Paper 250-27

SAS® Tools for Meta-Analysis

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ABSTRACT

This paper discusses meta-analysis, enumerates the circumstances under which it might or might not be appropriate, and mentions some SAS® tools which can be used for meta-analysis.

INTRODUCTION

Meta-Analysis has become increasingly popular in medicine, education, psychology and other social sciences, marketing and other business applications, and many other areas. Unfortunately, meta-analysis is probably used badly and without sufficient thought and care at least as much as it is used carefully and appropriately.

I never meta-analysis I liked

The above statement may possibly be an exaggeration. However, more thought, care, and expertise should go into most meta-analyses than usually does. Moreover meta-analyses by substantive experts without substantial collaboration by statisticians and experts in meta-analysis tends to produce questionable results. In this paper, we address the following issues:

1. What is a meta-analysis?
2. Why do a meta-analysis?
3. Who should do a meta-analysis?
4. How is a meta-analysis done?
5. When is a meta-analysis appropriate?
6. Where are tools available to do a meta-analysis?
7. Examples
8. Discussion

We have included an extensive bibliography at the end of this paper, in addition to a list of specific references.

WHAT IS A META-ANALYSIS?

Meta-analysis was invented by Eugene Glass (although he claims that this may be an historical accident), and has been characterized by him as a statistical analysis of statistical analyses. The New York Times in 1999 stated, "A meta-analysis aims at gleaning more information from existing data by pooling the results of smaller studies and applying one or more statistical techniques. The benefits or hazards that may not be detected in small studies can be found in meta-analysis that uses data from thousands of studies."

Rarely would we ever have *thousands* of studies, and there are many judgments and decisions along the way that need to be made while doing a meta-analysis, which influence the outcome and interpretation.

META-ANALYSIS FOR TWO TREATMENTS AND BINARY OUTCOME (WHEN YOU HAVE THE DATA)

Statistically, the simplest and most straightforward meta-analysis could be done if you had data from several studies, which contained exactly the same two groups or treatments, administered under exactly the same conditions, and you had a binary response variable. For example, the FDA generally requires at least *two* successful clinical trials to approve a new medication. It is not unknown for a pharmaceutical company to conduct a large clinical trial, at multiple centers or sites, and then randomly assign the centers to "Trial 1," and "Trial 2," before looking at the data. The pharmaceutical company now has two identical clinical trials, run under the same protocol, with the same outcome variable. (We will ignore the center or site effect for the moment.)

The advantage of the binary response variable is that the results are generally presented in articles as tables, and if you think carefully about it, if you have these tables, you can recover the observations (the tables are sufficient statistics).

Under such conditions, there are many well-known techniques for integrating such studies. One is the Mantel-Hanszel statistic. (Others would include calculating Chi-Squared statistics separately for each study and making use of the additivity of independent Chi-Squares to construct a global test, or to fit a logistic regression model with "study" as an effect, and examine the treatment effect in the context of that model.)

For example, suppose there are exactly two studies in the literature that test exactly the same hypothesis, under exactly the same conditions, with exactly the same outcome variable, and the papers contain tables of treatment and outcome (P and D are Placebo and Drug, and R and N are Remitted and Not remitted):

Study 1

	R	N	
P	24	3	27
D	58	30	88
	82	33	125

OR=4.14, χ^2=5.32

Study 2

	R	N	
P	16	57	73
D	2	10	12
	18	67	85

OR=1.40, χ^2=0.17

For each study, we have an odds ratio, which is a measure of the extent of the relationship, and we have a Chi-Squared test, which tests the null hypothesis that the distribution of responders is the same under the two treatments. We would like to integrate these results into one estimate of a common odds ratio, and perform one hypothesis test, using information from both studies.

If we were simply to lump the data together, we observe the following table:

Combined Studies

	R	N
P	40	60
D	60	40

OR=0.44, χ^2=8.00

Our estimated "lumped" odds ratio is 0.44, and our Chi-Squared test produces a Chi-Squared statistic of 8.00, which would lead to rejection of the null hypothesis. This is probably a wrong analysis. It assumes there is not treatment-by-study interaction, and that the response rates are the same in both studies.

The Mantel-Haenszel estimator of the common odds ratio estimates an odds ratio assumed to be homogeneous among both studies, and the Mantel-Haenszel test statistic tests the null hypothesis that the response rate is the same for the two treatments, after adjusting for possible differences in study response rates. In this case, our Mantel-Haenszel estimator of the common odds ratio is 2.85, and our Mantel-Haenszel test statistic is 4.65, which would lead to rejection of the null hypothesis. With categorical data and the same treatments in each study, we may extend these techniques to more than two treatments, and a categorical response with more than two outcomes.

