Supplementary Material for “A Joint Model for Unbalanced Nested Repeated Measures with Informative Drop-out Applied to Ambulatory Blood Pressure Monitoring Data”

S1. Exploratory Analyses

Participants may drop out of longitudinal studies for several reasons, known as loss to follow-up, due to disease development, treatment modifications and death. The difference in the drop-out rates between treatment arms may be due to perceived benefits. Table S1 below represents median survival time by group. Half of the control group dropped out over the 365 days (i.e., 1 year). However, half of the mild group dropped out over the first 273 days (i.e., 9 months). The severe group dropped out at an earlier time in which the median time to dropout was 21 days, corresponding to just after visit A.

Table S1. Study time to drop-out by group.

| Groups    | n  | Event | Median survival time (days) | 95% CI     |
|-----------|----|-------|-----------------------------|------------|
| Control   | 61 | 39    | 365                         | (273,365)  |
| Mild      | 61 | 39    | 273                         | (21,365)   |
| Severe    | 56 | 42    | 21                          | (21,365)   |

Baseline characteristics according to drop-out status for the 178 subjects are described in Table S2. During the study follow-up, 120 (67%) of subjects dropped out, including 32.5% of subjects with mild OSA and 35% subjects with serve OSA. There was no significant difference between baseline characteristics of subjects who completed the study period from those who dropped out. These results are in line with logistic regression analysis, which used drop-out status as the outcome variable as shown in Table S3. Even though logistic regression declares no statistically significant effect, it could be clinically meaningful. Specifically, patients in the severe group were 1.45 times more likely to drop out, compared to the control group. Additionally, White subjects were 1.06 times more likely to drop out, compared to non-White subjects. For each point increase in BMI z-score 11% were more likely to drop out. Table S4 shows characteristics of study cohort summarized by group. There was a difference in means of baseline body mass index (BMI) between groups. There is also an apparent difference between groups in terms of race, where the control group had a higher proportion of Whites, compared to the other groups.

Table S2. Baseline characteristics of the study cohort by drop-out status

|                  | Drop out No N=58 | Drop out Yes N=120 | P-value |
|------------------|------------------|--------------------|---------|
| Age in years     | 9.96 (2.03)      | 9.99 (2.52)        | 0.9     |
| BMI              | 0.66 (1.11)      | 0.87 (1.28)        | 0.3     |
| Mean of DBP      | 63.84 (4.35)     | 63.73 (5.36)       | 0.8     |
| Gender Male      | 41 (71%)         | 68 (57%)           | 0.1     |
| Race White       | 30 (52%)         | 63 (53%)           | 1       |
| Group Control    | 22 (38%)         | 39 (32.5%)         | 0.3     |
| Group Mild       | 22 (38%)         | 39 (32.5%)         |         |
| Group Severe     | 14 (24%)         | 42 (35%)           |         |

For continuous variables, mean (SD) and t-test
For categorical variables, frequency (%) and $\chi^2$ test
Table S3. Logistic regression model of drop-out status

| Baseline characteristics          | Estimate | Standard error | Odds Ratio | P-value |
|-----------------------------------|----------|----------------|------------|---------|
| Age (in years)                    | 0.01     | 0.07           | 1.00       | 0.9     |
| BMI (z-score)                     | 0.11     | 0.13           | 1.11       | 0.4     |
| DBP (1 mmHg per 24 hour period)   | -0.02    | 0.03           | 0.97       | 0.5     |
| Race (White)                      | -0.61    | 0.36           | 0.54       | 0.1     |
| Gender (Male)                     | 0.06     | 0.33           | 1.06       | 0.8     |
| Group (Mild)                      | -0.18    | 0.39           | 0.83       | 0.6     |
| Group (Severe)                    | 0.38     | 0.42           | 1.45       | 0.4     |

Table S4. Baseline characteristics of the study cohort by group.

| Characteristics          | Control N=61 | Mild N=61 | Severe N=56 | P-value |
|--------------------------|--------------|-----------|-------------|---------|
| Age (years)              | 10.30 (2.19) | 10.04 (2.45) | 9.56 (2.43) | 0.2     |
| BMI (z-score)            | 0.48 (1.05)  | 0.93 (1.24)  | 1.03 (1.33) | 0.024*  |
| Mean of DBP (mmHg/24 hour period) | 63.06 (5.53) | 63.76 (4.38) | 64.54 (5.10) | 0.3     |
| Race (White)             | 47 (77%)     | 32 (52%)    | 30 (54%)    | 0.007*  |
| Gender (Male)            | 30 (50%)     | 33 (54%)    | 30 (54%)    | 0.8     |

