PharmaSUG 2021 - Paper SA-062

SAS Proc Mixed: A Statistical Programmer's Best Friend in QoL Analyses

Janaki Manthena, Varsha Korrapati and Chiyu Zhang, Seagen Inc., Bothell WA

ABSTRACT

SAS PROC MIXED is a powerful procedure that can be used to efficiently and comprehensively analyze longitudinal data such as many patient-reported outcomes (PRO) measurements overtime, especially when missing data are prevalent. This paper illustrates the commonly used statements and options in this procedure when used in such analyses. We will present a statistical programmer's perspective on how to calculate Least Square (LS) Mean, Standard Error, difference in LS Means between treatment arms, and corresponding 95% confidence interval at each time point using this procedure. This will be demonstrated using examples of PROC MIXED focusing on both linear mixed models and pattern mixture models on imputed and original QLQ-C30 questionnaire data, respectively.

Keywords: PROC MIXED, Lsmeans, Standard Error, Lsmean Difference, Confidence Intervals, p-value, Change from baseline.

INTRODUCTION

The **PROC MIXED** was specifically designed to fit mixed effect models. It can model random and mixed effect data, repeated measures, spacial data, data with heterogeneous variances and autocorrelated observations. The MIXED procedure is more general than GLM in the sense that it gives a user more flexibility in specifying the correlation structures, particularly useful in repeated measures and random effect models.

PROC MIXED provides a variety of covariance structures to handle the following two scenarios.

- The first scenario can be generalized to include one set of clusters nested within another.
- The second scenario occurs in longitudinal studies, where repeated measurements are taken over time.

Alternatively, the repeated measures could be spatial or multivariate in nature.

SYNTAX FOR PROC MIXED:

```
proc mixed options;
   class variable-list;
   model dependent=fixed effects/ options;
   random random effects / options;
   repeated repeated effects / options;
   contrast 'label' fixed-effect values | random-effect values/ options;
   estimate 'label' fixed-effect values | random-effect values/ options;
   lsmeans fixed-effects / options;
run;
```

PROC MIXED statement:
Most often used options:

- The **method**=REML option calls the restricted maximum likelihood estimator for the model and is a default method. REML is selected because it typically provides less biased estimates of the variance components of the model than the full information maximum likelihood, particularly when there are many covariates.

- The **covtest** option on the proc mixed statement requests asymptotic standard errors and Wald-Z tests for covariance parameters (producing a table of output called “Covariance Parameter Estimates”). This option has SAS show hypothesis tests for the variance and covariance parts of the model in the output.
- If one specifies the **EMPIRICAL** option, PROC MIXED adjusts all standard errors and test statistics involving the fixed-effects parameters.

CLASS statement:
The CLASS statement names the classification variables to be used in the analysis. Classification variables can be either character or numeric. The procedure uses only the first 16 characters of a character variable. The display order of CLASS variable levels can be adjusted with the ORDER= option in the PROC MIXED statement.

MODEL statement:
The MODEL statement names a single dependent variable and the fixed effects. An intercept is included in the model by default. The NOINT option can be used to remove the intercept.
Often-used options:

- **DDFM**= option specifies the method for computing the denominator degrees of freedom for the tests of fixed effects.
- **SOLUTION**, for t-tests and standard errors for each fixed effect.
- **CL**, to output confidence intervals for fixed effect estimates.

RANDOM statement:
The RANDOM statement defines the random effects in the mixed model. In this statement we list predictors with random effects that vary randomly across the sampling units.
Often-used options:

- **SUBJECT**= creates block-diagonality and tells the mixed procedure what class variable denotes the grouping determining the individuals.
- **TYPE**= is used to specify covariance structure.
- **SOLUTION** requests solution for random-effects parameters.

