**Evaluating the Efficacy of Progabide in Seizure Reduction: A Placebo-Controlled, Double-Blinded Clinical Trial Using Generalized Estimating Equations**

**PORTFOLIO**

**Course: STP598, Clinical Trials**

**Instructor: Ming-Hung Kao**

**Author: Jiseon Yang**

2024

**ABSTRACT**

This double-blinded, placebo-controlled clinical trial assessed the efficacy of the anti-epileptic drug Progabide in 59 patients, analyzing seizure counts during an 8-week baseline and subsequent four 2-week periods post-treatment. Utilizing Generalized Estimating Equations (GEE) with an autoregressive (AR[1]) covariance structure for its low Quasi-Information Criterion (QIC), we identified Model 16 as optimal through backward selection. Significant treatment effects were explored using the CONTRAST statement and mean log baseline (mlb) calculations. Results confirm Progabide's effectiveness in reducing seizure frequency compared to placebo, with age and baseline seizures as critical factors in treatment response. The chosen GEE model effectively captures the dynamics of treatment effects over time, accounting for the repeated measures within subjects, thus providing robust insights into the drug’s therapeutic potential.

**INTRODUCTION**

We have a placebo-controlled, double-blinded clinical trial for studying the effectiveness of an anti-epileptic drug, Progabide. A total of 59 patients are randomized to receive an active treatment or placebo. Before the treatment, the number of seizures that each patient experienced during an 8-week baseline period is recorded. The seizure counts are also recorded over 4 consecutive 2-week periods following the treatment. We would like to know if there is any evidence of a difference in response profile between the treatment and placebo. Here, I built an appropriate model to study the effect of the treatment on the response profile. For model selection, Generalized Estimating Equations (GEE) were used to evaluate various covariance structures, and The AR(1) structure, which had the lowest Quasi-Information Criterion (QIC), was selected and the AR(1) covariate structure producing the lowest QIC was selected. Starting with a full model with AR(1), Model 16, which displayed the lowest QICu, was identified as the most appropriate, through backward selection. Detailed interaction effects were explored using the CONTRAST statement, and mean log baseline (mlb) was calculated to aid in interpreting the treatment effects, both with and without considering the baseline effect. The statistical evidence supports the efficacy of Progabide in reducing seizure frequency compared to placebo, with age and baseline seizure counts being important modifiers of this effect. The chosen GEE model with an AR(1) correlation structure provides a reliable understanding of treatment response profiles over time, accounting for repeated measures within subjects.

**PROCEDURES**

***Data preparation***: The data was obtained with ‘**seizures.csv**’. The class variables in the model include subject ‘**id**’, ‘**trt**’, and ‘**visit**’. I used the ‘**baseline**’ and ‘**age**’ as a covariate. In the analysis, the 'baseline' value was divided by 4 because it represents data collected over 8 weeks, whereas 'visit1' through 'visit4' represent data collected every 2 weeks with repeated measures. The response (**Y**) at the ith visit was counted and saved as ‘**cnt’**. The ‘**age**’ and ‘**baseline**’ were log-transformed to '**log\_age**' and **'log\_base**,' respectively. A variable ‘**cell**’ was created to indicate the (treatment, visit) combination by using CAT function. The long-form data set was prepared as shown below.

A screenshot of a cell

Description automatically generated

***Visualization of the data***: To check if a linear relationship between the log-response (Y) and the log-baseline (X) is reasonable, I plotted logcnt(Y) vs log\_base (X) for each treatment-visit cell using PROC SQPLOT. From the **figure** below, the assumption of a linear relation between ‘logcnt’ and ‘logbase’ does not seem unreasonable although higher order term may be considered.

