

A Statistical Analysis Macro Library in SAS®

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ABSTRACT

Statistical analysis plays a major role in pharmaceutical research. The SAS system provides many procedures that perform analysis, nonetheless it is typical to customize a procedure to fit each specific situation. This requires that a new procedure or program be written each time an analysis is performed. However, many types of analyses are programmed similarly, with only minor characteristics differentiating each customized procedure. These characteristics can be parameterized and the procedure abstracted to a macro routine.

This paper discusses a macro library of statistical analysis tools developed by STATPROBE, Inc. The core procedures of the macro tools use PROC FREQ for the analysis of categorical data. The macro tools accept a parameter list that includes input data set names, output data set names, variable identifiers, group identifiers, report titles, test identifier, and test options. This library provides statisticians with a set of tools that allows them to quickly produce analyses without the need to program. Each macro has an easy to use programmer interface based on standardized data set structures. The advantages to using these macro tools are increased efficiency and standardization.

INTRODUCTION

In the field of pharmaceutical research, statistical analysis is critical in formulating conclusions concerning the safety and effectiveness of a experimental product. Many statistical results are obtained using standard analyses. The SAS system provides built in procedures to run typical analytical tests.

This paper describes a macro library of standard analyses based on the SAS system. The macro library frees the statistician from ordinary SAS coding by providing an straightforward method to obtain results. This leaves the statistician unconfined to study the result rather than spending time involved with mundane programming.

The first section describes the types of statistical tests and analyses that are used in the clinical trial setting. The next section describes the macro library usage and the standard data set structures that are used. Each macro requires input data to follow a rather generic standard structure. There are various options in the macro usage to control the macro output, control the fields to be analyzed, and specify test parameters. These options are explained and described with example. The next section contains some explanations of the technical details relating to how the macros are programmed. Some of the design considerations are discussed in this section. The concluding section describes future work planned on the macro library and a SAS/AF user interface to the macro library.

STATISTICAL ANALYSIS

In the pharmaceutical industry, clinical trials are designed to test drugs and medical devices for effectiveness, safety, and optimal dosing regimens. A protocol for the clinical trial, or a model for the study, is written before the trial begins. The protocol defines in detail the type of patients required, the test article to be used, the set of objectives for the study, the time schedule for completing study procedures, the planned statistical analyses, and the data to be collected.

In comparative clinical trials, different dose levels of a test article or multiple treatment groups are compared. This is to determine the most effective and safest dosing regimen. A test drug is also frequently compared to either a placebo, no drug at all, or to a currently accepted drug for the specific indication, such as comparison of a test drug for pain relief to aspirin.

In a randomized clinical trial, patient numbers are defined and randomly assigned to different treatment groups before the study begins. A blinded trial is when the assignment of treatment groups to patient numbers is not disclosed until after the study completion when all patients have either completed or discontinued the study procedures. Investigators that participate in clinical trials typically consist of a group of medical doctors at a number of clinical sites. After a protocol is approved by the FDA, investigators enroll patients meeting the desired inclusion/exclusion criteria and start the study procedures outlined in the protocol. The data is recorded on case report forms or electronic media and put into a data base, where it is reviewed and finalized.

After all data is in a data base and treatment group assignments are disclosed, or the study is unblinded, the statistical analyses that compare characteristics of the treatment groups can be performed and interpreted. There are two basic types of data that statisticians typically analyze: Categorical data and continuous data. Categorical data is data that can be put into a finite number of categories, such as race or gender. Continuous data are data that are not categorized such as weight or age. Note that most continuous data can be categorized into a finite number of groups or ranges. In this paper, analyses of categorical data that can be performed by SAS PROC FREQ are emphasized.

Statistical analyses of categorical data can answer questions like:

- Are there statistically significant differences in the number of female patients between treatment groups?
- When separating patients into two categories by gender, are there any statistically significant differences between treatment groups with regards to race in either gender category?
- When looking at parameters that assess the effectiveness of the test article, are there statistically significant differences between treatment groups, is one treatment

more effective than the other(s), or are all the treatments of equal effectiveness?

