

Explanation of the R code

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```
source("R/dgm.r")
source("R/vis.r")
source("R/imp.r")
source("R/sim.r")
```

We first need to set up the data-generating mechanism to enable the generation of a non-randomized dataset with two treatments. By default, a total of 61 visits will be generated for each patient, with a frequency of one visit per month. The outcome at each visit (EDSS) is determined by the received treatment, the total treatment exposure time, and the age at baseline. In addition, random variation is added to the EDSS scores, with clustering by patient ID and by center ID.

```
simpars <- setup(delta_xt = -0.007)
```

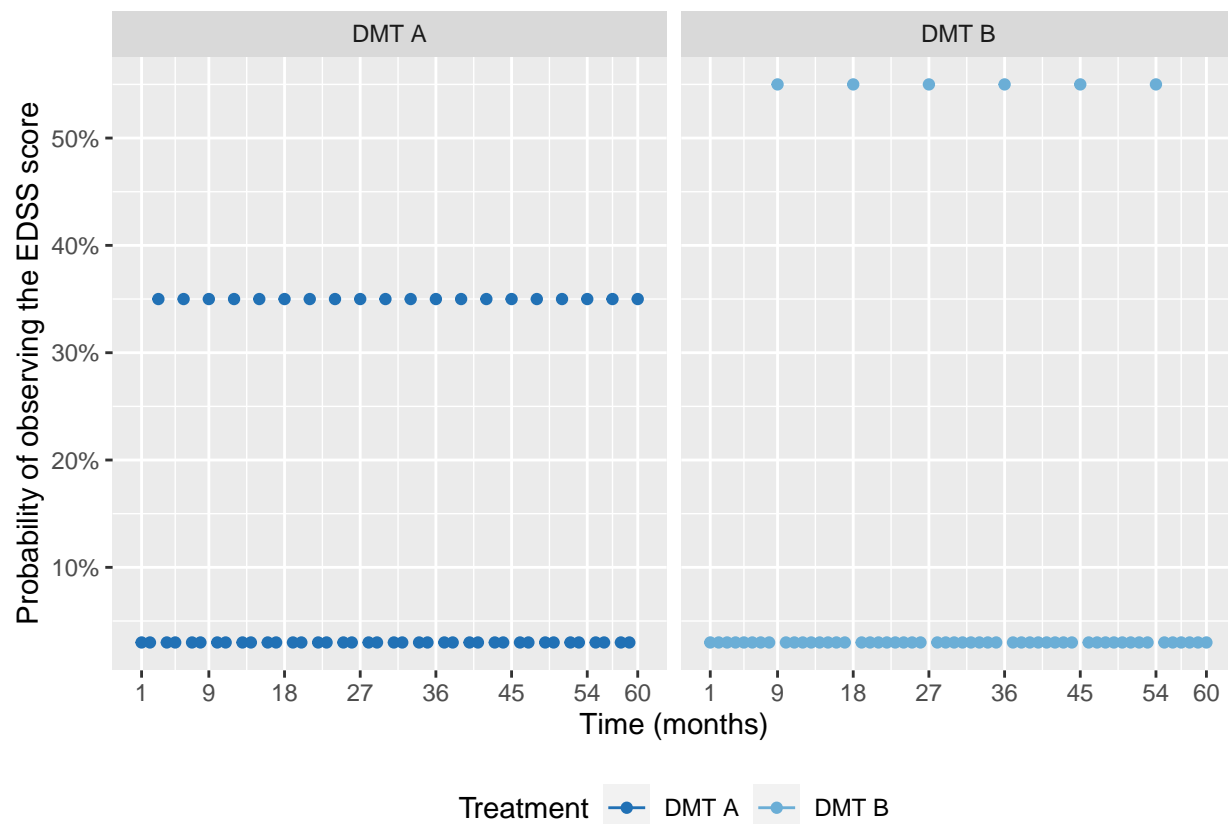
The configuration above ensures that the active treatment will reduce deterioration in EDSS by 0.007 points each day (as compared to the control treatment). We can now simulate a dataset:

```
dat <- sim_data(simpars)
head(dat)
```

```
##   centerid patid trt      age time edss
## 1         1     1  0 57.25648    0  7.5
## 2         1     1  0 57.25648    1  7.0
## 3         1     1  0 57.25648    2  7.5
## 4         1     1  0 57.25648    3  7.0
## 5         1     1  0 57.25648    4  7.0
## 6         1     1  0 57.25648    5  7.0
```

So far, the simulated dataset does not contain any missing visits. We can introduce irregular visit patterns by informatively censoring certain visits from `dat`. Several informative censoring functions are available from `R/dgm.r`. We will consider `censor_visits_7()`, which introduces the following visit pattern:

```
plot_md_pattern(simpars, censor_visits_7)
```



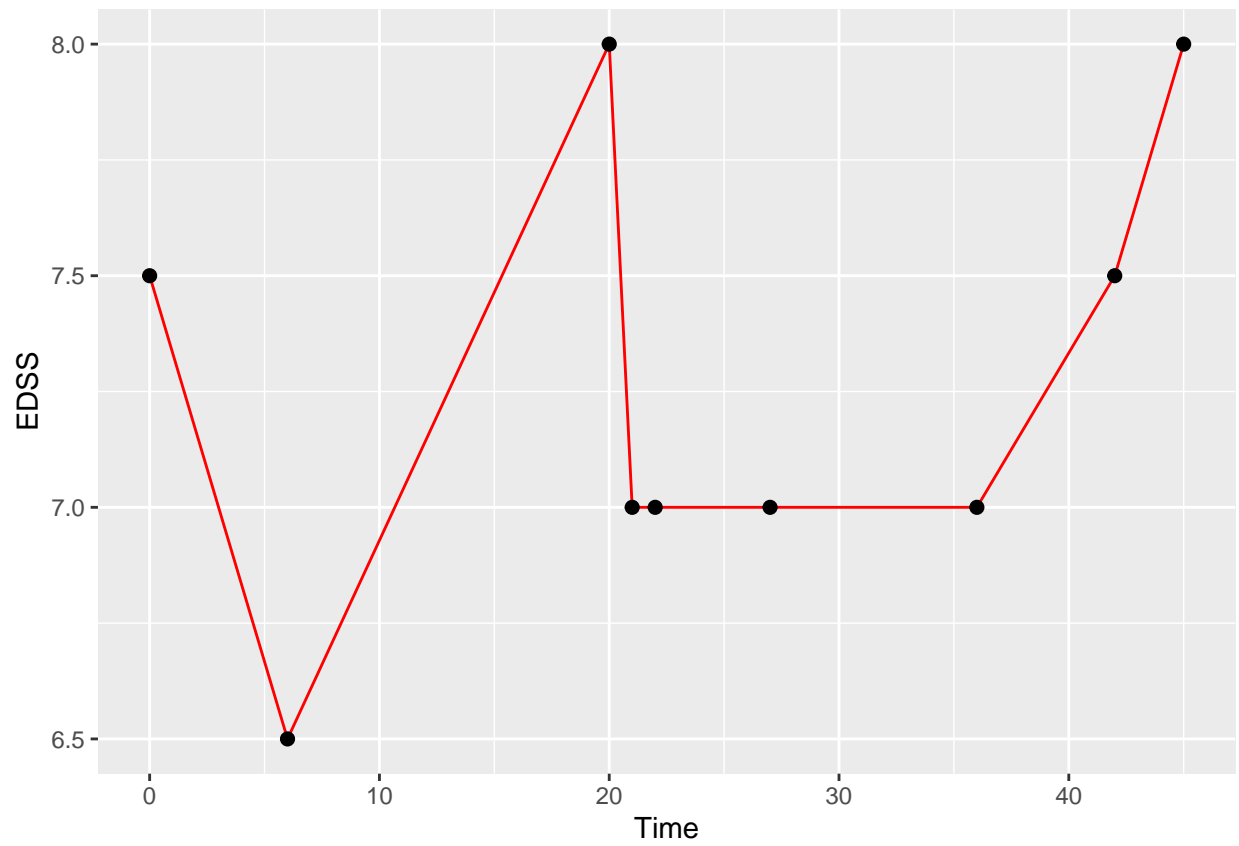
We can apply the informative visit process as follows:

