Homework for Lesson 13

In a clinical trials study 3 drugs (A,B,and C) were administered to patients with a chronic condition. The degree of improvement was recorded as the response. Each participant was given all three drugs over the course of the study. The order of drug administration to participants was determined by randomly assigning participants to one of 6 sequences. After a drug was given, patients were assessed after 2 days for their condition, and then after a 2 week washout period, were then given the next drug in their sequence. A total of 3 periods were used to complete the study. Two participants were assigned to each sequence.

The data are in the Excel file ‘Lesson 13 Homework Data.xlsx’.

1. Set up the covariate coding to include adjustment for carry-over effects in an ANCOVA

The cross-over design can be summarized as:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Period** | | |  |
| **Sequence** | **1** | **2** | **3** | **Abbreviation** |
| **1** | A | B | C | ABC |
| **2** | B | C | A | BCA |
| **3** | C | A | B | CAB |
| **4** | A | C | B | ACB |
| **5** | B | A | C | BAC |
| **6** | C | B | A | CBA |

We need now to add two columns to use an effect-type coding for the 3 treatment levels. We will use:

|  |  |  |
| --- | --- | --- |
|  | X1 | X2 |
| A | 1 | 0 |
| B | 0 | 1 |
| C | -1 | -1 |

After doing this, the first few rows are:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| period | seq | trt | id | response | x1 | x2 |
| 1 | ABC | A | 1 | 174 | 0 | 0 |
| 1 | ABC | A | 2 | 145 | 0 | 0 |
| 1 | ACB | A | 3 | 192 | 0 | 0 |
| 1 | ACB | A | 4 | 194 | 0 | 0 |
| 1 | BAC | B | 5 | 184 | 0 | 0 |
| 1 | BAC | B | 6 | 140 | 0 | 0 |
| 1 | BCA | B | 7 | 136 | 0 | 0 |
| 1 | BCA | B | 8 | 145 | 0 | 0 |
| 1 | CAB | C | 9 | 206 | 0 | 0 |
| 1 | CAB | C | 10 | 160 | 0 | 0 |
| 1 | CBA | C | 11 | 180 | 0 | 0 |
| 1 | CBA | C | 12 | 210 | 0 | 0 |
| 2 | ABC | B | 1 | 146 | 1 | 0 |
| 2 | ABC | B | 2 | 125 | 1 | 0 |
| 2 | ACB | C | 3 | 150 | 0 | 1 |
| 2 | ACB | C | 4 | 208 | 0 | 1 |
| 2 | BAC | A | 5 | 192 | -1 | -1 |
| 2 | BAC | A | 6 | 150 | -1 | -1 |
| 2 | BCA | C | 7 | 132 | 1 | 0 |
| 2 | BCA | C | 8 | 154 | 1 | 0 |
| 2 | CAB | A | 9 | 220 | 0 | 1 |
| 2 | CAB | A | 10 | 180 | 0 | 1 |
| 2 | CBA | B | 11 | 180 | -1 | -1 |
| 2 | CBA | B | 12 | 160 | -1 | -1 |
| 3 | ABC | C | 1 | 164 | 0 | 1 |
| 3 | ABC | C | 2 | 130 | 0 | 1 |
| 3 | ACB | B | 3 | 160 | -1 | -1 |
| 3 | ACB | B | 4 | 160 | -1 | -1 |

1. Run the model as a repeated measures analysis, explore candidate covariance structures and choose the best fit (use AICC for the assignment).

With various covariance structures, we get the following summary:

|  |
| --- |
| Covariance Summary |

| **Obs** | **Descr** | **CS** | **VC** | **SP** | **UN** | **AR1** |
| --- | --- | --- | --- | --- | --- | --- |
| **1** | -2 Res Log Likelihood | 220.6 | 237.3 | 215.4 | 215.4 | 227.6 |
| **2** | AIC (Smaller is Better) | 228.6 | 239.3 | 227.4 | 227.4 | 231.6 |
| **3** | AICC (Smaller is Better) | 230.7 | 239.5 | 232.3 | 232.3 | 232.2 |
| **4** | BIC (Smaller is Better) | 230.6 | 239.8 | 230.3 | 230.3 | 232.6 |

Based on AICC we use the CSH covariance structure.

