17
The Analgesic Trial

17.1 Introduction

Marginal models, fitted to the analgesic trial, introduced in Section 2.2, more specifically to the binary 'general satisfaction assessment' outcome ('GSABIN,' denoted by Y_{ij}), will be studied in Section 17.2. Section 17.3 describes subject-specific models fitted to the GSABIN outcome. A comparison between both methods is offered in Section 17.4. Some key programs are presented in Section 17.5. We should keep in mind that the actual outcome, GSA, is measured on a five-point ordinal scale. Ordinal outcomes is the topic of Chapter 18, and there also, a number of analyses of the analgesic trial will be offered.

Another issue deserves mention at this point. As is to be expected in patients with severe chronic pain, a good number drops out before the end of the study. Unless the very strong assumption of missingness completely at random (MCAR) is made, GEE is strictly speaking not valid in this case. MCAR is violated as soon as the reason for missingness is outcome related, even when the dependence is on observed outcomes. The missing data concepts are outlined in Chapter 26. Ways to extend GEE to overcome this problem are presented in Chapter 27, where these data will be considered again.

17.2 Marginal Analyses of the Analgesic Trial

The analgesic trial has been introduced in Section 2.2. The primary outcome in this one-armed trial is ordinally scored global satisfaction assessment (GSA). For the purpose of our analysis, we will consider a dichotomized version of (2.1):

$$\text{GSABIN} = \begin{cases} 1 \text{ if GSA} \leq 3 \text{ ('Very Good' to 'Moderate')}, \\ 0 \text{ otherwise.} \end{cases} \tag{17.1}$$

Preliminary analyses have indicated that, among a set of potential covariates, the linear and square effects of time t_{ij}, as well as the effect of baseline pain control assessment ('PCA0,' denoted X_i) are of importance. The marginal regression model so obtained is

$$\text{logit}[P(Y_{ij} = 1|t_{ij}, X_i)] = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 X_i. \tag{17.2}$$

Because there are four equally-spaced follow-up measurements, not only independence and exchangeable, but also autoregressive and unstructured working assumptions are consistent with the design of the study. Table 17.1 displays parameter estimates and standard errors for standard GEE (Section 8.2) , under a variety of working assumptions. Table 17.2 presents the results for alternating logistic regression (Section 8.6). Table 17.3 summarizes analyses from Tables 17.1 and 17.2 that are based on exchangeable working assumptions, and supplements them with the corresponding fits obtained from ordinary logistic regression, Prentice's method (Section 8.4) and the linearization method (Section 8.8). It is clear from Table 17.1 that all analyses agree closely in terms of parameter estimates and standard errors. Even between the empirically corrected and model-based standard errors, there is little difference. This may be due to the fact that the correlation is relatively small. However, given the size of the dataset, it is likely that the correlation is significantly different from zero. Exploring the correlation in a little more detail, we find for the three non-trivial correlation matrices:

$$R_{\text{EXCH}} = \begin{pmatrix} 1 & 0.22 & 0.22 & 0.22 \\ & 1 & 0.22 & 0.22 \\ & & 1 & 0.22 \\ & & & 1 \end{pmatrix},$$

$$R_{\text{AR}} = \begin{pmatrix} 1 & 0.25 & 0.06 & 0.02 \\ & 1 & 0.25 & 0.06 \\ & & 1 & 0.25 \\ & & & 1 \end{pmatrix},$$

TABLE 17.1. *Analgesic Trial. Parameter estimates (model-based standard errors; empirically corrected standard errors) for standard GEE under a variety of working assumptions: IND (independence), EXCH (exchangeable), AR (autoregressive), UN (unstructured).*

