Variance Ratio Estimation using the PrecMod SAS Macro

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ABSTRACT

When comparing two groups, the first thing that comes to the analyst's mind is to compare means. However, it may become necessary to compare group dispersions such as the variance, between the two groups to show equivalence, especially in a regulatory setting. The user is taken through the much vaunted PrecMod SAS macro to show how this can be done easily using the SAS System.

INTRODUCTION

When comparing means from two independent normally-distributed groups, appropriate statistical tests will use the difference as the statistic of choice since location distance is of interest. Similarly, when one compares the differences in dispersion statistics such as the variance (and standard deviation) between two independent normally-distributed groups, we get that $\sigma_1^2 = \sigma_2^2$, which, mathematically, can be written as

$$\frac{\sigma_1^2}{\sigma_2^2}=1 \quad (1)$$

or in other words, a variance ratio. Since the sample variance is distributed as a chi-square probability distribution with n-1 degrees of freedom, then the ratio of two chi-square distributions is an F probability distribution. The next section expands this theorem sketch (i.e., set of results).

THEORY

The sampling distribution of the sample variance is distributed as a chi-square probability distribution with n-1 degrees of freedom as follows (Hald, 1952):

Let **X** be a random variable distributed as a normal probability distribution with mean μ and variance σ^2. That is,

$$X \sim N(\mu, \sigma^2) \quad (2)$$

Then, the $X_1, X_2, \ldots, X_n$ random sample from **X** will give a sample mean of

$$\bar{X} = \frac{1}{n}\sum_{i=1}^{n} X_i \quad (3)$$

and sample variance of

$$S^2 = \frac{1}{n-1}\sum_{i=1}^{n}(X_i - \bar{X})^2 \quad (4)$$

then

$$\bar{X} \; and \; S^2 \; are \; independent \text{ (Basu, 1955)} \quad (5)$$

and

$$\frac{(n-1)\cdot S^2}{\sigma^2} = \frac{\sum_{i=1}^{n}(X_i-\bar{X})^2}{\sigma^2} \sim \chi^2_{df=n-1} \quad (6)$$

where n is the sample size, S is the sample standard deviation, σ is the population standard deviation, df is the degrees of freedom equal to n-1 and the twiddle symbol "∼" is read as "is distributed as". This can be read as "the term on the left in (6) is distributed as (i.e., "∼") a chi-square probability distribution with degrees of freedom equal to n-1".

Next, if we have two random independent random variables $\mathbf{X_1}$ and $\mathbf{X_2}$, it follows from (1) and (6) that the ratio of the variance distributions for $\mathbf{X_1}$ and $\mathbf{X_2}$, is an F probability distribution with numerator degrees of freedom (df_1) equal to n_1-1 and denominator degrees of freedom (df_2) equal to n_2-1 (Ross, 1987):

$$\frac{\chi^2_{n_1-1}/(n_1-1)}{\chi^2_{n_2-1}/(n_2-1)} = \frac{S_1^2}{S_2^2} = F_{(df_1=n_1-1,\ df_2=n_2-1)} = F_{(\upsilon_1,\ \upsilon_2)} \quad (7)$$

with $v_1 = n_1 - 1 \; and \; v_2 = n_2 - 1$ for simplicity.

HYPOTHESIS TESTING

Next, we wish to produce a statistical hypothesis test that tests the equality of two independent population variances. For this test, we posit the null hypothesis as follows:

$$H_0: \sigma_1^2 = \sigma_2^2 \; (= \sigma^2) \tag{8}$$

which translates to the variance ratio being equal to 1 from (1):

$$H_0: \frac{\sigma_1^2}{\sigma_2^2}=1 \tag{9}$$

Against a two-sided alternative that the variances are not the same:

$$H_A: \sigma_1^2 \neq \sigma_2^2 \tag{10}$$

with the test statistic defined from (7) as:

$$F_{Observed} = \frac{S_1^2}{S_2^2} \tag{11}$$

which is then compared to an F distribution with $n_1 - 1$ numerator and $n_2 - 1$ denominator degrees of freedom and/or a confidence interval can be constructed as shown later below.

To use this test, there are two main assumption requirements (R_A and R_B):

R_A. Both parent populations are normally distributed;

R_B. The populations are independent.

We next see how to satisfy the assumptions.