The SAS® code required to produce this analysis would be:

```
Proc freq data=bothdata;
  Table study*response*trt / cmh;
  Weight cellfreq;
Run;
```

This assumes that the data are stored one SAS® observation per cell, and a variable called *cellfreq* contains the number of observations per cell. (Mantel and Haenszel produced many statistical tests in their careers, and this one, in FREQ, is called the Cochran-Mantel-Haenszel test, and is obtained with the CMH option.)

As we stated earlier, this is not the only potential meta-analysis for this situation. One could use the additivity of independent Chi-Squared statistics to construct a Chi-Squared statistic based on all the studies. One could fit a logistic regression model, with study as an effect, using these data. This has the advantage of using a model to which other information, such as covariates, could be added if available. If one wanted to treat the study as a random effect, one could fit mixed logistic regression models using SAS® procedures such as NLMIXED and SAS® macros such as %GLIMMIX.

Note that this was a **m**eta-**a**nalysis with the **d**ata (MAD), as opposed to a **m**eta-**a**nalysis from the **l**iterature (MAL), which would usually mean that one did not have the data, but had only the summary statistics presented in the articles.

META-ANALYSIS FOR CONTINUOUS VARIABLES (WHEN NORMAL-THEORY CONDITIONS ARE MET) (WHEN YOU HAVE THE DATA)

Suppose we have the same situation, except that the response variable is continuous, and we are willing to make normal-theory assumptions and use the Analysis of Variance (ANOVA) for analysis. That is, suppose we have in the literature two identical studies, following the same protocol, using the same treatments, using the same response variable, and suppose once again that we can obtain the data. We could then fit a mixed model (if we wanted to treat study as a random effect), using PROC MIXED, or an ANOVA model (if we wanted to treat study as a fixed effect), using PROC GLM.. Consider the following data from two studies:

	Study 1				Study 2		
Rx	n	Mean	Std	Rx	n	Mean	Std
D	40	15.45	8.74	D	40	13.50	9.82
P	40	13.03	10.38	P	40	9.08	10.40

If we were to examine the data for these two separately, we would observe the following results:

Study 1	Study 2
F(1,78) = 1.28, P < 0.2619	F(1,78) = 3.83, P < 0.0539

We can combine the data from both studies (160 observations in total) and obtain combined means and standard deviations:

	Combined Studies		
Rx	n	Mean	Std
D	80	14.475	9.289
P	80	11.055	10.514

We can fit a mixed model, with study as a random effect, using SAS® PROC MIXED:

```
Proc mixed data=whatever;
  Class trt study;
  Model response=trt;
  Random study;
  Lsmeans trt;
Run;
```

The results of the hypothesis test produced by this analysis are F(1,157)=4.85, P < 0.0292.

Note that in this case (because we made up the data that way) in each of the individual studies we failed to reject the null hypothesis of no difference between treatment means, while in the meta-analysis, we rejected the null hypothesis. That probably resulted from both the fact that with the studies combined we had more error degrees of freedom, as well as the fact that we adjusted for the study effect.

WHAT ABOUT DOING A META-ANALYSIS WHEN YOU DON'T HAVE THE DATA?

Suppose we have the same situations, except that the articles we're reading about the studies are all we have. We do not have the raw data. Let's suppose that the articles contain the cell frequencies (if we have a categorical response) , or contain sample sizes, means, standard deviations (if we have a continuous response). As stated earlier, for a categorical response, the raw data are recoverable from the tables, so we won't discuss categorical data further here. (If you don't have the tables, but have sample sizes, and either odds ratios or relative risks, you can recover the data.) For continuous data, the sample sizes, means, and standard deviations are a set of sufficient statistics, from which we can calculate everything we need to obtain the analysis above.

WHY DO A META-ANALYSIS?

We perform meta-analyses because we often have a lot of information, from many studies, sometimes contradictory, and meta-analysis offers us *a tool* to help us integrate this. However, we should always remember that meta-analysis is only a tool, and it is simply one of many tools we use to help us understand what a literature is trying to tell us, if anything.

A meta-analysis may increase statistical power, resolve uncertainty, improve estimates of effect size, and may in fact be able to address questions not posed when the studies were designed. However, a meta-analysis is only as good as the studies that it comprise it, and as good as the many decisions that were made when designing and performing the meta-analysis, such as which studies to include, whether and how to assess quality of the studies, the measure(s) of effect, and the

ability of the meta-analysts to understand both the statistical, substantive, and methodological issues both in the original studies and in the meta-analysis. *Further, as new studies become available, meta-analyses need frequent updating.* A meta-analysis containing only old information may not be very useful.

WHO SHOULD DO A META-ANALYSIS?

The team which does a meta-analysis needs to include persons with expertise in the substantive area, research methods used for the research included in the meta-analysis, statistics used in such studies, and meta-analysis methodology. Sometimes several of these may in fact be the same person. For example, in a meta-analysis of psychiatry clinical trials of novel antipsychotics, it may be that the team member who knows the substantive area (a psychiatrist) and who knows research methods in that area (a psychiatric clinical trials researcher) may in fact be the same person.