For continuous variables, mean (SD) and ANOVA test
For categorical variables, frequency (%) and χ² test
*Significance level of 0.05
S2. Overview of Shared Parameter Modeling with Informative Drop-Out

Accurately modeling the missing data mechanisms responsible for drop-out in a longitudinal study is often necessary to combat biased estimation of the mean response. There are three types of missing data mechanisms based on the relationship between the probability of missingness and the actual values (observed or unobserved).

For notational convenience, let \( Y_i \) be the longitudinal outcome vector for \( i^{th} \) subject \( (i = 1, 2, \ldots, N) \) recorded at times \( t_1, t_2, \ldots, t_k \), let \( y_i^o \) and \( y_i^m \) be the vectors of observed and missing outcomes, respectively. The missing data pattern is described by the response indicator \( R_i \) (e.g., \( R_i = 1 \) denoting a missed outcome for subject \( i \) and is 0 otherwise). Further, let \( b_i \) be a vector of random effects for the \( i^{th} \) subject. The missing data mechanism is then characterized by the conditional distribution \( f(r|y, \phi) \), where \( \phi \) denotes relevant model parameters, with three different missing data mechanisms. Missing completely at random (MCAR) implies that missingness does not depend on both unobserved and observed data elements of \( y \) such that \( f(r|y, \phi) = f(r|\phi) \) for all \( y, \phi \). Missing at random (MAR) implies that the missingness depends only on the observed components \( y^o \) of the response such that \( f(r|y, \phi) = f(r|y^o, \phi) \) for all \( y^o, \phi \). Missing Not at Random (MNAR) implies that the missingness depends on the unobserved values \( y^m \) perhaps in addition to the observed data \( y^o \) of the response such that \( f(r|y, \phi) = f(r|y^o, y^m) \). The MCAR and MAR mechanisms are ignorable, in the sense that analysis can be done using the observed data only. On the other hand, MNAR mechanisms are nonignorable.

Three classes of statistical methods have been developed to handle MNAR in longitudinal studies: selection models, pattern mixture models and shared parameter models. The most common joint model method is the shared parameter model in which the associations between the longitudinal outcome and the risk of drop-out are characterized by shared random effects \( b_i \). The shared parameter model has been studied extensively. In the shared parameter model the joint distribution of \( Y_i, R_i \), and \( b_i \) can be written as:

\[
f(y_i, r_i|\phi, b_i) = f(y_i|\beta, \sigma^2; b_i)f(r_i|\gamma; b_i)f(b_i|D) \tag{1}
\]

where \( \phi = (\beta, \sigma^2; \gamma; D) = (\phi_y; \phi_r; \phi_b) \) is the vector containing the parameters of each one of the density functions; \( D \) is a covariance matrix for the random effects. The key assumption is that the missingness and longitudinal models are assumed independent given this set of random effects. Imposing that all associations are induced by the random effects \( b_i \), the density for the longitudinal outcome \( Y_i \) conditional on \( b_i \), \( f(y_i|b_i) \), can be written as a product of the densities for the observed and unobserved outcomes. Specifically, \( f(y_i|b_i) = f(y_i^o|b_i)f(y_i^m|b_i) \). Under these assumptions, and since both the random effects \( b_i \) and missing outcome \( y_i^m \) are unobserved, they must be integrated to obtain the joint likelihood function as follows

\[
f(y_i, r_i|\phi, b_i) = \int_{y^m} \int_b f(y_i^o, y_i^m, r_i; \phi)db_idy_i^m
\]

\[
= \int_{y^m} \int_b f(y_i^o|\phi_y; b_i)f(r_i|\phi_r; b_i)f(b_i; \phi_b)db_idy_i^m
\]

\[
= \int_b f(y_i^o|\phi_y; b_i)f(r_i|\phi_r; b_i)f(b_i; \phi_b)\left\{ \int_{y^m} f(y_i^m|\phi_y; b_i)dy_i^m \right\} db_i
\]

\[
= \int_b f(y_i^o|\phi_y; b_i)f(r_i|\phi_r; b_i)f(b_i; \phi_b)db_i \tag{2}
\]

where \( f(y_i^o|\phi_y; b_i) \) denotes the probability density function of unbalanced repeated measurements on the \( i^{th} \). And \( f(r_i|\phi_r; b_i) \) is the probability density function of the continuous time to drop-out process. Under equation (2), a model for longitudinal repeated measure
S3. Model Adequacy

