



Two-level models for binary outcomes

The data

To illustrate the application of the mixed-effects ordinal logistic regression model to longitudinal data, data from the NIMH Schizophrenia Collaborative Study on treatment related changes in overall severity are used. Specifically, Item 79 of the Inpatient Multidimensional Psychiatric Scale (IMPS; Lorr & Klett, 1966) was used. Item 79, "Severity of Illness," (IMPS79) was scored as: 1 = normal, or not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill. An ordinal mixed-effects model, with the seven ordered categories recoded into four, is given in the section dealing with ordinal variables. In the present example, scores have been recoded to a dichotomous variable, where scores up to, but excluding 3.5 were coded 0, and scores of 3.5 or higher were coded 1. The value "0" is associated with measurements classified as normal, borderline, mildly, or moderately mentally ill, while the value "1" was assigned to measurements corresponding to "markedly ill" through "most extremely ill." In this study, patients were randomly assigned to receive one of four medications: placebo, chlorpromazine, fluphenazine, or thioridazine. Since previous analyses (Longford, 1993, and Gibbons & Hedeker, 1994) revealed similar effects for the three anti-psychotic drug groups, they were combined in the present analysis. Finally, again based on previous analysis, to linearize the relationship of the IMPS79 scores over time, a square root transformation of time was chosen.

Data for the first 10 participants on most of the variables used in this section are shown below in the form of a SuperMix spreadsheet file, named **schizx1.ss3**.

The variables of interest are:

- ID indicates the subject (437 patients in total).
- Imps79 represents the original score on Item 79 of the Inpatient Multidimensional Psychiatric Scale.
- Imps79D is a recoded version of the same scale, but in binary form, with coding as discussed above.

	(A) Patient	(B) Imps79	(C) Imps79	(D) Imps79	(E) TxDrug	(F) Week	(G) SqrtWeek	(H) Tx*SWeek
1	1103	5.50	1	4	1	0	0.00	0.00
2	1103	3.00	0	2	1	1	1.00	1.00
3	1103	-9.00	-9	-9	1	2	1.41	1.41
4	1103	2.50	0	2	1	3	1.73	1.73
5	1103	-9.00	-9	-9	1	4	2.00	2.00
6	1103	-9.00	-9	-9	1	5	2.24	2.24
7	1103	4.00	1	2	1	6	2.45	2.45
8	1104	6.00	1	4	1	0	0.00	0.00
9	1104	3.00	0	2	1	1	1.00	1.00
10	1104	-9.00	-9	-9	1	2	1.41	1.41

- Imps790 is also a recoded version of the same scale, but with the 7 original categories reduced to four.
- TxDrug indicates the treatment group, where 1 indicates membership in the treatment group, and 0 membership in the control group.
- Week represents the time during the course of the study when a specific measurement was made, and ranges between 0 and 6.
- SqrtWeek is the square root of Week.
- Tx*SWeek is the product of the treatment group and the square root of Week.

In this data file, each subject's data consist of seven lines, these being the repeated measurements on seven occasions. Notice that there are missing value codes (-9) for some subjects at specific time points. The data from these time points will not be used in the analysis, but data from these subjects at other time points where there are no missing data will be used in the analysis. Thus, for inclusion into the analysis, a subject's data (both the dependent variable and all model covariates being used in a particular analysis) at a specific time point must be complete. The number of repeated observations per subject then depends on the number of time points for which there are non-missing data for that subject. The specification of missing data codes will be illustrated in the model specification section to follow.

The models

Continuous outcomes

A general two-level model for a continuous response variable y depending on a set of r predictors x_1, x_2, \dots, x_r can be written in the form

$$y_{ij} = \mathbf{x}'_{ij} \boldsymbol{\beta}_i + \mathbf{w}'_{ij} \boldsymbol{\alpha} + \mathbf{e}_{ij}$$

Where $i=1,2,\dots,N$ denotes the level-2 units, and $j=1,2,\dots,n_i$ the level-1 units. In this context, y_{ij} represents the response of individual j , nested within level-2 unit i . The model shown here consists of a fixed and a random part. The fixed part of the model is represented by the vector product $\mathbf{w}'_{ij}\boldsymbol{\alpha}$, where \mathbf{w}'_{ij} is a typical row of the design matrix of the fixed part of the model with, as elements, a subset of the r predictors. The vector $\boldsymbol{\alpha}$ contains the fixed, but unknown parameters to be estimated. $\mathbf{x}'_{ij}\boldsymbol{\beta}_i$, and e_{ij} denote the random part of the model at levels 2 and 1 respectively. For example, \mathbf{x}'_{ij} represents a typical row of the design matrix of the random part at level 2, and $\boldsymbol{\beta}_i$ the vector of random level-2 effects to be estimated. It is assumed that $\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \dots, \boldsymbol{\beta}_N$ are independently and identically distributed (i.i.d.) with mean vector $\mathbf{0}$ and covariance matrix $\boldsymbol{\Phi}_{(2)}$. Similarly, the e_{ij} are assumed i.i.d., with mean vector $\mathbf{0}$ and covariance matrix $\sigma^2\mathbf{I}$.

