used: 0.95
```

2. MMRM, unstructured covariance

Table: Adjusted means for the all2 data set with drop-out analysed with MMRM

```
model_lsmeans_mmrm
```

```
 trt avisit emmean    SE   df lower.CL upper.CL
 1   Week 2  -4.10 0.900 47.0    -5.91    -2.29
 2   Week 2  -5.29 0.899 47.0    -7.10    -3.48
 1   Week 4  -6.42 0.974 46.5    -8.38    -4.46
 2   Week 4  -8.52 0.951 44.8   -10.43    -6.60
 1   Week 8  -9.73 1.142 40.4   -12.03    -7.42
 2   Week 8 -12.62 1.114 40.1   -14.88   -10.37

Confidence level used: 0.95
```

3. LOCF

```r
all2.locf <- all2 %>% filter(!is.na(chgdrop)) %>%
  dplyr::group_by(subject) %>%
  dplyr::mutate( drop=max(week) )

all2.locf<-all2.locf %>% dplyr::filter(week==drop)

ancova <- aov(change ~ basval + trt, data = all2.locf)
summary(ancova)
```

```
            Df Sum Sq Mean Sq F value Pr(>F)
basval       1    1.8    1.82   0.053 0.8185
trt          1  114.2  114.20   3.342 0.0739 .
Residuals   47 1606.1   34.17
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```r
ancova$coefficients
```

```
(Intercept)      basval        trt2
-8.69460273  0.02497994 -3.02800963
```

Table: Mean values for change from baseline of LOCF analysis

Characteristic	**Arm 1**, N = 25	**Arm 2**, N = 25
change	-8.20 (5.50)	-11.24 (6.06)

4. J2R imputation

```r
# Define the names of key variables in the data set
set_mi<-set_vars(
  subjid = "subject",
  visit = "avisit",
  outcome = "chgdrop",
  group = "group",
  covariates = c("basval * avisit", "group * avisit")
)

vars_an<-set_mi
vars_an$covariates <- "basval"
```

```r
# Define the imputation strategy for each subject with at least one missing observation
dat_ice <- all2 %>%
  arrange(subject, avisit) %>%
  filter(is.na(chgdrop)) %>%
  group_by(subject) %>%
  slice(1) %>%
  ungroup() %>%
  select(subject, avisit) %>%
  mutate(strategy = "JR")

# Define the imputation method
method <- method_bayes(
  burn_in = 200,
  burn_between = 5,
  n_samples = 100,
  seed = 072407
)

draw_all2<-draws(data=all2, data_ice = dat_ice, vars=set_mi, method=method, ncores = 1, qu

imputeObj <- impute(
  draw_all2,
  references = c("Arm 1" = "Arm 1", "Arm 2" = "Arm 1")
)

imputed_all2 <- extract_imputed_dfs(imputeObj)

anaObj <- analyse(
  imputeObj,
  vars = vars_an
)
```

Table: Estimates from jump to reference J2R imputation

```r
poolObj <- pool(anaObj)
as.data.frame(poolObj)
```

```
       parameter        est        se        lci        uci         pval
1     trt_Week 2  -1.189928 1.2864325  -3.780746  1.4008900 3.598958e-01
2 lsm_ref_Week 2  -4.125036 0.9088264  -5.955372 -2.2947002 4.178855e-05
3 lsm_alt_Week 2  -5.314964 0.9088264  -7.145300 -3.4846279 5.199440e-07
```

```
4     trt_Week 4  -1.920738 1.3711052  -4.689028  0.8475529 1.687137e-01
5 lsm_ref_Week 4  -6.404449 0.9777849  -8.379818 -4.4290798 7.521493e-08
6 lsm_alt_Week 4  -8.325187 0.9654627 -10.274069 -6.3763039 8.265733e-11
7     trt_Week 8  -2.211225 1.6967275  -5.649685  1.2272346 2.005871e-01
8 lsm_ref_Week 8  -9.656881 1.2244745 -12.142348 -7.1714149 2.770935e-09
9 lsm_alt_Week 8 -11.868107 1.1717638 -14.238826 -9.4973871 1.948658e-12
```

5. Change from J2R to CIR Use the additional argument update_strategies in the impute function.