To compare the adequacy of the joint model and two-stage approach, we examined three different criteria, based on observed and practiced values of log(DBP). Specifically, mean absolute error (MAE), root mean-square error (RMSE) and mean absolute percentage error (MAPE) were computed as follows:

$$MAE = \frac{1}{N} \sum_{i=1}^{N} |y_i - \hat{y}_i|$$ (3)

$$RMSE = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (y_i - \hat{y}_i)^2}$$ (4)

$$MAPE = \frac{100}{N} \sum_{i=1}^{N} \left| \frac{y_i - \hat{y}_i}{y_i} \right|$$ (5)

where $y_i$, and $\hat{y}_i$ are the observed value of the $i^{th}$ response, and fitted value of the $i^{th}$ response.

Table S5. Model comparison results.

| Metrics | Joint Model | Two-stage |
|---------|-------------|-----------|
| MAE     | 0.096       | 0.085     |
| RMSE    | 0.124       | 0.110     |
| MAPE    | 2.3%        | 2.0%      |

Statistics of mean absolute error (MAE), root mean square error (RMSE), and mean absolute percentage error (MAPE)
S4. Additional Model Coefficients

The following tables include remaining coefficients from model fitting in the main manuscript.

Table S6. The coefficients of the transformed natural cubic spline functions for the two-stage approach

| Parameter       | Estimate | SE  | T-value | P-value |
|-----------------|----------|-----|---------|---------|
| ns1             | 9.365    | 0.926 | 10.115  | 0.000 * |
| ns2             | 13.056   | 0.596 | 21.905  | 0.000*  |
| ns3             | 9.159    | 0.488 | 18.776  | 0.000*  |
| ns4             | 3.227    | 0.831 | 3.884   | 0.000*  |
| ns5             | 5.408    | 0.337 | 16.049  | 0.000*  |
| VisitB          | -0.010   | 0.018 | -0.566  | 0.571   |
| VisitC          | -0.020   | 0.019 | -1.076  | 0.282   |
| VisitD          | -0.002   | 0.022 | -0.095  | 0.924   |
| groupMild       | -0.033   | 0.020 | -1.653  | 0.098   |
| groupSevere     | 0.019    | 0.020 | 0.945   | 0.345   |
| ns1:VisitB      | 0.168    | 1.417 | 0.119   | 0.905   |
| ns2:VisitB      | 1.880    | 0.905 | 2.078   | 0.038   |
| ns3:VisitB      | 2.377    | 0.745 | 3.193   | 0.001*  |
| ns4:VisitB      | 1.247    | 1.271 | 0.981   | 0.326   |
| ns5:VisitB      | 0.273    | 0.513 | 0.532   | 0.595   |
| ns1:VisitC      | 3.231    | 1.508 | 2.142   | 0.032*  |
| ns2:VisitC      | 3.520    | 0.961 | 3.664   | 0.000*  |
| ns3:VisitC      | 2.350    | 0.791 | 2.968   | 0.003*  |
| ns4:VisitC      | 1.178    | 1.350 | 0.872   | 0.383   |
| ns5:VisitC      | -0.331   | 0.542 | -0.610  | 0.542   |
| ns1:VisitD      | 1.873    | 1.726 | 1.085   | 0.278   |
| ns2:VisitD      | 2.263    | 1.097 | 2.063   | 0.039*  |
| ns3:VisitD      | 0.770    | 0.909 | 0.848   | 0.397   |
| ns4:VisitD      | 1.701    | 1.548 | 1.098   | 0.272   |
| ns5:VisitD      | 1.290    | 0.623 | 2.071   | 0.038*  |
| ns1:groupMild   | 2.869    | 1.323 | 2.169   | 0.030*  |
| ns2:groupMild   | 2.443    | 0.857 | 2.850   | 0.004*  |
| ns3:groupMild   | 1.990    | 0.707 | 2.814   | 0.005*  |
| ns4:groupMild   | 3.684    | 1.187 | 3.104   | 0.002*  |
| ns5:groupMild   | -0.697   | 0.488 | -1.429  | 0.153   |