REPEATED statement:
The repeated statement is used in PROC MIXED to specify the covariance structure of the error term. The repeated effect must be categorical and has to appear in the class statement and the data has to be sorted accordingly. We must indicate all missing response variables with periods in the input data set unless they all fall at the end of a subject’s repeated response profile.
Often-used options:

- Option **TYPE** in the REPEATED statement specifies the type of the error correlation structure.
- **SUBJECT** option is needed to identify observations that are correlated.

CONTRAST/ESTIMATE statement:
The **CONTRAST** statement provides a mechanism for obtaining composite hypothesis tests. It is patterned to include ***random-effects*** along with ***label***, ***fixed-effects,*** and ***values***. The contrast statement tests involve linear combinations of fixed and/or random effects. The **ESTIMATE** statement is used just like **CONTRAST** statement to obtain custom estimates.

LSMEANS statement:
LSMEANS computes the least squares means of fixed effects. The standard errors are adjusted for the covariance parameters in the model. LS-means can be computed for any effect in the MODEL statement that involves CLASS variables. You can specify multiple effects in one LSMEANS statement or in multiple

LSMEANS statements, and all LSMEANS statements must appear after the MODEL statement. The ADJUST option requests a multiple comparison adjustment for the p-values and confidence limits for the differences of LS-mean. If only comparisons with a control level are needed then in addition to the ADJUST option, PDIFF=control should be used.

Often-used options:

- **CL** option requests that t-type confidence limits be constructed for each of the LS-means.
- **PDIFF** option requests that differences of the LS-means be displayed.

ANALYSIS OF EORTC-QLQ-C30 CHANGE FROM BASELINE ON QUALITY-OF-LIFE SUBSCALE SCORES USING LINEAR MIXED MODEL

In the oncology therapeutic area, we often see quality of life as an endpoint. Quality of life is measured on various scales like the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), EQ-5D-5L/EQ-5D-3L, etc. The QLQ-C30 consists of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale and a number of single items assessing additional symptoms commonly reported by cancer patients. Steps involved in calculation of Least Square (LS) Mean, standard error, difference in LS Means between treatment arms, P-value and corresponding 95% confidence interval are explained in the context of Quality-of-Life data collected on the global health status / QoL sub scale of QLQ-C30 CRFs at each time point using PROC MIXED.

Desired Change from Baseline Output

Analysis of EORTC-QLQ-C30 Change from Baseline on Global Health Status Subscale Score
Using Linear Mixed Models
ITT Analysis Set

				TRT A vs. TRT B		
Scale	Visit	TRT A N=4	TRT B N=4	LS Mean Difference(SE)	95% C.I. for Diff. in LS Means	p-value
Global Health Status / QoL						
	Baseline					
	N	4	4			
	LS Mean (SE)	41.67(10.44)	37.50 (18.08)	4.17 (20.88)	(-46.92, 55.26)	0.848
	Change from Baseline to Cycle 2					
	N	4	4			
	LS Mean (SE)	26.61 (4.23)	17.69 (26.63)	8.92 (27.00)	(-48.05, 65.89)	0.745
	Change from Baseline to Cycle 3					
	N	4	4			
	LS Mean (SE)	19.66 (3.55)	59.35 (2.88)	-39.69 (4.61)	(-49.42, -29.96)	<0.0001

Step 1: The programmer has to understand the input data set variables and make sure all variables required for the model are present in the data set. A dummy ADQLQC30 data set with each subject's Global Health Status/QoL scores at different timepoints (cycle 1, 2, 3, 4, and EOT) is shown below for demonstration purposes.

