PharmaSUG China 2018 - Paper 48

Statistical Programming Analysis of Percentage of Responders in Alzheimer's Disease

Yan Liu, MSD, Beijing, China

ABSTRACT

Alzheimer's disease (AD) is primarily a disease of cognition, but it can also lead to deficits in function, including activities of daily living and behavioral abnormalities, particularly in more advanced stages of the disease. This paper introduces an efficacy model to analyze AD, which determines responders based on ADAS-Cog and ADCS-ADL scores by using a linear regression, and the analysis of proportion of responders will be conducted using logistic regression model.

INTRODUCTION

Alzheimer's disease (AD), also referred to simply as Alzheimer's, is a chronic neurodegenerative disease that usually starts slowly and worsens over time. It is the cause of 60–70% of cases of dementia. The most common early symptom is difficulty in remembering recent events (short-term memory loss). As the disease deteriorates , symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behaviors.

ADAS-COG AND ADAS-ADL:

- **ADAS-Cog=Alzheimer's Disease Assessment Scale Cognitive subscale**
  The cognitive subscale (ADAS-Cog) includes 11 tasks that include both subject-completed tests and observer-based assessments. Together these tasks assess the cognitive domains of memory, language, and praxis. Specific tasks (Table 1) include Word Recall, Naming Objects and Fingers, Commands, Constructional Praxis, Ideational Praxis, Orientation, Word Recognition, and Language.

  ADAS-Cog Computation:

1	2	3	4	5	6	7	8	9	10	11
10	5	5	5	5	8	12	5	5	5	5

  Total: (0-70)

  Notes:

  For LOCF(Last Observation Carried Forward) purposes, only carry forward the entire subscore, not parts of the subscore (e.g. for Q1, only carry forward the entire Q1 subscore, not the individual trial scores.)

  Subquestion Notes:

  Q1 (Immediate Word Recall):
  If any of the three trials is missing, compute the subscore as the average of the non-missing trials.
  Take the average of the number of not recalled of the three trials. Apply standard rounding.
  Q2 (Commands):
  Score the number incorrect.
  Q3 (Constructional Praxis):
  If "No recognizable…" box is selected for all four figures score a 5. Otherwise, score 1 for each incorrect response or "No recognizable…" attempt.
  Q4 (Naming Objects and Fingers):
  0 = 0-2 items (objects and fingers) named incorrectly
  1 = 3-5 items (objects and fingers) named incorrectly
  2 = 6-8 items (objects and fingers) named incorrectly
  3 = 9-11 items (objects and fingers) named incorrectly
  4 = 12-14 items (objects and fingers) named incorrectly
  5 = 15-17 items (objects and fingers) named incorrectly

Q5 (Ideational Praxis):
Score the number incorrect.
Q6 (Orientation):
Score the number incorrect.
Q7 (Word Recognition):
Min (number incorrect, 12).
Q8 (Remembering Instructions):
0 = 0 reminders needed.
1 = 1 reminder needed.
2 = 2 reminders needed.
3 = 3 or 4 reminders needed.
4 = 5 or 6 reminders needed.
5 = 7 or more reminders needed.
Q9 (Spoken Language Ability):
As mapped.
Q10 (Word Finding Ability):
As mapped.
Q11 (Comprehension of Spoken Language):
As mapped.

- **ADCS-ADL=Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory**
  The Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory (ADCS-ADL) is a frequently used functional endpoint in clinical trials for AD that assesses patient functional ability on the basis of informant ratings of patient performance on a variety of everyday tasks (Table 2).

  ADCS-ADL Computation:

  Basic ADL: Q1-Q6 (0-22)
  Instrumental ADL: Q7-Q23 (0-56)
  Total ADL: Q1-Q23 (0-78)

  Subquestion Notes:

  For all subquestions, all mapped values of 999 are to be scored as 0.
  For LOCF purposes, any and all missing sub-subquestions within a subquestion are considered in total as one missing subquestion (e.g. if 18A and 18B are missing, then this is considered as one missing subquestion for the purposes of the missing count).
  When attempting to sum subquestions, if any of the subquestions are missing then the sum is missing.

