Paper 209-28

P-Value Generation Simplified with a Single SAS® Macro

Pete Anderson, Quintiles, Inc., Kansas City, Missouri
Chris Hord, Quintiles, Inc., Kansas City, Missouri

ABSTRACT

P-values can be generated for a vast number of statistical tests, and many SAS procedures facilitate their computation. In the pharmaceutical industry, clinical trials often require tables presenting descriptive statistics and p-value results for baseline data analyses. Although important, such tables constitute a small portion of the universe of reports for which the programmer is responsible, and therefore are only produced on a periodic basis. To minimize the need for programmers to re-evaluate the various procedures for computing p-values every time such a table is needed, we developed a SAS macro to consolidate the p-value generation code. This macro currently incorporates p-value computations from several SAS procedures, including: chi-square, Cochran-Mantel-Haenszel, and Fisher's exact tests (PROC FREQ); a Kruskal-Wallis test (PROC NPAR1WAY); and a rank ANOVA test (PROC MIXED). The macro easily accommodates additional statistical tests using a modular approach that simplifies validation. The macro also facilitates reporting by merging the p-value results with pertinent descriptive statistic datasets and by ensuring uniform p-value formats. Since code syntax for some procedures varies between SAS versions, the macro ensures proper syntax is applied. The macro requires SAS/STAT®; the paper is written for SAS programmers of any experience level.

INTRODUCTION

In order to better understand the role of p-values in statistical reporting, some basic background information may be useful. In the pharmaceutical industry, many randomized clinical trials are conducted to compare the efficacy and/or safety among two or more treatment groups in subjects with a particular disease or illness. In randomized clinical trials with a parallel group design, subjects are randomized to one of the treatments included in the study. Before efficacy or safety is evaluated, it is often desirable to compare characteristics between the samples of subjects assigned to each treatment group at baseline, that is, before the subjects receive study treatment. In fact, the International Conference on Harmonisation (ICH) issued a guideline, ICH E3 *Structure and Content of Clinical Study Reports*, for the pharmaceutical industry that states "Group data for the critical demographic and baseline characteristics of the patients…should be presented…and comparability of the treatment groups for all relevant characteristics should be displayed by use of tables or graphs...". Although statistical analyses of efficacy and safety data are of interest in clinical trials, the scope of this paper is limited to baseline data to simplify the discussion.

Demographic data, such as gender, race, age, and weight, are one type of data collected at baseline that can be compared among the treatment groups. Such comparisons can be made through the use of descriptive statistics (percentage, mean, standard deviation, minimum, median, maximum, etc.) with statistical tests to examine potential baseline imbalances. The statistical tests of select baseline variables generate p-values, with a significant difference among treatment groups noted if the p-value is below a preset level, for example 0.05.

Baseline data variables can be categorical or continuous in scale. A categorical variable is one for which the measurement scale consists of a set of categories (for example, female or male for gender). Continuous variables can take on values on a continuous scale, while discrete variables have a more finite range of values. Actual measurement of continuous variables occurs in a discrete manner, due to limitations in measuring instruments. In practice, discretely measured variables that can assume a large number of values are often treated as continuous for the purpose of statistical testing (for example, age and weight). These different variable types lead to the need for different statistical tests. For example, chi-square, Cochran-Mantel-Haenszel, and Fisher's exact tests are used to produce p-values for categorical variables, while Kruskal-Wallis and rank ANOVA tests are used for continuous variables. The particular test to be used is selected by the statistician, based on characteristics of the sample and the variable of interest.

While statistical testing in clinical trials can be quite complicated, the tests for baseline data are more straightforward and lend themselves to standardized programming. Tables are routinely required which present p-value results from the baseline data analyses along with pertinent descriptive statistics (for example, percentages for categorical variables or means and standard deviations for continuous variables). Some tables (such as demographics) present both continuous and categorical variables. The specific test chosen by the statistician for any given variable may vary from one study to another, based on sample size or other characteristics. Hence, although the SAS code required to produce p-values from the five tests mentioned earlier is not complex, the programmer must become proficient with the test syntax and idiosyncrasies of all three procedures (FREQ, MIXED and NPAR1WAY) needed to run these five tests. Furthermore, the syntax varies between different SAS versions for the Fisher's exact and rank ANOVA tests. To streamline the production of baseline tables that feature p-values, and to make the production of such tables more programmer-friendly (especially for the statistically-challenged) we developed a SAS macro (%pval) to consolidate the p-value generation code and to standardize the syntax across versions of SAS. As a bonus, the macro also automates the merging of the p-value result with the baseline descriptive statistics and formats the p-values for reporting.