- When looking at parameters that assess the safety of the test article, are there statistically significant differences between treatment groups, is one treatment safer than the other(s), or with regards to safety are all the treatments the same?

When doing categorical statistical analyses, the statistician is looking for statistically significant differences in characteristics between treatment groups. Based on standard statistical theory, a statistical test is chosen considering the question posed, the design of the study, and the type of data available. A value is calculated, called a probability value (or p-value), which is compared to a significance level called alpha. If the p-value calculated from the statistic is less than or equal to alpha then there is a statistically significant difference between treatment groups. Commonly used values for alpha are 0.05 and 0.1.

Some of the most commonly used statistical tests in the pharmaceutical industry for categorical data analysis are the Fisher's Exact Test, the chi-square statistics, and the Cochran-Mantel-Haenszel statistics. These tests are regularly used to detect differences in characteristics between treatment groups and are invaluable when analyzing categorical baseline characteristics, efficacy results, and safety results. These tests include nonparametric as well as parametric tests. Parametric statistical methods assume that samples are drawn from populations with known probability distributions. Nonparametric statistical methods assume only that the treatment assignments are random.

Fisher's Exact Test is a nonparametric test for comparing independent samples of categorical data. This test is useful for small sample sizes. Fisher's Exact two-tailed statistic tests whether or not the proportion of observations with a certain characteristic is the same across two or more treatment groups. The left-tailed or right-tailed Fisher's Exact statistic is used for 2x2 tables only, and it tests whether or not the proportion of observations with a certain characteristic in one treatment group is less than or the equal to the proportion in the other treatment group.

The Pearson chi-square statistic, the continuity-adjusted chi-square statistic, the likelihood-ratio chi-square statistic, and the Mantel-Haenszel chi-square statistic are parametric tests for comparing independent samples of categorical data. The Pearson chi-square statistic tests for differences between proportions. The continuity adjusted chi-square test, for 2x2 tables only, is very similar to the Pearson chi-square test and is used for small sample sizes. The likelihood-ratio chi-square test tests for general association. The Mantel-Haenszel chi-square statistic tests for linear association; this statistic is only appropriate when variables are ordinal. If the too many cells have an expected count of less than five the chi-square tests may not be valid.

There are three Cochran-Mantel-Haenszel (CMH) test statistics: the nonzero correlation statistic, the general association statistic, and the row mean scores differ statistic. These statistics are used to assesses the association between two characteristics, A and B, while controlling for a specified stratum. The CMH statistics are based on scores. There are four basic types of scores to choose from: Table scores, rank scores, ridit scores, and modified ridit scores. Table scores give parametric analyses. Rank, ridit, and modified ridit scores give nonparametric analyses. The nonzero correlation statistic, also called the Mantel-Haenszel statistic, is a one

degree of freedom test of linear association where at least one of A and B characteristics must be ordinal for the statistic to be interpretable. The general association statistic uses nominal data and is also a test for association between A and B within stratum. The row mean scores differ statistic, also known as the ANOVA statistic, uses A and B, one as ordinal and one as nominal. When there is only one stratum the row mean scores differ statistic is equivalent to the Kruskal-Wallis statistic, when using nonparametric scores, and the one-way ANOVA, when using parametric scores.

USING THE MACRO LIBRARY

The production version of the macro library has five statistical macros available. Table 1 describes the macro names and purpose.

Macro Name	Purpose
EXACT	Fisher's Exact Tests
CHISQ	chi-square tests
CMH	Cochran-Mantel-Haenszel tests
ALL	Calculates all the statistics of the three previous macros
COUNT	calculates a contingency table

Table 1. Description of macro library

The output from any one of these macros can be either the standard SAS generated output, a data set containing the numbers output by the standard SAS generated output, or both. The macros can also give a general interpretation of the statistical test.

Table 2 details the parameters used in the macros. Not all parameters are needed in each macro. The next section on programming the macro library describes in more detail the parameters used in each macro.