  Q1 - Q5: As mapped.

  Q6: Q6=sum(ORRES6A, ORRES6B). As mapped. If one of ORRES6A or ORRES6B is missing then Q6=.

  (Note that the paper form doesn't require 6A to be answered, but that 6A should always be present on the database anyway, due to the way the mapping was designed.)

  Q7: As mapped.

  Q8: If ORRES08 in (0, 999) then Q8=0 else if ORRES08=998 then Q8=sum(ORRES08A, ORRES08B, ORRES08C).
  If ORRES08=998 and one of ORRES08A, ORRES08B, or ORRES08C is missing then Q8=.

  Q9-Q15: As mapped.

  Q16: If ORRES16 in (0, 999) then Q16=0 else if ORRES16=998 then Q16=sum(ORRES16A, ORRES16B).
  If ORRES16=998 and one of ORRES16A or ORRES16B is missing then Q16=.

  Q17: As mapped.

  Q18: If ORRES18I=0 then Q18=0

```
       else if ORRES18I=998 then do;
 if ORRESS18 in (0,999) then Q18=0;
else if ORRESS18=998 then Q18= sum(ORRES18A, ORRES18B, ORRES18C)
else if ORRES18=. then Q18=.;
       end;
```

if ORRES18I=998 and ORRESS18=998 and one of ORRES18A, ORRES18B, or ORRES18C is missing then Q18=.

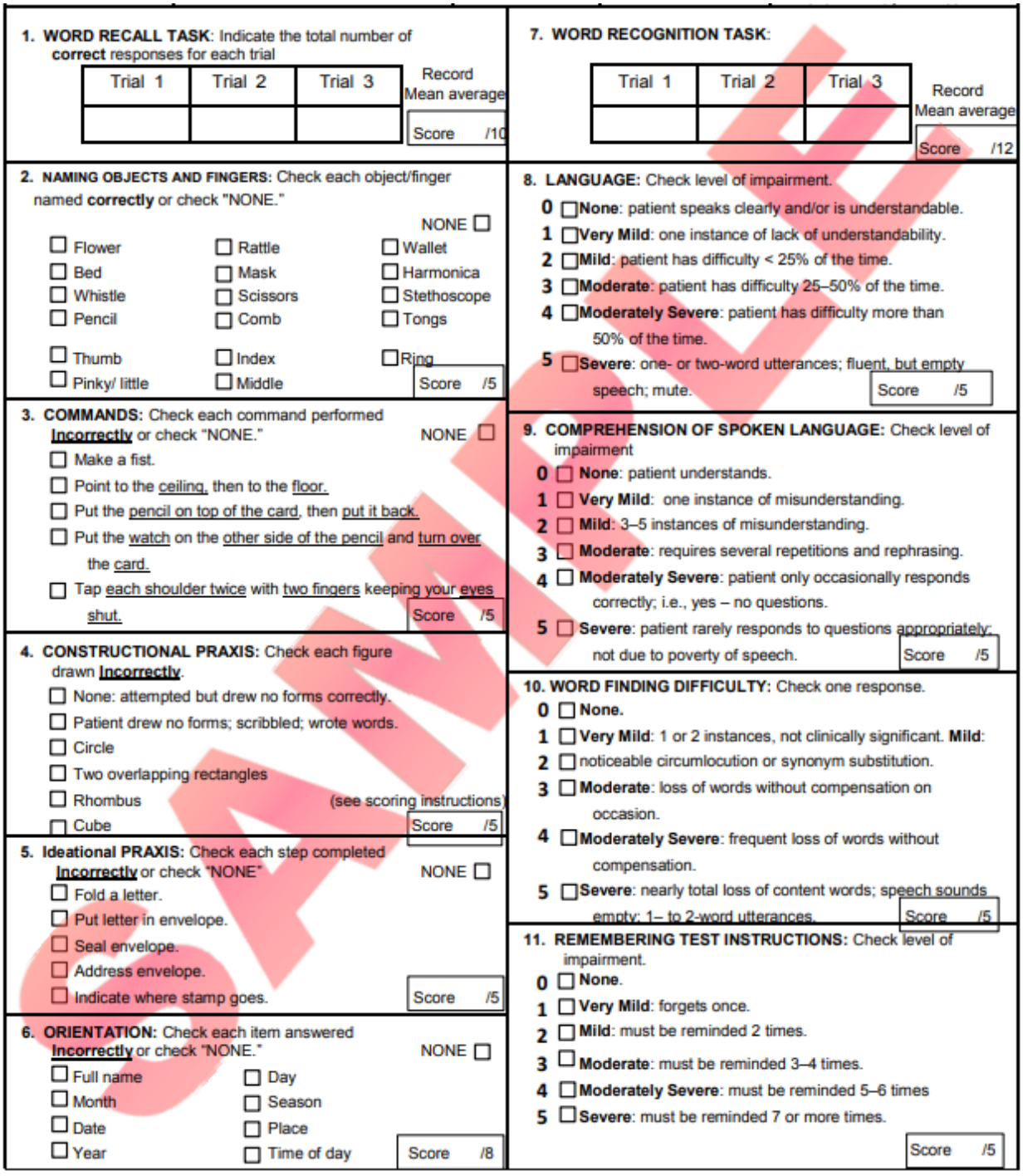
Q19: If ORRES19 in (0, 999) then Q19=0 else if ORRES19=998 then Q19= sum(ORRES19A, ORRES19B, ORRES19C).
If ORRES19=998 and one of ORRES19A, ORRES19B, or ORRES19C is missing then Q19=.

