MULTILOG Example #2

SUDAAN Statements and Results Illustrated

- GEE model-fitting with multinomial outcomes
- Correlations, R options
- Standard error, SEMETHOD option
- CUMLOGIT option
- CONDMARG

Input Data Set(s): CROSS.SSD

Example

Evaluate data from a crossover clinical trial conducted by 3M Health Care Ltd. Use multinomial logistic regression to evaluate the clarity of leaflet instructions in the study. Treatment group and study period are the independent variables.

This example highlights the use of the PROC statement options (R and SEMETHOD) to implement GEE model-fitting techniques for cluster-correlated experimental data with multinomial outcomes.

This example also highlights the estimation of the model-adjusted risk and risk ratio via conditional marginal proportions (ADJRR option on CONDMARG statement). It also provides confidence limits for the model-adjusted risk, new in Release 11.

Solution

Qualitative responses in a cross-over clinical trial are often ordinal. For example, such responses might be "relief," "slight relief," or "no relief" in studies of painkiller effectiveness. Due to the nature of cross-over studies, repeated measurements on the same subject are likely to be correlated. The intrasubject correlation must be considered in order to make valid inferences about the treatment effect.

Data for this example are from a two-treatment, two-period crossover study conducted by 3M Health Care Ltd. (Ezzet and Whitehead, 1991) to compare the suitability of two inhalation devices (A and B) in patients who are currently using a standard inhaler device delivering salbutamol. ***Exhibit 1*** shows the structure of the data.

Exhibit 1. Structure of the Leaflet Clarity Data

Patient	Period	Treatment	Y = Clarity
1	1	1 = New	1 = Easy
1	2	2 = Standard	1 = Easy
2	1	1	1 = Easy
2	2	2	2 = Rereading
3	1	2	3 = Not Clear
3	2	1	2 = Rereading
4	1	2	4 = Confusing
4	2	1	1 = Easy
.	.	.	.
.	.	.	.
.	.	.	.

N = 572 records on the file, (286 clusters, two records per cluster).

Variables in the regression models include:

TREATMENT: 1 or 2
PERIOD: 1 or 2.

The accompanying output contains results from the following SUDAAN procedures.

- PROC RECORDS: contents of the data set (***Exhibit 2***).
- PROC CROSSTAB: descriptive statistics; distribution of the four-level ordinal outcome across treatment group; and test for trend between leaflet clarity and treatment (***Exhibit 5***).
- PROC MULTILOG: proportional odds and multinomial logit regression of treatment and period effects on leaflet clarity. In the proportional odds model, we model the probability of increasing clarity across treatment group and study period (1 vs. 2). In the multinomial logit model, we model the probability of being in each of the first three levels of CLARITY vs. the last (***Exhibit 10***).

This example was run in SAS-Callable SUDAAN, and the SAS program and *.LST files are provided.

Exhibit 2. SAS Program Code for PROC RECORDS

```
libname in v604 "c:\10winbetatest\examplemanual\multilog";

options nocenter pagesize=70 linesize=95;
proc format;
  value treat 1="Inhalant A"
              2="Inhalant B";
  value clarity 1="Easy"
                2="Rereading"
                3="Not Clear"
                4="Confusing";

data one; set in.cross;
proc sort data=one; by person;

PROC RECORDS DATA=one FILETYPE=SAS CONTENTS COUNTREC NOPRINT;
```

Exhibit 3. First Page of RECORDS Output

```
                                S U D A A N
            Software for the Statistical Analysis of Correlated Data
           Copyright      Research Triangle Institute     November 2011
                                Release 11.0.0


SAS Record File ONE
Variables
Name          Type       Output     Description
                         Format
-----------------------------------------------
PERSON        Numeric    F12.0      PERSON
TREAT         Numeric    F12.0      TREAT
SEQUENCE      Numeric    F12.0      SEQUENCE
PERIOD        Numeric    F12.0      PERIOD
CLARITY       Numeric    F12.0      CLARITY

Number of records on file :    572
```

Exhibit 3 indicates that there are 572 records (one record for each person and treatment occasion) on the SAS data set. The outcome of interest is CLARITY of leaflet instructions, coded as follows: 1=Easy; 2=Rereading required; 3=Not clear; and 4=Confusing.

Exhibit 4. PROC CROSSTAB Code

```
PROC CROSSTAB DATA=one FILETYPE=SAS;
NEST _ONE_ PERSON;
WEIGHT _ONE_;

CLASS TREAT CLARITY;
TABLES TREAT*CLARITY;
TEST TCMH;

SETENV DECWIDTH=4 COLWIDTH=10 LABWIDTH=15;
PRINT NSUM / ATEST=default STYLE=NCHS nsumfmt=f10.0 adffmt=f8.0 atestvalfmt=f5.2
             apvalfmt=f8.4;
RFORMAT treat treat.;
RFORMAT clarity clarity.;
RTITLE "Frequency Distribution and Trend Test for Inhaler Device Cross-Over Study";
RFOOTNOTE "Ezzett and Whitehead, 1991";
```

Exhibit 5. First Page of CROSSTAB Output

```
                                S U D A A N
            Software for the Statistical Analysis of Correlated Data
           Copyright      Research Triangle Institute     November 2011
                                Release 11.0.0


DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method,
Assuming a With Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: PERSON


Number of observations read    :    572    Weighted count :      572
Denominator degrees of freedom :    285
```

Exhibit 5 indicates that there are 572 records on the file. The variable PERSON is the primary sampling unit (cluster).

Exhibit 6. CLASS Variable Frequencies (TREAT)

```
Frequencies and Values for CLASS Variables

by: TREAT.
---------------------------------------
TREAT           Frequency         Value
---------------------------------------
Ordered
  Position:
  1                   286    Inhalant A
Ordered
  Position:
  2                   286    Inhalant B
---------------------------------------
```

Exhibit 7. CLASS Variable Frequencies (CLARITY)

```
Frequencies and Values for CLASS Variables

by: CLARITY.
---------------------------------------
CLARITY         Frequency        Value
---------------------------------------
Ordered
  Position:
  1                   358         Easy
Ordered
  Position:
  2                   189    Rereading
Ordered
  Position:
  3                    17    Not Clear
Ordered
  Position:
  4                     8    Confusing
---------------------------------------
```