Within this hierarchical framework, the effects of TxDrug, SqrtWeek, and Tx*SWeek can be used to predict the Imps79 score for the case where Imps79 is a continuous variable. The corresponding model may be expressed as

$$\text{Imps79}_{ij} = \alpha_0 + \alpha_1 * \text{TxDrug}_{ij} + \alpha_2 * \text{SqrtWeek}_{ij} + \alpha_3 * \text{Tx*SWeek}_{ij} + \beta_{i0} + e_{ij}$$

where α_0 denotes the average expected Imps79 score, and α_1, α_2 , and α_3 indicate the estimated coefficients associated with the fixed part of the model which contains the predictor variables TxDrug, SqrtWeek, and Tx*SWeek. The random part of the model is represented by β_{i0} and e_{ij} , which denote the variation in average score over patients and between measurements nested within patients at the lowest level of the hierarchy.

Binary outcomes

In the current example, the outcome variable is Imps79D, which is of a binary nature. The original scores on Item 79 of the Inpatient Multidimensional Psychiatric Scale have been recoded to a dichotomous variable, where scores up to, but excluding 3.5 were coded 0, and scores of 3.5 or higher were coded 1. In this case, the predicted value of the outcome can be viewed as the predicted probability that Imps79D is 1. Due to this, predicted values outside the interval (0,1) would not be meaningful and a model constraining predicted values to lie within this interval would be appropriate, in contrast with the model for a continuous outcome (see above) where predicted values outside this interval would be interpretable. In addition, the assumption of normality at level 1 is not realistic, as the level-1 random effect can only assume one of two values: 0 or 1. This random effect can thus not have homogeneous variance.

In order to insure that the predicted value lies within the (0,1) interval, a transformation of the level-1 predicted probability can be used. For the binary case considered here, we have

$$\text{Prob}(\text{Imps79D}_{ij} = 1 | \boldsymbol{\alpha}, \boldsymbol{\beta}_i) = \frac{e^{\eta_{ij}}}{1 + e^{\eta_{ij}}}$$

where η_{ij} represents the log of the odds of success, and (for the current model) can be expressed as

$$\eta_{ij} = \alpha_0 + \alpha_1 * \text{TxDrug}_{ij} + \alpha_2 * \text{SqrtWeek}_{ij} + \alpha_3 * \text{Tx} * \text{SWeek}_{ij} + \beta_{i0} + e_{ij}.$$

This transformation, commonly referred to as the logit link function, constrains $\text{Prob}(y_{ij} = 1 | \boldsymbol{\beta})$ to lie in the interval (0,1).

Example: Logistic regression with a random intercept

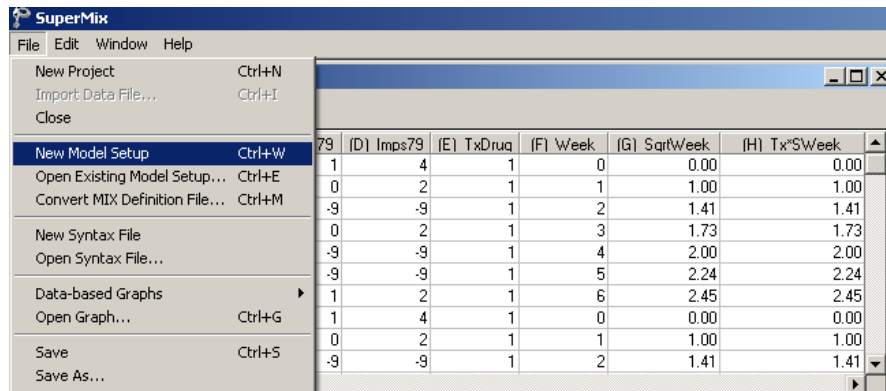
The model is fitted to the data in **schizx1.ss3**. The first step is to create the **ss3** file **schizx1.ss3** from an Excel spreadsheet named **schizx1.xls**. This is accomplished as follows:

- Use the **File, Import Data File** option to activate the display of an **Open** dialog box.
- Browse for the file **schizx1.xls** in the **Examples, Binary** folder.
- Select the file and click the **Open** button to return to the main SuperMix window, where the contents of the Excel spreadsheet are displayed as the SuperMix system file with default name **schizx1.ss3**.