Parameter	Parameter Description
data	Input data set name. The default input data set name is <i>data</i> .
output	Output data set name for statistics. The default output data set name is <i>output</i> .
cmhscore	Type of scores. The default is null.
byvars	By variables, parameter(s) to create subgroups for analysis. The default is null.
tables	The parameters to be analyzed and put into contingency tables separated by an asterisk (*).
weight	Parameter to weight observations in the data set by. The default is null.
print	Print output from SAS generated FREQ procedure. Possible values are YES or NO. The default is NO.
report	Print report. Possible values are YES or NO. The default is YES report.
title1	Text for the first title. The default text is dependent on the macro.
title2	Text for the second title. The default text is "REPORT OF RESULTS".
explain	Print out a general interpretation. Possible values are YES or NO. The default is YES.
alpha	Statistical significance level to compare the p-values to for the explanation. The default is 0.05.

Table 2. List of macro parameters

A typical data set structure to run the macros on would have one record per patient and contain fields corresponding to investigator, treatment group, and patient number. In addition, there would be demographics fields like gender, race, and age. Other possible fields might include an initial diagnosis, descriptions about medical history and other study specific fields. The macros are written in a completely generic manner, therefore the names of the data set variables do not effect the macro execution.

```

      CHI-SQUARE TEST
      REPORT OF RESULTS

      P-value
      for
      Chi-Square

      0.36281

      The p-value 0.362806 for the Pearson Chi-Square test is not
      statistically significant for alpha = .05
  
```

Diagram 1. Partial output from the CHISQ macro

Diagram 1 shows partial output from the CHISQ macro. The entire output is quite long and not appropriate for display in this paper, however diagram 1 shows how the interpretive text appears as a footnote in the macro report.

PROGRAMMING THE MACRO LIBRARY

The macro library consists of five high level macros for users of the library and one core macro that performs the PROC FREQ. Users are encouraged to use the high level macros because these macros have reporting and interpretive capability. However, users also have access to the core macro.

The system was designed with five high level macros to supply the user with five options. The options are to run no test and simply compute crosstabulation tables, run one of three possible tests, or run all three tests. Each of the five macros run the core macro first and then do additional processing. The core macro, `do_test`, is displayed in diagram 2.

The macro `do_test` has ten key-word parameters, six of which are defaulted to null. The default values for the parameters `data` and `output` are 'data' and 'output', respectively. The default parameter for `test` is 'NONE'. This is the case that where only crosstabulation tables are generated. The default for the `print` parameter is 'NO', which would suppress printing the output from the PROC FREQ.

The `do_test` macro first sets titles using the `title1` and `title2` parameters. We have found in most cases that two titles are sufficient for reports generated, however should the need arise, it would be easy to support additional titles. As the core procedure continues to execute, it runs a PROC FREQ. Different code is conditionally executed based on the values of various macro parameters. The macro ends by resetting the titles.

```

%Macro do_test( data = data,
               output = output,
               test = NONE,
               scores = ,
               byvars = ,
               tables = ,
               weight = ,
               print = NO,
               title1 = ,
               title2 = );

  Title;
  Title1 "&title1";
  Title2 "&title2";

  Proc freq data = &data
    %If %upcase(&print) = NO %then %do;
      noprint
    %End;
  ;
  %If &byvars^ = %then %do;
    By &byvars;
  %End;
  Tables &tables
  %If %upcase(&test)^ = NONE %then %do;
    /
    %If &scores^ = %then %do;
      scores = &scores
    %End;
    &test
    %If &weight^ = %then %do;
      Weight &weight;
    %End;
  %End;
  ;
  %If &output^ = %then %do;
    Output out = &output &test;
  %End;
Run;
Title;
%Mend do_test;
  
```

Diagram 2. Core procedure for the macro library

The higher level macros execute the core procedure then perform optional processing to report and interpret the results. Diagram 3 shows the code for the exact macro.

After the `do_test` macro is invoked, the values of the report and output macro are checked to determine if the user wants a report. A report is generated if the value of `report` is YES and the value of `output` is not null. To generate a report, first the titles are assigned using the parameters `title1` and `title2`. The next step is to run PROC REPORT on the output data set from the `do_test` macro invocation. The report results for the exact macro is an uncomplicated summary of the p-values for the statistics.