*Significance level of 0.05
Table S6 continued. The coefficients of the transformed natural cubic spline functions for the two-stage approach

| Parameter         | Estimate | SE    | T-value | P-value |
|-------------------|----------|-------|---------|---------|
| ns1:groupSevere   | -0.780   | 1.336 | -0.584  | 0.559*  |
| ns2:groupSevere   | -1.679   | 0.857 | -1.960  | 0.050*  |
| ns3:groupSevere   | 0.541    | 0.704 | 0.769   | 0.442   |
| ns4:groupSevere   | -0.015   | 1.201 | -0.012  | 0.990   |
| ns5:groupSevere   | -0.627   | 0.488 | -1.285  | 0.199   |
| VisitB:groupMild  | 0.013    | 0.026 | 0.488   | 0.625   |
| VisitC:groupMild  | 0.023    | 0.029 | 0.803   | 0.422   |
| VisitD:groupMild  | -0.035   | 0.031 | -1.128  | 0.259   |
| ns1:VisitB:groupMild | -0.052 | 0.027 | -1.894  | 0.058   |
| ns2:VisitB:groupMild | -0.028 | 0.030 | -0.935  | 0.350   |
| ns3:VisitB:groupMild | -0.042 | 0.035 | -1.206  | 0.228   |
| ns4:VisitB:groupMild | -1.628 | 2.080 | -0.782  | 0.434   |
| ns5:VisitB:groupMild | -1.706 | 1.340 | -1.273  | 0.203*  |
| VisitC:groupMild  | -0.291   | 1.501 | -0.184  | 0.854   |
| VisitD:groupMild  | -0.953   | 1.315 | -0.725  | 0.468   |
| ns1:VisitD:groupMild | -1.226 | 2.219 | -0.553  | 0.581   |
| ns2:VisitD:groupMild | -0.843 | 0.891 | -0.947  | 0.344   |
| ns3:VisitD:groupMild | 2.652 | 0.827 | 3.206   | 0.001*  |
| ns4:VisitD:groupMild | 0.224 | 2.477 | 0.090   | 0.928   |
| ns5:VisitD:groupMild | 2.062 | 1.582 | -0.184  | 0.854   |
| ns1:groupSevere   | -0.291   | 1.501 | -0.184  | 0.854   |
| ns2:groupSevere   | -0.953   | 1.315 | -0.725  | 0.468   |
| ns3:groupSevere   | -1.226   | 2.219 | -0.553  | 0.581   |
| ns4:groupSevere   | -0.843   | 0.891 | -0.947  | 0.344   |
| ns5:groupSevere   | 2.652    | 0.827 | 3.206   | 0.001*  |
| ns1:groupSevere   | 0.224    | 2.477 | 0.090   | 0.928   |
| ns2:groupSevere   | 2.062    | 1.582 | -0.184  | 0.854   |
| ns3:groupSevere   | 0.224    | 2.477 | 0.090   | 0.928   |
| ns4:groupSevere   | 2.062    | 1.582 | -0.184  | 0.854   |
| ns5:groupSevere   | 2.062    | 1.582 | -0.184  | 0.854   |

*Significance level of 0.05
Table S7. The coefficients of the transformed natural cubic spline functions for the joint model