SUBJID	IPI	HISTOLGY	TRT	PARAM	AVAL	VISIT	ABLFL	BASE	CHG
101	2-3	ALK-positive sALCL	A	Global Health Status/QoL	50	Baseline	Y	50	0
101	2-3	ALK-positive sALCL	A	Global Health Status/QoL	58.3333	Cycle 2		50	8.3333
101	2-3	ALK-positive sALCL	A	Global Health Status/QoL	50	Cycle 3		50	0
101	2-3	ALK-positive sALCL	A	Global Health Status/QoL	66.6667	Cycle 4		50	16.6667
101	2-3	ALK-positive sALCL	A	Global Health Status/QoL	66.6667	EOT		50	16.6667
102	2-3	ALK-positive sALCL	A	Global Health Status/QoL	16.6667	Baseline	Y	16.6667	0
102	2-3	ALK-positive sALCL	A	Global Health Status/QoL	66.6667	Cycle 2		16.6667	50
102	2-3	ALK-positive sALCL	A	Global Health Status/QoL	66.6667	Cycle 4		16.6667	50
102	2-3	ALK-positive sALCL	A	Global Health Status/QoL	83.3333	EOT		16.6667	66.6666
103	2-3	ALK-positive sALCL	A	Global Health Status/QoL	16.6667	Baseline	Y	16.6667	0
103	2-3	ALK-positive sALCL	A	Global Health Status/QoL	83.3333	Cycle 2		16.6667	66.6666
103	2-3	ALK-positive sALCL	A	Global Health Status/QoL	58.3333	Cycle 3		16.6667	41.6666
103	2-3	ALK-positive sALCL	A	Global Health Status/QoL	83.3333	Cycle 4		16.6667	66.6666
103	2-3	ALK-positive sALCL	A	Global Health Status/QoL	83.3333	EOT		16.6667	66.6666
104	2-3	ALK-positive sALCL	B	Global Health Status/QoL	16.6667	Baseline	Y	16.6667	0
104	2-3	ALK-positive sALCL	B	Global Health Status/QoL	16.6667	Cycle 2		16.6667	0
104	2-3	ALK-positive sALCL	B	Global Health Status/QoL	100	Cycle 3		16.6667	83.3333
104	2-3	ALK-positive sALCL	B	Global Health Status/QoL	66.6667	Cycle 4		16.6667	50
105	2-3	All Other Histologies	A	Global Health Status/QoL	41.6667	Baseline	Y	41.6667	0
105	2-3	All Other Histologies	A	Global Health Status/QoL	66.6667	Cycle 2		41.6667	25
105	2-3	All Other Histologies	A	Global Health Status/QoL	66.6667	Cycle 3		41.6667	25
105	2-3	All Other Histologies	A	Global Health Status/QoL	83.3333	Cycle 4		41.6667	41.6666
105	2-3	All Other Histologies	A	Global Health Status/QoL	33.3333	EOT		41.6667	-8.3334
106	2-3	ALK-positive sALCL	A	Global Health Status/QoL	83.3333	Baseline	Y	83.3333	0
106	2-3	ALK-positive sALCL	A	Global Health Status/QoL	75	Cycle 2		83.3333	-8.3333
106	2-3	ALK-positive sALCL	A	Global Health Status/QoL	58.3333	Cycle 3		83.3333	-25
106	2-3	ALK-positive sALCL	A	Global Health Status/QoL	83.3333	Cycle 4		83.3333	0
106	2-3	ALK-positive sALCL	A	Global Health Status/QoL	100	EOT		83.3333	16.6667
107	2-3	All Other Histologies	B	Global Health Status/QoL	58.3333	Baseline	Y	58.3333	0
107	2-3	All Other Histologies	B	Global Health Status/QoL	100	Cycle 2		58.3333	41.6667
107	2-3	All Other Histologies	B	Global Health Status/QoL	100	Cycle 3		58.3333	41.6667
107	2-3	All Other Histologies	B	Global Health Status/QoL	100	Cycle 4		58.3333	41.6667
107	2-3	All Other Histologies	B	Global Health Status/QoL	100	EOT		58.3333	41.6667
108	2-3	All Other Histologies	A	Global Health Status/QoL	41.6667	Baseline	Y	41.6667	0
108	2-3	All Other Histologies	A	Global Health Status/QoL	58.3333	Cycle 2		41.6667	16.6666
108	2-3	All Other Histologies	A	Global Health Status/QoL	66.6667	Cycle 3		41.6667	25
108	2-3	All Other Histologies	A	Global Health Status/QoL	66.6667	Cycle 4		41.6667	25
108	2-3	All Other Histologies	A	Global Health Status/QoL	75	EOT		41.6667	33.3333