	(A) Patient	(B) Imps79	(C) Imps79	(D) Imps79	(E) TxDrug	(F) Week	(G) SqrtWeek	(H) Tx*SWeek
1	1103	5.50	1	4	1	0	0.00	0.00
2	1103	3.00	0	2	1	1	1.00	1.00
3	1103	-9.00	-9	-9	1	2	1.41	1.41
4	1103	2.50	0	2	1	3	1.73	1.73
5	1103	-9.00	-9	-9	1	4	2.00	2.00
6	1103	-9.00	-9	-9	1	5	2.24	2.24
7	1103	4.00	1	2	1	6	2.45	2.45
8	1104	6.00	1	4	1	0	0.00	0.00
9	1104	3.00	0	2	1	1	1.00	1.00
10	1104	-9.00	-9	-9	1	2	1.41	1.41

Setting up the analysis

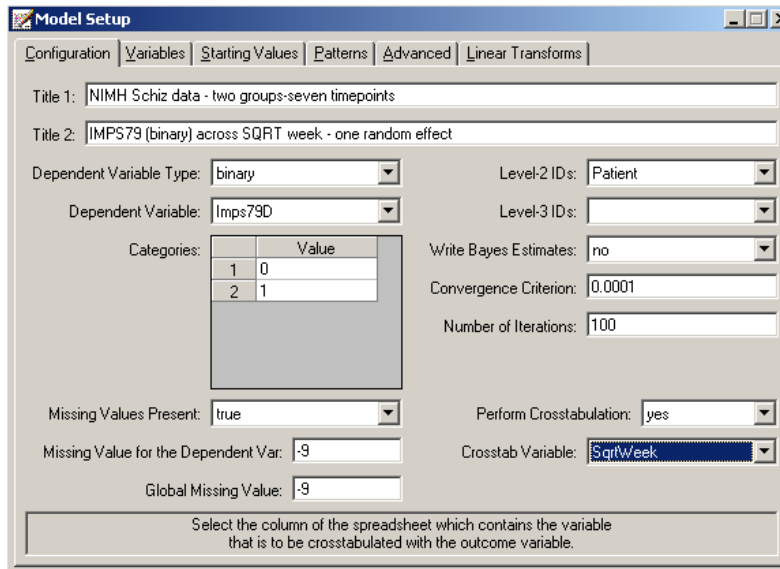
The next step is to describe the model to be fitted. We use the SuperMix interface to provide the model specifications. From the main menu bar, select the **File, New Model Setup** option.



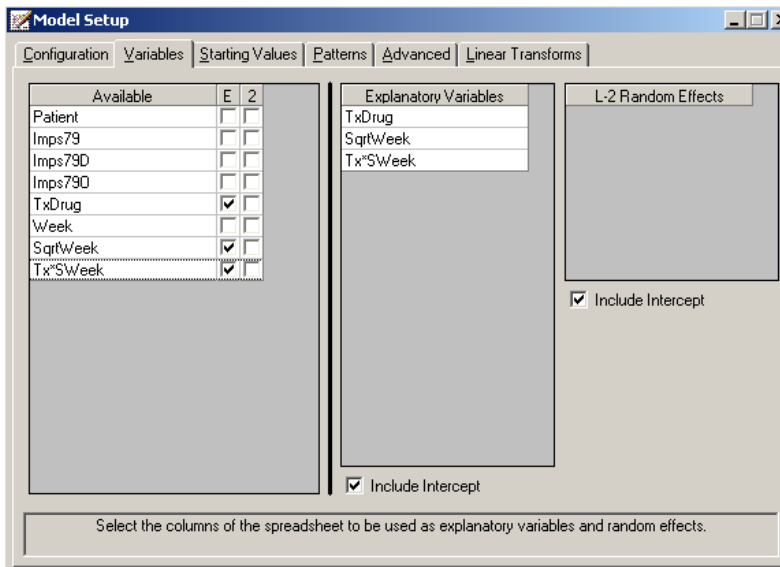
The **Model Setup** window that appears has six tabs. In this example, three of these tabs are used in model specification.

As a first step, select the dichotomous outcome variable Imps79D from the **Dependent Variable** drop-down list box on the **Configuration** screen. Specify the type of outcome as binary using the **Dependent Variable Type** drop-down list box. Once this selection is made, the **Categories** grid is displayed. As there are missing data in the **ss3** file for both outcome and potential predictors, set the **Missing Values Present** drop-down list box to true. Once this is done, the **Missing Values for Dependent Var** and **Global Missing Value** text boxes are displayed. Enter the value -9 into both these boxes.