```
dat_ice_CIR <- dat_ice %>%
  mutate(strategy = ifelse(strategy == "JR", "CIR", strategy))

imputeObj_CIR <- impute(
  draw_all2,
  references = c("Arm 1" = "Arm 1", "Arm 2" = "Arm 1"),
  update_strategy = dat_ice_CIR
)

anaObj_CIR <- analyse(
  imputeObj_CIR,
  vars = vars_an
)
```

Table: Estimates from copy increments in reference CIR imputation

```
poolObj_CIR <- pool(anaObj_CIR)
as.data.frame(poolObj_CIR)
```

```
       parameter        est        se        lci        uci         pval
1     trt_Week 2  -1.189928 1.2864325  -3.780746  1.4008900 3.598958e-01
2 lsm_ref_Week 2  -4.125036 0.9088264  -5.955372 -2.2947002 4.178855e-05
3 lsm_alt_Week 2  -5.314964 0.9088264  -7.145300 -3.4846279 5.199440e-07
4     trt_Week 4  -2.014793 1.3710976  -4.782582  0.7529964 1.492281e-01
5 lsm_ref_Week 4  -6.389437 0.9827301  -8.375095 -4.4037784 8.988973e-08
6 lsm_alt_Week 4  -8.404230 0.9687489 -10.359825 -6.4486346 7.096096e-11
7     trt_Week 8  -2.609022 1.6166710  -5.879658  0.6616141 1.146759e-01
8 lsm_ref_Week 8  -9.646948 1.1739906 -12.026748 -7.2671472 8.012076e-10
9 lsm_alt_Week 8 -12.255969 1.1568184 -14.598416 -9.9135228 7.351873e-13
```

Now, you can first of all repeat the analysis on the *all2* data set to see if you can manage it. Or you go directly to the next step and apply methods to the *high2* data set.

One starting point for the *high2* data set as the structure is a little bit different:

First, fill in missing visits. This was not necessary in the *all2* data set. This can be done with the expand_locf function of the rbmi package. Note, *change* is the outcome variable and not *chgdrop* as in *all2*

```
high2 <- high2 %>% ungroup()

high2_expand <- expand_locf(
  high2,
  subject = levels(high2$subject),
  avisit = levels(high2$avisit),
  vars = c("basval","trt","group"),
  group = c("subject"),
  order = c("subject", "avisit")
)
```

6.6.3 Solution for high2 data set

First, fill in missing visits. This was not necessary in the *all2* data set. Note, *change* is the outcome variable and not *chgdrop* as in *all2*

```
high2 <- high2 %>% ungroup()

high2_expand <- expand_locf(
  high2,
  subject = levels(high2$subject),
  avisit = levels(high2$avisit),
  vars = c("basval","trt","group"),
  group = c("subject"),
  order = c("subject", "avisit")
)
```

1. Complete case

```
high2.cc<- high2 %>% dplyr::filter(drop==8)

fit_cc <- mmrm::mmrm(
  formula = change ~ basval*avisit + trt*avisit + us(avisit | subject),
  data = high2.cc,
  control = mmrm_control(method = "Kenward-Roger")
```

```
)

summary(fit_cc)
```

```
mmrm fit

Formula:     change ~ basval * avisit + trt * avisit + us(avisit | subject)
Data:        high2.cc (used 649 observations from 130 subjects with maximum 5
timepoints)
Covariance:  unstructured (15 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
  3693.8   3736.9  -1831.9   3663.8

Coefficients:
                     Estimate Std. Error        df t value Pr(>|t|)
(Intercept)           3.26341    1.33919 127.00000   2.437   0.0162 *
basval               -0.29475    0.07287 127.00000  -4.045 9.03e-05 ***
avisitWeek 2         -0.11631    1.40264 127.74000  -0.083   0.9340
avisitWeek 4         -0.77525    1.56814 127.01000  -0.494   0.6219
avisitWeek 6         -3.27487    1.59347 127.01000  -2.055   0.0419 *
avisitWeek 8         -3.94403    1.69295 127.01000  -2.330   0.0214 *
trt2                 -0.06433    0.81571 127.00000  -0.079   0.9373
basval:avisitWeek 2  -0.11719    0.07647 128.03000  -1.532   0.1279
basval:avisitWeek 4  -0.18029    0.08533 127.01000  -2.113   0.0366 *
basval:avisitWeek 6  -0.10859    0.08671 127.01000  -1.252   0.2127
basval:avisitWeek 8  -0.06299    0.09212 127.01000  -0.684   0.4954
avisitWeek 2:trt2    -0.32364    0.85100 127.17000  -0.380   0.7043
avisitWeek 4:trt2    -1.07631    0.95516 127.01000  -1.127   0.2619
avisitWeek 6:trt2    -1.35403    0.97059 127.01000  -1.395   0.1654
avisitWeek 8:trt2    -1.65323    1.03118 127.01000  -1.603   0.1114
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 1  Week 2  Week 4  Week 6  Week 8
Week 1 21.0337 16.0819 13.3827 12.2436 13.2340
Week 2 16.0819 34.0261 22.4388 20.5555 20.0298
```