A graph of different colored lines

Description automatically generated

***Model building***:

For model selection, I used Generalized Estimating Equations (GEE) and evaluated different covariance structures: independence, AR(1), exchangeable, and unstructured. The response cnt was modeled as a function of treatment, visit, log-transformed age (log\_age), and log-transformed baseline (log\_base), along with all their interactions in all levels between the terms. The data follow a Poisson distribution. The scale parameter is estimated from the Pearson chi-square statistic, adjusting for overdispersion if present. The three covariance structures were compared. The structure with the lowest Quasi-Information Criterion (QIC) was selected, which was AR(1).

A screenshot of a computer code

Description automatically generated

Starting with a full model that included all main effects and potential interactions, I used a stepwise approach to remove non-significant terms, beginning with the highest-order interactions and closely observing changes in QICu values. The QICu values, obtained by the backward selection with AR(1), were compared and the **Model 16** showed the lowest value and was thus determined to be the best fit.

A screenshot of a computer

Description automatically generated

***Analysis the data with the selected model 16***: The final analysis was conducted using PROC GENMOD with this model and studied the differences among treatments (Progabide and placebo). To examine the interaction effects in more detail, the **CONTRAST** statement in PROC GENMOD was used, along with the calculation of mlb (mean log baseline), to assist in interpreting the treatment effects in relation to the average baseline seizure count.

A screenshot of a data sheet

Description automatically generated A screenshot of a data sheet

Description automatically generated

A screenshot of a computer

Description automatically generated

Exp (0.3669)= 1.4433 🡺 ratio between two means

A math equation with numbers

Description automatically generated with medium confidence

First line (trt-wald): treatment effect at logbase=0

2nd line (trt-wald at mean); treatment effect at logbase=&mlb

**RESULTS and DISCUSSION**

The final model is shown below:

**ln(E[*cntijk*​]) = *γ* + *τj*​ + *ρk* ​+ (*β*0 ​\* log\_base) + (*β*1​ \* log\_age) + (*β*2​ \* log\_base \* *τj*​) + (*β*3​ \* log\_base \* visit*k*​) + (*β*4 ​\* log\_age \* visit*k*​)**

Alternatively,

**ln(*E*[*Yijk*​]) = *γ* + *τj* ​+ *ρk*​ + *β*0​ln(*xi*​) + *β*1​ln(age*i*​) + *β*2*j*​\**τj\**​ln(*xi*​) + *β*3*k\**​*ρk\**​ln(*xi*​) + *β*4*k\**​*ρk\**​ln(age*i)*​**

where:

* *γ* : the overall intercept.
* *τj*​ : the effect of the treatment *j* (where *j*=0 for placebo, *j*=1 for Progabide).
* *ρk*​ : the effect of the *k*-th visit.
* *xi*​ : (the seizure count in the baseline period) / 4, for the *i*-th patient.
* *β*0​ : the coefficient for the main effect of the log-baseline seizure count.
* *β*1​ : the coefficient for the main effect of log-age.
* *β*2*j*​ : the coefficient for the interaction between treatment (j) and log-baseline seizure count.
* *β*3*k*​ : the coefficient for the interaction between visit (k) and log-baseline seizure count.
* *β*4*k*​ : the coefficient for the interaction between visit (k) and log-age.

1. **Treatment Effect**: The result show that the test for H0: τ0=τ1 showed that with a p-value of 0.0093, there is a significant treatment effect of treatment on the response (seizure counts).
2. **Age Effects**: The age of patients (log\_age) were found to be significant (p = 0.066), suggesting variability in seizure counts across different ages and visit periods.
3. **Baseline Seizure Count**: The log-baseline seizure count (log\_base, p=0.0072) and its interaction with treatment (log\_base\*trt, p=0.0441) were significant, indicating the importance of the initial severity of the condition in the response to treatment.
4. **Treatment Efficacy**: The log odds of seizure counts for patients on placebo is 0.3669 units higher than for those on the Progabide, on the logarithmic scale. Wald tests conducted at mean logbase levels suggest the point estimate of the mean ratio (µ₀/µ₁) = Exp{L^T B.hat} = exp(β₁), the ratio of seizure counts between the placebo and treatment groups, is e^ 0.3669 = 1.4433 (p = 0.0337). This indicates that the mean seizure counts in the placebo group is 1.443 times that of the treatment group assuming all other variables are held constant. Thus, the results imply that treatment with Progabide has a substantial effect on reducing the frequency of seizures in patients with epilepsy.
5. **Contrast results**: Since there is interaction effect, “at mean" contrasts are used to estimate the effect of a treatment at the average value of log-base. The results indicates the significant effect of treatment at the mean level of log\_base in the model. Thus, there is a statistically significant difference between treatment levels and this effect remains significant even when considering the average levels of log\_base in this model.