Using the heterogeneous compound symmetry (type=CSH) covariance structure because it provided a better fit compared to UN or CS or AR(1).

To see the adjustment on the treatment means, we can compare the LSmeans for a reduced model that does not contain the carry-over covariates.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| LSMeans | | | | | | |
| Full Model with Covariates | | |  | Reduced Model (without carry-over covariates) | | |
| Effect | DIET | Estimate |  | Effect | DIET | Estimate |
| DRUG | A | 182.67 |  | DRUG | A | 182.08 |
| DRUG | B | 160.14 |  | DRUG | B | 158.09 |
| DRUG | C | 165.18 |  | DRUG | C | 167.83 |

1. Test for the overall significance of carry-over effects.

To test for the overall significance of carry-over effects, we can drop the carry-over covariates (x1 and x2 in our example) and re-run the ANOVA. Because the reduced model is a subset of the full model that includes the covariates, we can construct a likelihood ratio test.



SAS output for the Full model with carry-over covarates is:

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 220.6 |
| **AIC (Smaller is Better)** | 228.6 |
| **AICC (Smaller is Better)** | 230.7 |
| **BIC (Smaller is Better)** | 230.6 |

and for the reduced model without the carry-over covariates is:

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 235.4 |
| **AIC (Smaller is Better)** | 243.4 |
| **AICC (Smaller is Better)** | 245.3 |
| **BIC (Smaller is Better)** | 245.3 |

ΔG2 = 235.4 – 220.6 = 14.8

We also know:

χ2(.05,2)=5.991

we conclude that there are significant carry-over effects.

1. Submit a single document with your name and the computer output supporting your analysis.

The computer output is:

The Mixed Procedure

| **Model Information** | |
| --- | --- |
| **Data Set** | WORK.TRIAL |
| **Dependent Variable** | response |
| **Covariance Structure** | Heterogeneous Compound Symmetry |
| **Subject Effect** | id(seq) |
| **Estimation Method** | REML |
| **Residual Variance Method** | None |
| **Fixed Effects SE Method** | Kenward-Roger |
| **Degrees of Freedom Method** | Kenward-Roger |

| **Class Level Information** | | |
| --- | --- | --- |
| **Class** | **Levels** | **Values** |
| **per** | 3 | 1 2 3 |
| **seq** | 6 | ABC ACB BAC BCA CAB CBA |
| **trt** | 3 | A B C |
| **id** | 12 | 1 2 3 4 5 6 7 8 9 10 11 12 |

| **Dimensions** | |
| --- | --- |
| **Covariance Parameters** | 4 |
| **Columns in X** | 15 |
| **Columns in Z** | 0 |
| **Subjects** | 12 |
| **Max Obs per Subject** | 3 |

| **Number of Observations** | |
| --- | --- |
| **Number of Observations Read** | 36 |
| **Number of Observations Used** | 36 |
| **Number of Observations Not Used** | 0 |

| **Iteration History** | | | |
| --- | --- | --- | --- |
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 237.27138165 |  |
| **1** | 2 | 220.62937524 | 0.00002399 |
| **2** | 1 | 220.62718816 | 0.00000006 |
| **3** | 1 | 220.62718242 | 0.00000000 |

|  |
| --- |
| Convergence criteria met. |

| **Estimated R Matrix for id(seq) 1 ABC** | | | |
| --- | --- | --- | --- |
| **Row** | **Col1** | **Col2** | **Col3** |
| **1** | 450.45 | 418.93 | 376.07 |
| **2** | 418.93 | 646.57 | 450.56 |
| **3** | 376.07 | 450.56 | 521.04 |

| **Estimated R Correlation Matrix for id(seq) 1 ABC** | | | |
| --- | --- | --- | --- |
| **Row** | **Col1** | **Col2** | **Col3** |
| **1** | 1.0000 | 0.7763 | 0.7763 |
| **2** | 0.7763 | 1.0000 | 0.7763 |
| **3** | 0.7763 | 0.7763 | 1.0000 |

| **Covariance Parameter Estimates** | | |
| --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** |
| **Var(1)** | **id(seq)** | 450.45 |
| **Var(2)** | **id(seq)** | 646.57 |
| **Var(3)** | **id(seq)** | 521.04 |
| **CSH** | **id(seq)** | 0.7763 |