Q20: If ORRES20 in (0, 999) then Q20=0 else if ORRES20=998 then Q20=sum(ORRES20A, ORRES20B).
If ORRES20=998 and one of ORRES20A or ORRES20B is missing then Q20=.

Q21: As mapped.

Q22: Use ORRES22 only, as mapped. Ignore ORRES22A.

Q23: As mapped.



1. **WORD RECALL TASK**: Indicate the total number of **correct** responses for each trial

Trial 1	Trial 2	Trial 3	Record Mean average
			Score /10

2. **NAMING OBJECTS AND FINGERS:** Check each object/finger named **correctly** or check "NONE."

NONE ☐

☐ Flower	☐ Rattle	☐ Wallet
☐ Bed	☐ Mask	☐ Harmonica
☐ Whistle	☐ Scissors	☐ Stethoscope
☐ Pencil	☐ Comb	☐ Tongs
☐ Thumb	☐ Index	☐ Ring
☐ Pinky/ little	☐ Middle	

Score /5

3. **COMMANDS:** Check each command performed **Incorrectly** or check "NONE." NONE ☐

- ☐ Make a fist.
- ☐ Point to the ceiling, then to the floor.
- ☐ Put the pencil on top of the card, then put it back.
- ☐ Put the watch on the other side of the pencil and turn over the card.
- ☐ Tap each shoulder twice with two fingers keeping your eyes shut.

Score /5

4. **CONSTRUCTIONAL PRAXIS:** Check each figure drawn **Incorrectly**.

- ☐ None: attempted but drew no forms correctly.
- ☐ Patient drew no forms; scribbled; wrote words.
- ☐ Circle
- ☐ Two overlapping rectangles
- ☐ Rhombus
- ☐ Cube

(see scoring instructions)

Score /5

5. **Ideational PRAXIS:** Check each step completed **Incorrectly** or check "NONE" NONE ☐

- ☐ Fold a letter.
- ☐ Put letter in envelope.
- ☐ Seal envelope.
- ☐ Address envelope.
- ☐ Indicate where stamp goes.

