

```

%_mprintto;
options notes nosource;
proc datasets lib=work nolist memtype=data kill; quit;
/* Standard - leave this */
%let TFL_Part=%scan(&_SASPROGRAMFILE,-3,%str(/));

/* Standard - leave this */
data _null_;
    tmp="%TFL_Part";
    if tmp not in ("dev" "qc") then call symput("TFL_Part", "prod");
    call symput('TFLpath', compress("&_SASPROGRAMFILE",""));
run;
%put NOTE:
=====;
%put NOTE: Covance Study Number : 000000106324;
%put NOTE: Client Protocol ID   : ZRHR-REXC-03-EU;
%put NOTE: Program Name        : tfl_anlneqrisk.sas;
%put NOTE: Purpose              : Analysis of Relationship between NEQ
and Risk markers Day 5;
%put NOTE: ;
%put NOTE: Input Data           : ADAM.ADBX;
%put NOTE: Output               : ;
%put NOTE: Macros Called        : _MPRINTTO;
%put NOTE: ;
%put NOTE: Programmed by        : cvn_ahall;
%put NOTE: Creation Date        : 2014-06-1;
%put NOTE: SAS Version          : 9.3;
%put NOTE: ;
%put NOTE: == Latest Run
=====;
%put NOTE: Run by                : &sysuserid;
%put NOTE: Date/Time             :
%sysfunc(putn(%sysfunc(date()),e8601da.))T%sysfunc(putn(%sysfunc(time()),
e86011z.));
%put NOTE: ;
%put NOTE: == Modification History
=====;
%put NOTE: Date      Initials   No. Reason;
%put NOTE: 01Aug2014  AMH        1) Correct output file names;
%put NOTE: 01Aug2014  AMH        2) Center output;
%put NOTE: 01Aug2014  AMH        3) Add where clause used to dataset;
%put NOTE: 05Sep2014  APH        4) Show regression lines for THS 2.2
and CC arms in overall plot;
%put NOTE:                               5) Show p-value from comparison of
slopes for THS 2.2 and CC arms;
%put NOTE:                               6) Add footnote to explain that
regression lines are only shown on individual plots when slope is
significant;
%put NOTE: 15SEP2014  APH        7) Move figure and title footnotes
outside of plot;
%put NOTE:                               8) Output dataset used in figure to xls
sheet;
%put NOTE: 31OCT2014  APH        9) Add p-value to pages 1-3;

```

```

%put NOTE:
=====;
options notes source source2 nofullstimer validvarname=upcase missing=' '
NOQUOTELENMAX/*turn off warnings about quoted strings too long*/;
ods _all_ close;
ods listing;

*=====;
* START OF PROGRAM CODE                                     ;
*=====;

*****;
* read in data ;
*****;
*****;
/* Calculate totals for products */

/*formats macro and appendix output macros*/
%include
"/cvn/projects/prj/development/000000106324/dev/adhoc/TMPLTMIX.sas";

/* Standard - leave this */
data _null_;
    tmp("&TFL_Part";
        if tmp not in ("dev" "qc") then call symput("TFL_Part", "prod");
        call symput('TFLpath', compress("&_SASPROGRAMFILE",""));
run;

data adsl;
    set adam.adsl(where=(fasfl='Y'));
    if index(trt01a,'THS 2.2') then colord=1;
    output;
    if index(trt01a,'CC') then colord=2;
    output;
    if index(trt01a,'SA') then colord=3;
    output;
run;

proc sort data=adsl nodupkey out=adsl1;
    by colord subjid;
run;

proc freq data=adsl1(where=(not missing(colord))) noprint;
    table colord/ out =totals2(drop=percent rename=(count=total));
run;

data _null_;
    set totals2;
    call symput('tot'||strip(put(colord,best.)),strip(put(total,best.)));
run;