Exhibit 8. Treatment by Clarity Cross-Classification

```
Variance Estimation Method: Taylor Series (WR)

Frequency Distribution and Trend Test for Inhaler Device Cross-Over Study

Sample Size

by: TREAT, CLARITY.
-------------------------------------------------------------------------------------
TREAT                CLARITY
                          Total         Easy    Rereading    Not Clear    Confusing
-------------------------------------------------------------------------------------
Total                       572          358          189           17            8
Inhalant A                  286          211           71            2            2
Inhalant B                  286          147          118           15            6
-------------------------------------------------------------------------------------
Ezzett and Whitehead, 1991
```

Exhibit 9. Test for Linear Trend Between Treatment and Leaflet Clarity

```
Variance Estimation Method: Taylor Series (WR)

Frequency Distribution and Trend Test for Inhaler Device Cross-Over Study

  Test Statistics for Stratum-Adjusted Hypotheses
  Variable TREAT by Variable CLARITY

------------------------------------------------
Hypothesis Test
   Test Statistic               Test
                          DF    Value    P-Value
------------------------------------------------
CMH Trend
   Wald-F                  1    41.92     0.0000
------------------------------------------------
Ezzett and Whitehead, 1991
```

The CROSSTAB procedure produced the frequency distribution of CLARITY across treatment (***Exhibit 8***) and performed a test for linear trend between treatment group and leaflet clarity (***Exhibit 9***). The frequency distribution indicates that the Inhaler A leaflet is easier to read than Inhaler B. The test for linear trend between treatment and leaflet clarity reveals that the tendency for Inhaler A to be easier to read is significant. This effect accounts for the correlations of observations within person, but is unadjusted for the effect of Period.

We report on four sets of MULTILOG programming statements. The first three MULTILOG runs are fit using the proportional odds model (CUMLOGIT link) with various options, and the last run is fit using the generalized logit model (GENLOGIT link). The CUMLOGIT link models the log-odds that CLARITY $\leq k$, where k=1,...,K-1 (or the tendency for the assessment of the leaflet instructions to be less confusing). The GENLOGIT link models the log-odds that CLARITY=k vs. K (or the log-odds that CLARITY is easy, requires rereading, or not clear vs. confusing). The CUMLOGIT option produces common slopes but separate intercepts for each of the K-1 = 3 cutpoints, while the GENLOGIT option produces a separate logit equation (intercepts and slopes) for each of the three cutpoints.

Runs with CUMLOGIT Link (Proportional Odds Model):

1. SEMETHOD=ZEGER and R=INDEPENDENT—Implements the GEE model-fitting technique under an independent working assumption and a robust variance estimator.
2. SEMETHOD=ZEGER and R=EXCHANGEABLE—Implements the GEE model-fitting technique under exchangeable working correlations and a robust variance estimator.
3. SEMETHOD=MODEL and R=EXCHANGEABLE—Implements the GEE model-fitting technique under exchangeable working correlations and a model-based, or naive, variance estimator. When R=Exchangeable is specified in conjunction with SEMETHOD=Model, variances are then computed as if the exchangeable working correlation assumption were correct.

Run with GENLOGIT Link (Generalized Logit Model):

1. SEMETHOD=ZEGER and R=INDEPENDENT—Implements the GEE model-fitting technique under an independent working assumption and a robust variance estimator.

In each run, the NEST statement indicates that PERSON is the cluster variable. The WEIGHT statement indicates equal sampling weights of 1.0 for each person and measurement occasion.

In MULTILOG, the CLASS statement contains the dependent variable and all covariates that are to be modeled as categorical covariates.

The MODEL statement specifies the categorical dependent variable CLARITY on the left of the "=" sign (with levels 1, 2, 3, and 4), and regressors on the right:

- TREAT (1=Inhalant A, 2=Inhalant B);
- PERIOD (1 vs 2);
- CLARITY (1=Easy, 2=Requires Rereading, 3=Not Clear, 4=Confusing).

The default Wald-*F* test is used for all tests of hypotheses.

The CONDMARG statement requests the conditional marginal proportion (*model-adjusted risk*) for each level of treatment. The ADJRR option on the CONDMARG statement computes the *model-adjusted risk ratio* for treatment (Inhalant A vs. B).

We include multiple PRINT statements, all of which are optional. Multiple PRINT statements allow us to set up different default print environments (SETENV statements) for different PRINT groups. The PRINT statements are used in this example to request the PRINT groups of interest; to calculate individual statistics of interest, and in some cases, change the default labels for those statistics; and to specify a variety of formats for those printed statistics. Without the PRINT statement, default statistics are produced from each PRINT group, with default formats.

The SETENV statements are optional. They set up default formats for printed statistics and further manipulate the printout to the needs of the user.

The RFORMAT statements associate the SAS formats with the variables used in the procedure. The RLABEL statement defines variable labels for use in the current procedure only. Without the RLABEL statement, SAS variable labels would be produced if already defined.

Exhibit 10. MULTILOG Code (CUMLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
PROC MULTILOG DATA=one FILETYPE=SAS SEMETHOD=ZEGER R=INDEPENDENT;
  NEST _ONE_ PERSON;
  WEIGHT _ONE_;

  CLASS CLARITY TREAT PERIOD;
  MODEL CLARITY = TREAT PERIOD / CUMLOGIT;
  CONDMARG treat / adjrr;

  SETENV LABWIDTH=28 COLWIDTH=7 DECWIDTH=4 COLSPCE=2 TOPMGN=0;
  PRINT  BETA SEBETA DEFT="Design Effect" T_BETA P_BETA /
         RISK=default TESTS=default deftfmt=f6.2
         orfmt=f6.3 loworfmt=f7.3 uporfmt=f7.3
         t_betafmt=f6.2 waldffmt=f6.2 dffmt=f7.0;

  SETENV LABWIDTH=22 COLWIDTH=7 DECWIDTH=4 COLSPCE=1 TOPMGN=0;
  PRINT / COND_MRG=default condmrgfmt=f11.4 lowcmfmt=f6.4 upcmfmt=f6.4
          t_cndmrgfmt=f8.2;

  SETENV LABWIDTH=40 COLWIDTH=5 DECWIDTH=3 COLSPCE=3 TOPMGN=0;
  PRINT COND_RR="Risk Ratio" / CONDRISK=default;