Effect	Parameter	IND	EXCH
Intercept	β_1	2.80(0.49;0.47)	2.92(0.49;0.46)
Time	β_2	-0.79(0.39;0.34)	-0.83(0.34;0.33)
Time^2	β_3	0.18(0.08;0.07)	0.18(0.07;0.07)
Basel. PCA	β_4	-0.21(0.09;0.10)	-0.23(0.10;0.10)
Correlation	ρ	—	0.22
Effect	Parameter	AR	UN
Intercept	β_1	2.94(0.49;0.47)	2.87(0.48;0.46)
Time	β_2	-0.90(0.35;0.33)	-0.78(0.33;0.32)
Time^2	β_3	0.20(0.07;0.07)	0.17(0.07;0.07)
Basel. PCA	β_4	-0.22(0.10;0.10)	-0.23(0.10;0.10)
Correlation	ρ	0.25	—
Correlation (1,2)	ρ_{12}		0.18
Correlation (1,3)	ρ_{13}		0.25
Correlation (1,4)	ρ_{14}		0.20
Correlation (2,3)	ρ_{23}		0.18
Correlation (2,4)	ρ_{24}		0.18
Correlation (3,4)	ρ_{34}		0.46

and

$$R_{\text{UN}} = \begin{pmatrix} 1 & 0.18 & 0.25 & 0.20 \\ & 1 & 0.18 & 0.18 \\ & & 1 & 0.46 \\ & & & 1 \end{pmatrix},$$

with obvious notation. Inspecting R_{UN}, it is clear that AR may be a working assumption, different from the true structure. EXCH looks more promising as a simplification to UN, even though it looks like ρ_{34} is higher than the others, while the others might well be equal to one another. Two remarks are in place. First, the above reasoning is irrelevant for the validity of GEE since the working assumptions are allowed to be incorrect, the only aspect that might be jeopardized being efficiency. This is clearly not the case in this analysis. Second, if one were interested in the correlation structure as such, there is no means within the standard GEE framework to make formal inferences about the correlation structure.

To overcome this, let us study the results for ALR in Table 17.2. Apart from exchangeability, an unstructured odds ratio model is assumed (termed

TABLE 17.2. *Analgesic Trial. Parameter estimates and empirically corrected standard errors for ALR under a variety of log odds ratio structure: EXCH (exchangeable), FULLCLUST (unstructured), and ZREP (a user-defined design).*

Effect	Parameter	EXCH	FULLCLUST	ZREP
Intercept	β_1	2.98(0.46)	2.92(0.46)	2.92(0.46)
Time	β_2	-0.87(0.32)	-0.80(0.32)	-0.80(0.32)
Time^2	β_3	0.18(0.07)	0.17(0.06)	0.17(0.07)
Basel. PCA	β_4	-0.23(0.22)	-0.24(0.10)	-0.24(0.10)
Log OR	α	1.43(0.22)		
Log OR(1,2)	α_{12}		1.13(0.33)	
Log OR(1,3)	α_{13}		1.56(0.39)	
Log OR(1,4)	α_{14}		1.60(0.42)	
Log OR(2,3)	α_{23}		1.19(0.37)	
Log OR(2,4)	α_{24}		0.93(0.42)	
Log OR(3,4)	α_{34}		2.44(0.48)	
Log OR par.	α_0			1.26(0.23)
Log OR par.	α_1			1.17(0.47)

'fullclust' in the SAS procedure GENMOD). As stated earlier, the odds ratios now have a standard error associated to them. It is clear that some of our conjectures, based on the correlations in Table 17.1 are confirmed straightaway. For example, the exchangeable log odds ratio is significantly different from zero, and so are all the odds ratios in the unstructured model. There is also a hint that α_{34} is different from the others, with all others being equal. To confirm this, a formal test is necessary. An easy approach is to consider a Wald test for the null hypothesis

$$H_0 : \alpha_{12} = \alpha_{13} = \alpha_{14} = \alpha_{23} = \alpha_{24}.$$

A Wald test statistic for this null hypothesis would assume the form

$$W = (C\boldsymbol{\alpha})'(CVC')^{-1}(C\boldsymbol{\alpha})', \tag{17.3}$$

where $\boldsymbol{\alpha} = (\alpha_{12}, \alpha_{13}, \alpha_{14}, \alpha_{23}, \alpha_{24}, \alpha_{34})'$, C is an appropriate contrast matrix:

$$C = \begin{pmatrix} 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 \end{pmatrix}, \tag{17.4}$$

and V is the asymptotic covariance matrix of the log odds ratio parameters. An estimate for the matrix V is given in the SAS output by way of the