```
Week 4 13.3827 22.4388 34.9214 27.3814 25.0059
Week 6 12.2436 20.5555 27.3814 33.6239 30.2604
Week 8 13.2340 20.0298 25.0059 30.2604 39.6554
```

```r
model_lsmeans <- emmeans::emmeans(fit_cc, ~trt*avisit, weights = "proportional")
model_lsmeans
```

```
 trt avisit emmean    SE  df lower.CL upper.CL
 1   Week 1  -1.91 0.595 127    -3.08   -0.731
 2   Week 1  -1.97 0.550 127    -3.06   -0.885
 1   Week 2  -4.08 0.756 126    -5.58   -2.585
 2   Week 2  -4.47 0.702 127    -5.86   -3.080
 1   Week 4  -5.85 0.764 127    -7.36   -4.336
 2   Week 4  -6.99 0.706 127    -8.38   -5.591
 1   Week 6  -7.09 0.749 127    -8.57   -5.607
 2   Week 6  -8.51 0.692 127    -9.88   -7.138
 1   Week 8  -6.96 0.811 127    -8.56   -5.352
 2   Week 8  -8.67 0.750 127   -10.16   -7.191

Confidence level used: 0.95
```

2. MMRM

```r
fit_mmrm <- mmrm::mmrm(
  formula = change ~ basval*avisit + trt*avisit + us(avisit | subject),
  data = high2,
  control = mmrm_control(method = "Kenward-Roger")
)

summary(fit_mmrm)
```

```
mmrm fit

Formula:     change ~ basval * avisit + trt * avisit + us(avisit | subject)
Data:        high2 (used 830 observations from 200 subjects with maximum 5
timepoints)
Covariance:  unstructured (15 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML
```

```
Model selection criteria:
     AIC      BIC   logLik deviance
  4779.1   4828.6  -2374.6   4749.1

Coefficients:
                     Estimate Std. Error        df t value Pr(>|t|)
(Intercept)           3.33421    1.12651 196.97000   2.960  0.00346 **
basval               -0.27934    0.05962 196.97000  -4.685  5.2e-06 ***
avisitWeek 2         -0.15400    1.17265 181.53000  -0.131  0.89566
avisitWeek 4         -1.00849    1.35934 172.12000  -0.742  0.45916
avisitWeek 6         -3.27037    1.53582 166.05000  -2.129  0.03470 *
avisitWeek 8         -3.93835    1.65523 140.95000  -2.379  0.01868 *
trt2                 -0.04273    0.64969 196.97000  -0.066  0.94763
basval:avisitWeek 2  -0.08292    0.06254 181.91000  -1.326  0.18659
basval:avisitWeek 4  -0.10700    0.07290 173.67000  -1.468  0.14396
basval:avisitWeek 6  -0.01321    0.08198 165.55000  -0.161  0.87216
basval:avisitWeek 8   0.01778    0.08902 143.32000   0.200  0.84197
avisitWeek 2:trt2    -0.61015    0.69414 181.41000  -0.879  0.38057
avisitWeek 4:trt2    -1.41851    0.81728 175.52000  -1.736  0.08438 .
avisitWeek 6:trt2    -2.31835    0.91503 165.19000  -2.534  0.01222 *
avisitWeek 8:trt2    -2.47738    0.99465 143.57000  -2.491  0.01389 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 1  Week 2  Week 4  Week 6  Week 8
Week 1 20.9961 17.1332 15.4142 15.3503 15.8717
Week 2 17.1332 35.2157 25.8380 25.5499 24.3926
Week 4 15.4142 25.8380 38.8771 33.0523 30.1128
Week 6 15.3503 25.5499 33.0523 43.7638 39.3236
Week 8 15.8717 24.3926 30.1128 39.3236 47.7371
```