| Parameter        | Mean   | SD      | 95% CrI                  |
|------------------|--------|---------|-------------------------|
| ns1              | 5.453  | 4.670   | (-2.661,16.07)          |
| ns2              | 8.239  | 5.377   | (-1.010,20.35)          |
| ns3              | 4.168  | 5.389   | (-5.117,16.210)         |
| ns4              | -0.714 | 4.664   | (-8.785,9.810)          |
| ns5              | 2.106  | 3.568   | (-3.970,10.04)          |
| VisitB.ns1       | 0.089  | 0.693   | (-1.257,1.456)          |
| VisitC.ns1       | 1.941  | 1.010   | (-0.049,3.941)          |
| VisitD.ns1       | 0.633  | 1.425   | (-2.200,3.486)          |
| VisitB.ns2       | 1.759  | 0.584   | (0.612,2.900)*          |
| VisitC.ns2       | 2.538  | 0.729   | (1.119,3.963)*          |
| VisitD.ns2       | 1.630  | 0.968   | (-0.228,3.591)          |
| VisitB.ns3       | 2.109  | 0.567   | (1.034,3.240)           |
| VisitC.ns3       | 1.644  | 0.668   | (0.337,3.009)*          |
| VisitD.ns3       | 0.475  | 0.854   | (-1.179,2.118)          |
| VisitB.ns4       | 1.184  | 0.655   | (-0.096,2.477)          |
| VisitC.ns4       | -0.114 | 0.937   | (-1.959,1.749)          |
| VisitD.ns4       | 0.721  | 1.299   | (-1.838,3.316)          |
| VisitB.ns5       | -0.156 | 9.976   | (-19.560,19.420)        |
| VisitC.ns5       | 0.013  | 9.905   | (-18.780,19.36)         |
| VisitD.ns5       | 0.041  | 9.869   | (-19.462,19.344)        |
| groupMild.ns1    | 0.063  | 9.879   | (-19.381,19.460)        |
| groupMild.ns2    | -0.245 | 0.483   | (-1.204,0.724)          |
| groupMild.ns3    | -0.915 | 1.077   | (-3.023,1.228)          |
| groupMild.ns4    | 0.977  | 0.677   | (-0.344,2.288)          |
| groupMild.ns5    | -1.929 | 0.900   | (-3.674,-0.151)         |

*A 95% CrI (credible interval) that excludes zero indicates significance at the 0.05 level
Table S7 continued. The coefficients of the transformed natural cubic spline functions for the joint model

| Parameter              | Mean   | SD    | 95%CrI       |
|------------------------|--------|-------|--------------|
| groupSevere.ns1        | -0.014 | 10.048| (-19.601,19.390) |
| groupSevere.ns2        | -0.784 | 0.480 | (-1.705,0.173)  |
| groupSevere.ns3        | 0.538  | 1.065 | (-1.508,2.642)  |
| groupSevere.ns4        | 0.501  | 0.690 | (-0.824,1.872)  |
| groupSevere.ns5        | -0.480 | 0.890 | (-2.205,1.320)  |
| groupMild.VisitB.ns1   | -0.142 | 1.010 | (-2.178,1.781)  |
| groupMild.VisitC.ns1   | -3.997 | 1.467 | (-6.884,-1.226) |
| groupMild.VisitD.ns1   | -1.246 | 2.029 | (-5.271,2.626)  |
| groupSevere.VisitB.ns1 | 0.954  | 1.049 | (-1.139,2.986)  |
| groupSevere.VisitC.ns1 | -0.641 | 1.514 | (-3.579,2.286)  |
| groupSevere.VisitD.ns1 | 1.956  | 2.119 | (-2.129,6.178)  |
| groupMild.VisitB.ns2   | -0.887 | 0.875 | (-2.600,0.8315) |
| groupMild.VisitC.ns2   | -3.204 | 1.088 | (-5.332,-1.073) |
| groupMild.VisitD.ns2   | -1.263 | 1.403 | (-4.014,1.408)  |
| groupSevere.VisitB.ns2 | 1.114  | 0.901 | (-0.681,2.923)  |
| groupSevere.VisitC.ns2 | -0.349 | 1.117 | (-2.480,1.830)  |
| groupSevere.VisitD.ns2 | 3.667  | 1.475 | (0.811,6.611)^* |

*A 95% CrI (credible interval) that excludes zero indicates significance at the 0.05 level

Table S7 continued. The coefficients of the transformed natural cubic spline functions for the joint model