'covb' option in the REPEATED statement and equals:

$$\widehat{V} = \begin{pmatrix} 0.107 & 0.023 & 0.023 & 0.030 & 0.033 & 0.008 \\ 0.023 & 0.149 & 0.068 & 0.016 & 0.012 & 0.026 \\ 0.023 & 0.068 & 0.176 & 0.012 & 0.033 & 0.054 \\ 0.030 & 0.016 & 0.012 & 0.135 & 0.074 & 0.032 \\ 0.033 & 0.012 & 0.033 & 0.074 & 0.178 & 0.069 \\ 0.008 & 0.026 & 0.054 & 0.032 & 0.069 & 0.231 \end{pmatrix}. \tag{17.5}$$

Computing the Wald test statistic (17.3), using the estimated $\alpha_{j_1 j_2}$ parameters, yields $W = 2.04$ (4 d.f., $p = 0.7284$). Hence, the first five log odds ratio parameters can be considered equal. Given this, it is of interest to see whether these common parameters differ from the remaining one, α_{34}. A convenient null hypothesis then is

$$H_0 : \frac{1}{5}(\alpha_{12} + \alpha_{13} + \alpha_{14} + \alpha_{23} + \alpha_{24}) = \alpha_{34}.$$

A corresponding contrast matrix is

$$C = (1, 1, 1, 1, 1, -5). \tag{17.6}$$

The corresponding Wald test statistic equals $W = 6.35$ (1 d.f., $p = 0.0117$) and hence we can conclude that there is a pair of distinct odds ratios: a common one for the first five, and then the sixth one. Should one test the null hypothesis whether the exchangeable model is a tolerable simplification of the unstructured one, then C in (17.4) would be augmented with an additional row $(0, 0, 0, 0, 1, -1)$ and the corresponding 6 d.f. Wald test statistic equals 8.93 ($p = 0.1119$). This need not be considered a contradiction: the 6 d.f. dilutes the power associated with the single degree of freedom contrast (17.6), by combining it with 5 non-significant contrasts, given by (17.4).

The so-obtained final model is presented in the column labeled 'ZREP' in Table 17.2, where now:

$$\begin{aligned} \alpha_{12} = \alpha_{13} = \alpha_{14} = \alpha_{23} = \alpha_{24} &= \alpha_0, \\ \alpha_{34} &= \alpha_0 + \alpha_1. \end{aligned}$$

At the odds ratio level:

$$\begin{aligned} \widehat{\psi}_{12} = \widehat{\psi}_{13} = \widehat{\psi}_{14} = \widehat{\psi}_{23} = \widehat{\psi}_{24} &= \widehat{\psi}_0 = 3.53, \\ \widehat{\psi}_{34} &= \widehat{\psi}_0 \cdot \widehat{\psi}_1 = 11.36. \end{aligned}$$

Note that the Z-statistic associated with α_0 is highly significant ($p < 0.0001$), even though the estimated value may seem moderate. The Z test for α_1 produces a p-value of $p = 0.0119$, in perfect agreement with the corresponding Wald test, obtained above.

Although not commonly done, we could present the "odds ratio matrices" based on the models in Table 17.2:

$$\Psi_{\text{EXCH}} = \left\{ \begin{array}{cccc} 1 & 4.18 & 4.18 & 4.18 \\ & 1 & 4.18 & 4.18 \\ & & 1 & 4.18 \\ & & & 1 \end{array} \right\},$$

$$\Psi_{\text{UN}} = \left\{ \begin{array}{cccc} 1 & 3.10 & 4.76 & 4.95 \\ & 1 & 3.29 & 2.53 \\ & & 1 & 11.47 \\ & & & 1 \end{array} \right\},$$

and

$$\Psi_{\text{ZREP}} = \left\{ \begin{array}{cccc} 1 & 3.53 & 3.53 & 3.53 \\ & 1 & 3.53 & 3.53 \\ & & 1 & 11.36 \\ & & & 1 \end{array} \right\}.$$

Curly braces are used rather than parentheses, to avoid confusion with a correlation or covariance matrix. In summary, the 'ZREP' structure is adequate for the odds ratios, it is not necessary to spend 6 unstructured parameters. Although exchangeability is off, the discrepancy is not very large, and there certainly is no strong impact on the marginal model parameter estimates.