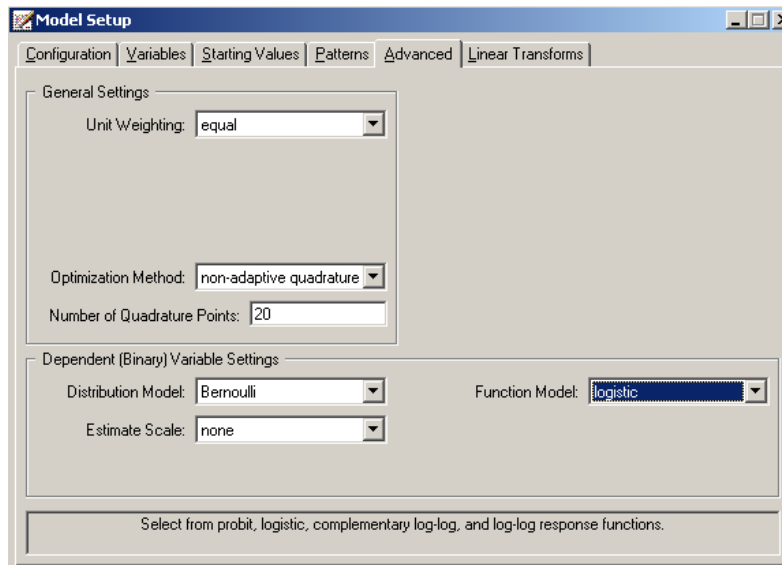
The patient identification variable is used to define the hierarchical structure of the data, and is selected as the Level-2 ID from the **Level-2 IDs** drop-down list box. Enter a title for the analysis in the **Title 1** and **Title 2** text boxes. Request a crosstabulation of the outcome variable and the predictor SqrtWeek by setting the **Perform Crosstabulation** and **Crosstab Variable** drop-down list boxes to **yes** and SqrtWeek respectively.



The **Variables** screen is used to specify the fixed and random effects to be included in the model. Start by selecting the explanatory (fixed) variables TxDrug, SqrtWeek, and Tx*SWeek by checking the check boxes in the **E** column of the **Available** grid.



After selecting all the explanatory variables, the random effect(s) at level 2 must be selected. By default, the model will include a random intercept, as indicated by the check box for **Include Intercept** in the **L-2 Random Effects** grid. The intercept is assumed to vary randomly over higher levels of the hierarchy, while the slopes of the predictors TxDrug, SqrtWeek and the interaction between treatment and the square root of the treatment time, Tx*SWeek, are assumed to be adequately described by common, fixed coefficients that do not vary across patients.



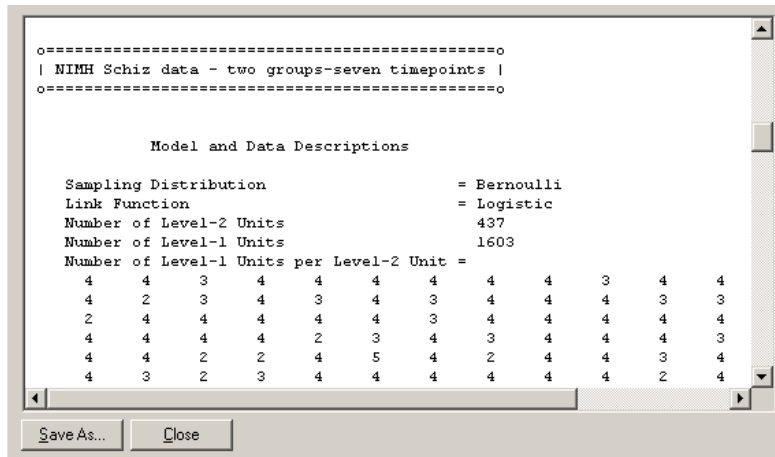
Next, click on the **Advanced** tab. This screen is used to specify additional settings for the case where the outcome variable is ordered. Set the **Function model** to **logistic**, and request the use of 20 non-adaptive quadrature points for estimation by entering the number 20 in the **Number of Quadrature Points** text box. No changes are made to the **Unit Weighting** box. Default settings for this option will be used in the analysis. The completed **Advanced** screen is shown above.

Before running the analysis, the model specifications have to be saved. Select the **File, Save** option, and provide a name for the model specification file. Run the analysis by selection the **Run** option from the **Analysis** menu.