Step 2: Derive **baseline estimates**.

a. Subset for baseline records:

```
data qlqc1;
      set adqlqc30;
      where ablfl eq 'Y';
run;
```

b. Derive **baseline estimates** using the model below. BASE (baseline score) is the dependent variable and TRT (treatment) the independent variable in this model:

```
ods output lsmeans=bs_lsmean diffs=bs_lsdiff;
proc mixed data=qlqc1 method=reml covtest noclprint;
      by param;
      class subjid trt visit;
      model base=trt /solution;
      lsmeans trt/ cl pdiff;
run;
```

bs_lsmean: bs_lsmean is the Lsmeans object from the ODS Output statement. This data set has a statistics estimate (LS means), stdErr (standard error), Probt (p-value), Lower (lower confidence interval), and Upper (upper confidence interval) for respective treatments at baseline.

Least Squares Means

Effect	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT	A	41.6667	10.4398	6	3.99	0.0072	0.05	16.1215	67.2119
TRT	B	37.5000	18.0822	6	2.07	0.0834	0.05	-6.7456	81.7456

PARAM	Effect	TRT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Global Health Status/QoL	TRT	A	41.66668333	10.43977733	6	3.99	0.0072	0.05	16.12146847	67.2118982
Global Health Status/QoL	TRT	B	37.5	18.08222475	6	2.07	0.0834	0.05	-6.745610032	81.74561003

bs_lsdiff: bs_lsdiff is the DIFFS object from the ODS Output statement. This data set has a statistics estimate (LS means difference), stdErr (standard error), Probt (p-value), Lower (lower confidence interval), and Upper (upper confidence interval) between 2 treatment groups (TRT A vs TRT B) at baseline.

Differences of Least Squares Means

Effect	TRT	_TRT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT	A	B	4.1667	20.8796	6	0.20	0.8484	0.05	-46.9237	55.2571

PARAM	Effect	TRT	_TRT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Global Health Status/QoL	TRT	A	B	4.166683333	20.87955465	6	0.20	0.8484	0.05	-46.92374639	55.25711306

c. If an analysis requires additional covariates along with the TRT variable, add those covariates to class and model statements. For example, let's say the above output needs stratification

factors IPI and HISTLOGY as covariates in addition to TRT. In that scenario, the following code would replace the code in section b:

```
ods output lsmeans=bs_lsmean diffs=bs_lsdiff;
proc mixed data=qlqc1 method=reml covtest noclprint;
      by param;
      class subjid trt visit ipi histolgy;
      model base=trt ipi histolgy/solution;
      lsmeans trt/ cl pdiff;
run;
```

Please note that bs_lsmean and bs_lsdiff from section b and section c have similar structure and processing.

Step 3: Derive **post-baseline estimates**.

a. Subset for post-baseline records:

```
data qlqc2;
      set adqlqc30;
      where ablfl ne 'Y';
run;
```

b. Derive **post-baseline estimates** using the model below. CHG (change from baseline score) is the dependent variable and BASE (baseline score), TRT (treatment), VISIT (visit), and the interaction between TRT and VISIT are independent variables in this model:

```
ods output lsmeans=pb_lsmean diffs=pb_lsdiff;
proc mixed data=qlqc2 method=reml covtest empirical;
      by param;
      class subjid trt visit;
      model chg=base trt visit trt*visit;
      random intercept/ subject=subjid;
      repeated visit/ subject=subjid type=ar(1);
      lsmeans trt*visit/ cl pdiff;
run;
```

pb_lsmean: pb_lsmean is the Lsmeans object from the ODS Output statement. This data set has the statistics estimate (LS means), stdErr (standard error), Probt (P value), Lower (lower confidence interval), and Upper (upper confidence interval) for respective treatments and visits.