Testing Assumption R_A: Both parent populations are normally distributed

A visual inspection using graphical methods with a trained eye can be the first step in declaring normality in each of the comparison samples (Park, 2015). The visual inspection can be buttressed with direct testing of R_A. The analyst should be aware that parametric tests for normality may be overly conservative with larger sample sizes and liberal with smaller sample sizes (Royston, 1991; Oztuna et al., 2006; Thode, 2002; Steinskog, 2007; Ghasemi and Zahediasl, 2012). This means that one should not readily discard a normality judgement from a visual inspection that fails the direct calculation. However, failing both visual and direct testing of normality will require a data transformation (McDonald, 2015).

Testing Assumption R_B: Both populations are independent

This is less of a test and more of a theoretical/existential exercise in that if two population measurements do not come from the same sample or item being measured, then we can assume that the two populations are independent.

INTERVAL ESTIMATION

In general, a two-sided (1-α)·100% confidence interval for the true variance ratio $\frac{\sigma_1^2}{\sigma_2^2}$ for two normally distributed populations is:

$$\frac{1}{F_{(\alpha/2)}(n_1-1,n_2-1)} \cdot \frac{S_1^2}{S_2^2} < \frac{\sigma_1^2}{\sigma_2^2} < F_{(\alpha/2)}(n_2 - 1, n_1 - 1)\frac{S_1^2}{S_2^2} \tag{12}$$

where $F_{(\alpha/2)}(v_1, \; v_2)$ is the F probability distribution at significance level α with v_1 numerator and v_2 denominator degrees of freedom.

PRECMOD SAS MACRO

The PrecMod SAS macro is an automated precision calculation tool for random effects models when multiple similar levels of precision results are desired (Canchola and Hemyari, 2016). It provides for repetitive/recursive precision estimation that would normally require application of the same code to multiple groups or levels, thus saving time and effort.

Initial presentation of the PrecMod SAS macro at the PharmaSUG 2016 (Denver, Colorado), included required inputs for main precision estimation. However, the report deferred presentation of the variance ratio option inputs. This paper fills this gap and exhibits the variance ratio option.

Recall from Canchola and Hemyari (2016) that the PrecMod macro call input specifications were (yellow highlighted inputs focus our attention for the present discourse):

```
%PrecMod(InData    = ,          ❶
         ByVars    = ,          ❷
         ClassVars = ,          ❸
         DepVar    = ,          ❹
         IndepVars = ,          ❺
         Random    = ,          ❻
         Method    = REML ,     ❼
         OutData   = ,          ❽
         FlagVar   = ,          ❾
         FlagValue = ,          ❿
         EquTest   = N    ,     ⓫
         Alpha     = 0.05 ,     ⓬
         InsType   = ,          ⓭
         Logged    = "Yes");    ⓮
```

and macro parameters presented there were defined in Table 1 below.

Parameter #	Macro Parameter	General Macro Parameter Description	Specifications / Defaults	Example
❶	InData	SAS input data set (permanent or temporary)	< previous data set >	anadata.valid
❷	ByVars	"By" processing variable	< empty >	instrument cap_avg cpavglog
❸	ClassVars	Categorical or Class Variables	[Required]	site day run
❹	DepVar	Dependent Variable	[Required]	Logconc
❺	IndepVars	Independent Fixed Variables	< typically empty >	
❻	Random	Independent Random Variables	[Required]	site day run
❼	Method	Optimization method	REML, MLE, MIVQUE() / REML	REML
❽	OutData	Output SAS data set (permanent or temporary)	[Required]	anadata.mixed
❾	FlagVar	Any data flag or indicator variable	< empty >	dvlflag
❿	FlagValue	Value for FlagVar for subsetting	< empty >	DVL
⓫	EquTest	Test for Equivalency for Two Systems/Items Indicated	N	Y
⓬	Alpha	Statistical Significance Level	0 < α < 1.0 / 0.05	0.05
⓭	InsType	Declare a variable for instrument type, variables should match input variables. Required for ⓫ EquTest.	< empty >	Group/Instrument
⓮	Logged	If "Yes", macro will use correct percent coefficient of variation (%CV) formula	"No"	"Yes"

Table 1. PrecMod SAS Macro Parameter Specifications and defaults (from Canchola and Hemyari, 2016)

PRACTICAL EXAMPLE

For completeness, we recall the presented analysis of 1855 sample reproducibility data for a HIV-1 PCR assay test evaluated at six titer/concentration levels across the following factors (yellow highlighted inputs focus the additions or differences from the original PrecMod presentation used for the present discourse):

- **Lot:** 3 manufactured reagent lots
- **Site/Instrument:** 3 test sites; 1 instrument per site
- **Operator:** 2 operators performing testing at each site
- **Day/Run:** 5 days per lot for each operator; 1 run per day

- **Within-Day/run:** 3 replicates for each HIV-1 RNA concentration

Two different operators were at each of 3 test sites each performed 5 days of testing with each of 3 lots of reagents.