Score /5

6. **ORIENTATION:** Check each item answered **Incorrectly** or check "NONE." NONE ☐

☐ Full name	☐ Day
☐ Month	☐ Season
☐ Date	☐ Place
☐ Year	☐ Time of day

Score /8

7. **WORD RECOGNITION TASK**:

Trial 1	Trial 2	Trial 3	Record Mean average
			Score /12

8. **LANGUAGE:** Check level of impairment.

- 0 ☐ **None**: patient speaks clearly and/or is understandable.
- 1 ☐ **Very Mild**: one instance of lack of understandability.
- 2 ☐ **Mild**: patient has difficulty < 25% of the time.
- 3 ☐ **Moderate**: patient has difficulty 25–50% of the time.
- 4 ☐ **Moderately Severe**: patient has difficulty more than 50% of the time.
- 5 ☐ **Severe**: one- or two-word utterances; fluent, but empty speech; mute.

Score /5

9. **COMPREHENSION OF SPOKEN LANGUAGE:** Check level of impairment

- 0 ☐ **None**: patient understands.
- 1 ☐ **Very Mild**: one instance of misunderstanding.
- 2 ☐ **Mild**: 3–5 instances of misunderstanding.
- 3 ☐ **Moderate**: requires several repetitions and rephrasing.
- 4 ☐ **Moderately Severe**: patient only occasionally responds correctly; i.e., yes – no questions.
- 5 ☐ **Severe**: patient rarely responds to questions appropriately; not due to poverty of speech.

Score /5

10. **WORD FINDING DIFFICULTY:** Check one response.

- 0 ☐ **None.**
- 1 ☐ **Very Mild**: 1 or 2 instances, not clinically significant. **Mild**:
- 2 ☐ noticeable circumlocution or synonym substitution.
- 3 ☐ **Moderate**: loss of words without compensation on occasion.
- 4 ☐ **Moderately Severe**: frequent loss of words without compensation.
- 5 ☐ **Severe**: nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.

Score /5

11. **REMEMBERING TEST INSTRUCTIONS:** Check level of impairment.

- 0 ☐ **None.**
- 1 ☐ **Very Mild**: forgets once.
- 2 ☐ **Mild**: must be reminded 2 times.
- 3 ☐ **Moderate**: must be reminded 3–4 times.
- 4 ☐ **Moderately Severe**: must be reminded 5–6 times
- 5 ☐ **Severe**: must be reminded 7 or more times.