```
misdat <- censor_visits_7(dat)
subset(misdat, patid == 1)
```

```
##      centerid patid trt      age time edss
## 1           1     1   0 57.25648    0  7.5
## 7           1     1   0 57.25648    6  6.5
## 21          1     1   0 57.25648   20  8.0
## 22          1     1   0 57.25648   21  7.0
## 23          1     1   0 57.25648   22  7.0
## 28          1     1   0 57.25648   27  7.0
## 37          1     1   0 57.25648   36  7.0
## 43          1     1   0 57.25648   42  7.5
## 46          1     1   0 57.25648   45  8.0
```

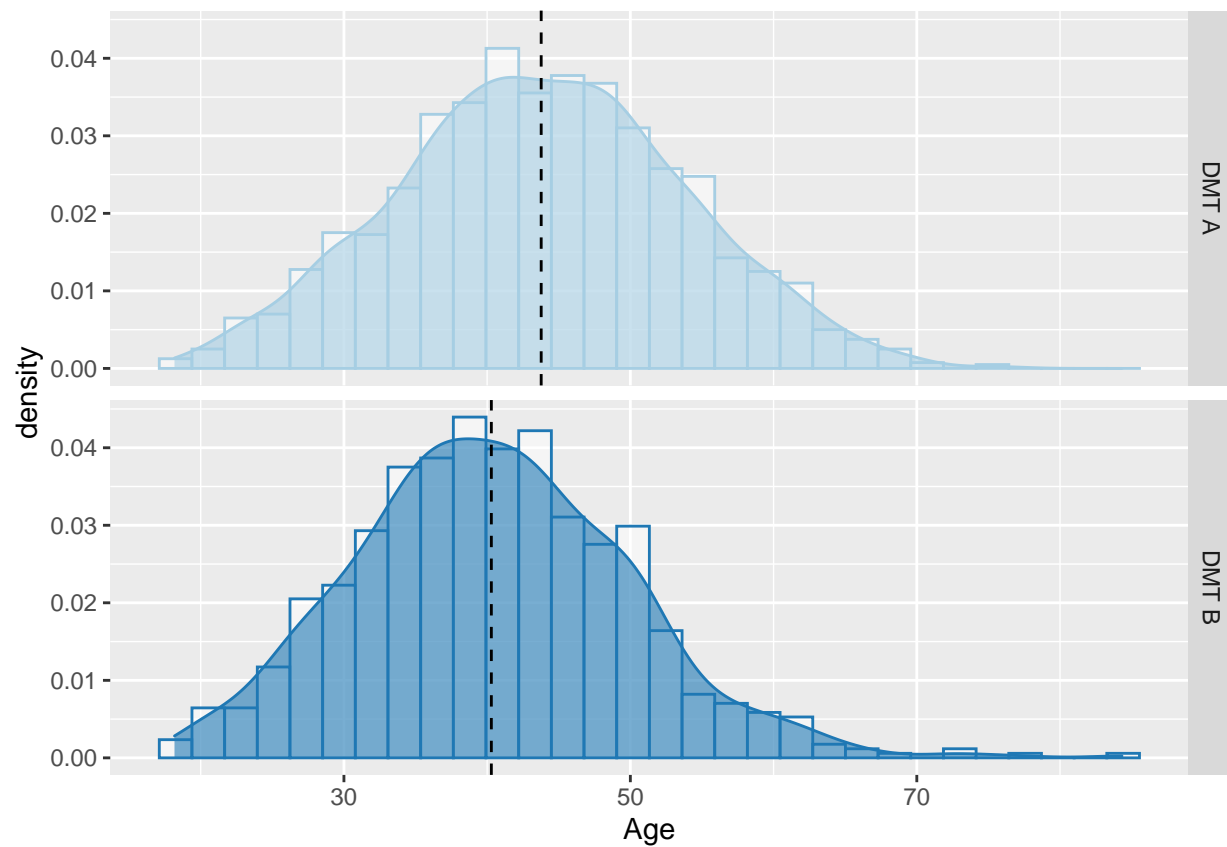
The observed EDSS trajectory of patient with `patid=1` is then as follows:

```
plot_example_trajectory(misdat, sel_patid = 1)
```



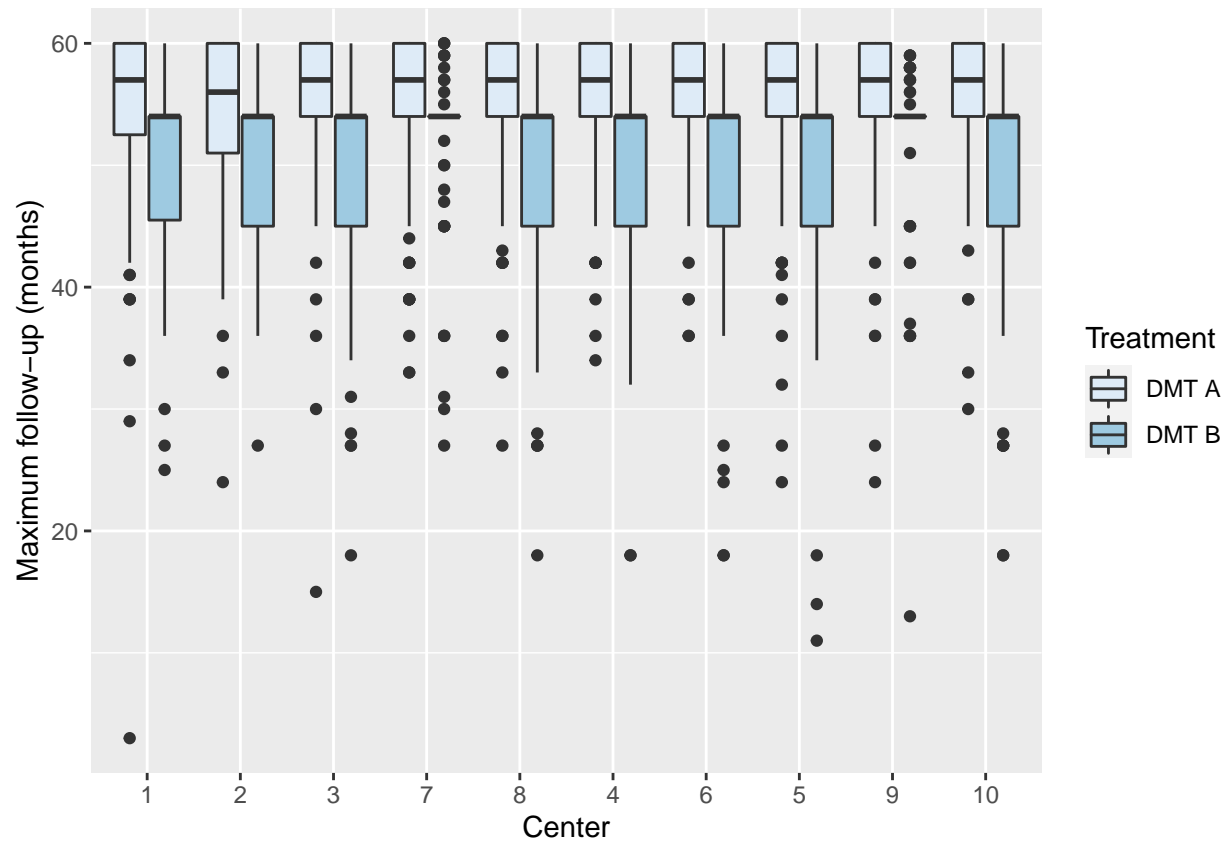
We can also visualize the age distribution across the treatment groups:

```
plot_dens_x(misdat, x_var = "age", x_label = "Age")
```



We can visualize the total follow-up for each center:

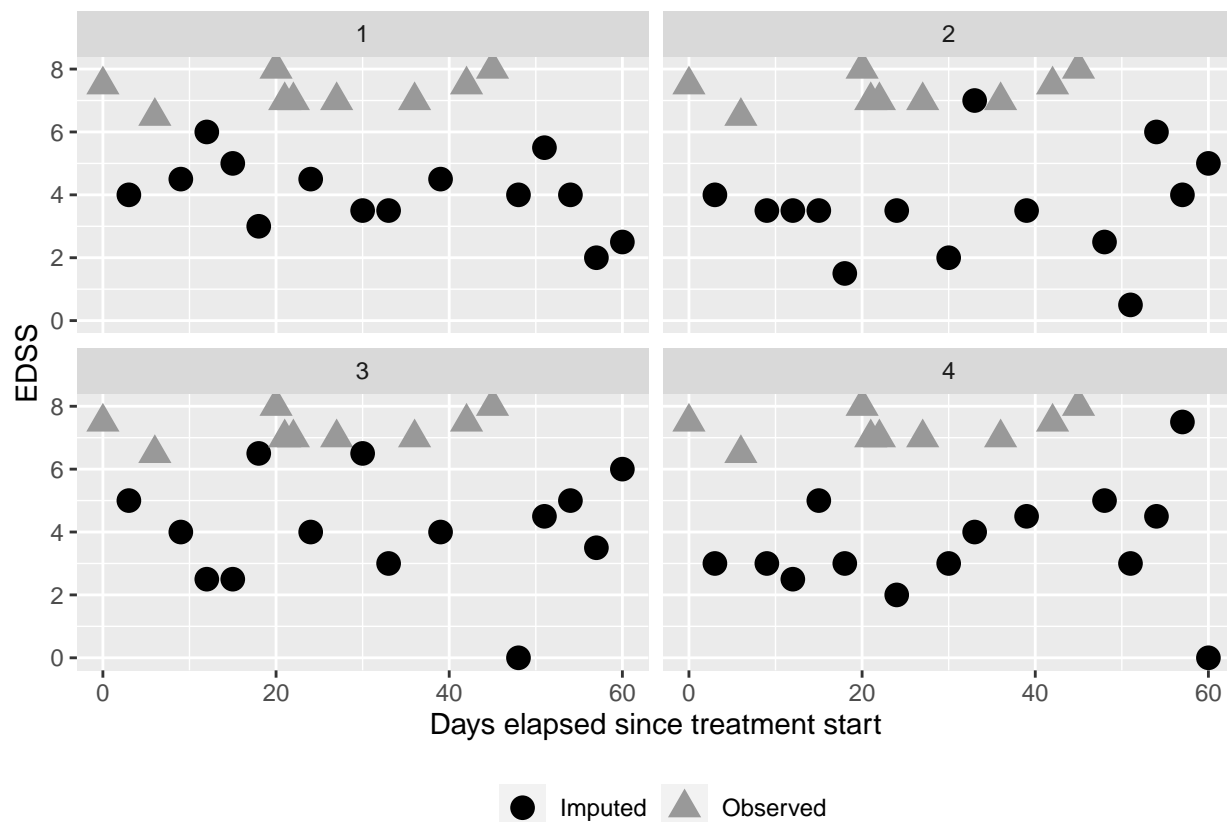
```
plot_max_fup(misdat)
```



We can now generate an imputed dataset using the `mice` software package. We will only generate imputed values on a 3-month grid.

```
imptimes <- seq(0, 60, by = 3)
imp <- impute(misdat, times = imptimes, maxit = 1)

# Visualize the imputed trajectory of one patient
plot_imputed_trajectories(imp, sel_patid = 1)
```



Finally, we can run a simulation study to assess the ability of the imputation model to recover the missing EDSS scores and to estimate the treatment effect. Since no Gibbs sampler is needed in this case, we implemented a faster version that bypasses the need of MICE and generates 10 imputed datasets simultaneously.

```
sim <- run_sim(simpars, censor_visits_7, seed = 101)
```

```
## |
```

```
sim
```

```
##   delta_xt sim_id system_name system_machine      R_version
## 1   -0.007   101    Windows      x86-64 R version 4.0.2 (2020-06-22)
## 2   -0.007   101    Windows      x86-64 R version 4.0.2 (2020-06-22)
## 3   -0.007   101    Windows      x86-64 R version 4.0.2 (2020-06-22)
## 4   -0.007   101    Windows      x86-64 R version 4.0.2 (2020-06-22)
## 5   -0.007   101    Windows      x86-64 R version 4.0.2 (2020-06-22)
##               method est_logHR   est_HR est_HR_CIl est_HR_CIl_u window
## 1             Reference -0.3707462 0.6902191 0.5994803 0.7946924      3
## 2              LOCF -0.3376605 0.7134375 0.6132510 0.8299913      3
## 3             Rounding -0.3172183 0.7281717 0.6215991 0.8530162      3
## 4             LME-CE (PMM) -0.3307769 0.7185456 0.6256175 0.8257436      3
## 5 LME-CE (EDSS conversion) -0.2477846 0.7809786 0.6853083 0.8901705      3
##   confirmation nobs_imputed      rmse
## 1              1           0 0.0000000
```

## 2	1	29516 0.6190101
## 3	1	29516 0.5496179
## 4	1	29516 0.4930344
## 5	1	29516 0.5129522