```

```

data bxin;
set adam.adbx;
where fasfl='Y' and not missing(aval) and avisitn=105
      and paramcd in
('UNEQ24U','UNEQCRE','UTXB224U','UTXB2CRE','UPGF2CRE','UPGF224U');
      if index(paramcd,'CRE') then rel=1;
      else rel=2;
run;

/*merge NEQ to risk marker dataset*/
proc sql;
create table anal as
select a.*, b.param as compar, b.aval as neq
from bxin as a, bxin as b
where index(b.paramcd,'UNEQ') and index(a.paramcd,'UNEQ')=0 and
a.usubjid=b.usubjid and a.rel=b.rel
order by paramn, rel;
quit;

data anal1;
attrib complab length=$200;
set anal;
by paramn rel;
complab=trim(left(compar))||' vs. '||trim(left(param));
retain comp;
if first.paramn or first.rel then comp+1;
run;

%fmt(datain=anal1, start=trtan, label=trta, name=trt);
%fmt(datain=anal1, start=comp, label=complab, name=comp);

data final;
set anal1;
format trtan trt. comp comp. ;
run;

proc sort data=final;by comp trtan;run;

title1 j=1 "PAGESPLIT"; /*do not change*/
title2 j=1 'Proc GLM Procedure';
title3 j=1 '#byval1';
title4 j=1 '#byval2';
TITLE5 J=L "The where clause used on the dataset adam.adbx: fasfl='Y' and
anl02fl='Y'";
%let tflno=L_15_04_04_57(NEQRISK); /* 1) AMH 01Aug2014 */

%mixout1(fileout=/cvn/projects/prj/data/000000106324/TFL/&TFL_Part./&tflno);

options ps=20;
options nobyline;

```

```

proc glm data=final order=internal;
by comp trtan;
model aval= neq / solution;
output out=pred1 p=pred r=resid;
ods output Parameterestimates=parms1;
ods output OverallANOVA=pvall1;
run;

/*Residual Plots*/
title5 j=1 'Residual Plots';
options ps=27; /*change this for proc plot*/

proc rank data=pred1 out=resid1 normal=vw ;
by comp trtan;
ranks nscore;
var resid;
run;

proc plot data=resid1 hpercent=50;
by comp trtan;
plot resid*pred / vref=0;
plot resid*nscore;
run;
quit;
/*treatment comparisons model*/
title;
title1 j=1 "PAGESPLIT"; /*do not change*/
title2 j=1 'Proc GLM Procedure';
title3 j=1 '#byvall1';

proc glm data=final(where=(trtan<3)) order=internal ;
by comp;
class trtan;
model aval= trtan neq neq*trtan / solution ;
output out=pred2 p=pred r=resid;
ods output Parameterestimates=parms2(where=(parameter='NEQ*TRTAN THS
2.2'));
run;

/*Residual Plots*/
title4 j=1 'Residual Plots';
options ps=27; /*change this for proc plot*/

proc rank data=pred1 out=resid1 normal=vw ;
by comp trtan;
ranks nscore;
var resid;
run;

proc plot data=resid1 hpercent=50;
by comp trtan;
plot resid*pred / vref=0;
plot resid*nscore;
run;

```

```

quit;

%mixout2(blankn=60, halfblnk=N,title=Listing 15.4.4.57 Statistical
Analysis of Relationship Between NEQ and Risk Markers on Day 5 - FAS);

ods rtf close;
ods results on;
ods path reset;

/*merge pvalue to parameter estimates*/
proc sql;
create table out1 as
select a.*, b.probf as pval1
from parms1 as a, pval1 as b
where a.parameter='NEQ' and missing(b.probf)=0 and a.comp=b.comp and
a.trtan=b.trtan
order by comp, trtan;
quit;

/*Manipulate datasets for output*/
/*_____*/
data tabout;
length rand $50 slope $50 pval $50;
set out1(in=a drop=parameter) parms2(in=b) ;
if a then do;
ord=trtan;
rand=left(put(trtan,trt.));
if pval1<0.001 then pval='<0.001';
else pval=compress(put(pval1,8.3));
end;
if b then do;
ord=4;
rand='THS 2.2 vs. CC';
if probt<0.001 then pval='<0.001';
else pval=compress(put(probt,8.3));
end;
slope=compress(put(estimate,8.2));
run;

/* Standard - macro for paging */
%macro outrtf(blankn=60, halfblnk=N, ref=);

%if &halfblnk=N %then %let halfblnk=;
%else %if &halfblnk=Y %then %let halfblnk=\~;

/* Standard - just change the number to match the listing you're working
on. Also change the letters in the*/
/* bracket, eg ccb = current cigarette brands. Make sure to do this at
the top of the code too. */

%let tflno=T_15_02_04_57(NEQRISK);

/* Standard - leave this */
%let TFL_Part=%scan(&_SASPROGRAMFILE,-3,%str(/));