Score /5

Table 1. Sample ADAS-Cog Form

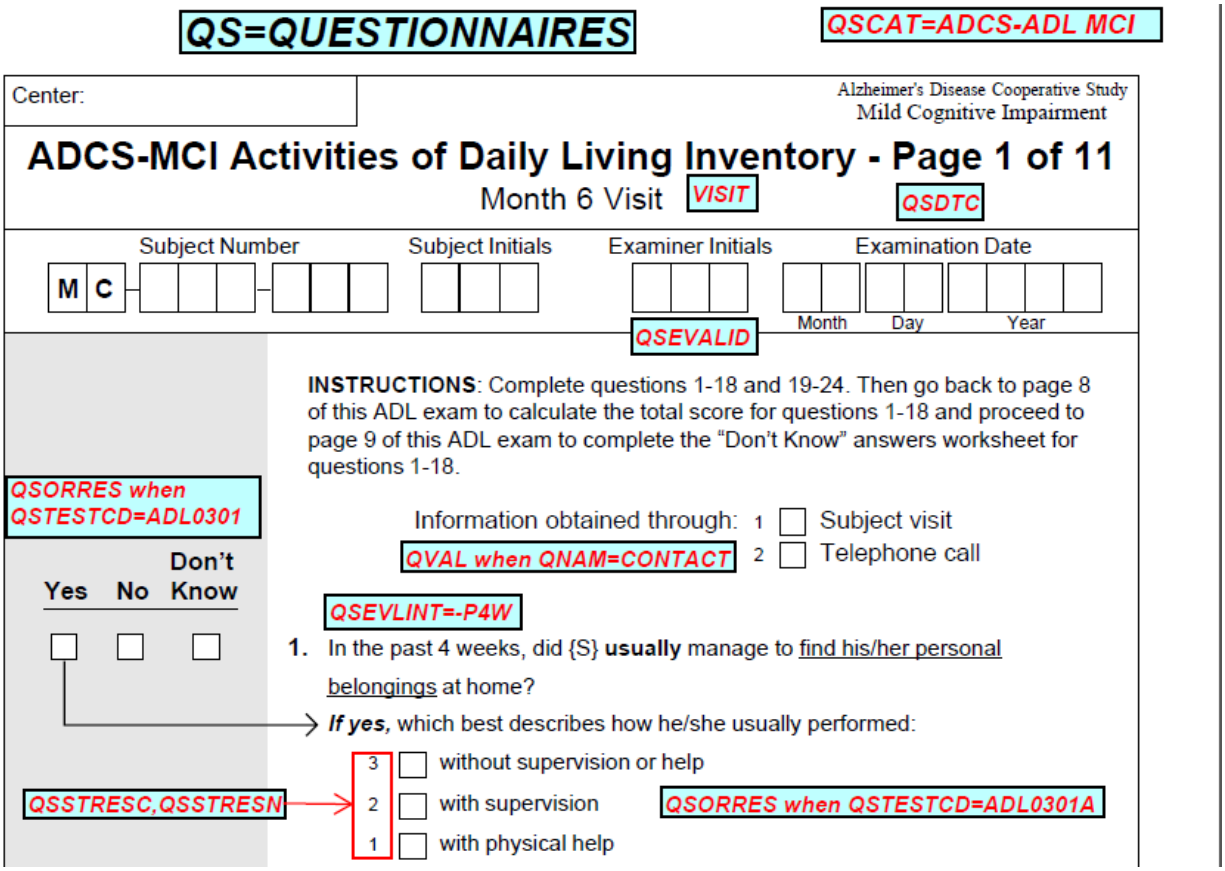


Table 2. Sample ADCS-ADL Form

IDENTIFY THE RESPONDERS VIA LINEAR REGRESSION

In order to determine which subjects are responders, a linear regression will be conducted, on the subject level, yielding an estimated 78-week rate of change (ie, a slope) for each subject. Each subject must meet three criteria in order to be declared as a 78-week responder. Each subject must have: 1) ADAS-Cog and ADCS-ADL responses at baseline and 78 weeks of treatment, 2) an ADAS-Cog slope less than 4.0 over 78 weeks, and 3) an ADCS-ADL slope greater than -6.3 over 78 weeks. A subject failing to meet any of these criteria will be designated as a Week 78 non-responder. Separate cumulative distribution plots will also be provided for each endpoint, with the 78-week CFB score on the x-axis.

Summary Statistics for Responder Analysis

	Group A (N = xxx)	Group B (N = xxx)	Group C (N = xxx)
ADAS-Cog subjects	n /m (%)	n /m (%)	n /m (%)
with a Baseline and Week 78 assessment	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx/xxx (xx.x)
with a slope[§] less than 4.0	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx/xxx (xx.x)
who were ADAS-Cog responders	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx/xxx (xx.x)
ADCS-ADL subjects		xxx/xxx (xx.x)	xxx/xxx (xx.x)
with a Baseline and Week 78 assessment	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx/xxx (xx.x)
with a slope[§] greater than - 6.3	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx/xxx (xx.x)
who were ADCS-ADL responders	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx/xxx (xx.x)
Overall Responders	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx/xxx (xx.x)

Table 1. Summary Statistics for Responder Analysis

SAS Code for defining the responder:

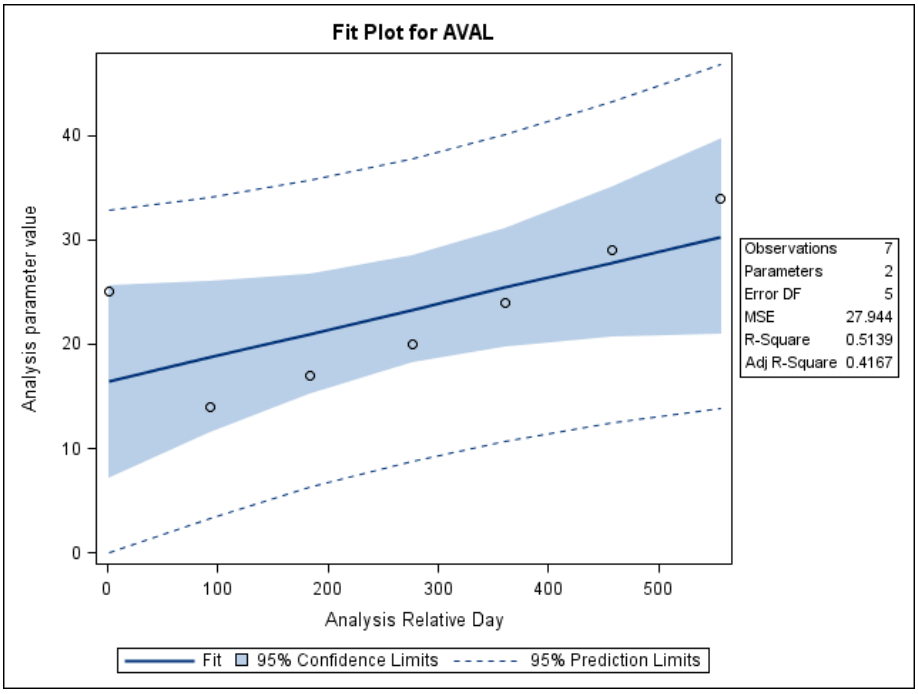
```
%let m18=548;
%macro e50_perform_reg(din, ep, dout);
data e50_week00 e50_week78;
set &din.;
  if (avisitn=0) and (aval^=.) then output e50_week00;
  else if (avisitn=9) and (aval^=.) then output e50_week78;
  keep usubjid;
run;
proc sort data=&din. out=e50in; by usubjid; run;
proc sort data=e50_week00;      by usubjid; run;
proc sort data=e50_week78;      by usubjid; run;
data e50_comp0(keep=usubjid trtgrp) e50_comp1(keep=qsgrpid trtgrp usubjid aval week ady);
  merge e50in(in=a) e50_week00(in=b) e50_week78(in=c);
  by usubjid;
  if (ady<-28) then ady=-28; *Set a floor for baseline records beyond one month prior to the first dose.;
  if (a) and (b) and (c) then output e50_comp1; else output e50_comp0;
run;
proc sort data=e50_comp0 out=e50_comp0_ nodupkey; by usubjid; run;
proc sort data=e50_comp1; by qsgrpid usubjid trtgrp; run;
ods output ParameterEstimates=e50_param;
proc reg data=e50_comp1; by qsgrpid usubjid trtgrp; model aval=ady; run;
data e50_slope;
   set e50_param;
   if (upcase(variable)='ADY');
  &ep._slope=&m18.*estimate;
  keep usubjid &ep._slope trtgrp;
run;
data &dout.; set e50_slope e50_comp0_; run;
%mend e50_perform_reg;

%e50_perform_reg(adasin_bp1, adas, adas_bp1_out);
%e50_perform_reg(adlin_bp1, adl, adl_bp1_out);

*Missing slope indicates non-completer and hence non-responder;
data resp_adasbp1;
  set adas_bp1_out;
  if (adas_slope=.) then adas_resp=0;
  else adas_resp=(adas_slope<4);
run;
data resp_adlbp1;
  set adl_bp1_out;  if (adl_slope=.)  then adl_resp=0;
  else adl_resp=(adl_slope>-6.3);
run;
%runmergeab(resp_adasba1, resp_adlba1, usubjid trtgrp);
```