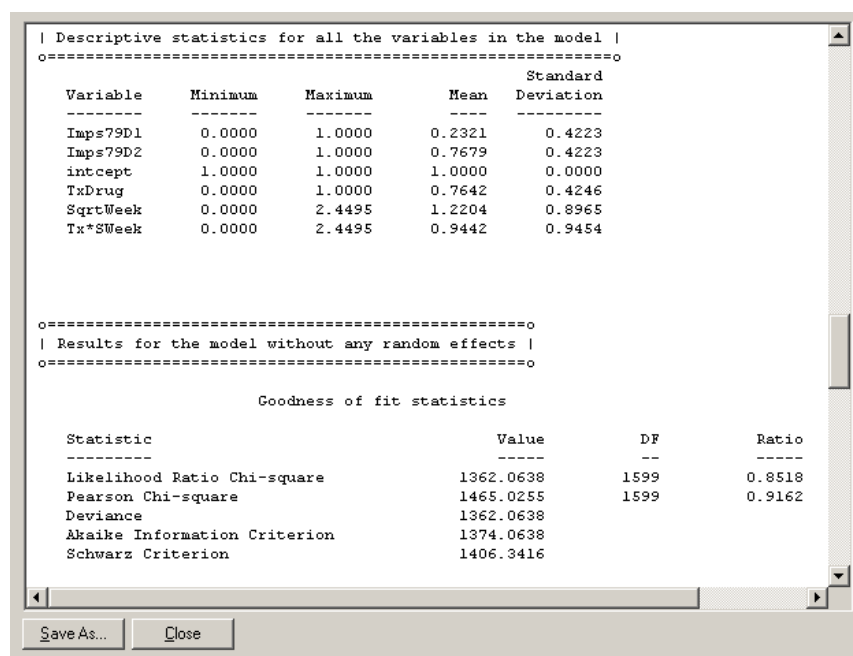
Discussion of results

Portions of the output file **schizx1.out** are shown below.

In the first section of the output file, a summary of the model specifications is provided. The use of a logistic response function (logit link function) is indicated. This is followed by a summary of the number of observations nested within each patient. The Level 2 observations entry corresponds to the number of patients for whom data were included in the analysis.



The data summary is followed by descriptive statistics for all the variables included in the model. We note that 23% of the patients had a value of 0 on the binary Imps79D score which indicates no or moderate signs of mental illness (Imps79D = 0).



The crosstabulation of the outcome variable and the predictor SqrtWeek requested on the **Variables** screen during model specification is listed next. We see that most of the measurements (1231) are from the higher, more ill, category of Imps79D. It is also noticeable that more data were obtained at the start, the fourth time point, and the end of the study than on the remaining occasions. The results for the model without any random effects serve as starting values for the iterative procedure.

SuperMix - [schizx1.out]

File Analysis Window Help

Crosstabulation of variable SQTWEEK by the response variable IMPS79D

SQTWEEK	IMPS79D		Total
	0.00	1.00	
0.00	6.0 (0.01)	428.0 (0.99)	434.0
1.00	67.0 (0.16)	359.0 (0.84)	426.0
1.41	5.0 (0.36)	9.0 (0.64)	14.0
1.73	108.0 (0.29)	266.0 (0.71)	374.0
2.00	7.0 (0.64)	4.0 (0.36)	11.0
2.24	6.0 (0.67)	3.0 (0.33)	9.0
2.45	173.0 (0.52)	162.0 (0.48)	335.0
Total	372.0	1231.0	1603.0

The output summarizing the estimated parameters after convergence is shown next. Sixteen iterations were required to obtain convergence. The estimates are shown in the column with heading Estimate, and correspond to the coefficients $\alpha_0, \alpha_1, \alpha_2$ and α_3 in the model specification. No estimate of the level-1 variance is given, as there is no single level-1 variance for this model.

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=====o
| Optimization Method: Non-Adaptive Quadrature |
=====o

Number of quadrature points =          20
Number of free parameters =           5
Number of iterations used =           5

-2lnL (deviance statistic) =          1249.73475
Akaike Information Criterion =         1259.73475
Schwarz Criterion =                   1286.63291

Estimated regression weights

Parameter      Estimate      Standard      z Value      P Value
-----
intcept        5.3905       0.6310       8.5431       0.0000
TxDrug         -0.0244      0.6539      -0.0374      0.9702
SqrtWeek       -1.5005      0.2908      -5.1605      0.0000
Tx*SWeek       -1.0158      0.3341      -3.0408      0.0024

Estimated level 2 variances and covariances

Parameter      Estimate      Standard      z Value      P Value
-----
intcept/intcept  4.4902       0.9480       4.7366      0.0000

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Save As... Close

The expected log-odds of having a high score at the end of the study period (Imps79D score of 1) for a patient from the control group (that is, TxDrug = Tx*SWeek = SqrtWeek = 0) is represented by the estimated intercept of 5.3905. The negative and significant coefficient for SqrtWeek indicates that the probability of having a high score decreases with time and more so when the interaction between receiving treatment and time is taken into account (Tx*SWeek = -1.0158, $p = 0.0024$). There is also evidence of significant random variation in the intercepts over patients.