For this example, the specification for the PrecMod SAS macro was as follows with the test for equality of variances noted in test options, `EquTest`, `Alpha` and `InsType` (see yellow highlighted sections below for focus on the present discourse that highlight additions from the initial presentation in Canchola and Hemyari, 2016):

```
%PrecMod(InData    = DataSetIn ,                          ①
         ByVars    = GroupID titer_n titer_c logexp ,     ②
         ClassVars = dslot site operator day ,            ③
         DepVar    = logconc ,                            ④
         IndepVars = ,                                    ⑤
         Random    = dslot site operator day ,            ⑥
         Method    = REML ,                               ⑦
         OutData   = ResultsDat ,                         ⑧
         FlagVar   = dvlflag ,                            ⑨
         FlagValue = DVL ,                                ⑩
         EquTest   = Y     ,                              ⑪
         Alpha     = 0.05 ,                               ⑫
         InsType   = GroupID ,                            ⑬
         Logged    = "Yes") ;                             ⑭
```

Parameter #	Macro Parameter	General Macro Parameter Description	Example	Description
①	`InData`	SAS input data set	`DataSetIn`	Temporary SAS Input Data Set

②	`ByVars`	"By" processing variable	`titer_n`
			`titer_c`
			`logexp`
				Numeric titer
				Character titer
				Log_{10}(expected conc)

③	`ClassVars`	Categorical or Class Variables	`dslot`
			`site`
			`operator`
			`day`
				Lot factor
				Site factor
				Operator factor
				Day factor

④	`DepVar`	Dependent Variable	`Logconc`	Logarithm base 10 of Observed Concentration
⑤	`IndepVars`	Independent Fixed Variables	`< empty >`	No fixed variables
⑥	`Random`	Independent Random Variables	`dslot, site, operator, day`	Same variables as in ③ `ClassVars`
⑦	`Method`	Optimization method	`REML`	Restricted Maximum Likelihood
⑧	`OutData`	Output SAS data set	`ResultsDat`	Temporary SAS data set
⑨	`FlagVar`	Any data flag or indicator variable	`dvlflag`	Flag
⑩	`FlagValue`	Value for FlagVar for subsetting	`DVL`	Flag value for subset
⑪	`EquTest`	Test for Equivalency for Two Systems Indicated	`Y`	Equivalency testing is requested
⑫	`Alpha`	Statistical Significance Level	`0.05`	Standard two-sided

				significance
⑬	InsType	Declare a variable for instrument type, variables should match input variables	GroupID	"instrument" variable is declared since equivalency testing is requested (⑪ EquTest=Y)
⑭	Logged	If "Yes", macro will use correct percent coefficient of variation (%CV) formula	"Yes"	Since ④ DepVar is logged in original data, choose "Yes" here.

Table 2. PrecMod SAS macro parameter inputs for example of HIV-1 PCR assay test evaluated at six titer/concentration levels across lot, site, operator, day (from Canchola and Hemyari, 2016).

It was also indicated that additional coding could be added to format the results in a table using the SAS REPORT procedure (APPENDIX B, below).

RESULTS

Table 3 shows the results as formatted using the DATA step and PROC REPORT code in APPENDIX B.

HIV-1 RNA Concentration (log_{10} cp/mL)	Group/Instrument 1 (log_{10} cp/mL)			Group/Instrument 2 (log_{10} cp/mL)			Variance Ratio (Var1/Var2)	
Expected	Observed Group 1	No. of Tests [a] Group 1	Total Variance Group 1	Observed Group 2	No. of Tests [a] Group 2	Total Variance Group 2	Estimate	95% CI
6.699	6.683	141	0.028	6.663	123	0.027	0.953	(0.056,21.207)
5	4.970	134	0.010	4.954	131	0.007	0.728	(0.365,1.477)
3	2.989	132	0.019	2.979	134	0.011	0.574	(0.388,0.848)
2.602	2.538	123	0.010	2.537	144	0.010	0.997	(0.615,1.556)
2.301	2.259	129	0.022	2.257	138	0.016	0.717	(0.491,1.053)
1.699	1.630	137	0.067	1.616	126	0.072	1.077	(0.708,1.668)

Note: Results with detectable viral load are included in this table.
CI=Confidence Interval.
[a] Number of tests with detectable viral load.