```

```

/* Standard - leave this */
data _null_;
    tmp="&TFL_Part";
    if tmp not in ("dev" "qc") then call symput("TFL_Part", "prod");
    call symput('TFLpath', compress("&_SASPROGRAMFILE",""));
run;

/*page numbers*/
data paging;
    set tabout;
    page=ceil(comp/2);
    %let tpage=2;
run;

/* Standard - leave this */
options number nodate orientation=landscape papersize=&p_pgsz missing='
' NOQUOTELNMAX/*turn off warnings about quoted strings too long*/;
ods escapechar='';
%let linetop = \brdrt\brdrs\brdrw30; * needs to be 1.5pt so calculated
in twips (1/20 pt) ;
%let linebot = \brdrb\brdrs\brdrw30;
%let linebot2 = \brdrb\brdrs\brdrw15;

ods path stdlib.tl06324 (read) ;
ods results off;
ods rtf toc_data/* contents*/
file="/cvn/projects/prj/data/000000106324/TFL/&TFL_Part./&tflno..rtf"
style=tl06324 startpage=yes headery=1440 footery=1440 ;
ods noproctitle;

%do i=1 %to &tpage;

ODS PROCLABEL = ' ';
title ;
footnote;
%let wd=0;

proc sort data=paging;by comp ord;run;

data comp;
    set paging end=eof;
    by comp ord;
    where page=&i;
    flag=1;
    _firtitl="Table 15.2.4.57 Statistical Analysis of Relationship
Between NEQ and Risk Markers on Day 5 - FAS";
    _upcas=(length(_firtitl)-
length(compress(_firtitl,'ABCDEFGHIJKLMNOPQRSTUVWXYZ')))/2;
    len=&blankn.-length("(Page &i of &tpage)");
    if eof then do;
        call symput('_FSRTITL', trim(left(_firtitl)));
    end;

```

```

        call symput('_blankn', compress(put(len,best.)));
    end;
    drop _firtitl _upcas len;
run;

ods listing close;

* most set up in template others below;
* title arial 12pt bold with 12pt paragraph space below;
* all headers to be arial 11pt bold;
* data arial 10pt;
* headers to be central, text values left aligned and numeric centered
around decimal point;
/* Update with your variables as needed */
proc report data = comp headline headskip missing nowd spanrows split =
'#'
%IF &I=1 %THEN %DO; CONTENTS=' ' %END; %ELSE %DO; CONTENTS='' %END;;
    column flag page comp ord rand slope pval;

    define flag / order noprint;
        define page          / order order = internal noprint;
        define comp          / group order=internal style={just=left
cellwidth=14cm} "Relationship";
        define ord           / order order=internal noprint;
        define rand          / display style={just=left cellwidth=3cm}
"Randomization#Arm";
        define slope         / display style={just=C/*d*/ cellwidth=2cm}
style(header)={just=center} "Slope";
        define pval          / display style={just=C/*d*/ cellwidth=2cm}
style(header)={just=center} "P-Value"; /* 2) AMH 01Aug2014 */

        break after page / page;

        break before flag / page %IF &I=1 %THEN %DO;
            CONTENTS="&_FSRTITL" %END; %ELSE %DO; CONTENTS='' %END;;

        compute before page / style={protectspecialchars=off};
            line "&linetop";
        endcomp;

        compute before _page_ / style={just=left protectspecialchars=off};
            line "\b\fs24\sa24&_FSRTITL." ; * \b = bold, \fs24 is font
size 12pt, \sa24 is space after 12pt;
            line "&linebot";
        endcomp;

        compute after comp;
            line ' ';
        endcomp;

        compute after _page_ / style={just=left protectspecialchars=off
pretext="&linetop."};

```

```

line "Note: CC = Conventional cigarettes; SA = Smoking abstinence; THS =
Tobacco Heating System.";
line "Note: Model for each arm separately was: Biomarker = NEQ
for each arm separately. P-value for test of  $R^2=0$ ";
line "Model for THS 2.2 vs CC was: Biomarker = NEQ +
randomization arm + NEQ*randomization arm. P-value for significance of
NEQ*randomization arm. Slope estimate is the difference in slopes (THS
2.2 - CC)";

line "";
line "Appendix &ref.";
line "Path: &TFLpath." &_blankn.*"\~\~" "(Page &i of
&tpage)";
line "Program Run: &sysdate &sysuserid Program Status:
&status";
endcomp;

run;
%end;
ods rtf close;
ods results on;
ods path reset;

%mend outrtf;

%outrtf(blankn=60, halfblnk=N, ref=15.4.4.57);

/*Figure Output*/
/*
_____*/

%macro figout(comp=,out=,title=);

/*Macrolise Pvalues from models above used to determine if to draw
rgression line*/
data _null_;
set pval1;
where not missing(probfb) and comp=&comp;
if probfb<0.05 then call symput('reg' || compress(put(trtan,z1.)),1);
else call symput('reg' || compress(put(trtan,z1.)),0);
run;

/* 5) APH 05SEP2014 */
DATA _NULL_;
SET PAGING(WHERE=(INDEX(RAND,'vs')));
CALL SYMPUT('PVAL' || COMPRESS(PUT(COMP,Z1.)),COMPRESS(PVAL));
RUN;

%let reg4=0; /*no regression line on Overall plot*/