```r
model_lsmeans <- emmeans::emmeans(fit_mmrm, ~trt*avisit, weights = "proportional")
model_lsmeans
```

```
 trt avisit emmean    SE  df lower.CL upper.CL
 1   Week 1  -1.61 0.458 197    -2.52   -0.711
 2   Week 1  -1.66 0.459 197    -2.56   -0.752
 1   Week 2  -3.24 0.609 191    -4.44   -2.036
 2   Week 2  -3.89 0.613 193    -5.10   -2.681
 1   Week 4  -4.52 0.656 182    -5.81   -3.223
```

```
 2   Week 4  -5.98 0.656 182    -7.27   -4.684
 1   Week 6  -5.12 0.718 168    -6.53   -3.701
 2   Week 6  -7.48 0.715 166    -8.89   -6.067
 1   Week 8  -5.24 0.785 149    -6.79   -3.686
 2   Week 8  -7.76 0.762 139    -9.26   -6.251

Confidence level used: 0.95
```

3. LOCF

```
high2.locf<-high2 %>% dplyr::filter(week==drop)

ancova <- aov(change ~ basval + trt, data = high2.locf)
summary(ancova)
```

```
             Df Sum Sq Mean Sq F value  Pr(>F)
basval        1    483   483.3   9.709 0.00211 **
trt           1    241   241.4   4.851 0.02880 *
Residuals   197   9805    49.8
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
ancova$coefficients
```

```
(Intercept)      basval        trt2
  0.3536399  -0.2648315  -2.2086854
```

```
high2.locf %>% ungroup() %>%
  select(change, group) %>%
  tbl_summary(by = group,
              statistic = list(
                all_continuous() ~ "{mean} ({sd})"),
              digits = all_continuous() ~ 2 )
```

Characteristic	**Arm 1**, N = 100	**Arm 2**, N = 100
change	-4.22 (6.38)	-6.72 (7.90)

4. J2R

```r
set_mi<-set_vars(
  subjid = "subject",
  visit = "avisit",
  outcome = "change",
  group = "group",
  covariates = c("basval * avisit", "group * avisit")
)

vars_an<-set_mi
vars_an$covariates <- "basval"

dat_ice <- high2_expand %>%
  arrange(subject, avisit) %>%
  filter(is.na(change)) %>%
  group_by(subject) %>%
  slice(1) %>%
  ungroup() %>%
  select(subject, avisit) %>%
  mutate(strategy = "JR")

method <- method_bayes(
  burn_in = 200,
  burn_between = 5,
  n_samples = 100,
  seed = 072407
)

draw_high2<-draws(data=high2_expand, data_ice = dat_ice, vars=set_mi, method=method, ncore

imputeObj <- impute(
  draw_high2,
  references = c("Arm 1" = "Arm 1", "Arm 2" = "Arm 1")
)

imputed_high2 <- extract_imputed_dfs(imputeObj)

anaObj <- analyse(
  imputeObj,
  vars = vars_an
)
```

Table: Estimates from copy jump to reference J2R imputation