**CONCLUSION**

The statistical evidence supports the efficacy of Progabide in reducing seizure frequency compared to placebo, with age and baseline seizure counts being important modifiers of this effect. The chosen GEE model with an AR(1) correlation structure provides a reliable understanding of treatment response profiles over time, accounting for repeated measures within subjects.

**SAS CODES**

dm "output;clear;log;clear;odsresults;clear";

**options** ls=75 ps=2000 formdlim='\*' nodate nonumber nocenter;

*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* I. data \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\**

*\* --- data set ---;*

**data** seizure;

infile 'C:\Users\jyang\OneDrive - Arizona State University\10 Classes\_OneDrive\2024\_STP598\_Clinical Trials\Computing\Topic4\seizures.csv' dlm=',' firstobs=2;

input id trt age baseline visit1-visit4;

**run**;

**proc** **print**;

title 'HW5-4';

**run**;

*%macro* univfmt;

**data** uniseizure (keep=id trt age baseline visit cnt cell); %\* only keep the useful variables in the final **data** set;

set seizure; %\* create the **data** set using the previously created seizure **data** set;

baseline = baseline/4; %\* adjust for the number of weeks for baseline;

*%do* i = **1** *%to* **4**; %\* create two new variables, namely 'visit' and 'cnt';

visit = &i.; %\* the ith visit;

cnt = visit&i.; %\* the response at the ith visit;

cell = cat(trt,visit);%\* Use CAT function to create a variable to indicate the (treatment, visit) combination;

output; %\* create a record with the current variables in the **data** set;

*%end*;

**run**;

*%mend*;

%univfmt;

*\* --- data preparation for log-linear model---;*

**data** uniseizure;

set uniseizure;

log\_age = log(age); */\* Log-transform age \*/*

log\_base = log(baseline); \*Log-transform baseline, log(x);

logcnt=log(cnt+**1**); \*obtain log(y) but avoid log(y=0);

**run**;

*\* --- sorting the data ---;*

**proc** **sort** data=uniseizure;

by trt visit;

**run**;

*\* --- visualization ---;*

*\* Visualize the data to check for linearity between log count and log baseline;*

ods graphics / attrpriority=none;

**proc** **sgplot** data=uniseizure;

styleattrs datalinepatterns=(solid);

**loess** y=logcnt x=log\_base / group=cell; */\* Replace cell with appropriate grouping variable if needed \*/*

**run**;

*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* II. Build model \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\**

*\* using PROC GENMOD with GEE for repeated measures*

*\* 1) independence structure, dispersion parameter, phi;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt = trt|visit log\_age|trt|visit log\_base|trt|visit / link=log type3 d=poisson scale=p; */\*A|B|C = A B C AB BC CA ABC \*/*

repeated subject=id(trt) / type=indep within=visit modelse; */\* Assuming independence \*/*

ods select GEEModPEst GEEFitCriteria;

ods output GEEModPEst=out1 GEEFitCriteria=out2;

**run**;

*\* From OUT1, we create a macro variable &phi to store the estimated sqrt(\phi);*

**proc** **sql**;

select estimate into :phi

from out1

where parm='Scale';

**quit**;

*\* Select an error structure with QIC: store QIC value for independent correlation structure;*

**proc** **sql**;

select value into :QICind

from out2

where criterion='QIC';