Table 3. Variance Ratio (Var1/Var2) Comparing Variances of Group 1 with Group 2 for HIV-1 RNA Concentration (log10 cp/mL) from Tests with Detectable Viral Load.

INTERPRETATION

Table 3 shows the estimation of the variance ratio comparing Instrument 1 with Instrument 2 (and associated 95% confidence interval for each "Expected" level. By producing a 95% confidence interval, we are implicitly testing at the 0.05 significance level. Therefore, if the 95% confidence interval excludes 1.0, then the two instruments are different at a 0.05 significance level (i.e., p-value < 0.05). Otherwise, if the 95% confidence interval includes 1.0, we say the two instrument variances are not different from each other (p-value ≥ 0.05).

From Table 3, it can be seen that the third level ("Expected"=3), the 95% confidence interval excludes 1 on the lower end (i.e., 0.388 to 0.848). Therefore, we can declare that the two instruments are different in variation at the "Expected" level 3 log_{10} cp/mL.

On the other hand, since the remaining confidence intervals in Table 3 (other than "Expected" level 3) contain 1.0, we declare the instruments not different from each other in terms of their variances for those levels.

CONCLUSION

We presented the motivation, theory and example for performing variance ratio estimation and testing. From the initial PrecMod SAS macro presentation (Canchola and Hemyari, 2016), we saw that the random effects linear model were fit to the data for the estimation of variance components for each factor in the model. The variance estimates were then used to derive the variance estimates for each instrument or group. We used the MIXED procedure and added coding to calculate confidence intervals for the variance components using the corrected degrees of freedom (Satterthwaite, 1946). Since there may be more than one level in a study for the calculations, we coded the macro to iterate over any number of grouping levels. Finally, we provided an example that showed how to calculate and interpret the variance components results obtained by the PrecMod SAS macro and provided a framework for reporting the results.