  RFORMAT treat treat.;
  RFORMAT clarity clarity.;
  RTITLE "Proportional Odds Model for Inhaler X-Over (Independent, Robust)";
  RFOOTNOTE "Ezzett and Whitehead, 1991";
```

Exhibit 11. First Page of MULTILOG Output (CUMLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
                              S U D A A N
           Software for the Statistical Analysis of Correlated Data
          Copyright      Research Triangle Institute    November 2011
                               Release 11.0.0


DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method,
Assuming a With Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: PERSON


Independence parameters have converged in 4 iterations

Number of observations read       :    572    Weighted count:      572
Observations used in the analysis :    572    Weighted count:      572
Denominator degrees of freedom    :    285


Maximum number of estimable parameters for the model is  5

File ONE contains  286 Clusters
 286 clusters were used to fit the model
Maximum cluster size is   2 records
Minimum cluster size is   2 records


Sample and Population Counts for Response Variable CLARITY
Based on observations used in the analysis
  Easy     :  Sample Count      358    Population Count       358
  Rereading:  Sample Count      189    Population Count       189
  Not Clear:  Sample Count       17    Population Count        17
  Confusing:  Sample Count        8    Population Count         8
```

CLARITY is the outcome variable in the model, while TREAT and PERIOD are covariates. ***Exhibit 11*** indicates that there are 572 records on the file, corresponding to 286 clusters, with a minimum and maximum cluster size of two (since this is a two-period crossover design). There are no missing values in the data set and no SUBPOPN statement to subset the analysis, so all observations on the file are used in fitting the model. SUDAAN displays the frequency distribution of the response in the data and the number of iterations needed to estimate the regression coefficients.

Exhibit 12. CLASS Variable Frequency Distributions (CLARITY)

```
Frequencies and Values for CLASS Variables

by: CLARITY.
--------------------------------------
CLARITY         Frequency        Value
--------------------------------------
Ordered
  Position:
  1                   358         Easy
Ordered
  Position:
  2                   189    Rereading
Ordered
  Position:
  3                    17    Not Clear
Ordered
  Position:
  4                     8    Confusing
--------------------------------------
```

Exhibit 13. CLASS Variable Frequency Distributions (TREAT)

```
Frequencies and Values for CLASS Variables

by: TREAT.
---------------------------------------
TREAT           Frequency         Value
---------------------------------------
Ordered
  Position:
  1                   286    Inhalant A
Ordered
  Position:
  2                   286    Inhalant B
---------------------------------------
```

Exhibit 14. CLASS Variable Frequency Distributions (PERIOD)

```
Frequencies and Values for CLASS Variables

by: PERIOD.
-----------------------------------
PERIOD          Frequency    Value
-----------------------------------
Ordered
  Position:
  1                   286        1
Ordered
  Position:
  2                   286        2
-----------------------------------
```

Exhibit 15. Estimated Regression Coefficients (CUMLOGIT link, with R=Independent, SEMETHOD=Zeger

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Independent, Robust)

------------------------------------------------------------------------------
CLARITY (cum-logit),
  Independent Variables and                                          P-value
  Effects                      Beta                  Design   T-Test   T-Test
                               Coeff.    SE Beta     Effect   B=0      B=0
------------------------------------------------------------------------------
CLARITY (cum-logit)
  Intercept 1: Easy             0.1110    0.1383      0.88     0.80    0.4229
  Intercept 2: Rereading        2.7657    0.2357      1.03    11.74    0.0000
  Intercept 3: Not Clear        3.9464    0.3638      0.95    10.85    0.0000
TREAT
  Inhalant A                    1.0137    0.1566      0.78     6.47    0.0000
  Inhalant B                    0.0000    0.0000       .        .       .
PERIOD
  1                            -0.1512    0.1565      0.80    -0.97    0.3347
  2                             0.0000    0.0000       .        .       .
------------------------------------------------------------------------------
Ezzett and Whitehead, 1991
```

Exhibit 15 displays the estimated regression coefficients for the proportional odds model and indicates that Inhaler A is significantly clearer in its leaflet instructions than Inhaler B (p=0.0000, t-test). This is reflected in the positive regression coefficient estimate (1.0137) and in the estimated odds ratio (2.756), below (***Exhibit 15***). In other words, the odds of being ≤ any response level k are increased almost threefold over Inhaler B. Note that the three intercept terms in the model are non-decreasing, because they are cumulative over the categories of the response (*i.e.*, intercept 1 = *easy*; 2 = *easy or rereading required*; 3 = *easy, rereading, or not clear*). The fitted proportional odds model is as follows:

$$\log\left[\frac{prob(Y \le k)}{prob(Y > k)}\right] = 0.11_{k=1} + 2.77_{k=2} + 3.95_{k=3} + 1.01 \cdot TREAT - 0.1512 \cdot PERIOD$$

where TREAT and PERIOD are converted to 0-1 indicator variables, because of their appearance on the CLASS statement.

Note the design effect of 0.78 for the treatment parameter (***Exhibit 15***). We expect design effects less than 1.0 for treatment parameters nested within the cluster, as occurs in many repeated measures designs. This indicates that an improvement in precision was obtained because of the cross-over design and that SUDAAN was able to recognize this gain.

Exhibit 16. ANOVA Table (CUMLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Independent, Robust)
-----------------------------------------------------------

Contrast                      Degrees
                              of                 P-value
                              Freedom   Wald F   Wald F
-----------------------------------------------------------
OVERALL MODEL                       5    54.52    0.0000
MODEL MINUS INTERCEPT               2    21.07    0.0000
TREAT                               1    41.88    0.0000
PERIOD                              1     0.93    0.3347
-----------------------------------------------------------
Ezzett and Whitehead, 1991
```

Exhibit 17. Default Odds Ratios (CUMLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Independent, Robust)