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 220.6 |
| **AIC (Smaller is Better)** | 228.6 |
| **AICC (Smaller is Better)** | 230.7 |
| **BIC (Smaller is Better)** | 230.6 |

| **Null Model Likelihood Ratio Test** | | |
| --- | --- | --- |
| **DF** | **Chi-Square** | **Pr > ChiSq** |
| 3 | 16.64 | 0.0008 |

| **Type 3 Tests of Fixed Effects** | | | | |
| --- | --- | --- | --- | --- |
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **per** | 2 | 15.1 | 0.67 | 0.5270 |
| **trt** | 2 | 18.6 | 9.60 | 0.0014 |
| **seq** | 5 | 6.3 | 1.71 | 0.2604 |
| **x1** | 1 | 17.8 | 0.20 | 0.6637 |
| **x2** | 1 | 18.3 | 2.99 | 0.1009 |

| **Least Squares Means** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Effect** | **trt** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| **trt** | **A** | 182.67 | 6.8445 | 9.03 | 26.69 | <.0001 |
| **trt** | **B** | 160.14 | 6.8437 | 8.98 | 23.40 | <.0001 |
| **trt** | **C** | 165.18 | 6.8445 | 9.03 | 24.13 | <.0001 |

| **Differences of Least Squares Means** | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Effect** | **trt** | **\_trt** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** | **Adjustment** | **Adj P** |
| **trt** | **A** | **B** | 22.5295 | 5.3967 | 18.9 | 4.17 | 0.0005 | Tukey-Kramer | 0.0015 |
| **trt** | **A** | **C** | 17.4929 | 5.4001 | 18.2 | 3.24 | 0.0045 | Tukey-Kramer | 0.0117 |
| **trt** | **B** | **C** | -5.0366 | 5.3967 | 18.9 | -0.93 | 0.3625 | Tukey-Kramer | 0.6266 |

|  |
| --- |
| Compound Symmetry |

The Mixed Procedure

| **Model Information** | |
| --- | --- |
| **Data Set** | WORK.TRIAL |
| **Dependent Variable** | response |
| **Covariance Structure** | Heterogeneous Compound Symmetry |
| **Subject Effect** | id(seq) |
| **Estimation Method** | REML |
| **Residual Variance Method** | None |
| **Fixed Effects SE Method** | Kenward-Roger |
| **Degrees of Freedom Method** | Kenward-Roger |

| **Class Level Information** | | |
| --- | --- | --- |
| **Class** | **Levels** | **Values** |
| **per** | 3 | 1 2 3 |
| **seq** | 6 | ABC ACB BAC BCA CAB CBA |
| **trt** | 3 | A B C |
| **id** | 12 | 1 2 3 4 5 6 7 8 9 10 11 12 |

| **Dimensions** | |
| --- | --- |
| **Covariance Parameters** | 4 |
| **Columns in X** | 15 |
| **Columns in Z** | 0 |
| **Subjects** | 12 |
| **Max Obs per Subject** | 3 |

| **Number of Observations** | |
| --- | --- |
| **Number of Observations Read** | 36 |
| **Number of Observations Used** | 36 |
| **Number of Observations Not Used** | 0 |

| **Iteration History** | | | |
| --- | --- | --- | --- |
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 237.27138165 |  |
| **1** | 2 | 220.62937524 | 0.00002399 |
| **2** | 1 | 220.62718816 | 0.00000006 |
| **3** | 1 | 220.62718242 | 0.00000000 |