```



```

proc sort data=final(where=(comp=&comp)) out=fig; by comp trtan; run;

data figpag;
  set fig;
if comp in (1,3) then param=trim(left(substr(param,1,index(param,'(')-
1)))||
  "^{unicode '000a'x}"||trim(left(substr(param,index(param,'('))));
  page=trtan;
  output;
  page=4;
  output;
run;
%let tpage=4;

/*Calculate correlation coefficeints*/
proc sort data=figpag; by page; run;

proc corr data=figpag;
by page;
var aval neq;
ods output PearsonCorr=corr;
run;

data test;
set corr;
where variable='NEQ';
call symput('corr' || compress(put(page,best.)),compress(put(aval,8.4)));
IF PAVAL LT 0.001 THEN CALL
SYMPUT('PVALC' || COMPRESS(put(PAGE,BEST.)),COMPRESS('<0.001'));
ELSE CALL
SYMPUT('PVALC' || COMPRESS(put(PAGE,BEST.)),COMPRESS(put(PAVAL,PVALUE6.3)));
; /* 9) APH 31OCT2014 */
run;

/* Ensure ODS listing, html etc is turned off to prevent */
/* temporary or junk image files being produced */
title; footnote;
options notes source source2 nofullstimer validvarname=upcase
  nonumber nodate orientation=portrait papersize=&p_pgsize missing=' ';
ods graphics on; /* As we are effectively using ODS graphics we need to
ensure that it is turned on */
ods graphics / noborder height=14 cm width=16 cm; /* Removes border
around the image */
ods path reset;
ods exclude all;
/* please include styles template */
%let temp=/cvn/projects/prj/development/000000106324/dev/macro/;
%include "&temp.figtplt.sas";

%let blankn=70;
%macro graph();

```

```

%let ref=15.4.4.57;
%let tflno=F_15_01_02_&out(NEQRISK);

      /* 8) APH 15SEP2014 */
PROC SQL;
CREATE TABLE PLOT2 AS
SELECT PARAM, COMPLAB, SUBJIDN, NEQ, AVAL, PUT(TRTAN,TRT.) AS TRTAN
FROM FIGPAG;
QUIT;

PROC EXPORT
DATA=PLOT2
DBMS=XLSX
OUTFILE="/cvn/projects/prj/data/000000106324/TFL/&TFL_Part./&tflno..xlsx"
REPLACE;
SHEET=Sheet1;
RUN;
      /* 8) APH 15SEP2014 */

/* treatment column headers and footnotes */
ods rtf toc_data
file="/cvn/projects/prj/data/000000106324/TFL/&TFL_Part./&tflno..rtf"
style=t106324_g startpage=yes headery=1440 footery=1440;

%do i=1 %to &tpage;

      data plot;
        set figpag end=eof;
        where page = &i;
        call symput("trt",trim(left(put(trtan,trt)))));
        %if &i=4 %then %do; call symput("trt","Overall. (P-value for
comparison of slopes between THS 2.2 and CC = &pval&comp..)"); %end;
        call symput("xlab",trim(left(compar)));
        call symput("ylab1",trim(left(param)));
        /* Amend title as needed */
        _firtitl="&title";
        if eof then do;
          call symput('_FSRTITL', trim(left(_firtitl)));
        end;
        /* 4) APH 05SEP2014 */
        %IF &I=4 %THEN %DO;
          IF TRTAN NE 3 THEN DO;
            NEQ2=NEQ;
            AVAL2=AVAL;
          END;
        %END;

        drop _firtitl ;
      run;

proc template;
  define statgraph temp;
    beginngraph /;