-----------------------------------------------------------
CLARITY (cum-logit),                      Lower     Upper
  Independent Variables and               95%       95%
  Effects                        Odds     Limit     Limit
                                 Ratio    OR        OR
-----------------------------------------------------------
CLARITY (cum-logit)
  Intercept 1: Easy               1.117     0.851     1.467
  Intercept 2: Rereading         15.889     9.992    25.267
  Intercept 3: Not Clear         51.750    25.288   105.903
TREAT
  Inhalant A                      2.756     2.025     3.751
  Inhalant B                      1.000     1.000     1.000
PERIOD
  1                               0.860     0.632     1.170
  2                               1.000     1.000     1.000
-----------------------------------------------------------
Ezzett and Whitehead, 1991
```

This output contains the main effects tests for the proportional odds model (***Exhibit 16***), in addition to the estimated odds ratios and their 95% confidence limits (***Exhibit 17***). The Wald-*F* test indicates that the treatment effect is significant (p=0.0000), after adjusting for the period effect. The odds ratio of 2.756 does not contain the null value of 1.0.

Below are the conditional marginal proportions (model-adjusted risks) for each treatment (***Exhibit 18***). Note that since the response variable has four categories, we get the model-adjusted probability of being in *each* category, separately for each Inhalant. In this table, it's clear that Inhalant A skews the distribution toward the Easy to Read category (74%), while Inhalant B is divided between Easy to Read

and Requires Rereading (51% and 43%, respectively). A small probability exists in each of the Not Clear and Confusing categories for each Inhalant, although less so for Inhalant A.

Exhibit 18. Conditional Marginal Proportions (CUMLOGIT link, with R=Independent, SEMETHOD=Zeger)

Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Independent, Robust)

CLARITY Conditional Marginal #1	Conditional Marginal	SE	Lower 95% Limit	Upper 95% Limit	T:Marg=0	P-value
Easy						
TREAT						
Inhalant A	0.7406	0.0258	0.6867	0.7881	28.71	0.0000
Inhalant B	0.5088	0.0296	0.4508	0.5667	17.21	0.0000
Rereading						
TREAT						
Inhalant A	0.2354	0.0240	0.1915	0.2857	9.82	0.0000
Inhalant B	0.4276	0.0274	0.3747	0.4822	15.59	0.0000
Not Clear						
TREAT						
Inhalant A	0.0165	0.0043	0.0099	0.0276	3.82	0.0002
Inhalant B	0.0431	0.0110	0.0259	0.0709	3.91	0.0001
Confusing						
TREAT						
Inhalant A	0.0075	0.0028	0.0036	0.0155	2.71	0.0072
Inhalant B	0.0204	0.0072	0.0102	0.0404	2.85	0.0046

Ezzett and Whitehead, 1991

The next table contains the model-adjusted risk ratio (Inhalant A vs. Inhalant B) within each category of response (***Exhibit 19***). The risk of being Easy to Read is *increased* by 45.5% (RR=1.455) for Inhalant A vs. B. In addition, the risk of being in each of the more confusing categories is *reduced* for Inhalant A vs. B—risk ratios vary from 0.368 to 0.550, indicating a *reduction* in risk of 45% or more. None of the confidence intervals contain the null value of 1.0.

Exhibit 19. Model-Adjusted Risk Ratios (CUMLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Independent, Robust)

------------------------------------------------------------------------
CLARITY
   Conditional Marginal Risk Ratio #1                    Lower   Upper
                                          Risk           95%     95%
                                          Ratio      SE  Limit   Limit
------------------------------------------------------------------------
Easy
   TREAT
     Inhalant A vs. Inhalant B           1.455   0.088  1.293   1.639
Rereading
   TREAT
     Inhalant A vs. Inhalant B           0.550   0.054  0.454   0.667
Not Clear
   TREAT
     Inhalant A vs. Inhalant B           0.383   0.057  0.286   0.514
Confusing
   TREAT
     Inhalant A vs. Inhalant B           0.368   0.057  0.271   0.499
------------------------------------------------------------------------
Ezzett and Whitehead, 1991
```

In the next set of programming statements (***Exhibit 20***), we request SEMETHOD=ZEGER and R=EXCHANGEABLE to implement GEE under exchangeable working correlations. All other statements remain as previously for the proportional odds model (CUMLOGIT link).

Exhibit 20. MULTILOG Code (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Zeger)

```
PROC MULTILOG DATA=one FILETYPE=SAS SEMETHOD=ZEGER R=EXCHANGE;
  NEST _ONE_ PERSON;
  WEIGHT _ONE_;

  CLASS CLARITY TREAT PERIOD;
  MODEL CLARITY = TREAT PERIOD / CUMLOGIT;
  CONDMARG treat / adjrr;

  SETENV LABWIDTH=28 COLWIDTH=7 DECWIDTH=4 COLSPCE=2 TOPMGN=0;
  PRINT / BETAS=default RISK=default TESTS=default RHOS=default
          orfmt=f6.3 loworfmt=f7.3 uporfmt=f7.3
          t_betafmt=f6.2 waldffmt=f6.2 dffmt=f7.0;

  SETENV LABWIDTH=22 COLWIDTH=7 DECWIDTH=4 COLSPCE=1 TOPMGN=0;
  PRINT / COND_MRG=default condmrgfmt=f11.4 lowcmfmt=f6.4 upcmfmt=f6.4
          t_cndmrgfmt=f8.2;

  SETENV LABWIDTH=40 COLWIDTH=5 DECWIDTH=3 COLSPCE=3 TOPMGN=0;
  PRINT COND_RR="Risk Ratio" / CONDRISK=default;

  RFORMAT treat treat.;
  RFORMAT clarity clarity.;
  RTITLE "Proportional Odds Model for Inhaler X-Over (Exchangeable, Robust)";
  RFOOTNOTE "Ezzett and Whitehead, 1991";
```

Exhibit 21. First Page of MULTILOG Output (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Zeger)

```
                              S U D A A N
           Software for the Statistical Analysis of Correlated Data
          Copyright      Research Triangle Institute      November 2011
                               Release 11.0.0


DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method,
Assuming a With Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: PERSON
    Cluster Identification Variables: _ONE_    PERSON


Independence parameters have converged in 4 iterations

Step 1 parameters have converged in 5 iterations.

Number of observations read       :    572    Weighted count:      572
Observations used in the analysis :    572    Weighted count:      572
Denominator degrees of freedom    :    285


Maximum number of estimable parameters for the model is  5

File ONE contains  286 Clusters
 286 clusters were used to fit the model
Maximum cluster size is   2 records
Minimum cluster size is   2 records


Sample and Population Counts for Response Variable CLARITY
Based on observations used in the analysis
  Easy     :  Sample Count      358    Population Count       358
  Rereading:  Sample Count      189    Population Count       189
  Not Clear:  Sample Count       17    Population Count        17
  Confusing:  Sample Count        8    Population Count         8
```

The starting parameter estimates, computed in the usual way under the naive assumption of independence, converged to a solution in four iterations (***Exhibit 21***). The Step 1 GEE estimates, which update the independence estimates with the estimated correlation structure, converged in five iterations.