|  |
| --- |
| Convergence criteria met. |

| **Estimated R Matrix for id(seq) 1 ABC** | | | |
| --- | --- | --- | --- |
| **Row** | **Col1** | **Col2** | **Col3** |
| **1** | 450.45 | 418.93 | 376.07 |
| **2** | 418.93 | 646.57 | 450.56 |
| **3** | 376.07 | 450.56 | 521.04 |

| **Estimated R Correlation Matrix for id(seq) 1 ABC** | | | |
| --- | --- | --- | --- |
| **Row** | **Col1** | **Col2** | **Col3** |
| **1** | 1.0000 | 0.7763 | 0.7763 |
| **2** | 0.7763 | 1.0000 | 0.7763 |
| **3** | 0.7763 | 0.7763 | 1.0000 |

| **Covariance Parameter Estimates** | | |
| --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** |
| **Var(1)** | **id(seq)** | 450.45 |
| **Var(2)** | **id(seq)** | 646.57 |
| **Var(3)** | **id(seq)** | 521.04 |
| **CSH** | **id(seq)** | 0.7763 |

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 220.6 |
| **AIC (Smaller is Better)** | 228.6 |
| **AICC (Smaller is Better)** | 230.7 |
| **BIC (Smaller is Better)** | 230.6 |

| **Null Model Likelihood Ratio Test** | | |
| --- | --- | --- |
| **DF** | **Chi-Square** | **Pr > ChiSq** |
| 3 | 16.64 | 0.0008 |

| **Type 3 Tests of Fixed Effects** | | | | |
| --- | --- | --- | --- | --- |
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **per** | 2 | 15.1 | 0.67 | 0.5270 |
| **trt** | 2 | 18.6 | 9.60 | 0.0014 |
| **seq** | 5 | 6.3 | 1.71 | 0.2604 |
| **x1** | 1 | 17.8 | 0.20 | 0.6637 |
| **x2** | 1 | 18.3 | 2.99 | 0.1009 |

|  |
| --- |
| Variance Components |

The Mixed Procedure

| **Model Information** | |
| --- | --- |
| **Data Set** | WORK.TRIAL |
| **Dependent Variable** | response |
| **Covariance Structure** | Variance Components |
| **Subject Effect** | id(seq) |
| **Estimation Method** | REML |
| **Residual Variance Method** | Parameter |
| **Fixed Effects SE Method** | Kenward-Roger |
| **Degrees of Freedom Method** | Kenward-Roger |

| **Class Level Information** | | |
| --- | --- | --- |
| **Class** | **Levels** | **Values** |
| **per** | 3 | 1 2 3 |
| **seq** | 6 | ABC ACB BAC BCA CAB CBA |
| **trt** | 3 | A B C |
| **id** | 12 | 1 2 3 4 5 6 7 8 9 10 11 12 |

| **Dimensions** | |
| --- | --- |
| **Covariance Parameters** | 1 |
| **Columns in X** | 15 |
| **Columns in Z** | 0 |
| **Subjects** | 12 |
| **Max Obs per Subject** | 3 |

| **Number of Observations** | |
| --- | --- |
| **Number of Observations Read** | 36 |
| **Number of Observations Used** | 36 |
| **Number of Observations Not Used** | 0 |

| **Iteration History** | | | |
| --- | --- | --- | --- |
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 237.27138165 |  |
| **1** | 1 | 237.27138165 | 0.00000000 |

|  |
| --- |
| Convergence criteria met. |

| **Covariance Parameter Estimates** | | |
| --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** |
| **per** | **id(seq)** | 442.58 |