| Parameter              | Mean   | SD    | 95%CrI       |
|------------------------|--------|-------|--------------|
| groupMild.VisitB.ns3   | -0.062 | 0.442 | (-0.921,0.796) |
| groupMild.VisitC.ns3   | 0.016  | 0.515 | (-0.978,1.030) |
| groupMild.VisitD.ns3   | 1.002  | 0.654 | (-2.942,2.274) |
| groupMild.VisitB.ns4   | -1.351 | 0.481 | (-2.279,-0.409) |
| groupMild.VisitC.ns4   | -1.213 | 0.679 | (-2.576,0.113) |
| groupMild.VisitD.ns4   | -1.315 | 0.934 | (-3.177,0.491) |
| groupSevere.VisitB.ns4 | -0.574 | 0.991 | (-2.519,1.357) |
| groupSevere.VisitC.ns4 | -0.155 | 1.391 | (-2.949,2.466) |
| groupSevere.VisitD.ns4 | 1.236  | 1.902 | (-2.569,4.946) |
| groupMild.VisitB.ns5   | 0.091  | 10.157| (-19.51,19.931)|
| groupMild.VisitC.ns5   | -0.124 | 10.023| (-19.650,19.870)|
| groupMild.VisitD.ns5   | -0.027 | 10.048| (-19.580,19.880)|
| groupSevere.VisitC.ns5 | 0.055  | 10.065| (-19.883,2.20)|
| groupMild.VisitD.ns5   | 0.075  | 10.150| (-19.580,20.050)|
| groupSevere.VisitD.ns5 | 0.042  | 9.996 | (-19.670,19.781)|