Exhibit 22. Estimated Intracluster Correlation Matrix (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Zeger)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Robust)

Correlation Matrix

------------------------------------------------------------
CLARITY                       CLARITY
                                                       Not
                                 Easy   Rereading     Clear
------------------------------------------------------------
Easy                           0.2156
Rereading                     -0.1975      0.2069
Not Clear                     -0.0564     -0.0168    0.1427
------------------------------------------------------------
Ezzett and Whitehead, 1991
```

The estimated correlation structure is contained in the above table (***Exhibit 22***). Note that for a four-level response variable, a cluster size of two, and an exchangeable correlation model, there are exactly six unique correlation estimates. SUDAAN prints the lower portion of the symmetric 3x3 matrix. These estimates indicate that the correlation between the "*Easy to Read*" categories on both treatments (Y_{i1s}, Y_{i1t}) was 0.2156, and the correlation between the "*Rereading*" categories on both treatments (Y_{i2s}, Y_{i2t}) was 0.2069. Therefore, the most frequently occurring pairs are identical outcomes. The smaller negative correlations indicate that crossing response categories from Inhaler A to Inhaler B are not as likely as remaining in the same response category on each treatment.

Exhibit 23. Estimated Regression Coefficients (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Zeger)

Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Robust)

by: CLARITY (cum-logit), Independent Variables and Effects.

CLARITY (cum-logit), Independent Variables and Effects	Beta Coeff.	SE Beta	Lower 95% Limit Beta	Upper 95% Limit Beta	T-Test B=0	P-value T-Test B=0
CLARITY (cum-logit)						
Intercept 1: Easy	0.1085	0.1379	-0.1630	0.3801	0.79	0.4320
Intercept 2: Rereading	2.7424	0.2344	2.2809	3.2039	11.70	0.0000
Intercept 3: Not Clear	3.9568	0.3639	3.2405	4.6731	10.87	0.0000
TREAT						
Inhalant A	1.0140	0.1562	0.7066	1.3214	6.49	0.0000
Inhalant B	0.0000	0.0000	0.0000	0.0000	.	.
PERIOD						
1	-0.1531	0.1556	-0.4594	0.1531	-0.98	0.3258
2	0.0000	0.0000	0.0000	0.0000	.	.

Ezzett and Whitehead, 1991

Exhibit 23 presents the regression coefficient estimates under the exchangeable correlation structure. We see that the regression estimates are slightly larger and the variance estimates are slightly smaller compared to the independence working assumption shown previously. However, the results are qualitatively the same. Inhaler A is significantly clearer in its leaflet instructions than Inhaler B. Both working assumptions are valid no matter what the true correlation structure, since SUDAAN is using the robust variance estimates (SEMETHOD=ZEGER) for computing variance and testing hypotheses.

Exhibit 24. ANOVA Table (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Zeger)

Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Robust)

Contrast	Degrees of Freedom	Wald F	P-value Wald F
OVERALL MODEL	5	54.47	0.0000
MODEL MINUS INTERCEPT	2	21.19	0.0000
TREAT	1	42.16	0.0000
PERIOD	1	0.97	0.3258

Ezzett and Whitehead, 1991

Exhibit 24 summarizes the main effects tests under the exchangeable correlation working assumption. Again, these results are qualitatively similar to the working independence model with robust variance estimates.

Exhibit 25. Default Odds Ratios (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Zeger)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Robust)
```

CLARITY (cum-logit), Independent Variables and Effects	Odds Ratio	Lower 95% Limit OR	Upper 95% Limit OR
CLARITY (cum-logit)			
Intercept 1: Easy	1.115	0.850	1.462
Intercept 2: Rereading	15.524	9.786	24.627
Intercept 3: Not Clear	52.290	25.546	107.033
TREAT			
Inhalant A	2.757	2.027	3.749
Inhalant B	1.000	1.000	1.000
PERIOD			
1	0.858	0.632	1.165
2	1.000	1.000	1.000

```
Ezzett and Whitehead, 1991
```

Exhibit 25 indicates that the odds ratios and 95% confidence limits for the exchangeable working assumption are identical to the independence working model. Modeling the correlations under exchangeability did not significantly improve the efficiency of the parameter estimates in this example.

Exhibit 26. Conditional Marginal Proportions (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Zeger)

Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Robust)

CLARITY Conditional Marginal #1	Conditional Marginal	SE	Lower 95% Limit	Upper 95% Limit	T:Marg=0	P-value
Easy						
TREAT						
Inhalant A	0.7400	0.0258	0.6861	0.7876	28.65	0.0000
Inhalant B	0.5080	0.0295	0.4500	0.5658	17.19	0.0000
Rereading						
TREAT						
Inhalant A	0.2354	0.0239	0.1916	0.2856	9.85	0.0000
Inhalant B	0.4270	0.0274	0.3741	0.4816	15.57	0.0000
Not Clear						
TREAT						
Inhalant A	0.0172	0.0045	0.0103	0.0286	3.83	0.0002
Inhalant B	0.0448	0.0113	0.0271	0.0732	3.96	0.0001
Confusing						
TREAT						
Inhalant A	0.0074	0.0028	0.0036	0.0154	2.70	0.0073
Inhalant B	0.0202	0.0071	0.0101	0.0402	2.84	0.0048

Ezzett and Whitehead, 1991

The conditional marginal proportions (model-adjusted risks) for each treatment (with 95% confidence intervals) are contained in ***Exhibit 26***. The results are very similar to working independence.

Exhibit 27. Model-Adjusted Risk Ratios (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Zeger)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Robust)
```

CLARITY
Conditional Marginal Risk Ratio #1

	Risk Ratio	SE	Lower 95% Limit	Upper 95% Limit
Easy				
TREAT				
Inhalant A vs. Inhalant B	1.457	0.088	1.294	1.640
Rereading				
TREAT				
Inhalant A vs. Inhalant B	0.551	0.054	0.455	0.668
Not Clear				
TREAT				
Inhalant A vs. Inhalant B	0.383	0.057	0.286	0.513
Confusing				
TREAT				
Inhalant A vs. Inhalant B	0.367	0.057	0.271	0.498

Ezzett and Whitehead, 1991

Exhibit 27 contains the model-adjusted risk ratio (Inhalant A vs. Inhalant B) within each category of response. The results are very similar to working independence.

Below are the results from the exchangeable correlations model using the model-based variance-covariance matrix of the estimated regression coefficients. The model-based variance is the $\boldsymbol{M}_0^{-1}$ matrix, or the outside portion of the robust variance estimate, $\boldsymbol{M}_0^{-1} = [\,\boldsymbol{D}'\boldsymbol{V}^{-1}\boldsymbol{D}\,]^{-1}$, where $\boldsymbol{D} = \partial\boldsymbol{\pi}_i / \partial\boldsymbol{\beta}$ is the vector of first partial derivatives of the response probabilities, $\boldsymbol{\pi}_i$, with respect to the regression coefficients, β. In this case, the model-based variance estimate is computed assuming that the exchangeable working correlation assumption were correct. To obtain the model-based results, we specify SEMETHOD=MODEL on the PROC statement.

Exhibit 28. MULTILOG Code (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Model)

```
PROC MULTILOG DATA=one FILETYPE=SAS SEMETHOD=MODEL R=EXCHANGE;
  NEST _ONE_ PERSON;
  WEIGHT _ONE_;