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 237.3 |
| **AIC (Smaller is Better)** | 239.3 |
| **AICC (Smaller is Better)** | 239.5 |
| **BIC (Smaller is Better)** | 239.8 |

| **Null Model Likelihood Ratio Test** | | |
| --- | --- | --- |
| **DF** | **Chi-Square** | **Pr > ChiSq** |
| 0 | 0.00 | 1.0000 |

| **Type 3 Tests of Fixed Effects** | | | | |
| --- | --- | --- | --- | --- |
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **per** | 2 | 24 | 0.22 | 0.8008 |
| **trt** | 2 | 24 | 3.08 | 0.0644 |
| **seq** | 5 | 24 | 5.01 | 0.0028 |
| **x1** | 1 | 24 | 0.08 | 0.7839 |
| **x2** | 1 | 24 | 0.98 | 0.3313 |

|  |
| --- |
| Unstructured |

The Mixed Procedure

| **Model Information** | |
| --- | --- |
| **Data Set** | WORK.TRIAL |
| **Dependent Variable** | response |
| **Covariance Structure** | Unstructured |
| **Subject Effect** | id(seq) |
| **Estimation Method** | REML |
| **Residual Variance Method** | None |
| **Fixed Effects SE Method** | Kenward-Roger |
| **Degrees of Freedom Method** | Kenward-Roger |

| **Class Level Information** | | |
| --- | --- | --- |
| **Class** | **Levels** | **Values** |
| **per** | 3 | 1 2 3 |
| **seq** | 6 | ABC ACB BAC BCA CAB CBA |
| **trt** | 3 | A B C |
| **id** | 12 | 1 2 3 4 5 6 7 8 9 10 11 12 |

| **Dimensions** | |
| --- | --- |
| **Covariance Parameters** | 6 |
| **Columns in X** | 15 |
| **Columns in Z** | 0 |
| **Subjects** | 12 |
| **Max Obs per Subject** | 3 |

| **Number of Observations** | |
| --- | --- |
| **Number of Observations Read** | 36 |
| **Number of Observations Used** | 36 |
| **Number of Observations Not Used** | 0 |

| **Iteration History** | | | |
| --- | --- | --- | --- |
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 237.27138165 |  |
| **1** | 2 | 217.53860311 | 0.01451595 |
| **2** | 1 | 215.95882559 | 0.00468715 |
| **3** | 1 | 215.47083288 | 0.00088082 |
| **4** | 1 | 215.38556550 | 0.00004730 |
| **5** | 1 | 215.38136087 | 0.00000017 |
| **6** | 1 | 215.38134636 | 0.00000000 |

|  |
| --- |
| Convergence criteria met. |

| **Estimated R Correlation Matrix for id(seq) 1 ABC** | | | |
| --- | --- | --- | --- |
| **Row** | **Col1** | **Col2** | **Col3** |
| **1** | 1.0000 | 0.7174 | 0.9269 |
| **2** | 0.7174 | 1.0000 | 0.7215 |
| **3** | 0.9269 | 0.7215 | 1.0000 |

| **Covariance Parameter Estimates** | | |
| --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** |
| **UN(1,1)** | **id(seq)** | 469.96 |
| **UN(2,1)** | **id(seq)** | 374.77 |
| **UN(2,2)** | **id(seq)** | 580.67 |
| **UN(3,1)** | **id(seq)** | 475.09 |
| **UN(3,2)** | **id(seq)** | 411.05 |
| **UN(3,3)** | **id(seq)** | 559.01 |

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 215.4 |
| **AIC (Smaller is Better)** | 227.4 |
| **AICC (Smaller is Better)** | 232.3 |
| **BIC (Smaller is Better)** | 230.3 |

| **Null Model Likelihood Ratio Test** | | |
| --- | --- | --- |
| **DF** | **Chi-Square** | **Pr > ChiSq** |
| 5 | 21.89 | 0.0005 |

| **Type 3 Tests of Fixed Effects** | | | | |
| --- | --- | --- | --- | --- |
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **per** | 2 | 8.34 | 0.92 | 0.4344 |
| **trt** | 2 | 10.6 | 19.29 | 0.0003 |
| **seq** | 5 | 6.11 | 1.40 | 0.3407 |
| **x1** | 1 | 10.6 | 0.11 | 0.7443 |
| **x2** | 1 | 11.4 | 5.05 | 0.0454 |

|  |
| --- |
| Autoregressive Lag 1 |

The Mixed Procedure

| **Model Information** | |
| --- | --- |
| **Data Set** | WORK.TRIAL |
| **Dependent Variable** | response |
| **Covariance Structure** | Autoregressive |
| **Subject Effect** | id(seq) |
| **Estimation Method** | REML |
| **Residual Variance Method** | Profile |
| **Fixed Effects SE Method** | Kenward-Roger |
| **Degrees of Freedom Method** | Kenward-Roger |