*A 95% CrI (credible interval) that excludes zero indicates significance at the 0.05 level
S5. WinBUGS code for the Joint Model

```plaintext
## Beginning of model
model {
  # loop over Studynr Mixed-effects model with multivariate normal
  # distribution on random effects, mean are 0 and unknown variance
  for (i in 1:n.ID){
    b0[i, 1]<-0
    b0[i, 2]<-0
    b0[i, 3]<-0
    B[i, 1:3] ~ dmnorm(b0[i,1:3], isigma[,])
  }
  # loop over measurements within each Studynr
  for( j in 1:ID.obs[i]){ DBP[i,j]~dnorm(muy[i,j],tauy)
  }
  # Likelihood function
  muy[i,j]<-B[i,1]+B[i,2]*visit[i,j]+B[i,3]*time[i,j]+
  Bn[i,j]+BnB[i,j]*B[i,j]+BnV[i,j]*visit[i,j]+
  BnG[i,j]+BnG[i,j]*group[i]+
  BnGV[i,j]*group[i]*visit[i,j]
  # z-matrix for ns(time)
  Bn[i,j]<-GS1*Z1[i,j]+GS2*Z2[i,j]+GS3*Z3[i,j]+ GS4*Z4[i,j]+
  GS5*Z5[i,j]
  # z-matrix for ns(time,5)*visits
  BnV1[i,j]<-VisitB.GS1*Z1[i,j]*visit.B[i,j]+
  VisitC.GS1*Z1[i,j]*visit.C[i,j]+ VisitD.GS1*Z1[i,j]
  *visit.D[i,j]
  BnV2[i,j]<-VisitB.GS2*Z2[i,j]*visit.B[i,j]+
  VisitC.GS2*Z2[i,j]*visit.C[i,j]+VisitD.GS2*Z2[i,j]
  *visit.D[i,j]
  BnV3[i,j]<-VisitB.GS3*Z3[i,j]*visit.B[i,j]+
  VisitC.GS3*Z3[i,j]*visit.C[i,j]+VisitD.GS3*Z3[i,j]
  *visit.D[i,j]
  BnV4[i,j]<-VisitB.GS4*Z4[i,j]*visit.B[i,j]+
  VisitC.GS4*Z4[i,j]*visit.C[i,j]+VisitD.GS4*Z4[i,j]
  *visit.D[i,j]
  BnV5[i,j]<-VisitB.GS5*Z5[i,j]*visit.B[i,j]+
  VisitC.GS5*Z5[i,j]*visit.C[i,j]+VisitD.GS5*Z5[i,j]
  *visit.D[i,j]
  # z-matrix for ns(time,5)*groups
  BnG[i,j]<-groupMild.GS1*Z1[i,j]*groupmild[i]+groupSevere.GS1*Z1[i,j]*groupsevere[i]
  BnG[i,j]<-groupMild.GS2*Z2[i,j]*groupmild[i]+groupSevere.GS2*Z2[i,j]*groupsevere[i]
  BnG[i,j]<-groupMild.GS3*Z3[i,j]*groupmild[i]+groupSevere.GS3*Z3[i,j]*groupsevere[i]
  BnG[i,j]<-groupMild.GS4*Z4[i,j]*groupmild[i]+groupSevere.GS4*Z4[i,j]*groupsevere[i]
  BnG[i,j]<-groupMild.GS5*Z5[i,j]*groupmild[i]+groupSevere.GS5*Z5[i,j]*groupsevere[i]
  # z-matrix for ns(time,5)*groups*visits
  BnGV[i,j]<-groupMild.VisitB.GS1*Z1[i,j]*groupmild[i]
```
*visit.B[i,j]+groupMild.VisitC.GS1*Z1[i,j]*groupmild[i]
*visit.C[i,j]+groupMild.VisitD.GS1*Z1[i,j]*groupmild[i]*visit.D[i,j]
BnGV2[i,j]<-groupSevere.VisitB.GS1*Z1[i,j]*groupsevere[i]
*visit.B[i,j]+
groupSevere.VisitC.GS1*Z1[i,j]*groupsevere[i]*visit.C[i,j]+
groupSevere.VisitD.GS1*Z1[i,j]*groupsevere[i]*visit.D[i,j]
BnGV3[i,j]<-groupMild.VisitB.GS2*Z2[i,j]*groupmild[i]
*visit.B[i,j]+
groupMild.VisitC.GS2*Z2[i,j]*groupmild[i]*visit.C[i,j]+
groupMild.VisitD.GS2*Z2[i,j]*groupmild[i]*visit.D[i,j]
BnGV4[i,j]<-groupSevere.VisitB.GS2*Z2[i,j]*groupsevere[i]
*visit.B[i,j]+
groupSevere.VisitC.GS2*Z2[i,j]*groupsevere[i]*visit.C[i,j]+
groupSevere.VisitD.GS2*Z2[i,j]*groupsevere[i]*visit.D[i,j]
BnGV5[i,j]<-groupMild.VisitB.GS3*Z3[i,j]*groupmild[i]
*visit.B[i,j]+
groupMild.VisitC.GS3*Z3[i,j]*groupmild[i]*visit.C[i,j]+
groupMild.VisitD.GS3*Z3[i,j]*groupmild[i]*visit.D[i,j]
BnGV6[i,j]<-groupSevere.VisitB.GS3*Z3[i,j]*groupsevere[i]
*visit.B[i,j]+
groupSevere.VisitC.GS3*Z3[i,j]*groupsevere[i]*visit.C[i,j]+
groupSevere.VisitD.GS3*Z3[i,j]*groupsevere[i]*visit.D[i,j]
BnGV7[i,j]<-groupMild.VisitB.GS4*Z4[i,j]*groupmild[i]
*visit.B[i,j]+
groupMild.VisitC.GS4*Z4[i,j]*groupmild[i]*visit.C[i,j]+
groupMild.VisitD.GS4*Z4[i,j]*groupmild[i]*visit.D[i,j]
BnGV8[i,j]<-groupSevere.VisitB.GS4*Z4[i,j]*groupsevere[i]
*visit.B[i,j]+
groupSevere.VisitC.GS4*Z4[i,j]*groupsevere[i]*visit.C[i,j]+
groupSevere.VisitD.GS4*Z4[i,j]*groupsevere[i]*visit.D[i,j]
BnGV9[i,j]<-groupMild.VisitB.GS5*Z5[i,j]*groupmild[i]
*visit.B[i,j]+
groupMild.VisitC.GS5*Z5[i,j]*groupmild[i]*visit.C[i,j]+
groupMild.VisitD.GS5*Z5[i,j]*groupmild[i]*visit.D[i,j]
BnGV10[i,j]<-groupSevere.VisitB.GS5*Z5[i,j]*groupsevere[i]
*visit.B[i,j]+
groupSevere.VisitC.GS5*Z5[i,j]*groupsevere[i]*visit.C[i,j]+
groupSevere.VisitD.GS5*Z5[i,j]*groupsevere[i]*visit.D[i,j]
} # for j

## Weibull sub-model / sharing random effects ##
t.obs[i]~ dweib(shape, mut[i]) I(t.cen[i],)
log(mut[i])<- Intercept.surv+Age_bs.surv*Age[i]+GenderMi.surv*GenderM[i]+groupMild.surv*groupmild[i]+
groupSevere.surv*groupsevere[i]+alpha_b0i*B[i,1]+alpha_b0ij*B[i,2]+alpha_b0ik*B[i,3]
} # for i