  CLASS CLARITY TREAT PERIOD;
  MODEL CLARITY = TREAT PERIOD / CUMLOGIT;
  CONDMARG treat / adjrr;

  SETENV LABWIDTH=28 COLWIDTH=7 DECWIDTH=4 COLSPCE=2 TOPMGN=0;
  PRINT / BETAS=default RISK=default TESTS=default RHOS=default
          orfmt=f6.3 loworfmt=f7.3 uporfmt=f7.3
          t_betafmt=f6.2 waldffmt=f6.2 dffmt=f7.0;

  SETENV LABWIDTH=22 COLWIDTH=7 DECWIDTH=4 COLSPCE=1 TOPMGN=0;
  PRINT / COND_MRG=default condmrgfmt=f11.4 lowcmfmt=f6.4 upcmfmt=f6.4
          t_cndmrgfmt=f8.2;

  SETENV LABWIDTH=40 COLWIDTH=5 DECWIDTH=3 COLSPCE=3 TOPMGN=0;
  PRINT COND_RR="Risk Ratio" / CONDRISK=default;

  RFORMAT treat treat.;
  RFORMAT clarity clarity.;
  RTITLE "Proportional Odds Model for Inhaler X-Over (Exchangeable, Model-Based)";
  RFOOTNOTE "Ezzett and Whitehead, 1991";
```

Exhibit 29. First Page of MULTILOG Output (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Model)

```
                              S U D A A N
           Software for the Statistical Analysis of Correlated Data
          Copyright      Research Triangle Institute    November 2011
                               Release 11.0.0


DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method,
Assuming a With Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: PERSON
    Cluster Identification Variables: _ONE_    PERSON


Independence parameters have converged in 4 iterations
Step 1 parameters have converged in 5 iterations.

Number of observations read       :    572    Weighted count:      572
Observations used in the analysis :    572    Weighted count:      572
Denominator degrees of freedom    :    285


Maximum number of estimable parameters for the model is  5

File ONE contains  286 Clusters
 286 clusters were used to fit the model
Maximum cluster size is   2 records
Minimum cluster size is   2 records


Sample and Population Counts for Response Variable CLARITY
Based on observations used in the analysis
  Easy     :  Sample Count      358    Population Count       358
  Rereading:  Sample Count      189    Population Count       189
  Not Clear:  Sample Count       17    Population Count        17
  Confusing:  Sample Count        8    Population Count         8
```

Exhibit 30. Estimated Intracluster Correlation Matrix (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Model)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Model-Based)

Correlation Matrix
------------------------------------------------------------
CLARITY                      CLARITY
                                                      Not
                                Easy   Rereading     Clear
------------------------------------------------------------
Easy                          0.2156
Rereading                    -0.1975      0.2069
Not Clear                    -0.0564     -0.0168    0.1427
------------------------------------------------------------
Ezzett and Whitehead, 1991
```

The estimated correlation matrix (***Exhibit 30***) under exchangeability is unaffected by the choice of robust vs. model-based variance estimation.

Exhibit 31. Estimated Regression Coefficients (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Model)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Model-Based)

-------------------------------------------------------------------------------
CLARITY (cum-logit),                          Lower     Upper
  Independent Variables and                   95%       95%               P-value
  Effects                    Beta             Limit     Limit     T-Test  T-Test
                             Coeff.  SE Beta   Beta      Beta      B=0     B=0
-------------------------------------------------------------------------------
CLARITY (cum-logit)
  Intercept 1: Easy          0.1085  0.1415  -0.1700    0.3871     0.77    0.4437
  Intercept 2: Rereading     2.7424  0.2363   2.2773    3.2074    11.61    0.0000
  Intercept 3: Not Clear     3.9568  0.3510   3.2658    4.6478    11.27    0.0000
TREAT
  Inhalant A                 1.0140  0.1577   0.7035    1.3245     6.43    0.0000
  Inhalant B                 0.0000  0.0000   0.0000    0.0000      .       .
PERIOD
  1                         -0.1531  0.1555  -0.4593    0.1530    -0.98    0.3256
  2                          0.0000  0.0000   0.0000    0.0000      .       .
-------------------------------------------------------------------------------Ezzett and
Whitehead, 1991
```

The output above (***Exhibit 31***) contains the estimated regression coefficients computed under exchangeability and the estimated standard errors calculated as if the exchangeable working assumption were correct. The standard errors are roughly the same as with the robust variance estimator for these data, indicating that the exchangeable correlation assumption is close to truth.

Exhibit 32. ANOVA Table (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Model)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Model-Based)

-----------------------------------------------------
Contrast                    Degrees
                            of                P-value
                            Freedom  Wald F   Wald F
-----------------------------------------------------
OVERALL MODEL                    5    54.35    0.0000
MODEL MINUS INTERCEPT            2    21.08    0.0000
TREAT                            1    41.33    0.0000
PERIOD                           1     0.97    0.3256
-----------------------------------------------------
Ezzett and Whitehead, 1991
```

The main effects tests are computed under exchangeability, using the model-based variance approach (***Exhibit 32***). Results are essentially the same as with the robust variance estimator.

Exhibit 33. Default Odds Ratios (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Model)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Model-Based)

-----------------------------------------------------------
CLARITY (cum-logit),                      Lower     Upper
  Independent Variables and               95%       95%
  Effects                        Odds     Limit     Limit
                                 Ratio    OR        OR
-----------------------------------------------------------
CLARITY (cum-logit)
  Intercept 1: Easy               1.115     0.844     1.473
  Intercept 2: Rereading         15.524     9.751    24.715
  Intercept 3: Not Clear         52.290    26.202   104.352
TREAT
  Inhalant A                      2.757     2.021     3.760
  Inhalant B                      1.000     1.000     1.000
PERIOD
  1                               0.858     0.632     1.165
  2                               1.000     1.000     1.000
-----------------------------------------------------------
Ezzett and Whitehead, 1991
```

The estimated odds ratios and their 95% confidence limits are computed under exchangeability, using the model-based variance approach (***Exhibit 33***). Odds ratios are unaffected by the choice of robust vs. model-based variance estimates, and estimated confidence limits are essentially the same as with the robust variance estimator.

Exhibit 34. Conditional Marginal Proportions (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Model)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Model-Based)
```

CLARITY Conditional Marginal #1	Conditional Marginal	SE	Lower 95% Limit	Upper 95% Limit	T:Marg=0	P-value
Easy						
TREAT						
Inhalant A	0.7400	0.0259	0.6859	0.7877	28.55	0.0000
Inhalant B	0.5080	0.0293	0.4504	0.5654	17.31	0.0000
Rereading						
TREAT						
Inhalant A	0.2354	0.0237	0.1919	0.2852	9.92	0.0000
Inhalant B	0.4270	0.0278	0.3734	0.4823	15.38	0.0000
Not Clear						
TREAT						
Inhalant A	0.0172	0.0047	0.0100	0.0293	3.66	0.0003
Inhalant B	0.0448	0.0111	0.0274	0.0723	4.05	0.0001
Confusing						
TREAT						
Inhalant A	0.0074	0.0026	0.0038	0.0147	2.88	0.0042
Inhalant B	0.0202	0.0068	0.0104	0.0389	2.99	0.0031

```
Ezzett and Whitehead, 1991
```

The conditional marginal proportions and SEs are unaffected by the choice of correlation structure in this example (***Exhibit 34***). Conclusions concerning differences in clarity of instructions between Inhalants are unchanged from the working independence assumption.