The REG Procedure

Model: MODEL1

Dependent Variable: AVAL Analysis parameter value

Group ID=ADASCOG Unique Subject Identifier=xxxxxxx TRTGRP=Group B



LOGISTIC REGRESSION

The analysis of the proportion of Week 78 responders will be conducted using logistic regression model with region, treatment, gender, APOE genotype (APOE 4 positive, APOE 4 negative), baseline use of Vitamin E (0-400 IU/day, > 400 IU/day), baseline AD medication (use of AChEI or memantine, no use of AChEI or memantine), and study cohort (Safety Cohort, Main Cohort), with the baseline values of MMSE and age included as continuous covariates. The odds ratios, corresponding 95% CIs, and P-values will be estimated from this model. In the event that the model fails to converge, terms will be sequentially removed from the model (until convergence is obtained) in the following order: study cohort, gender, geographic region, baseline use of Vitamin E, APOE genotype, baseline AD medication.

SAS Code for logistic regression:

```
***Create global macro variables to hold the population proportions for use in the
estimate statements.;
data _null_;
  set lptda.effcov;
  call symput("reg1",reg1);       call symput("reg2",reg2);
  call symput("reg3",reg3);       call symput("reg4",reg4);
  call symput("sex1",sex1);           call symput("sex2",sex2);
  call symput("apoe0",apoe0);         call symput("apoe1",apoe1);
  call symput("bgadtrt0",bgadtrt0);   call symput("bgadtrt1",bgadtrt1);
  call symput("cohort1",cohort1);     call symput("cohort2",cohort2);
  call symput("vit1",vit1);           call symput("vit2",vit2);
  call symput("agemean",agemean);     call symput("mmsemean",mmsemean);
run;

***Create global macro variables to hold the population proportions for use in the
estimate statements.;
%let coeff_string_bp=reggrpn &reg1. &reg2. &reg3. &reg4. sexn &sex1. &sex2. apoe4psn
&apoe0. &apoe1. bgadtr2n &bgadtrt0. &bgadtrt1. cohortn &cohort1. &cohort2.   vitegr1n
&vit1. &vit2. mmseval &mmsemean. ageyears &agemean.;

ods listing close;ods output estimates=e27_esr type3=e27_lrsft3au;
   proc genmod data=adsl_and_e27inbp1 desc;
```

```
   class trtgrp reggrpn sexn apoe4psn bgadtr2n cohortn vitegr1n;
   model resp = trtgrp reggrpn sexn apoe4psn bgadtr2n cohortn vitegr1n mmseval
   ageyears /d=b type3;
   estimate 'Group A' int 1 trtgrp 1 0 0 &coeff_string_bp. / alpha=0.05;
   estimate 'Group B' int 1 trtgrp 0 1 0 &coeff_string_bp. / alpha=0.05;
   estimate 'Group C' int 1 trtgrp 0 0 1 &coeff_string_bp. / alpha=0.05;
   estimate 'Group A vs. Group C' trtgrp 1 0 -1 / alpha=0.05;
   estimate 'Group B vs. Group C' trtgrp 0 1 -1 / alpha=0.05;
   run;
ods listing;
```

Logistic Regression for Responder Analysis

	Observed	Model-Based‡
Treatment	n / m (%)	% (95% CI)
Group A	xxx/xxx (xx.x)	xxx/xxx (xx.x)
Group B	xxx/xxx (xx.x)	xxx/xxx (xx.x)
Group C	xxx/xxx (xx.x)	xxx/xxx (xx.x)
Treatment Comparisons§		
	Odds Ratio (95% CI)	p-value
Group A vs. Group C	x.xx (x.xx, x.xx)	x.xxxx
Group B vs. Group C	x.xx (x.xx, x.xx)	x.xxxx

Table 2. Logistic Regression for Responder Analysis

REFERENCES

SAS Help and Documentation: http://support.sas.com/documentation/onlinedoc/91pdf/index_913.html

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Name: Yan Liu
Enterprise: MSD R&D China
Address: 1-13F, Building 21 Rongda Road, Wangjing R&D Base, Zhongguancun Electronic Zone West Zone, Chaoyang District
City, State ZIP: Beijing 100012, China
Work Phone: 1058609402
E-mail: yan.liu14@merck.com