### priors Regression coefficients for longitudinal sub-model
### (fixed effects)
GS1~dnorm(0,0.01) GS2~dnorm(0,0.01) GS3~dnorm(0,0.01)
GS4~dnorm(0,0.01) GS5~dnorm(0,0.01) VisitB.GS1~dnorm(0,0.01)
VisitC.GS1~dnorm(0,0.01) VisitD.GS1~dnorm(0,0.01)
VisitB.GS2 \sim \text{dnorm}(0,0.01) \quad \text{VisitC.GS2} \sim \text{dnorm}(0,0.01)
VisitD.GS2 \sim \text{dnorm}(0,0.01) \quad \text{VisitB.GS3} \sim \text{dnorm}(0,0.01)
VisitC.GS3 \sim \text{dnorm}(0,0.01) \quad \text{VisitD.GS3} \sim \text{dnorm}(0,0.01)
VisitB.GS4 \sim \text{dnorm}(0,0.01) \quad \text{VisitC.GS4} \sim \text{dnorm}(0,0.01)
VisitD.GS4 \sim \text{dnorm}(0,0.01) \quad \text{VisitB.GS5} \sim \text{dnorm}(0,0.01)
VisitC.GS5 \sim \text{dnorm}(0,0.01) \quad \text{VisitD.GS5} \sim \text{dnorm}(0,0.01)

\text{groupMild.GS1} \sim \text{dnorm}(0,0.01) \quad \text{groupSevere.GS1} \sim \text{dnorm}(0,0.01)
\text{groupMild.GS2} \sim \text{dnorm}(0,0.01) \quad \text{groupSevere.GS2} \sim \text{dnorm}(0,0.01)
\text{groupMild.GS3} \sim \text{dnorm}(0,0.01) \quad \text{groupSevere.GS3} \sim \text{dnorm}(0,0.01)
\text{groupMild.GS4} \sim \text{dnorm}(0,0.01) \quad \text{groupSevere.GS4} \sim \text{dnorm}(0,0.01)
\text{groupMild.GS5} \sim \text{dnorm}(0,0.01) \quad \text{groupSevere.GS5} \sim \text{dnorm}(0,0.01)

\text{groupMild.VisitB.GS1} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitC.GS1} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitD.GS1} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitB.GS1} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitC.GS1} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitD.GS1} \sim \text{dnorm}(0,0.01)

\text{groupMild.VisitB.GS2} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitC.GS2} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitD.GS2} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitB.GS2} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitC.GS2} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitD.GS2} \sim \text{dnorm}(0,0.01)

\text{groupMild.VisitB.GS3} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitC.GS3} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitD.GS3} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitB.GS3} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitC.GS3} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitD.GS3} \sim \text{dnorm}(0,0.01)

\text{groupMild.VisitB.GS4} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitC.GS4} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitD.GS4} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitB.GS4} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitC.GS4} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitD.GS4} \sim \text{dnorm}(0,0.01)

\text{groupMild.VisitB.GS5} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitC.GS5} \sim \text{dnorm}(0,0.01)
\text{groupMild.VisitD.GS5} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitB.GS5} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitC.GS5} \sim \text{dnorm}(0,0.01)
\text{groupSevere.VisitD.GS5} \sim \text{dnorm}(0,0.01)

### Survival ###
\text{Intercept.surv} \sim \text{dnorm}(0,0.01)
\text{Age_bs.surv} \sim \text{dnorm}(0,0.01)
\text{GenderMi.surv} \sim \text{dnorm}(0,0.01)
\text{groupMild.surv} \sim \text{dnorm}(0,0.01)
\text{groupSevere.surv} \sim \text{dnorm}(0,0.01)

### Associations parameter ###
\text{alpha_b0i} \sim \text{dnorm}(0,0.01)
\text{alpha_b0ij} \sim \text{dnorm}(0,0.01)
\text{alpha_b0ik} \sim \text{dnorm}(0,0.01)

# Shape parameter for full Weibull model
\text{shape} \sim \text{dgamma}(0.01,0.01)

# Residual error variance (random effects)
```r
tau ~ dgamma(0.001, 0.001)
sigma.tau <- 1/tau
# Wishart prior for the inverse variance-covariance 3x3 matrix
# (random effects)
# with R as a mean value
isigma[1:3, 1:3] ~ dwish(R[,], 3)
# Covariance matrix (random effects)
sigma[1:3, 1:3] <- inverse(isigma[,])
}  # for model
```