Estimated unit-specific probabilities

To evaluate the expected effect of TxDrug, SqrtWeek, and Tx*SWeek on the predicted probability that the Imps79D score is equal to 1, we use the expression for the predicted log odds of success given earlier

$$\hat{\eta}_{ij} = \hat{\alpha}_0 + \hat{\alpha}_1 \times \text{TxDrug}_{ij} + \hat{\alpha}_2 \times \text{SqrtWeek}_{ij} + \hat{\alpha}_3 \times \text{Tx} \times \text{SWeek}_{ij}.$$

For a typical measurement from any patient from the control group at the beginning of the study period (TxDrug = SqrtWeek = Tx*SWeek = 0) we have

$$\hat{\eta}_{ij} = \hat{\alpha}_0.$$

For a typical measurement from any patient from the treatment group at the beginning of the study period, $\hat{\eta}_{ij}$ can be expressed as

$$\begin{aligned} \hat{\eta}_{ij} &= \hat{\alpha}_0 + \hat{\alpha}_1 \times \text{TxDrug}_{ij} \\ &= \hat{\alpha}_0 + \hat{\alpha}_1. \end{aligned}$$

Using the estimates of $\hat{\alpha}_0$ and $\hat{\alpha}_1$ of 5.3905 and -0.0244 respectively as obtained for the current analysis, we can calculate the subject-specific probability of an Imps79D score of 1 as

$$\begin{aligned} \text{Prob}(\text{Imps79D}_{ij} = 1 \mid \text{TxDrug} = \text{SqrtWeek} = \text{Tx} \times \text{SWeek} = 0) &= \frac{e^{5.3905}}{1 + e^{5.3905}} \\ &= 0.9955 \end{aligned}$$

and

$$\begin{aligned} \text{Prob}(\text{Imps79D}_{ij} = 1 \mid \text{TxDrug} = 1; \text{SqrtWeek} = \text{Tx} \times \text{SWeek} = 0) &= \frac{e^{5.3905 - 0.0244}}{1 + e^{5.3905 - 0.0244}} \\ &= 0.9953 \end{aligned}$$

respectively.

On the other end of the scale in terms of time, we can consider patients from both control and treatment groups at the end of the study period. For both groups, this corresponds to a value of 2.45 on the variable SqrtWeek.

For a typical measurement from any patient from the control group at the end of the study period we have

$$\begin{aligned} \hat{\eta}_{ij} &= \hat{\alpha}_0 + \hat{\alpha}_2 \times \text{SqrtWeek}_{ij} \\ &= \hat{\alpha}_0 + 2.45 \times \hat{\alpha}_2 \\ &= 1.7143. \end{aligned}$$

For a typical measurement from any patient from the treatment group at the end of the study period, $\hat{\eta}_{ij}$ can be expressed as

$$\begin{aligned} \hat{\eta}_{ij} &= \hat{\alpha}_0 + \hat{\alpha}_1 \times \text{TxDrug}_{ij} + \hat{\alpha}_2 \times \text{SqrtWeek}_{ij} + \hat{\alpha}_3 \times \text{Tx} * \text{SWeek}_{ij} \\ &= \hat{\alpha}_0 + \hat{\alpha}_1 + 2.45 \left(\hat{\alpha}_2 + \hat{\alpha}_3 \right) \\ &= -0.7988. \end{aligned}$$

In Table 3.2, the predicted probabilities of a high post-treatment Imps79D score are given for patients from both experimental groups at selected time points during the study period.

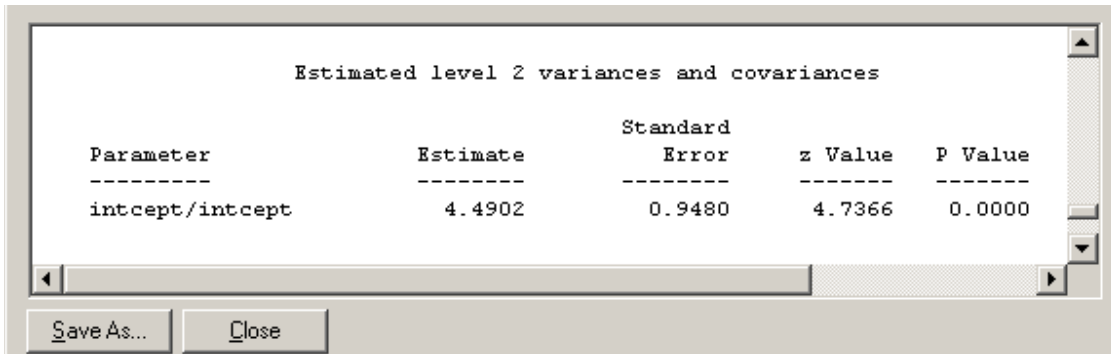
We conclude that the diagnoses for both control and treatment groups improved over the seven week study period. There is, however, a marked decrease in $P(\text{Imps79D}) = 1$ for the treatment group. Looking at the differences of probabilities at the end of the trial, we can draw the conclusion that the treatment effect is highly significant.