MACRO OVERVIEW

The %pval SAS macro was primarily developed to streamline the production of baseline tables presenting p-values with descriptive statistics. The macro incorporates p-value computations from three SAS procedures commonly used for such analyses, including: chi-square, Cochran-Mantel-Haenszel, and Fisher's exact tests using PROC FREQ; a Kruskal-Wallis test using PROC NPAR1WAY; and a rank ANOVA test using PROC MIXED after first ranking the dependent variable using PROC RANK (see Table 1).

The %pval macro was developed with the following program flow:

1. Define the macro and keyword parameters.
2. Determine the statistical test to be performed.
3. Determine the SAS version being executed.
4. Conduct the statistical test with appropriate SAS procedure and version-specific syntax.
5. Create output dataset with p-value result.
6. Merge p-value output dataset with pre-existing dataset of descriptive statistics (if available).
7. Format the p-value for reporting.

A call to the macro runs one statistical test for one specified variable. Hence, any statistical test for any baseline variable requested by the statistician is easily generated by another call to the macro. If a test is needed that is not currently handled by the macro, it can be easily added since the macro was designed using a modular structure.

The %pval macro automatically adjusts for variations in the syntax between SAS versions 6 and 8 for the Fisher's exact and rank ANOVA tests. In particular, the name for the output dataset variable storing the p-value result differs between these versions. Table 1

displays the appropriate p-value variable name for the five statistical tests used in the macro for SAS Version 6.12 versus 8.02, as well as other code syntax which differs between the two versions.

Table 1. P-value Variable Name by Statistical Test

Data Type	*Statistical Test*	*PROC*	*SAS Version*	*P-value Variable*
categorical	chi-square	FREQ	6.12/ 8.02	p_pchi
	Cochran-Mantel-Haenszel (general association)	FREQ	6.12/ 8.02	p_cmhga
	Fisher's exact	FREQ	6.12	p_exact2
			8.02	xp2_fish
continuous	Kruskal-Wallis	NPAR 1WAY	6.12/ 8.02	p_kw
	ANOVA (F-test)	MIXED*	6.12	p_f
			8.02	ProbF

* PROC MIXED code for creating the output dataset also differs between SAS Versions 6.12 and 8.02 as follows:
Version 6.12: make 'tests' out=_pval;
Version 8.02: make 'tests3' out=_pval;
Version 8.02 alternative: ODS output tests3=_pval;

MACRO CALL

The call to the %pval macro takes the following form:

```
%pval(indata=,
      outdata=,
      subset=,
      poolvar=,
      trtvar=,
      depvar=,
      test=,
      outvar=)
```

The %pval macro has a parameter list comprised of eight keyword parameters, as described below:

indata
Required - name of SAS dataset with one record per subject to be used as input for the SAS procedure.

outdata
Optional - name of output SAS dataset to contain p-value.

subset
Optional - code to identify subset of subjects for analysis.

poolvar
Optional - name of pooled investigative site variable to use as an adjustment factor in some statistical tests.

trtvar
Required - name of treatment group variable.

depvar
Required - name of dependent variable to be tested (for example, gender or age).

test
Required - identifier for statistical test to be performed, including the following values:

CHISQ = chi-square test
CMH = Cochran-Mantel-Haenszel test
FISHER = Fisher's exact test
KW = Kruskal-Wallis test
ANOVA = rank ANOVA test.

outvar
Optional - name of formatted p-value result variable; macro assigns a variable name if not defined by user.

The SAS dataset passed to the %pval macro via the *indata* macro parameter should contain one record per subject with, at a minimum, variables for subject number, treatment group, and the baseline variable(s) of interest. For a baseline table summarizing multiple variables, it is advantageous to include all variables to be analyzed in the input dataset. If needed for the analysis, a subsetting variable and/or pooled investigative site variable should also be included in the dataset. Table 2 presents select observations from a sample input SAS dataset.

Table 2. Sample Input SAS Dataset

obs	subno	trt_grp	gender	age	disp	poolinv
1	101/001	A	M	32	1	1
2	101/002	B	F	55	1	1
3	101/003	A	M	24	2	1
. . .	. . .	. . .	. . .	. . .	. . .	. . .
58	105/001	B	F	46	1	5
59	105/002	B	F	19	2	5
60	105/003	A	M	60	1	5

If a SAS dataset of descriptive statistics has been produced for the variable of interest prior to the macro call, the user may pass this dataset to the macro via the *outdata* macro parameter. The macro will then merge the p-value with the descriptive statistics using the same dataset name. Since only one variable of interest is processed per macro call, a uniquely named dataset of descriptive statistics should be created prior to the macro call for each variable for which both descriptive statistics and a p-value are to be presented. If a dataset of descriptive statistics has not been previously created or accompanying descriptive statistics are not desired, the macro will create an output dataset containing only the p-value. This output dataset will be named as defined by the user via the *outdata* parameter.