```

```

/* we can change the alignment of text using halign=, text
attributes can also be set */
/*          entrytitle halign=left "&_FSRTITL."  /* 7) APH
15SEP2014 */
/*          entrytitle " " /* 7) APH 15SEP2014 */
/* textattrs options include size, color, font, weight and
style */
/* the default text attributes are picked up from the default
rtf styles template */
/* this can be changed using style= in the ods rtf statement
*/

          entrytitle halign=left "Study Arm: &trt" /*
              layout overlay /
              %if &i=4 %then

XAXISOPTS=(label="&xlab");
              %else XAXISOPTS=(label="&xlab^{unicode
'000a'x}Correlation Coefficient = &&corr&i (P-value = &&pvalc&i)"); /*
9) APH 31OCT2014 */
              YAXISOPTS=(label="&ylab1");
              %if &&reg&i=1 %then modelband 'conf' / name='band'
display=(fill) legendlabel='95% Confidence Limits';
              scatterplot x=neq y=aval / index=trtan group=trtan
name='trt';
              %if &&reg&i=1 %then regressionplot x=neq y=aval / name='line'
alpha=.05 clm='conf' legendlabel='Linear regression line';

              %if &i=4 %then %do;
                  discretelegend "trt" / across=1 /* 4) APH05SEP2014
*/
                  REGRESSIONPLOT X=NEQ2 Y=AVAL2 / GROUP=TRTAN
LINEATTRS=(PATTERN=SOLID) NAME='LINE2' LEGENDLABEL='Linear regression
line';
              %end;
              %if &&reg&i=1 %then discretelegend "line" "band" / across=1
;;
                  endlayout;
/* footnotes work using the same option as the entrytitle
statement */
/* 7) APH 15SEP2014 */
/*          entryfootnote halign=left "Note: CC = Conventional cigarettes;
SA = Smoking abstinence; THS = Tobacco Heating System." /*
/*          ENTRYFOOTNOTE HALIGN=LEFT "Note: Regression lines only shown on
separate study arm plots where a significant result was found for the
slope (see Table 15.2.4.57)."; /* 6) APH 05SEP2014 */
/*          entryfootnote " " /*
/*          entryfootnote halign=left "Appendix &ref." / /*
/*          entryfootnote halign=left "Path: &TFLpath." halign=right
"(Page &i of &tpage)" / /*
/*          entryfootnote halign=left "Program Run: &sysdate &sysuserid
Program Status: &status" / /*
/* 7) APH 15SEP2014 */

          endgraph;

```

```

        end;
run;

/* 7) APH 15SEP2014 */
ods select all;
ods escapechar='^';
ODS RTF PREPAGE="^S={outputwidth=100% just=l font_size=12pt
font_weight=bold background=white foreground=black
font_face=arial}^R/RTF'\QL' &_FSRTITL.";

proc sgrender data=plot template=temp objectlabel=''; /* applies the
above template to the specified data */
format trtan trt. ;
run;

/* 7) APH 15SEP2014 */
ODS RTF TEXT="^S={outputwidth=100% just=l font_size=9pt background=white
foreground=black font_face=arial}^R/RTF'\QL' Note: CC = Conventional
cigarettes; THS = Tobacco Heating System.";
ODS RTF TEXT="^S={outputwidth=100% just=l font_size=9pt background=white
foreground=black font_face=arial}^R/RTF'\QL' Note: Regression lines only
shown on separate study arm plots where a significant result was found for
the slope (see Table 15.2.4.57).";
ODS RTF TEXT="^S={outputwidth=100% just=l font_size=9pt background=white
foreground=black font_face=arial}^R/RTF'\QL' &ref.";
ODS RTF TEXT="^S={outputwidth=100% just=l font_size=9pt background=white
foreground=black font_face=arial}^R/RTF'\QL' Path: &TFLpath.
(Page &i of &tpage)";
ODS RTF TEXT="^S={outputwidth=100% just=l font_size=9pt background=white
foreground=black font_face=arial}^R/RTF'\QL' Program Run: &sysdate
&sysuserid Program Status: &status";

/* 7) APH 15SEP2014 */

%end;
ods markup close;
/*ods rtf close; */
ods path reset;

%mend graph;
%graph;
ods exclude all;
ods _all_ close;

%mend;

%figout(comp=1,out=40,
title=%str(Figure 15.1.2.40 Scatterplot of 8-epi-PGF2^{unicode alpha}
Urinary Concentration Adjusted for Creatinine vs. NEQ Urinary
Concentration Adjusted for Creatinine - FAS));

%figout(comp=2,out=41,

```

```
title=%str(Figure 15.1.2.41 Scatterplot of Urinary 8-epi-PGF2^{unicode  
alpha} Quantity Excreted over 24 hours vs. Urinary NEQ Quantity Excreted  
over 24 hours - FAS));
```

```
%figout(comp=3,out=42,  
title=%str(Figure 15.1.2.42 Scatterplot of 11-DTX-B2 Urinary  
Concentration Adjusted for Creatinine vs. NEQ Urinary Concentration  
Adjusted for Creatinine - FAS));
```

```
%figout(comp=4,out=43,  
title=%str(Figure 15.1.2.43 Scatterplot of Urinary 11-DTX-B2 Quantity  
Excreted over 24 hours vs. Urinary NEQ Quantity Excreted over 24 hours -  
FAS));
```

```
proc printto ; run;
```

```
*=====;  
* END OF PROGRAM CODE ;  
*=====;
```