| **Class Level Information** | | |
| --- | --- | --- |
| **Class** | **Levels** | **Values** |
| **per** | 3 | 1 2 3 |
| **seq** | 6 | ABC ACB BAC BCA CAB CBA |
| **trt** | 3 | A B C |
| **id** | 12 | 1 2 3 4 5 6 7 8 9 10 11 12 |

| **Dimensions** | |
| --- | --- |
| **Covariance Parameters** | 2 |
| **Columns in X** | 15 |
| **Columns in Z** | 0 |
| **Subjects** | 12 |
| **Max Obs per Subject** | 3 |

| **Number of Observations** | |
| --- | --- |
| **Number of Observations Read** | 36 |
| **Number of Observations Used** | 36 |
| **Number of Observations Not Used** | 0 |

| **Iteration History** | | | |
| --- | --- | --- | --- |
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 237.27138165 |  |
| **1** | 2 | 227.64021093 | 0.00014923 |
| **2** | 1 | 227.62615329 | 0.00000025 |
| **3** | 1 | 227.62613034 | 0.00000000 |

|  |
| --- |
| Convergence criteria met. |

| **Estimated R Correlation Matrix for id(seq) 1 ABC** | | | |
| --- | --- | --- | --- |
| **Row** | **Col1** | **Col2** | **Col3** |
| **1** | 1.0000 | 0.6615 | 0.4376 |
| **2** | 0.6615 | 1.0000 | 0.6615 |
| **3** | 0.4376 | 0.6615 | 1.0000 |

| **Covariance Parameter Estimates** | | |
| --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** |
| **AR(1)** | **id(seq)** | 0.6615 |
| **Residual** |  | 496.72 |

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 227.6 |
| **AIC (Smaller is Better)** | 231.6 |
| **AICC (Smaller is Better)** | 232.2 |
| **BIC (Smaller is Better)** | 232.6 |

| **Null Model Likelihood Ratio Test** | | |
| --- | --- | --- |
| **DF** | **Chi-Square** | **Pr > ChiSq** |
| 1 | 9.65 | 0.0019 |

| **Type 3 Tests of Fixed Effects** | | | | |
| --- | --- | --- | --- | --- |
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **per** | 2 | 17.8 | 0.59 | 0.5668 |
| **trt** | 2 | 18.9 | 5.92 | 0.0101 |
| **seq** | 5 | 6.93 | 2.54 | 0.1288 |
| **x1** | 1 | 17.6 | 0.26 | 0.6193 |
| **x2** | 1 | 17.6 | 1.87 | 0.1888 |

|  |
| --- |
| Covariance Summary |

| **Obs** | **Descr** | **CS** | **VC** | **SP** | **UN** | **AR1** |
| --- | --- | --- | --- | --- | --- | --- |
| **1** | -2 Res Log Likelihood | 220.6 | 237.3 | 215.4 | 215.4 | 227.6 |
| **2** | AIC (Smaller is Better) | 228.6 | 239.3 | 227.4 | 227.4 | 231.6 |
| **3** | AICC (Smaller is Better) | 230.7 | 239.5 | 232.3 | 232.3 | 232.2 |
| **4** | BIC (Smaller is Better) | 230.6 | 239.8 | 230.3 | 230.3 | 232.6 |

|  |
| --- |
| Full Model, CSH, With covariates |

The Mixed Procedure

| **Model Information** | |
| --- | --- |
| **Data Set** | WORK.TRIAL |
| **Dependent Variable** | response |
| **Covariance Structure** | Heterogeneous Compound Symmetry |
| **Subject Effect** | id(seq) |
| **Estimation Method** | REML |
| **Residual Variance Method** | None |
| **Fixed Effects SE Method** | Kenward-Roger |
| **Degrees of Freedom Method** | Kenward-Roger |