```r
poolObj <- pool(anaObj)
as.data.frame(poolObj)
```

```
       parameter         est        se       lci        uci         pval
1      trt_Week 1 -0.04272539 0.6513099 -1.327240  1.2417894 9.477641e-01
2  lsm_ref_Week 1 -1.64363730 0.4593710 -2.549610 -0.7376649 4.367614e-04
3  lsm_alt_Week 1 -1.68636270 0.4593710 -2.592335 -0.7803903 3.118171e-04
4      trt_Week 2 -0.56805913 0.8694895 -2.283587  1.1474688 5.143679e-01
5  lsm_ref_Week 2 -3.29966757 0.6139776 -4.511086 -2.0882493 2.330387e-07
6  lsm_alt_Week 2 -3.86772670 0.6154448 -5.082087 -2.6533665 2.383863e-09
7      trt_Week 4 -1.23794505 0.9341607 -3.081702  0.6058116 1.868456e-01
8  lsm_ref_Week 4 -4.56691815 0.6705840 -5.890893 -3.2429436 1.703692e-10
9  lsm_alt_Week 4 -5.80486320 0.6575761 -7.102678 -4.5070482 1.090291e-15
10     trt_Week 6 -1.69994606 1.0170780 -3.707618  0.3077255 9.647476e-02
11 lsm_ref_Week 6 -5.21952895 0.7327090 -6.666472 -3.7725863 3.306987e-11
12 lsm_alt_Week 6 -6.91947501 0.7414260 -8.383999 -5.4549508 9.864655e-17
13     trt_Week 8 -1.72945373 1.1031354 -3.908286  0.4493783 1.189418e-01
14 lsm_ref_Week 8 -5.31618579 0.8094870 -6.916486 -3.7158856 9.139985e-10
15 lsm_alt_Week 8 -7.04563951 0.8266465 -8.680733 -5.4105457 2.995529e-14
```

Summary of results

Take the figure from the visualization part from day 1 to better understand what we have found here.

Table 6.3: Estimates for all methods

	Mean	Diff
Completers, Arm 1	-6.96	
Completers, Arm 2	-8.67	-1.71
MMRM, Arm 1	-5.24	
MMRM, Arm 2	-7.76	-2.52
LOCF, Arm 1	-4.22	
LOCF, Arm 1	-6.72	-2.50
J2R , Arm 1	-5.32	
J2R , Arm 1	-7.06	-1.74

7 Inferences from binary longitudinal data

In the previous chapters we focused on modeling the means over time from a continuous response vector. In clinical trials we often encounter cases, where our response is however not continuous, but rather discrete. Discrete data can stem from either count data, such that values are taken in (a subset) of the natural numbers, or ordinal data, where values represent distinct categories, or binary data. In the latter case only values 0 and 1 are taken and represent the presence or absence of a clinical status, such as alive or dead at time X, hospitalized or not hospitalized at time X or response or non-response on a specific scale at time X.

In this case we use *generalized linear models* for the analysis of discrete longitudinal data.

References

Bates, Douglas, Martin Mächler, Ben Bolker, and Steve Walker. 2015. "Fitting Linear Mixed-Effects Models Using lme4." *Journal of Statistical Software* 67 (1): 1–48. https://doi.org/10.18637/jss.v067.i01.

Carpenter, Roger, J. R., and M. G. Kenward. 2013. "Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation." *Journal of Biopharmaceutical Statistics*, October. https://doi.org/10.1080/10543406.2013.834911.

Fitzmaurice, Laird, G. M. 2011. *Applied Longitudinal Analysis*. Vol. 2. USA: New York, Wiley. https://doi.org/10.1002/9781119513469.

Gower-Page, Noci, C., and M. Wolbers. 2022. "Rbmi: A r Package for Standard and Reference-Based Multiple Imputation Methods." *Journal of Open Source Software*, June. https://doi.org/10.21105/joss.04251.

Kayembe, Jolani, M. T., and G. J. P. van Breukelen. 2022. "Imputation of Missing Covariates in Randomized Controlled Trials with Continuous Outcomes: Simple, Unbiased and Efficient Methods." *Journal of Biopharmaceutical Statistics*, September. https://doi.org/10.1080/10543406.2021.2011898.

Liang, Kung-Yee, and Scott L. Zeger. 2000. "Longitudinal Data Analysis of Continuous and Discrete Responses for Pre-Post Designs." *Sankhyā: The Indian Journal of Statistics, Series B (1960-2002)* 62 (1): 134–48. http://www.jstor.org/stable/25053123.

Mallinckrodt, Craig, and Ilya Lipkovich. 2016. *Analyzing Longitudinal Clinical Trial Data*. Chapman; Hall/CRC. https://doi.org/10.1201/9781315186634.

Roderick JA Little, Donald B. Rubin. 2019. *Statistical Analysis with Missing Data*. Vol. 3. USA: New York, Wiley. https://doi.org/10.1002/9781119482260.

Sabanes Bove, Daniel, Liming Li, Julia Dedic, Doug Kelkhoff, Kevin Kunzmann, Brian Matthew Lang, Christian Stock, et al. 2024. *Mmrm: Mixed Models for Repeated Measures*. https://openpharma.github.io/mmrm/.