Clearly, the various GEE methods provide virtually the same fit. Not only the empirically corrected standard errors, but also the model-based ones (not shown here, except for logistic regression), virtually coincide.

17.3 Random-effects Analyses of the Analgesic Trial

In this section, we will consider the random-effects counterparts of (17.2) from Section 17.2:

$$\begin{array}{rcl} Y_{ij}|b_i & \sim & \text{Bernoulli}(\pi_{ij}), \\ \text{logit}(\pi_{ij}) & = & \beta_0 + b_i + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 X_i, \end{array} \qquad (17.7)$$

where notation is used as in Section 14.7, i.e.,

$$\pi_{ij} = \text{logit}P(Y_{ij} = 1|b_i, t_{ij}, X_i).$$

Thus, a random intercept has been added to the linear predictor (17.2), producing a random-intercept logistic regression model. Apart from the

TABLE 17.3. *Analgesic Trial. Parameter estimates (empirically corrected standard errors) for ordinary logistic regression, standard GEE, Prentice's GEE, the linearization-based method, and ALR under exchangeable working assumptions. (The standard errors for logistic regression are the usual, uncorrected ones.)*

Effect	Parameter	Log. regr.	Standard	Prentice
Intercept	β_1	2.80(0.49)	2.92(0.46)	2.94(0.46)
Time	β_2	-0.79(0.39)	-0.83(0.33)	-0.84(0.33)
Time^2	β_3	0.18(0.08)	0.18(0.07)	0.18(0.07)
Basel. PCA	β_4	-0.21(0.09)	-0.23(0.10)	-0.23(0.10)
Correlation	ρ		0.21	0.26(0.05)
Effect	Parameter	Lineariz.	ALR	
Intercept	β_1	2.94(0.46)	2.98(0.46)	
Time	β_2	-0.84(0.33)	-0.87(0.32)	
Time^2	β_3	0.18(0.07)	0.18(0.07)	
Basel. PCA	β_4	-0.23(0.10)	-0.23(0.10)	
Corr.	ρ	0.26(0.04)		
Log OR	α		1.43(0.22)	

NTP data in Section 14.7, similar models were considered for the toenail data in Section 14.8. For the random effect b_i we assume that $b_i \sim N(0, \tau^2)$.

Model (17.7) was fitted to the analgesic trial data using MQL and PQL, combined with REML, by means of the SAS procedure GLIMMIX. Using the SAS procedure NLMIXED, numerical integration was employed, using both non-adaptive and adaptive quadrature, in both cases with 10 and 20 quadrature points. Results are summarized in Table 17.4. The parameter τ, the standard deviation of the random intercept, was included directly into the numerical integration based NLMIXED programs. Its square and associated precision, the variance of the random intercept, was obtained through the delta method. Of course, it is very easy to obtain it by an additional run of the NLMIXED procedure, upon a slight change of the program code. In addition to the SAS-based analyses, we fitted model (17.7) using the MIXOR package and the MLwiN package. The MIXOR program is in the public domain and can be downloaded from

`http://www.uic.edu/ hedeker/mixreg.html`.

It is developed for mixed-effects ordinal regression analysis, and hence in particular in the binary case, and has been documented extensively in Hedeker and Gibbons (1993, 1994, 1996). It performs numerical integration (Gaussian quadrature) and uses the Newton-Raphson algorithm to maximize the marginal likelihood. Technically, MIXOR is most directly comparable to NLMIXED. This is reflected in the parameter estimates but

TABLE 17.4. *Analgesic Trial. Parameter estimates (standard errors) for generalized linear mixed models, under MQL and PQL (combined with REML) in SAS, PQL1 and PQL2 in MLwiN, as well as with numerical integration, in SAS (I: non-adaptive with 10 quadrature points; II: non-adaptive with 20 quadrature points and adaptive with both 10 and 20 quadrature points) and using MIXOR.*