Least Squares Means

Effect	TRT	Visit	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT*VISIT	A	Cycle 2	26.6060	4.2346	17	6.28	<.0001	0.05	17.6718	35.5402
TRT*VISIT	A	Cycle 3	19.6616	3.5451	17	5.55	<.0001	0.05	12.1821	27.1410
TRT*VISIT	A	Cycle 4	33.5504	3.4356	17	9.77	<.0001	0.05	26.3019	40.7990
TRT*VISIT	A	EOT	32.1615	8.2690	17	3.89	0.0012	0.05	14.7155	49.6075
TRT*VISIT	B	Cycle 2	17.6852	26.6340	17	0.66	0.5156	0.05	-38.5077	73.8781
TRT*VISIT	B	Cycle 3	59.3518	2.8765	17	20.63	<.0001	0.05	53.2829	65.4208
TRT*VISIT	B	Cycle 4	42.6852	8.9655	17	4.76	0.0002	0.05	23.7697	61.6007
TRT*VISIT	B	EOT	47.7637	5.4039	17	8.84	<.0001	0.05	36.3625	59.1649

PARAM	Effect	TRT	VISIT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Global Health Status/QoL	TRT*VISIT	A	Cycle 2	26.6059847	4.234586367	17	6.28	0.0000	0.05	17.67178842	35.54018098
Global Health Status/QoL	TRT*VISIT	A	Cycle 3	19.66155137	3.54506409	17	5.55	0.0000	0.05	12.18211993	27.14098281
Global Health Status/QoL	TRT*VISIT	A	Cycle 4	33.5504347	3.4356216	17	9.77	0.0000	0.05	26.30190673	40.79896267
Global Health Status/QoL	TRT*VISIT	A	EOT	32.1615347	8.26896619	17	3.89	0.0012	0.05	14.71554102	49.60752838
Global Health Status/QoL	TRT*VISIT	B	Cycle 2	17.68518561	26.63403309	17	0.66	0.5156	0.05	-38.50771231	73.87808353
Global Health Status/QoL	TRT*VISIT	B	Cycle 3	59.35183561	2.876522088	17	20.63	0.0000	0.05	53.2829045	65.42076672
Global Health Status/QoL	TRT*VISIT	B	Cycle 4	42.68518561	8.965490609	17	4.76	0.0002	0.05	23.76965386	61.60071736
Global Health Status/QoL	TRT*VISIT	B	EOT	47.76371377	5.403890434	17	8.84	0.0000	0.05	36.36250155	59.16492598

pb_lsdiff: pb_lsdiff is the DIFFS object from the ODS Output statement. This data set has a statistics estimate (LS means difference), stdErr (standard error), Probt (P value), Lower (lower confidence interval), and Upper (upper confidence interval). TRT is the current treatment whereas _TRT is a model-generated variable which represents the treatment comparator. As per the above shell, we have to display results for TRT A vs TRT B at each timepoint, so select records with TRT=A and _TRT=B when VISIT=_VISIT.