Exhibit 35. Model-Adjusted Risk Ratios (CUMLOGIT link, with R=Exchangeable, SEMETHOD=Model)

Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

Proportional Odds Model for Inhaler X-Over (Exchangeable, Model-Based)

CLARITY

Conditional Marginal Risk Ratio #1	Risk Ratio	SE	Lower 95% Limit	Upper 95% Limit
Easy				
TREAT				
Inhalant A vs. Inhalant B	1.457	0.088	1.293	1.641
Rereading				
TREAT				
Inhalant A vs. Inhalant B	0.551	0.055	0.453	0.670
Not Clear				
TREAT				
Inhalant A vs. Inhalant B	0.383	0.058	0.285	0.515
Confusing				
TREAT				
Inhalant A vs. Inhalant B	0.367	0.057	0.270	0.499

Ezzett and Whitehead, 1991

The model-adjusted risk ratio and 95% CIs are unaffected by the choice of correlation structure in this example (***Exhibit 35***). Conclusions concerning differences in clarity of instructions between Inhalants are unchanged from the working independence assumption.

The last MULTILOG run in this example (***Exhibit 68***) is fit using the generalized logit model (GENLOGIT link). The GENLOGIT link models the log-odds that CLARITY=*k* vs. *K* (or the log-odds that CLARITY is easy, requires rereading, or is not clear vs. confusing). The GENLOGIT option produces a separate logit equation (intercepts and slopes) for each of the (*K*-1)=3 cutpoints.

The GENLOGIT model was run with the SEMETHOD=ZEGER and R=INDEPENDENT options, which implements the GEE model-fitting technique under an independent working assumption and a robust variance estimator.

Exhibit 36. MULTILOG Code (GENLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
PROC MULTILOG DATA=one FILETYPE=SAS SEMETHOD=ZEGER R=INDEPENDENT;
  NEST _ONE_ PERSON;
  WEIGHT _ONE_;

  CLASS CLARITY TREAT PERIOD;
  MODEL CLARITY = TREAT PERIOD / GENLOGIT;
  CONDMARG treat / adjrr;

  SETENV LABWIDTH=28 COLWIDTH=7 DECWIDTH=4 COLSPCE=2 TOPMGN=0;
  PRINT / BETAS=default RISK=default TESTS=default
          orfmt=f6.3 loworfmt=f7.3 uporfmt=f7.3
          t_betafmt=f6.2 waldffmt=f6.2 dffmt=f7.0 style=nchs;

  SETENV LABWIDTH=22 COLWIDTH=7 DECWIDTH=4 COLSPCE=1 TOPMGN=0;
  PRINT / COND_MRG=default condmrgfmt=f11.4 lowcmfmt=f6.4 upcmfmt=f6.4
          t_cndmrgfmt=f8.2;

  SETENV LABWIDTH=40 COLWIDTH=5 DECWIDTH=3 COLSPCE=3 TOPMGN=0;
  PRINT COND_RR="Risk Ratio" / CONDRISK=default;

  RFORMAT treat treat.;
  RFORMAT clarity clarity.;
  RTITLE "Generalized Logit Model for Inhaler X-OVER (Independent, Robust)";
  RFOOTNOTE "Ezzett and Whitehead, 1991";
```

The GENLOGIT option on the MODEL statement invokes the multinomial logit model based on the generalized logit link function. All other options remain the same as for the proportional odds model.

Exhibit 37. First Page of MULTILOG Output (GENLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
                              S U D A A N
           Software for the Statistical Analysis of Correlated Data
          Copyright      Research Triangle Institute    November 2011
                               Release 11.0.0


DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method,
Assuming a With Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: PERSON


Independence parameters have converged in 6 iterations

Number of observations read       :    572    Weighted count:      572
Observations used in the analysis :    572    Weighted count:      572
Denominator degrees of freedom    :    285


Maximum number of estimable parameters for the model is  9

File ONE contains  286 Clusters
 286 clusters were used to fit the model
Maximum cluster size is   2 records
Minimum cluster size is   2 records


Sample and Population Counts for Response Variable CLARITY
Based on observations used in the analysis
  Easy     :  Sample Count      358    Population Count       358
  Rereading:  Sample Count      189    Population Count       189
  Not Clear:  Sample Count       17    Population Count        17
  Confusing:  Sample Count        8    Population Count         8
```

Exhibit 38. Estimated Regression Coefficients (GENLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

Generalized Logit Model for Inhaler X-OVER (Independent, Robust)
```

CLARITY (log-odds) Independent Variables And Effects	Beta Coeff.	SE Beta	Lower 95% Limit Beta	Upper 95% Limit Beta	T-Test B=0	P-value T-Test B=0
Easy vs Confusing						
Intercept	3.5099	0.6858	2.1599	4.8599	5.12	0.0000
TREAT						
Inhalant A	1.4615	0.8254	-0.1631	3.0862	1.77	0.0777
Inhalant B	0.0000	0.0000	0.0000	0.0000	.	.
PERIOD						
1	-0.5593	0.7401	-2.0160	0.8975	-0.76	0.4505
2	0.0000	0.0000	0.0000	0.0000	.	.
Rereading vs Confusing						
Intercept	3.2510	0.6908	1.8914	4.6106	4.71	0.0000
TREAT						
Inhalant A	0.5919	0.8311	-1.0439	2.2277	0.71	0.4769
Inhalant B	0.0000	0.0000	0.0000	0.0000	.	.
PERIOD						
1	-0.4805	0.7456	-1.9480	0.9871	-0.64	0.5198
2	0.0000	0.0000	0.0000	0.0000	.	.
Not Clear vs Confusing						
Intercept	1.0089	0.7634	-0.4938	2.5115	1.32	0.1874
TREAT						
Inhalant A	-0.9159	1.1557	-3.1908	1.3590	-0.79	0.4287
Inhalant B	0.0000	0.0000	0.0000	0.0000	.	.
PERIOD						
1	-0.1527	0.8992	-1.9227	1.6173	-0.17	0.8653
2	0.0000	0.0000	0.0000	0.0000	.	.