The final section of the exact macro interprets the statistics. If the value of `explain` is YES and the value of `output` is not null, the macro will attempt to interpret the p-value. The first step in this section is to run PROC SQL and store the p-value in the local macro variable `pvalue`. The PROC SQL also compares the p-value to alpha and sets the text string stored in the local macro variable `signif` to 'is' for the significant case and 'is not' for the insignificant case. This text is used in an interpretive footnote statement.

```

%Macro exact( data = data,
              output = output,
              byvars = ,
              tables = ,
              weight = ,
              print = NO,
              report = YES,
              title1 = FISHERS EXACT TEST,
              title2 = REPORT OF RESULTS,
              explain = YES,
              alpha = .05);

%do _test(data = &data,
          output = &output,
          test = EXACT,
          byvars = &byvars,
          tables = &tables,
          weight = &weight,
          print = &print,
          title1 = &title1,
          title2 = &title2);

%If %upcase(&report) = YES and &output^ = %then %do;
  Title;
  Title1 "&title1";
  Title2 "&title2";

  Proc print data = &output label noobs;
  Run;
  Title;
%End;

%If %upcase(&explain) = YES and
&output^ = %then %do;
  %Local signif pvalue;
  Proc sql noprint;
  Select p_exact2 into:pvalue
  From &output;
  Select
    case
      when p_exact2 <= &alpha then 'is'
      else 'is not'
    end into:signif
  From &output;
  Quit;
%If &pvalue^ = . %then %do;
  Title;
  Title1 "&title1";
  Title2 "&title2";
  Footnote "The p-value &pvalue for the Fisher's Exact
  test %trim(&signif) statistically significant for
  alpha = &alpha";

  Proc report data = &output nowd;

  Run;
  Title;
  Footnote;
%End;
%Else
%Put WARNING: No statistics were calculated for test.;
%End;
%Mend exact;

```

Diagram 3. Code for the exact macro

The other macros in the system process in a similar manner and the complete code for these macros is not included here

for the sake of brevity. However, diagram 3 displays the macro declaration for the other macros.

```

%Macro chisq( data = data,
              output = output,
              byvars = ,
              tables = ,
              weight = ,
              print = NO,
              report = YES,
              title1 = CHI-SQUARE TEST,
              title2 = REPORT OF RESULTS,
              explain = YES,
              alpha = .05);

%Macro cmh( data = data,
             output = output,
             cmhscore = ,
             byvars = ,
             tables = ,
             weight = ,
             print = NO,
             report = YES,
             title1 = COCHRAN-MANTEL-HAENSZEL
             STATISTICS,
             title2 = REPORT OF RESULTS,
             explain = YES,
             alpha = .05);

%Macro all( data = data,
             output = output,
             cmhscore = ,
             byvars = ,
             tables = ,
             weight = ,
             print = NO,
             report = YES,
             title1 = ALL AVAILABLE TESTS,
             title2 = REPORT OF RESULTS,
             explain = YES,
             alpha = .05);

%Macro count( data = data,
               output = output,
               byvars = ,
               tables = ,
               weight = ,
               print = NO,
               report = YES,
               title1 = CROSSTABULATION TABLES,
               title2 = REPORT OF RESULTS);

```

Diagram 4. Declarations of other macros

The macros each have a different default value for the title1 parameter. There are some minor differences in parameter lists, nevertheless the basic processing is similar for each of the macros.

CONCLUSION

A macro library for statistical analysis can be a valuable tool for the statistician. Using the macro library promotes standardization and liberates the statistician from needing to know the proper rules and syntax for the low-level code.

As we continue to develop this macro library, we will add a set of macro tools based on PROC GLM to perform analysis of variance and regression. We also plan to develop macro tools

to perform pharmacokinetic analysis. After a broad set of tools have been developed, the next step will be to build a SAS/AF interface to the macro library. The user interface will further remove the statistician from the low level code, allowing them to concentrate their efforts on analysis rather than programming.

REFERENCES

SAS Institute, Inc. (1990), *SAS Procedures Guide, Version 6, Third Edition*, Cary, NC: SAS Institute Inc.

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