Differences of Least Squares Means

Effect	TRT	VISIT	_TRT	_VISIT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRT*VISIT	A	Cycle 2	A	Cycle 3	6.9444	4.5714	17	1.52	0.1471	0.05	-2.7004	16.5892
TRT*VISIT	A	Cycle 2	A	Cycle 4	-6.9445	2.3378	17	-2.97	0.0086	0.05	-11.8769	-2.0120
TRT*VISIT	A	Cycle 2	A	EOT	-5.5555	7.7745	17	-0.71	0.4846	0.05	-21.9583	10.8472
TRT*VISIT	A	Cycle 2	B	Cycle 2	8.9208	27.0028	17	0.33	0.7452	0.05	-48.0501	65.8917
TRT*VISIT	A	Cycle 2	B	Cycle 3	-32.7459	5.2966	17	-6.18	<.0001	0.05	-43.9206	-21.5711
TRT*VISIT	A	Cycle 2	B	Cycle 4	-16.0792	10.0080	17	-1.61	0.1265	0.05	-37.1941	5.0357
TRT*VISIT	A	Cycle 2	B	EOT	-21.1577	6.6780	17	-3.17	0.0056	0.05	-35.2471	-7.0684
TRT*VISIT	A	Cycle 3	A	Cycle 4	-13.8889	4.2431	17	-3.27	0.0045	0.05	-22.8411	-4.9367
TRT*VISIT	A	Cycle 3	A	EOT	-12.5000	9.3686	17	-1.33	0.1997	0.05	-32.2660	7.2660
TRT*VISIT	A	Cycle 3	B	Cycle 2	1.9764	26.8772	17	0.07	0.9422	0.05	-54.7295	58.6823
TRT*VISIT	A	Cycle 3	B	Cycle 3	-39.6903	4.6136	17	-8.60	<.0001	0.05	-49.4242	-29.9564
TRT*VISIT	A	Cycle 3	B	Cycle 4	-23.0236	9.6639	17	-2.38	0.0291	0.05	-43.4127	-2.6346
TRT*VISIT	A	Cycle 3	B	EOT	-28.1022	6.4156	17	-4.38	0.0004	0.05	-41.6379	-14.5664
TRT*VISIT	A	Cycle 4	A	EOT	1.3889	9.2997	17	0.15	0.8830	0.05	-18.2317	21.0095
TRT*VISIT	A	Cycle 4	B	Cycle 2	15.8652	26.8706	17	0.59	0.5627	0.05	-40.8268	72.5573
TRT*VISIT	A	Cycle 4	B	Cycle 3	-25.8014	4.5753	17	-5.64	<.0001	0.05	-35.4544	-16.1484
TRT*VISIT	A	Cycle 4	B	Cycle 4	-9.1348	9.6457	17	-0.95	0.3569	0.05	-29.4853	11.2158
TRT*VISIT	A	Cycle 4	B	EOT	-14.2133	6.3111	17	-2.25	0.0378	0.05	-27.5286	-0.8980
TRT*VISIT	A	EOT	B	Cycle 2	14.4763	27.9197	17	0.52	0.6108	0.05	-44.4290	73.3817
TRT*VISIT	A	EOT	B	Cycle 3	-27.1903	8.8550	17	-3.07	0.0069	0.05	-45.8727	-8.5079
TRT*VISIT	A	EOT	B	Cycle 4	-10.5237	12.2685	17	-0.86	0.4029	0.05	-36.4080	15.3607
TRT*VISIT	A	EOT	B	EOT	-15.6022	9.7549	17	-1.60	0.1281	0.05	-36.1832	4.9789
TRT*VISIT	B	Cycle 2	B	Cycle 3	-41.6666	29.4628	17	-1.41	0.1754	0.05	-103.83	20.4944
TRT*VISIT	B	Cycle 2	B	Cycle 4	-25.0000	17.6777	17	-1.41	0.1754	0.05	-62.2966	12.2966
TRT*VISIT	B	Cycle 2	B	EOT	-30.0785	21.3014	17	-1.41	0.1760	0.05	-75.0205	14.8634
TRT*VISIT	B	Cycle 3	B	Cycle 4	16.6666	11.7851	17	1.41	0.1754	0.05	-8.1977	41.5310
TRT*VISIT	B	Cycle 3	B	EOT	11.5881	8.2783	17	1.40	0.1796	0.05	-5.8777	29.0539
TRT*VISIT	B	Cycle 4	B	EOT	-5.0785	3.7795	17	-1.34	0.1967	0.05	-13.0525	2.8955