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APPENDIX B. Additional SAS code for formatting results from PrecMod SAS Macro for Variance Ratio

```
*-----------------------------------------------------------------------------
 Setup New ODS Template Definition
------------------------------------------------------------------------------ ;
ods path work.templat(update) sasuser.templat(read) sashelp.tmplmst(read) ;
ods path show ;

proc template ;
     define style print.chgRTF ;
        parent = styles.rtf ;
               * RTF automatically has border of 0.25 in ;
            style body from body /
                  leftmargin = 1 in
                  rightmargin = 0.5 in ;
            * Per specs from medical writing ;
            style table from table /
                  cellpadding = 2pt ;
         end ;
run ;

* Determine Operating System(PC or Server)-For Use with PROC FONTREG ;
%global winsys ;
%macro winsys ;
        %if &sysscpl=XP_PRO          %then %let winsys=WINDOWS ;
        %else %if &sysscpl = NET_ASRV %then %let winsys=WINDOWS ;
%mend winsys ;
%winsys ;

%put "winsys=" &winsys ;

* Register Fonts - WINNT: Server & WINDOWS: PC ;
proc fontreg mode=all msglevel=verbose ;
        fontfile "C:\WINDOWS\Fonts\TIMES.TTF" ;;
        fontfile "C:\WINDOWS\Fonts\ARIAL.TTF" ;
run;

*-------------------------------------------------------------------------------------------------
Start Programming:- Formats for the Columns in the Table
-------------------------------------------------------------------------------------------------;
/* Variables produced in ResultsDat_Ratio, a temporary SAS data set (won't use all but you can):
   NOTE:  later we can add the p-value if you're interested.
levelvar
titer_n
titer_c
logexp
ratio
ci_l_95 ci_u_95
mean1_md mean2_md
totvar1 totvar2
n1 n2
df1 df2
*/ ;

data Intext ( drop = levelvar titer_c mean1_md mean2_md df1 df2 totvar1 totvar2 ratio ci_l_95
                     ci_u_95 ci_l_95_1 ci_u_95_1 ) ;
    * save variables in this order in the data set ;
    retain titer_n logexp n1 mean1_md_1 totvar1_1 n2 mean2_md_1 totvar2_1 ratio_1 df1_1 df2_1
                     ci_95_1 ;
    set ResultsDat_Ratio ;

    * mean, rounded degrees of freedom and total variance for first group or instrument ;
    mean1_md_1 = put(mean1_md,8.3) ;
    df1_1      = put(df1,8.0)      ;
    totvar1_1  = put(totvar1,8.3)  ;

    * mean, rounded degrees of freedom and total variance for second group or instrument ;
    mean2_md_1 = put(mean2_md,8.3) ;
    df2_1      = put(df2,8.0)      ;
    totvar2_1  = put(totvar2,8.3)  ;
```

```
    * keeping variance ratio to three decimal places ;
    ratio_1 = put(ratio,8.3) ;

    * Confidence Intervals to 3 decimal places ;
    ci_l_95_1 = put(ci_l_95,8.3) ;
    ci_u_95_1 = put(ci_u_95,8.3) ;

    * Combining items ;
    * Add an asterisk if interval contains 1.0, indicating statistical significance at
      alpha=0.05 ;
    if ( ci_l_95_1 < 1 < ci_u_95 ) then
          ci_95_1 = compress("("|| ci_l_95_1 || ", " || ci_u_95_1 || ")*") ;
    else ;
          ci_95_1 = compress("("|| ci_l_95_1 || ", " || ci_u_95_1 || ")") ;
run ;
proc sort data = Intext ; by descending titer_n ; run ;


*-----------------------------------------------------------------
Output Reports:
----------------------------------------------------------------- ;
options orientation=landscape ;
ods listing close ;
ods escapechar = '~' ;
ods rtf file="<your path>\<your filename>.rtf" style=print.chgRTF bodytitle notoc_data ;

title ; footnote ;

proc report nowd data=Intext split='*'

     style(report)={just=center outputwidth=6.5 in}
     style(lines)=header {font_size=9pt font_face="Arial"
                 font weight=medium background=transparent just=left}
     style(header)=header{font_size=9pt font_face="Arial"
                 font_weight=bold   background=transparent}
     style(column)=header{font_size=9pt font_face="Arial"
                 font_weight=medium background=transparent just=center} ;

     columns ( ( "HIV-1 RNA Concentration*(log~{sub 10} cp/mL)" logexp )
                  ( "Group/Instrument 1*(log~{sub 10} cp/mL)" mean1_md_1 n1 totvar1_1 )
                  ( "Group/Instrument 2*(log~{sub 10} cp/mL)" mean2_md_1 n2 totvar2_1 )
               ( "Variance Ratio*(Var1/Var2)" ratio_1 ci_95_1 )
             ) ;

      define logexp / display "Expected" flow
                      style(header)={just=center}
                      style(column)={just=left protectspecialchars=off pretext="\qj\tqdec\tx350 "
cellwidth=0.90 in} ;

          define Mean1_md_1 / display "Observed*Group 1"  flow
                      style(header)={just=center}
                      style(column)={just=center protectspecialchars=off  cellwidth=0.60 in} ;

          define Mean2_md_1 / display "Observed*Group 2"  flow
                      style(header)={just=center}
                      style(column)={just=center protectspecialchars=off  cellwidth=0.60 in} ;

          define n1 / display "No. of*Tests~{super a}*Group 1" flow
                      style(header)={just=center}
                      style(column)={just=center protectspecialchars=off  cellwidth=0.50 in} ;

          define n2 / display "No. of*Tests~{super a}*Group 2" flow
                      style(header)={just=center}
                      style(column)={just=center protectspecialchars=off  cellwidth=0.50 in} ;

          define totvar1_1 / display "Total Variance*Group 1"  flow
                      style(header)={just=center}
                      style(column)={just=center protectspecialchars=off  cellwidth=0.60 in} ;

          define totvar2_1 / display "Total Variance*Group 2"  flow
                      style(header)={just=center}
```

```
                    style(column)={just=center protectspecialchars=off  cellwidth=0.60 in} ;


         define ratio_1 /display "Estimate" flow
                        style(header)={just=center}
                        style(column)={just=center protectspecialchars=off
pretext="\qj\tqdec\tx350 " cellwidth=0.70 in} ;

          define ci_95_1 /display "95% CI" flow
                        style(header)={just=center}
                        style(column)={just=center protectspecialchars=off  cellwidth=0.90 in}
;

        title1 j=c bold height=12pt f='Times'
              "Table X1.  Variance Ratio (Var1/Var2) Comparing Variances of Group 1 with " ;
        title2 j=c bold height=12pt f='Times'
              "Group 2 for HIV-1 RNA Concentration (log~{sub 10} cp/mL) from Tests with " ;
        title3 j=c bold height=12pt f='Times' "Detectable Viral Load" ;

     compute after _page_ / style=[protectspecialchars=off] ;
               line "Note: Results with detectable viral load are included in this table." ;
               line "CI=Confidence Interval. " ;
               line "~{super a }Number of tests with detectable viral load." ;
     endcomp;
run;
ods rtf close ;
ods listing ;
options orientation=portrait ;

/* ********************** END OF PROGRAM ********************** */
```