		Integrand approximation			
		SAS GLIMMIX		MLwiN	
Effect	Par.	MQL	PQL1	PQL1	PQL2
Intercept	β_1	2.91(0.53)	3.03(0.55)	3.02(0.55)	4.07(0.70)
Time	β_2	-0.83(0.39)	-0.87(0.41)	-0.87(0.41)	-1.17(0.48)
Time^2	β_3	0.18(0.08)	0.19(0.08)	0.19(0.08)	0.25(0.10)
Basel. PCA	β_4	-0.22(0.11)	-0.22(0.11)	-0.22(0.11)	-0.31(0.15)
Rand. int s.d.	τ	1.06(0.25)	1.04(0.23)	1.01(0.12)	1.61(0.15)
Rand. int var.	τ^2	1.12(0.53)	1.08(0.48)	1.02(0.25)	2.59(0.47)

		Numerical integration		
		SAS NLMIXED		
Effect	Par.	I	II	MIXOR
Intercept	β_1	4.07(0.71)	4.05(0.71)	4.05(0.55)
Time	β_2	-1.16(0.47)	-1.16(0.47)	-1.16(0.45)
Time^2	β_3	0.25(0.09)	0.24(0.09)	0.24(0.10)
Basel. PCA	β_4	-0.30(0.14)	-0.30(0.14)	-0.30(0.15)
Rand. int s.d.	τ	1.60(0.22)	1.59(0.21)	1.59(0.21)
Rand. int var.	τ^2	2.56(0.70)	2.53(0.68)	2.53(0.67)

not entirely in the standard errors, because MIXOR uses an approximation to the (empirical) information matrix, whereas NLMIXED uses numerical derivatives. MLwiN is the successor of an earlier DOS incarnation MLN, and is the implementation of the *multilevel modeling* approach, proposed in Bryk and Raudenbush (1992), Longford (1993), and Goldstein (1995). Kreft and de Leeuw (1998) provide a more informal and introductory approach to the subject. This modeling approach for hierarchical data (and hence in particular longitudinal data) is primarily used and known in the social sciences environment. While the language typically used to describe the model is somewhat different from the linear and generalized linear mixed model formalisms, it is very similar and a wide class of mixed models can be considered within the multilevel paradigm as well.

The MLwiN and MIXOR results are shown in Table 17.4 as well. Note that the MQL approximation is particularly bad in this case, and the parameter estimates are virtually the same as those obtained under GEE (Table 17.3). These results are more extreme than the ones obtained for the NTP data (Table 16.4). The main reason is that in the analgesic trial

the number of binary measurements per subject is small, such that the approximations on which MQL and PQL are based do not work particularly well. For more details, see Section 14.4. The results for PQL are a bit better. This phenomenon is generally observed, although the difference between them is often larger. Recall that MQL linearizes the link function around the expected linear predictor, thus effectively bringing the model for the pseudo-data closer to a marginal one than PQL. Between the two PQL1 based estimates, there hardly is a difference. An important difference is seen when switching from PQL1 to PQL2 (see Section 14.3 for details), effectively bringing the results in line with the numerical integration based ones. It is fair to say that even in a case like this, where the number of measurements per subjects is relatively small, PQL2 tends to produce good approximations.

Among the numerical integration based ones, there is little or no difference. First, even though Table 17.4 presents only three columns for this class of methods, six analyses were done. From the four analyses based on the SAS procedure NLMIXED, three coincide within the reported precision, with only non-adaptive quadrature and 10 quadrature points giving a slightly different result. The MIXOR based estimates are identical, within the reported precision, to the ones form SAS, group II. The only difference is seen in the standard errors: whereas SAS bases its estimates upon Fisher's information matrix, MIXOR uses an approximation. For more details, see the MIXOR website.

17.4 Comparing Marginal and Random-effects Analyses

In Section 17.2, we presented several marginal analyses and offered a comparison among them. The key message is that the results are very similar. In Section 17.3, random effects analyses were offered, based on the corresponding model. The numerical integration based methods are virtually identical, and so are the PQL2 based ones. MQL and PQL1 produce relatively poor approximations in this case.