PARAM	Effect	TRT	VISIT	_TRT	_VISIT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Global Health Status/QoL	TRT*VISIT	A	Cycle 2	A	Cycle 3	6.944433333	4.571400853	17	1.52	0.1471	0.05	-2.700379399	16.58924607
Global Health Status/QoL	TRT*VISIT	A	Cycle 2	A	Cycle 4	-6.94445	2.337842315	17	-2.97	0.0086	0.05	-11.87686613	-2.012033866
Global Health Status/QoL	TRT*VISIT	A	Cycle 2	A	EOT	-5.55555	7.774478798	17	-0.71	0.4846	0.05	-21.95826648	10.84716648
Global Health Status/QoL	TRT*VISIT	A	Cycle 2	B	Cycle 2	8.920799088	27.00279278	17	0.33	0.7452	0.05	-48.05011377	65.89171195
Global Health Status/QoL	TRT*VISIT	A	Cycle 2	B	Cycle 3	-32.74585091	5.296553463	17	-6.18	0.0000	0.05	-43.92060192	-21.57109991
Global Health Status/QoL	TRT*VISIT	A	Cycle 2	B	Cycle 4	-16.07920091	10.00795289	17	-1.61	0.1265	0.05	-37.19413583	5.035734005
Global Health Status/QoL	TRT*VISIT	A	Cycle 2	B	EOT	-21.15772906	6.677989226	17	-3.17	0.0056	0.05	-35.24705476	-7.068403368
Global Health Status/QoL	TRT*VISIT	A	Cycle 3	A	Cycle 4	-13.88888333	4.243125037	17	-3.27	0.0045	0.05	-22.84109464	-4.936672031
Global Health Status/QoL	TRT*VISIT	A	Cycle 3	A	EOT	-12.49998333	9.368579695	17	-1.33	0.1997	0.05	-32.26595872	7.265992049
Global Health Status/QoL	TRT*VISIT	A	Cycle 3	B	Cycle 2	1.976365754	26.87718035	17	0.07	0.9422	0.05	-54.72952803	58.68225954
Global Health Status/QoL	TRT*VISIT	A	Cycle 3	B	Cycle 3	-39.69028425	4.613619401	17	-8.60	0.0000	0.05	-49.42417033	-29.95639816
Global Health Status/QoL	TRT*VISIT	A	Cycle 3	B	Cycle 4	-23.02363425	9.663908449	17	-2.38	0.0291	0.05	-43.41269883	-2.634569657
Global Health Status/QoL	TRT*VISIT	A	Cycle 3	B	EOT	-28.1021624	6.415605204	17	-4.38	0.0004	0.05	-41.6379062	-14.5664186
Global Health Status/QoL	TRT*VISIT	A	Cycle 4	A	EOT	1.3889	9.299677524	17	0.15	0.8830	0.05	-18.23170451	21.00950451
Global Health Status/QoL	TRT*VISIT	A	Cycle 4	B	Cycle 2	15.86524909	26.87062517	17	0.59	0.5627	0.05	-40.82681448	72.55731266
Global Health Status/QoL	TRT*VISIT	A	Cycle 4	B	Cycle 3	-25.80140091	4.575276775	17	-5.64	0.0000	0.05	-35.45439112	-16.1484107
Global Health Status/QoL	TRT*VISIT	A	Cycle 4	B	Cycle 4	-9.134750912	9.645662243	17	-0.95	0.3569	0.05	-29.48531937	11.21581755
Global Health Status/QoL	TRT*VISIT	A	Cycle 4	B	EOT	-14.21327906	6.311133661	17	-2.25	0.0378	0.05	-27.52860718	-0.897950953
Global Health Status/QoL	TRT*VISIT	A	EOT	B	Cycle 2	14.47634909	27.91968029	17	0.52	0.6108	0.05	-44.42902731	73.38172548
Global Health Status/QoL	TRT*VISIT	A	EOT	B	Cycle 3	-27.19030091	8.855010323	17	-3.07	0.0069	0.05	-45.87273963	-8.50786219
Global Health Status/QoL	TRT*VISIT	A	EOT	B	Cycle 4	-10.52365091	12.2685309	17	-0.86	0.4029	0.05	-36.40798851	15.36068669
Global Health Status/QoL	TRT*VISIT	A	EOT	B	EOT	-15.60217906	9.754909662	17	-1.60	0.1281	0.05	-36.18323943	4.978881301
Global Health Status/QoL	TRT*VISIT	B	Cycle 2	B	Cycle 3	-41.66665	29.46277076	17	-1.41	0.1754	0.05	-103.8276627	20.49436272
Global Health Status/QoL	TRT*VISIT	B	Cycle 2	B	Cycle 4	-25	17.67766953	17	-1.41	0.1754	0.05	-62.29662255	12.29662255
Global Health Status/QoL	TRT*VISIT	B	Cycle 2	B	EOT	-30.07852815	21.30135451	17	-1.41	0.1760	0.05	-75.02045773	14.86340143
Global Health Status/QoL	TRT*VISIT	B	Cycle 3	B	Cycle 4	16.66665	11.78510123	17	1.41	0.1754	0.05	-8.197740171	41.53104017
Global Health Status/QoL	TRT*VISIT	B	Cycle 3	B	EOT	11.58812185	8.278348879	17	1.40	0.1796	0.05	-5.877667576	29.05391127
Global Health Status/QoL	TRT*VISIT	B	Cycle 4	B	EOT	-5.078528153	3.77948413	17	-1.34	0.1967	0.05	-13.05254265	2.89548634