**quit**;

*\*\* 2) the AR(1) structure by keeping the same \phi-hat;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt|visit log\_base|trt|visit /link=log type3 d=poisson scale=&phi. noscale;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods select GEEFitCriteria; \*Only present this result;

ods output GEEFitCriteria=out2; \*create output **data** sets to give the QIC;

title "Cov structure: AR(1)";

**run**;

**proc** **sql**;

select value into :QICar1

from out2

where criterion='QIC';

**quit**;

*\*\* 3) the exchangeable type covariance structure, i.e., compound symmetry;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt|visit log\_base|trt|visit /link=log type3 d=poisson scale=&phi. noscale;

repeated subject=id(trt) / type=cs within=visit;

ods select GEEFitCriteria;

ods output GEEFitCriteria=out2;

title "Cov structure: Exchangeable";

**run**;

**proc** **sql**;

select value into :QICcs

from out2

where criterion='QIC';

**quit**;

*\*\* 4) The unstrcuted covariance, not working well;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt|visit log\_base|trt|visit /link=log type3 d=poisson scale=&phi. noscale;

repeated subject=id(trt) / type=un within=visit;

title "Cov structure: Unstructured";

**run**;

title;

*\*\*\*\*\*\*\*\*\*\*\*\*\*\* III. Compare the three covariance structures \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\**

*\*\*\*\* AR(1) yields a slighly smaller QIC than CS;*

**data** \_null\_;

file **print**;

put "Indep.: &QICind"; \*-**1309**.**0017**;

put "AR(1) : &QICar1"; \*-**1309**.**4286** (smallest);

put "CS : &QICcs"; \*-**1309**.**2051**;

**run**;

*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* IV. backward selection with AR(1) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\**

*\* 1) AR(1);*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt|visit log\_base|trt|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q1

from out2

where criterion='QICu';

**quit**;

*\* 2) no three-way interaction;*

*\*\* Note. A|B|C @2 = A B C A\*B A\*C B\*C, i.e. up to 2-way interactions;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt|visit log\_base|trt|visit @**2** /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q2

from out2

where criterion='QICu';

**quit**;

*\* 3) elliminate log\_base\*visit;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt log\_age|visit log\_base|trt /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q3

from out2

where criterion='QICu';

**quit**;

*\* 4) elliminate log\_base\*trt;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt log\_age|visit log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q4

from out2

where criterion='QICu';

**quit**;

*\* 5) elliminate log\_age\*visit ;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt log\_base|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q5

from out2

where criterion='QICu';

**quit**;

*\* 6) elliminate log\_age\*trt ;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|visit log\_base|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q6

from out2

where criterion='QICu';

**quit**;

*\* 7) elliminate ..\*visit ;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt log\_base|trt /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q7

from out2

where criterion='QICu';

**quit**;

*\* 8) elliminate ..\*trt ;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|visit log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q8

from out2

where criterion='QICu';

**quit**;

*\* 9) elliminate age\*trt, base\*visit ;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|visit log\_base|trt /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q9

from out2

where criterion='QICu';

**quit**;

*\* 10) elliminate age\*visit, base\*trt ;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2;

**run**;

**proc** **sql**;

select value into :q10

from out2

where criterion='QICu';

**quit**;

*\* 11) w/o age\*.. base\*..;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt|visit log\_age log\_base /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q11

from out2

where criterion='QICu';

**quit**;

*\* 12) w/o trt\*visit;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|trt log\_age|visit log\_base|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q12

from out2

where criterion='QICu';

**quit**;

*\* 13)w/o trt\*visit, w/o base\*visit;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|trt log\_age|visit log\_base|trt /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q13

from out2

where criterion='QICu';

**quit**;

*\* 14)w/o trt\*visit, w/o base\*trt;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|trt log\_age|visit log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q14

from out2

where criterion='QICu';

**quit**;

*\* 15)w/o trt\*visit, w/o age\*visit;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|trt log\_base|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q15

from out2

where criterion='QICu';