Keyword parameters *subset* and *poolvar* are optional. *Subset* simply gives the user the opportunity to restrict analysis to a certain subset of subjects. For example, using the sample input dataset in Table 2, the analysis could be restricted to subjects having disp=1. *Poolvar* identifies a variable in the input dataset that will adjust the statistical analysis. For example, the poolinv variable in Table 2 can be used to adjust the analysis by pooled investigative site when needed.

The user must identify a variable for *trtvar* and *depvar* in the macro call. *Trtvar* names the input dataset variable that contains the treatment information for each subject (trt_grp in Table 1), while *depvar* names the input dataset variable to be analyzed (gender or age in Table 1). Recall that only one dependent variable is passed per call of the macro.

The user must identify the specific test to be performed via the keyword parameter *test;* this parameter is not case sensitive. It is incumbent upon the statistician to specify the appropriate test for a given variable, and the programmer to call the macro per those specifications.

The *outvar* macro parameter assigns a variable name to the p-value result. If the p-values for multiple tests are to be presented on one table, it is advantageous to provide the same variable name for *outvar* for each macro call.

EXAMPLE 1

The following macro call creates an output dataset containing descriptive statistics and the p-value result from a Fisher's exact test of gender:

```
%pval(indata=demog,
      outdata=gendrsum,
      subset=,
      poolvar=,
      trtvar=trt_grp,
      depvar=gender,
      test=fisher,
      outvar=p_val)
```

A sample output dataset created by the above macro call is displayed in Table 3. In this case, a SAS dataset of descriptive statistics for gender was created and named gendrsum prior to the %pval macro call, containing the variables type, stat, trt_A, and trt_B shown in Table 3. The %pval macro simply performs the Fisher's exact test and merges the resulting p-value variable with the existing gendrsum dataset.

Table 3. Sample Output SAS Dataset for a Fisher's Exact Test of Gender

obs	type	stat	trt_A	trt_B	p_val
1	Gender				0.4060
2	M	N(%)	20 (63)	21 (75)	
3	F	N(%)	12 (38)	7 (25)	

EXAMPLE 2

The following macro call creates an output dataset containing descriptive statistics and the p-value result from a rank ANOVA test of age:

```
%pval(indata=demog,
      outdata=agesum,
      subset=disp eq 1,
      poolvar=poolinv,
      trtvar=trt_grp,
      depvar=age,
      test=anova,
      outvar=p_val)
```

The output dataset created by the above macro call is displayed in Table 4. In this example, a SAS dataset of descriptive statistics for age was created and named agesum prior to the %pval macro call, containing the variables type, trt_A, and trt_B shown in Table 4. Next the input dataset is subset for subjects with a disposition value of 1. The %pval macro then performs the rank ANOVA test adjusted for pooled investigative site, and merges the resulting p-value variable with the existing agesum dataset.

Table 4. Sample Output SAS Dataset for a Rank ANOVA Test of Age

obs	type	trt_A	trt_B	p_val
1	Age			0.5016
2	N	28	24	
3	Mean	36.9	39.7	
4	Standard Deviation	16.0	14.5	
5	Minimum	18	18	
6	Median	35.5	40.0	
7	Maximum	63	65	

CONCLUSION

The %pval macro certainly simplifies the task of generating and reporting baseline analysis p-values. It centralizes the code from five statistical tests spanning three different SAS procedures into one simple, straightforward macro call. It frees the programmer from dealing with the insidious test-specific and version-specific syntax inherent in programming for these tests. The macro gives the programmer the flexibility to rapidly perform multiple tests, while providing the opportunity to subset the input dataset and adjust the tests for investigative site. The macro also formats the p-values for reporting, and automates the merging of the p-value with the descriptive statistics. Hence, the %pval macro streamlines the production of baseline tables that feature p-values, thus expediting the process and improving programmer productivity.

REFERENCES

International Conference on Harmonisation E3. Guideline on structure and content of clinical study reports. 28 November 1995.

SAS Institute Inc., *SAS® Macro Language: Reference, Version 6, First Edition,* Cary, NC: SAS Institute, Inc., 1997.

SAS Institute Inc., *SAS/STAT® User's Guide, Version 6, Fourth Edition, Volumes 1 and 2,* Cary, NC: SAS Institute, Inc., 1989.

SAS Institute Inc., *SAS/STAT® User's Guide, Version 8,* Cary, NC: SAS Institute, Inc., 1999.

SAS Institute Inc., *SAS® Procedures Guide, Version 6, Third Edition,* Cary, NC; SAS Institute, Inc., 1990.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dawn DuBois for reviewing and editing this paper, and Jacob Boyle for his contributions to the %pval macro.

CONTACT INFORMATION

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

Pete Anderson
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137
Work Phone: 816-767-6416
Email: pete.anderson@quintiles.com

Chris Hord
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137
Work Phone: 816-767-6414
Email: chris.hord@quintiles.com