When comparing marginal with random effects analyses, the discussion offered in Chapter 16 should be kept in mind. A key warning is that the two model families are rather different, and that the parameters have to be interpreted differently. This was exemplified in Sections 16.4 and 16.5. Nevertheless, for a random-intercept logistic regression, like the one considered here, (16.3) can be used to calculate an approximation to the ratio between the two sets of parameters. Using standard GEE1 from Table 17.3 and the integration based estimates from Table 17.4, the approximate factor from (16.3) is 1.37, the ratios between the two sets of parameter estimates are

(1.39, 1.40, 1.33, 1.30), and the corresponding ratios between the standard errors are (1.54, 1.42, 1.29, 1.40), providing good agreement between both.

17.5 Programs for the Analgesic Trial

In this section, we will present a few key programs for the analgesic trial.

17.5.1 Marginal Models with SAS

A standard GEE1 program, with unstructured working assumptions, linear and quadratic effects of time as well as an effect of baseline pain control assessment, is given by:

```
proc genmod data=m.gsa descending;
 class patid timecls;
 model gsabin = time|time pca0 / dist=b;
 repeated subject=patid / withinsubject=timecls
                          type=un covb corrw modelse;
run;
```

The corresponding ALR program would change the repeated statement to

```
 repeated subject=patid / withinsubject=timecls
                          logor=fullclust covb corrw modelse;
```

The empirically corrected estimates for the latter case are

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	2.9219	0.4583	2.0237	3.8201	6.38	<.0001
TIME	-0.7980	0.3207	-1.4266	-0.1694	-2.49	0.0128
TIME*TIME	0.1683	0.0648	0.0412	0.2953	2.60	0.0094
pca0	-0.2359	0.0960	-0.4241	-0.0478	-2.46	0.0140
Alpha1	1.1280	0.3278	0.4856	1.7705	3.44	0.0006
Alpha2	1.5631	0.3865	0.8056	2.3206	4.04	<.0001
Alpha3	1.6035	0.4192	0.7819	2.4251	3.83	0.0001
Alpha4	1.1864	0.3680	0.4652	1.9077	3.22	0.0013
Alpha5	0.9265	0.4218	0.0997	1.7533	2.20	0.0281
Alpha6	2.4387	0.4805	1.4970	3.3805	5.08	<.0001

Note, again, that a single panel contains both the marginal regression β parameters and the log odds ratio α parameters. The asymptotic covariance

matrix panel (not shown) can be used directly to construct Wald tests. Note that, while there is a CONTRAST statement in the GENMOD procedure, it does not support the use of the α parameters, even though it does support typical linear contrasts of β parameters, whether in the cross-sectional case, GEE, or ALR.

In Table 17.2, a user-defined log odds ratio structure was considered, where all of them where set equal to each other, except α_{34}, which was allowed to have an excess. The REPEATED statement for this case is

```
repeated subject=patid / withinsubject=timecls
                         logor=zrep(
                              (1 2) 1 0,
                              (1 3) 1 0,
                              (2 3) 1 0,
                              (2 4) 1 0,
                              (3 4) 1 1
                                   )
                         covb modelse;
```

The 'logor=zrep( )' option allows a flexible linear structure on the α parameters, producing a large number of covariance structures and providing flexibility to choose the most convenient one from among equivalent parameterizations. For example, changing the last line to `(3 4) 0 1` would specify α_2 to be the log odds ratio for the last pair, rather than the difference between that one and the earlier ones. A serial structure can be mimicked by means of this option. For example,

```
logor=zrep((1 2) 1,
           (1 3) 0.5,
           (1 4) 0.3333,
           (2 3) 1,
           (2 4) 0.5,
           (3 4) 1)
```

would produce odds ratios of the form

$$\psi_{j_1 j_2} = e^{\frac{1}{j_2 - j_1}\alpha} = \psi^{\frac{1}{j_2 - j_1}},$$

and these diminish as the time interval between measurements increases, when $\psi > 1$.