| **Class Level Information** | | |
| --- | --- | --- |
| **Class** | **Levels** | **Values** |
| **per** | 3 | 1 2 3 |
| **seq** | 6 | ABC ACB BAC BCA CAB CBA |
| **trt** | 3 | A B C |
| **id** | 12 | 1 2 3 4 5 6 7 8 9 10 11 12 |

| **Dimensions** | |
| --- | --- |
| **Covariance Parameters** | 4 |
| **Columns in X** | 15 |
| **Columns in Z** | 0 |
| **Subjects** | 12 |
| **Max Obs per Subject** | 3 |

| **Number of Observations** | |
| --- | --- |
| **Number of Observations Read** | 36 |
| **Number of Observations Used** | 36 |
| **Number of Observations Not Used** | 0 |

| **Iteration History** | | | |
| --- | --- | --- | --- |
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 237.27138165 |  |
| **1** | 2 | 220.62937524 | 0.00002399 |
| **2** | 1 | 220.62718816 | 0.00000006 |
| **3** | 1 | 220.62718242 | 0.00000000 |

|  |
| --- |
| Convergence criteria met. |

| **Estimated R Matrix for id(seq) 1 ABC** | | | |
| --- | --- | --- | --- |
| **Row** | **Col1** | **Col2** | **Col3** |
| **1** | 450.45 | 418.93 | 376.07 |
| **2** | 418.93 | 646.57 | 450.56 |
| **3** | 376.07 | 450.56 | 521.04 |

| **Estimated R Correlation Matrix for id(seq) 1 ABC** | | | |
| --- | --- | --- | --- |
| **Row** | **Col1** | **Col2** | **Col3** |
| **1** | 1.0000 | 0.7763 | 0.7763 |
| **2** | 0.7763 | 1.0000 | 0.7763 |
| **3** | 0.7763 | 0.7763 | 1.0000 |

| **Covariance Parameter Estimates** | | |
| --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** |
| **Var(1)** | **id(seq)** | 450.45 |
| **Var(2)** | **id(seq)** | 646.57 |
| **Var(3)** | **id(seq)** | 521.04 |
| **CSH** | **id(seq)** | 0.7763 |

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 220.6 |
| **AIC (Smaller is Better)** | 228.6 |
| **AICC (Smaller is Better)** | 230.7 |
| **BIC (Smaller is Better)** | 230.6 |

| **Null Model Likelihood Ratio Test** | | |
| --- | --- | --- |
| **DF** | **Chi-Square** | **Pr > ChiSq** |
| 3 | 16.64 | 0.0008 |

| **Type 3 Tests of Fixed Effects** | | | | |
| --- | --- | --- | --- | --- |
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **per** | 2 | 15.1 | 0.67 | 0.5270 |
| **trt** | 2 | 18.6 | 9.60 | 0.0014 |
| **seq** | 5 | 6.3 | 1.71 | 0.2604 |
| **x1** | 1 | 17.8 | 0.20 | 0.6637 |
| **x2** | 1 | 18.3 | 2.99 | 0.1009 |

| **Least Squares Means** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Effect** | **trt** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| **trt** | **A** | 182.67 | 6.8445 | 9.03 | 26.69 | <.0001 |
| **trt** | **B** | 160.14 | 6.8437 | 8.98 | 23.40 | <.0001 |
| **trt** | **C** | 165.18 | 6.8445 | 9.03 | 24.13 | <.0001 |

| **Differences of Least Squares Means** | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Effect** | **trt** | **\_trt** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** | **Adjustment** | **Adj P** |
| **trt** | **A** | **B** | 22.5295 | 5.3967 | 18.9 | 4.17 | 0.0005 | Tukey-Kramer | 0.0015 |
| **trt** | **A** | **C** | 17.4929 | 5.4001 | 18.2 | 3.24 | 0.0045 | Tukey-Kramer | 0.0117 |
| **trt** | **B** | **C** | -5.0366 | 5.3967 | 18.9 | -0.93 | 0.3625 | Tukey-Kramer | 0.6266 |