c. If the analysis requires additional covariates along with BASE (baseline score), TRT (treatment), VISIT (visit), and the interaction between TRT and VISIT, add those covariates to class and model statements. For example, let's say the above output needs stratification factors IPI and HISTLOGY as covariates in addition to BASE, TRT, VISIT, and TRT* VISIT. In that scenario, the following code would replace the code in section b:

```
ods output lsmeans=pb_lsmean diffs=pb_lsdiff;
proc mixed data=qlqc2 method=reml covtest empirical;
      by param;
      class subjid trt visit ipi histolgy;
      model chg=base trt visit ipi histolgy trt*visit;
```

```
        random intercept/ subject=subjid;
        repeated visit/ subject=subjid type=ar(1);
        lsmeans trt*visit/ cl pdiff;
run;
```

Please note that pb_lsmean and pb_lsdiff from section b and section c have similar structure and processing.

Note that the models used in this procedure may vary depending on the analysis requirement.

CONCLUSION

The usage of the MIXED procedure in the analysis of patient-reported outcomes and statements/options were described in this paper. These models can help users get a basic awareness of the MIXED procedure and implement it for various analyses.

REFERENCES

The MIXED Procedure: http://www.math.wpi.edu/saspdf/stat/chap41.pdf

Introduction to PROC MIXED: https://webpages.uidaho.edu/~brian/proc_mixed_documentation_uky.pdf

SAS Proc MIXED Syntax for Evaluating: https://dbauer.web.unc.edu/wp-content/uploads/sites/7494/2014/08/BauerSterba_appendix_SAS.pdf

ACKNOWLEDGMENTS

We would like to thank Michiel Hagendoorn, Balavenkata R. Pitchuka and Johnny Maruthavanan for their valuable feedback and constant support and guidance.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact authors at:

Janaki Manthena.
21823 - 30th Drive S.E.
Bothell, WA 98021
Jmanthena@seagen.com

Varsha Korrapati
21823 - 30th Drive S.E.
Bothell, WA 98021
Vkorrapati@seagen.com

Chiyu Zhang
21823 - 30th Drive S.E.
Bothell, WA 98021
Czhang@seagen.com