Table 3.2: Predicted probability of a high post-treatment Imps79D score

Square root of week (SqrtWeek)	Control group	Treatment group
0.00	0.9955	0.9953
1.73	0.9424	0.7336
2.45	0.8473	0.3103

Estimated population-average probabilities

Table 3.2 contains estimated unit (patient) specific probabilities. To obtain population-average probabilities, the estimated η_{ij} – values are divided by the square root of the design effect. These adjusted η_{ij} – values are subsequently used in the computation of the probabilities.



Finally, the random variation in intercept over patients is estimated at 4.477.

In addition to the standard output file **schizx1.out**, the **Write Bayes Estimates** drop-down list box on the **Configuration** screen of the **Model Setup** window was used to request Bayes estimates for the individual random terms. This is done by selecting the **means & (co)variances** option from the **Write Bayes Estimates** drop-down list box. These estimates are written to the file **schizx1.ba2**. The first few lines of this file are shown below.

Level-3 ID	Level-2 ID	Uij01	Cov(01,01)
1.00	1103.00	-1.375397	1.434063
1.00	1104.00	-2.826594	1.492193
1.00	1105.00	-2.750448	1.593848
1.00	1106.00	-4.407172	1.700419
1.00	1107.00	0.970126	2.795587
1.00	1108.00	1.931422	2.205989
1.00	1109.00	-2.826594	1.492193
1.00	1110.00	1.931422	2.205989
1.00	1111.00	0.105153	1.573764
1.00	1112.00	-1.310094	1.763492
1.00	1113.00	-1.375397	1.434063
1.00	1114.00	0.105153	1.573764
1.00	1115.00	0.970126	2.795587
1.00	1118.00	0.476509	3.448127
1.00	1119.00	0.092066	1.591734
1.00	1124.00	0.970126	2.795587
1.00	1125.00	-2.896372	1.505657
1.00	1129.00	-1.149182	1.614074
1.00	1136.00	0.592035	3.243141

Four pieces of information per patient are given:

- the level-3 ID (if any),
- the level-2 ID (patient number),
- the empirical Bayes estimate ($\hat{\beta}_{i0}$), and
- the estimated associated posterior variance of the patient estimate $\text{var}(\hat{\beta}_{i0})$.

From the data, we know that the first patient, with ID = 1103, was a member of the treatment group. On the other hand, the patient with ID = 1107 was assigned to the control group. At the beginning of the study, the predictor SqrtWeek and hence the interaction term Tx*SWeek were equal to zero. In both cases, the observed Imps79D score at the beginning of the study was equal to 1. Their empirical Bayes estimates were -1.3754 and 0.9701 respectively. For measurements from each of these patients, this implies

$$\begin{aligned}
 \text{Prob}(\text{Imps79D}_{ij} = 1 \mid \text{TxDrug} = 1, \text{SqrtWeek}=0, \text{ID}=1103) &= \frac{e^{5.3905-1.3754-0.0244}}{1 + e^{5.3905-1.3754-0.0244}} \\
 &= \frac{e^{3.9907}}{1 + e^{3.9907}} \\
 &= 0.9818
 \end{aligned}$$

and

$$\begin{aligned}
 \text{Prob}(\text{Imps79D}_{ij} = 1 \mid \text{TxDrug} = 0, \text{SqrtWeek}=0, \text{ID}=1107) &= \frac{e^{5.3905+0.9701}}{1 + e^{5.3905+0.9701}} \\
 &= 0.9983
 \end{aligned}$$

respectively.

Similarly, we find that at the end of the study

$$\begin{aligned}
 & \text{Prob}(\text{Imps79D}_{ij} = 1 \mid \text{TxDrug} = 1, \text{SqrtWeek}=2.45, \text{ID}=1103) \\
 &= \frac{e^{5.3905-1.3754-0.0244-1.5005(2.45)-1.0158(2.45)}}{1 + e^{5.3905-1.3754-0.0244-1.5005(2.45)-1.0158(2.45)}} \\
 &= \frac{e^{-2.1742}}{1 + e^{-2.1742}} \\
 &= 0.1021
 \end{aligned}$$

and

$$\begin{aligned}
 & \text{Prob}(\text{Imps79D}_{ij} = 1 \mid \text{TxDrug} = 0, \text{SqrtWeek}=2.45, \text{ID}=1107) = \frac{e^{5.3905+0.9701-1.5005(2.45)}}{1 + e^{5.3905+0.9701-1.5005(2.45)}} \\
 &= \frac{e^{2.6844}}{1 + e^{2.6844}} \\
 &= 0.9361.
 \end{aligned}$$

Using the empirical Bayes estimates for each patient, we can also obtain the predicted probability of improving. This probability, $\text{Prob}(\text{Imps79D}_{ij} = 0 \mid \text{ID} = i, i = 1, 2, \dots, N)$ is obtained as $1 - (\text{Prob}(\text{Imps79D}_{ij} = 1 \mid \text{ID} = i, i = 1, 2, \dots, N))$. In Figures 3.11 and 3.12 below, the predicted probabilities of improving for all measurements are shown, with a linear regression line showing the mean probability for each group.