```
Ezzett and Whitehead, 1991
```

Exhibit 38 presents the estimated regression coefficient vector and related statistics. Note that there are *three* separate logit equations in this model. So, for example, the logit equation for CLARITY=*Easy* vs. *Confusing* is as follows:

$$\log\left[\frac{\hat{\pi}_{EASY}}{\hat{\pi}_{CONFUSING}}\right] = 3.51 + 1.46 \cdot \text{TREAT} - 0.56 \cdot PERIOD,$$

where TREAT and PERIOD are converted to 0-1 indicator variables because of their appearance on the CLASS statement. The treatment effect appears to be largest when comparing the Easy vs. Confusing categories.

Exhibit 39. ANOVA Table (GENLOGIT link, with R=Independent, SEMETHOD=Zeger)

Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

Generalized Logit Model for Inhaler X-OVER (Independent, Robust)

Contrast	Degrees of Freedom	Wald F	P-value Wald F
OVERALL MODEL	9	25.90	0.0000
MODEL MINUS INTERCEPT	6	7.55	0.0000
INTERCEPT	.	.	.
TREAT	3	13.29	0.0000
PERIOD	3	0.48	0.6965

Ezzett and Whitehead, 1991

Exhibit 39 indicates that the treatment effect (now with 3 degrees of freedom in the multinomial logit model) is statistically significant, as in the proportional odds model.

Exhibit 40. Default Odds Ratios (GENLOGIT link, with R=Independent, SEMETHOD=Zeger)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

Generalized Logit Model for Inhaler X-OVER (Independent, Robust)

-----------------------------------------------------------
CLARITY (log-odds)                        Lower     Upper
   Independent Variables and              95%       95%
     Effects                    Odds      Limit     Limit
                                Ratio     OR        OR
-----------------------------------------------------------
Easy vs Confusing
   Intercept                   33.445     8.670   129.008
   TREAT
     Inhalant A                 4.313     0.850    21.893
     Inhalant B                 1.000     1.000     1.000
   PERIOD
     1                          0.572     0.133     2.453
     2                          1.000     1.000     1.000
Rereading vs Confusing
   Intercept                   25.816     6.628   100.546
   TREAT
     Inhalant A                 1.807     0.352     9.279
     Inhalant B                 1.000     1.000     1.000
   PERIOD
     1                          0.618     0.143     2.683
     2                          1.000     1.000     1.000
Not Clear vs Confusing
   Intercept                    2.742     0.610    12.323
   TREAT
     Inhalant A                 0.400     0.041     3.892
     Inhalant B                 1.000     1.000     1.000
   PERIOD
     1                          0.858     0.146     5.039
     2                          1.000     1.000     1.000
-----------------------------------------------------------
Ezzett and Whitehead, 1991
```

The estimated odds of being in the Easy vs. Confusing categories is increased more than fourfold (OR=4.31) for Inhaler A vs. Inhaler B (***Exhibit 40***). And the estimated odds of being in the Rereading vs. Confusing category is almost doubled (OR=1.81) for Inhalant A vs. B. This is in general agreement with the cumulative logit (proportional odds) model.

Below are the conditional marginal proportions (model-adjusted risks) for each treatment (***Exhibit 41***). Note that, since the response variable has four categories, we get the model-adjusted probability of being in *each* category separately for each Inhalant. In this table, it is clear that Inhalant A skews the distribution toward the Easy to Read category (74%), while Inhalant B is divided between Easy to Read and Requires Rereading (51% and 41%, respectively). A small probability exists in each of the Not Clear and Confusing categories for each Inhalant, although less so for Inhalant A.

These model-adjusted risks are very similar to those estimated under the CUMLOGIT link.

Exhibit 41. Conditional Marginal Proportions (GENLOGIT link, with R=Independent, SEMETHOD=Zeger)

Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

Generalized Logit Model for Inhaler X-OVER (Independent, Robust)

CLARITY Conditional Marginal #1	Conditional Marginal	SE	Lower 95% Limit	Upper 95% Limit	T:Marg=0	P-value
Easy						
TREAT						
Inhalant A	0.7380	0.0260	0.6837	0.7859	28.38	0.0000
Inhalant B	0.5147	0.0297	0.4562	0.5727	17.32	0.0000
Rereading						
TREAT						
Inhalant A	0.2483	0.0256	0.2015	0.3020	9.72	0.0000
Inhalant B	0.4132	0.0293	0.3571	0.4718	14.12	0.0000
Not Clear						
TREAT						
Inhalant A	0.0069	0.0050	0.0017	0.0281	1.39	0.1667
Inhalant B	0.0517	0.0130	0.0313	0.0842	3.97	0.0001
Confusing						
TREAT						
Inhalant A	0.0068	0.0046	0.0018	0.0252	1.48	0.1388
Inhalant B	0.0204	0.0088	0.0086	0.0473	2.31	0.0218

Ezzett and Whitehead, 1991

The next table contains the model-adjusted risk ratio (Inhalant A vs. Inhalant B) within each category of response (***Exhibit 42***). The risk of being Easy to Read is *increased* by 43% (RR=1.43) for Inhalant A vs. B. In addition, the risk of being in each of the more confusing categories is *reduced* for Inhalant A vs. B—risk ratios vary from 0.13 to 0.60, indicating a *reduction* in risk of 40% or more.

These model-adjusted risk ratios are very similar to those estimated under the CUMLOGIT link.

Exhibit 42. Model-Adjusted Risk Ratios (GENLOGIT link, with R=Independent, SEMETHOD=Zeger)

Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

Generalized Logit Model for Inhaler X-OVER (Independent, Robust)

CLARITY Conditional Marginal Risk Ratio #1	Risk Ratio	SE	Lower 95% Limit	Upper 95% Limit
Easy				
TREAT				
Inhalant A vs. Inhalant B	1.434	0.087	1.272	1.616
Rereading				
TREAT				
Inhalant A vs. Inhalant B	0.601	0.067	0.482	0.749
Not Clear				
TREAT				
Inhalant A vs. Inhalant B	0.133	0.095	0.033	0.540
Confusing				
TREAT				
Inhalant A vs. Inhalant B	0.332	0.271	0.067	1.653

Ezzett and Whitehead, 1991