Returning to the earlier program, the corresponding estimates are

```
            Analysis Of GEE Parameter Estimates
             Empirical Standard Error Estimates

                    Standard   95% Confidence
Parameter Estimate     Error       Limits            Z Pr > |Z|
```

```
Intercept    2.9215    0.4607    2.0186    3.8244     6.34    <.0001
TIME        -0.8021    0.3215   -1.4323   -0.1720    -2.49    0.0126
TIME*TIME    0.1701    0.0650    0.0427    0.2975     2.62    0.0089
pca0        -0.2351    0.0958   -0.4229   -0.0474    -2.46    0.0141
Alpha1       1.2640    0.2309    0.8115    1.7166     5.47    <.0001
Alpha2       1.1719    0.4660    0.2584    2.0853     2.51    0.0119
```

We see at a glance that both α parameters are significant.

For completeness, let us present a program for the linearization-based method (Section 8.8), using the GLIMMIX macro,

```
%glimmix(data=gsa, procopt=%str(method=ml noclprint),
   stmts=%str(
      class patid timecls;
      model gsabin = time|time pca0 / solution;
      repeated timecls / sub=patid type=un rcorr=3;
      ),
   error=binomial,
   link=logit);
```

The option 'rcorr=3' is added to the REPEATED statement, and not 'rcorr,' since the first two subjects have incomplete follow-up, and hence only a particular upper left block of the entire working correlation matrix would be given. The GLIMMIX procedure counterpart is

```
proc glimmix data=gsa method=RSPL empirical;
class patid timecls;
model gsabin (event='1') = time|time pca0
                           / dist=binary solution;
random _residual_ / subject=patid type=un;
run;
```

17.5.2 Random-effects Models with SAS

Shifting attention to the random-effects models, the MQL analysis is obtained using the GLIMMIX procedure code:

```
proc glimmix data=m.gsa method=RMPL;
class patid timecls;
model gsabin (event='1') = time|time pca0
                           / dist=binary solution;
random intercept / subject=patid type=un;
run;
```

Clearly, changing the method via 'method=RSPL' produces the PQL version. The integration-based methods are obtained using code of the form:

```
proc nlmixed data=m.gsa qpoints=10 noad;
```

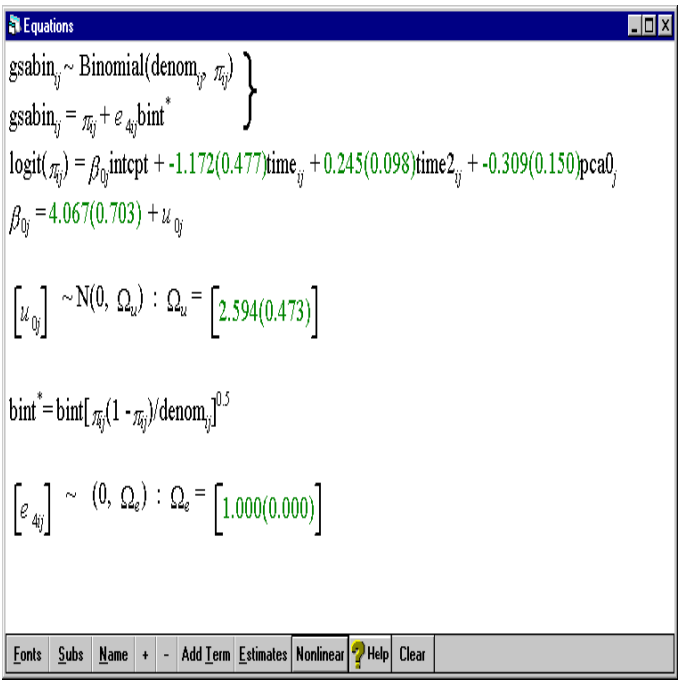

FIGURE 17.1. *Analgesic Trial. MLwIN Program for PQL2 without overdispersion parameter.*

```
parms beta0=4 beta1=-1 beta2=0.25 beta3=-0.25 tau=1.5;
theta = beta0 + b + beta1*time + beta2*time2 + beta3*pca0;
exptheta = exp(theta);
p = exptheta/(1+exptheta);
model gsabin ~ binary(p);
random b ~ normal(0,tau**2) subject=patid;
run;
```

Again, changing the 'qpoints=' option in the PROC NLMIXED statement, combined with inclusion or omission of the 'noad' option in the same statements, produces all of the analyses discussed in Section 17.3. When a probit rather than a logit link is desired, one merely adds the option 'link=probit' to the GENMOD and GLIMMIX programs. Here, however, one should remove the 'exptheta=' programming statement and replace the definition of p by 'p = probnorm(theta).'