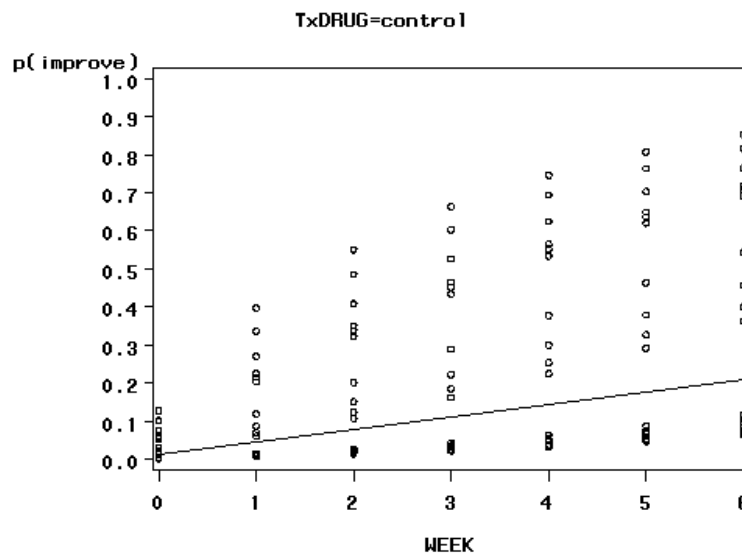


Figure 3.11: Predicted probability of improvement (control group)

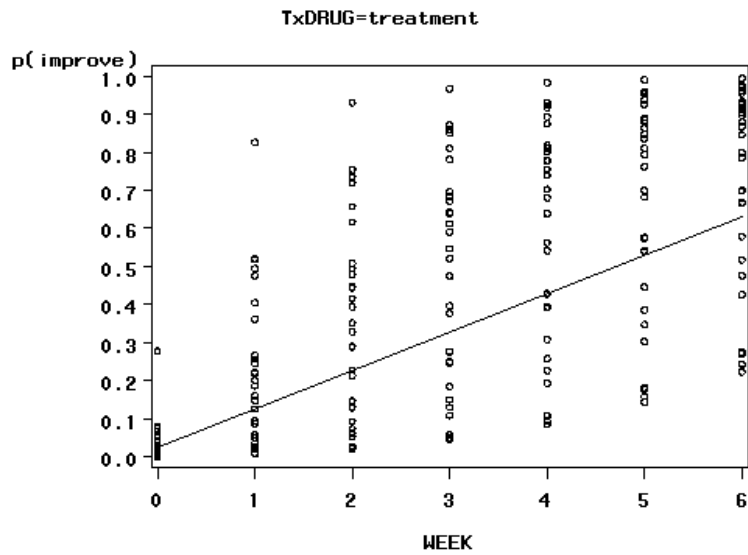


Figure 3.12: Predicted probability of improvement (treatment group)

For both groups, an increased probability of obtaining a predicted value of 0 on the outcome is observed. Recall that the value "0" is associated with measurements classified as normal, borderline, mildly, or moderately mentally ill, while the value "1" was assigned to measurements corresponding to "markedly ill" through "most extremely ill". However, the patients in the treatment group were much more likely to show improvement, as can be seen from the slopes of the regression lines for the groups in Figure 3.13.

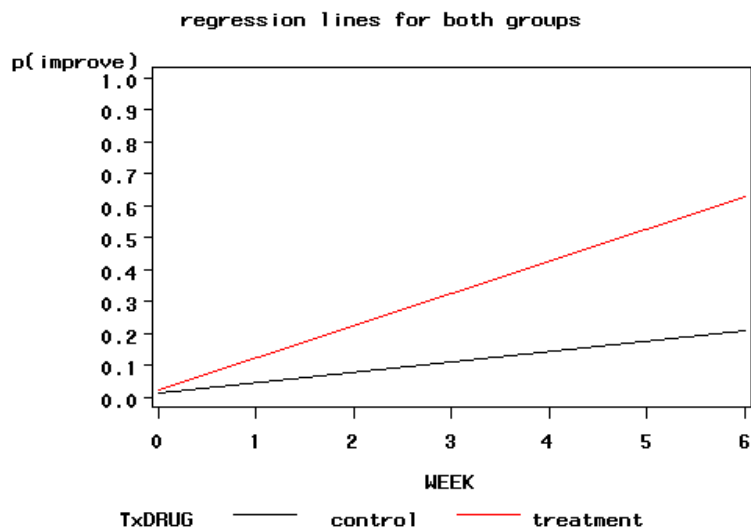


Figure 3.13: Regression lines for control and treatment groups