|  |
| --- |
| Reduced model, CSH, Without covariates |

The Mixed Procedure

| **Model Information** | |
| --- | --- |
| **Data Set** | WORK.TRIAL |
| **Dependent Variable** | response |
| **Covariance Structure** | Heterogeneous Compound Symmetry |
| **Subject Effect** | id(seq) |
| **Estimation Method** | REML |
| **Residual Variance Method** | None |
| **Fixed Effects SE Method** | Kenward-Roger |
| **Degrees of Freedom Method** | Kenward-Roger |

| **Class Level Information** | | |
| --- | --- | --- |
| **Class** | **Levels** | **Values** |
| **per** | 3 | 1 2 3 |
| **seq** | 6 | ABC ACB BAC BCA CAB CBA |
| **trt** | 3 | A B C |
| **id** | 12 | 1 2 3 4 5 6 7 8 9 10 11 12 |

| **Dimensions** | |
| --- | --- |
| **Covariance Parameters** | 4 |
| **Columns in X** | 13 |
| **Columns in Z** | 0 |
| **Subjects** | 12 |
| **Max Obs per Subject** | 3 |

| **Number of Observations** | |
| --- | --- |
| **Number of Observations Read** | 36 |
| **Number of Observations Used** | 36 |
| **Number of Observations Not Used** | 0 |

| **Iteration History** | | | |
| --- | --- | --- | --- |
| **Iteration** | **Evaluations** | **-2 Res Log Like** | **Criterion** |
| **0** | 1 | 250.46487451 |  |
| **1** | 2 | 235.39407707 | 0.00002536 |
| **2** | 1 | 235.39160772 | 0.00000009 |
| **3** | 1 | 235.39159919 | 0.00000000 |

|  |
| --- |
| Convergence criteria met. |

| **Covariance Parameter Estimates** | | |
| --- | --- | --- |
| **Cov Parm** | **Subject** | **Estimate** |
| **Var(1)** | **id(seq)** | 451.97 |
| **Var(2)** | **id(seq)** | 686.59 |
| **Var(3)** | **id(seq)** | 547.29 |
| **CSH** | **id(seq)** | 0.7392 |

| **Fit Statistics** | |
| --- | --- |
| **-2 Res Log Likelihood** | 235.4 |
| **AIC (Smaller is Better)** | 243.4 |
| **AICC (Smaller is Better)** | 245.3 |
| **BIC (Smaller is Better)** | 245.3 |

| **Null Model Likelihood Ratio Test** | | |
| --- | --- | --- |
| **DF** | **Chi-Square** | **Pr > ChiSq** |
| 3 | 15.07 | 0.0018 |

| **Type 3 Tests of Fixed Effects** | | | | |
| --- | --- | --- | --- | --- |
| **Effect** | **Num DF** | **Den DF** | **F Value** | **Pr > F** |
| **per** | 2 | 15.5 | 0.55 | 0.5866 |
| **trt** | 2 | 20.5 | 9.61 | 0.0011 |
| **seq** | 5 | 6.32 | 1.49 | 0.3135 |

| **Least Squares Means** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Effect** | **trt** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| **trt** | **A** | 182.08 | 6.8968 | 9.01 | 26.40 | <.0001 |
| **trt** | **B** | 158.09 | 6.8968 | 9.01 | 22.92 | <.0001 |
| **trt** | **C** | 167.83 | 6.8968 | 9.01 | 24.33 | <.0001 |

| **Differences of Least Squares Means** | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Effect** | **trt** | **\_trt** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** | **Adjustment** | **Adj P** |
| **trt** | **A** | **B** | 23.9977 | 5.5072 | 20.5 | 4.36 | 0.0003 | Tukey-Kramer | 0.0008 |
| **trt** | **A** | **C** | 14.2537 | 5.5072 | 20.5 | 2.59 | 0.0173 | Tukey-Kramer | 0.0439 |
| **trt** | **B** | **C** | -9.7440 | 5.5072 | 20.5 | -1.77 | 0.0917 | Tukey-Kramer | 0.2046 |