17.5.3 MIXOR

A small portion of the output, obtained when calling MIXOR, is:

```
MIXOR - The program for mixed-effects ordinal regression analysis
          (version 2)

Global Satisfaction Assessment
Response function: logistic
Random-effects distribution: normal

 ----------------------------------------------------------
 * Final Results - Maximum Marginal Likelihood Estimates *
 ----------------------------------------------------------

 Total Iterations  =  10
 Quad Pts per Dim  =  20
 Log Likelihood    =    -506.275
 Deviance (-2logL) =    1012.549
 Ridge             =       0.000

 Variable      Estimate  Stand. Error             Z        p-value
 --------    ----------  ------------    ----------   ------------
 intcpt         4.04741       0.71278       5.67835   0.00000  (2)
 Time          -1.16003       0.47453      -2.44457   0.01450  (2)
 Time2          0.24449       0.09678       2.52624   0.01153  (2)
 PCA0          -0.29971       0.15375      -1.94932   0.05126  (2)

 Random effect variance term (standard deviation)
 intcpt         1.59139       0.20578       7.73355   0.00000  (1)

 note: (1) = 1-tailed p-value
       (2) = 2-tailed p-value
```

At the end, an estimate of an approximate intracluster correlation is presented, based on both the random-intercept variance and the variance of the standard logistic density ($\pi^2/3$).

```
 Calculation of the intracluster correlation
 -------------------------------------------
 residual variance = pi*pi / 3 (assumed)
 cluster  variance = (1.591 * 1.591) =  2.533

 intracluster correlation =  2.533 / ( 2.533 + (pi*pi/3)) = 0.435
```

However, the basis for this calculation is not very strong and caution is needed with its use (Laenen *et al* 2004). These authors suggested it is better to calculate an intraclass correlation coefficient based on the observed outcomes, rather than in terms of the latent variable. However, in most cases no constant would be obtained, not even when there is a random intercept only.

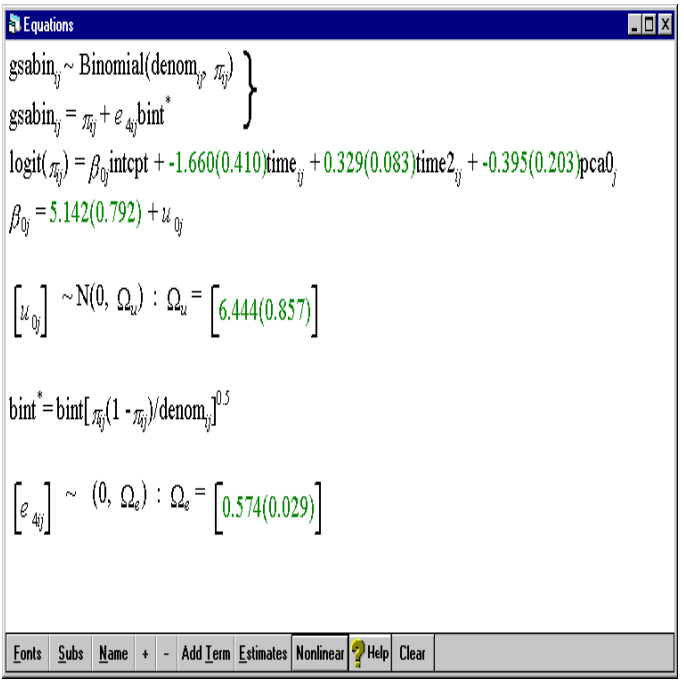

FIGURE 17.2. *Analgesic Trial. MLwIN Program for PQL2 with overdispersion parameter.*

17.5.4 MLwiN

MLwiN is a windows-driven program. The model is constructed in algebraic format, whereafter the unknown parameters are estimated. A random-intercepts logistic model would be called a two-level model within this setting, where the levels refer to the subject level on the one hand and the measurement within subject level on the other hand. There is a wide variety of options available for such aspects as the estimation method, the presence or absence of overdispersion, etc. Two example programs are provided in Figures 17.1–17.2.