**quit**;

*\* 16)w/o trt\*visit, w/o age\*trt;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|visit log\_base|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q16

from out2

where criterion='QICu';

**quit**;

*\* 17)w/o trt\*visit, w/o ..\*visit;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|trt log\_base|trt /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q17

from out2

where criterion='QICu';

**quit**;

*\* 18)w/o trt\*visit, w/o age\*visit w/o base\*trt;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q18

from out2

where criterion='QICu';

**quit**;

*\* 19)w/o trt\*visit, w/o age\*trt w/o base\*visit;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|visit log\_base|trt /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q19

from out2

where criterion='QICu';

**quit**;

*\* 20)w/o trt\*visit, w/o ..\*trt;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|visit log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q20

from out2

where criterion='QICu';

**quit**;

*\* 21)w/o interactions;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age log\_base /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

**proc** **sql**;

select value into :q21

from out2

where criterion='QICu';

**quit**;

*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* V. Compare the QICu for the above models;*

**data** \_null\_;

file **print**;

put "mean1(full): &q1";

put "mean2(no 3-int): &q2";

put "mean3(w/o log\_base\*visit): &q3";

put "mean4(w/o log\_base\*trt): &q4";

put "mean5(w/o log\_age\*visit): &q5";

put "mean6(w/o log\_age\*trt): &q6";

put "mean7(w/o ..\*visit): &q7";

put "mean8(w/o ..\*trt): &q8";

put "mean9(w/o age\*trt, base\*visit): &q9";

put "mean10(w/o age\*visit, base\*trt): &q10";

put "mean11(no 2-int): &q11";

put "mean12(w/o trt\*visit): &q12";

put "mean13(mean12 w/o base\*visit): &q13";

put "mean14(mean12 w/o base\*trt): &q14";

put "mean15(mean12 w/o age\*visit): &q15";

put "mean16(mean12 w/o age\*trt): &q16";

put "mean17(mean12 w/o ..\*visit): &q17";

put "mean18(mean15 w/o base\*trt): &q18";

put "mean19(mean16 w/o base\*visit): &q19";

put "mean20(mean12 w/o ..\*trt): &q20";

put "mean21(w/o): &q21";

**run**;

*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* VI. analyze the data with Model 16 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*;*

*\* 16) model 16: w/o trt\*visit, w/o age\*trt;*

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|visit log\_base|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit corrw;

ods output GEEFitCriteria=out2; \*create output **data** sets;

**run**;

*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* VII. study trt difference \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*;*

**proc** **sql**;

select avg(log\_base) into :mlb

from uniseizure;

**quit**;

ods trace on;

**proc** **genmod** data=uniseizure;

class id trt visit;

**model** cnt= trt visit log\_age|visit log\_base|trt log\_base|visit /link=log type3 d=poisson scale=p;

repeated subject=id(trt) / type=ar(**1**) within=visit corrw;

contrast 'trt-score' trt **1** **-1**; \*treatment effect at logbase=0 with **score** method;

contrast 'trt-wald' trt **1** **-1** /wald; \*treatment effect at logbase=0 with Wald method;

estimate 'trt-wald' trt **1** **-1** ; \*estimates of treatment effect at logbase=0 with Wald method;

contrast 'trt-score at mean' trt **1** **-1** log\_base\*trt &mlb. - &mlb.; \*score test at logbase=&mlb. (the mean of logbase);

contrast 'trt-wald at mean' trt **1** **-1** log\_base\*trt &mlb. - &mlb./wald; \*at logbase=&mlb. (the mean of logbase);

estimate 'trt-wald at mean' trt **1** **-1** log\_base\*trt &mlb. - &mlb.;

ods select Estimates Contrasts;

**run**;

ods trace off;

*\* The Wald estimates suggest that the point estimate of mean ratio (mu\_0/mu\_1)=exp(L'beta) at mean logbase*

is **1**.**4433**;

**quit**;