HOW IS A META-ANALYSIS DONE?

The following has been attributed to Mark Twain, and also to Bismarck: "There are two things you should never watch being made. The law, and sausage." Perhaps meta-analysis should be added to the list. We illustrated two meta-analyses using original data earlier in this paper, illustrating the statistical aspects of performing a meta-analysis, but there is a great deal to performing meta-analyses than that. There are generally at least 7 steps to performing a meta-analysis:

1. Decide on the topic.
2. Decide on the hypothesis being tested.
3. Review the literature for all studies which test that hypothesis. While this literature review may begin with a computerized search of the literature, such searches may miss important studies. Therefore other methods, such as careful study of the references in articles, examination of papers, abstracts, and presentations not published, and other sources of unpublished (including government agencies, and rejected submissions). This needs to be done carefully to minimize bias.
4. Evaluate each study carefully, to decide whether it is of sufficient quality to be worthy of inclusion, and whether it includes sufficient information to be included. This includes attention to endpoints, choice of the measure of effect size, and other information about quality. This task, too, needs to be done carefully to minimize bias.
5. Create a database containing the information necessary for the analyses.
6. Perform the meta-analysis
7. Interpret the results.

We will discuss each of these separately.

DECIDE ON A TOPIC

Generally, a topic which might be appropriate is one for which the question is clearly focused, for which literature is available, and is of some importance. The research question should be focused, and you should consider beforehand the criteria you will use to include and exclude studies.

DECIDE ON THE HYPOTHESIS TO BE TESTED

This should probably be done in concert with deciding on a topic. One would not want to decide on a topic if there is no reasonable hypothesis that could be tested using the existing studies. It is difficult to decide which is the chicken and which is the egg.

REVIEW THE LITERATURE

A good meta-analysis should begin with a good review of the literature. You should make an effort to obtain studies from all sources, such as the published literature, unpublished literature, presentations, non-public sources, etc., to attempt to minimize bias.

EVALUATE THE STUDIES

The meta-analysis you do is no better than the choice of the studies that comprise it. Each study should pass some minimal pre-set requirements, and a careful assessment of the quality of the study should be made. A check-list and form on which you can record such information is sometimes helpful, and you could well use a spreadsheet for this recording tool, so that this check-list may actually become the database. You should attend to assessment of the heterogeneity of the studies, and any important cofounders. You should record something about the treatment methods, so you can judge ultimately how to include a relatively homogeneous set of studies (if that is what you desire) in your analyses. Many studies will use similar but not identical endpoints, and you have to translate them into some common measure of effect size, along with a measure of precision, and a sample size.

For continuous endpoints, that usually means differences between means expressed in standard deviation units, and sample sizes. For binary endpoints, that usually means odds ratios, or relative risks. In the medical meta-analysis literature, a measure sometimes used is the "number needed to treat," or NNT, which is the number of patients needed to be treated to prevent an additional adverse event, or for one additional patient to benefit. (This is the reciprocal of the absolute risk reduction.)

One object of this activity is to reduce bias, which could result from publication bias (the probability of publication may be higher for a positive study than for a negative study) Studies which have been published multiple times may be more likely to be discovered, and worse, it may not be obvious that several different articles may in fact all come from the same study. Several "studies" may share a control group, and that may not be obvious. Studies done published in languages other than English may be less likely to be found. Unpublished data may help reduce this bias. Bias may also result from the manner in which subjects were recruited or ascertained, inclusion or exclusion criteria, or confounding. Trials which are observational may be more subject to bias than experimental trials. There are diagnostic tools, such as funnel plots, and funnel plot regression, which may aid in discovering bias.

Quality may be variable among studies. A study with a large sample size is, all other things being equal, of higher quality because, all other things being equal, measures are more precise, and power is higher. An evaluator who knows the area, knows the literature, and knows the methodology used in the research may be able to make judgments about quality. How one deals with quality issues is another affair. Most meta-analyses, unfortunately, choose to ignore quality (aside from any quality judgments that enter into whether to include the study in the meta-analysis). Another possibility (not done frequently enough) is to weight the analysis by some measure of quality. Sample size is most often used as a weight, but there are many other things besides sample size which affect quality, and some judgment of quality may be better than no judgment. One can attempt to predict effect size from quality measures (using measures such as regression) in an attempt to judge whether the variation in quality appears to be affecting the results. Plots are often helpful.

CREATE A DATABASE

Many meta-analysis tools include a form that can be handy to use to record information about the studies. Some of these are incorporated directly into the software. For use with SAS®, it is

often useful to simply make a spreadsheet where the columns include the information abstracted from each study. This spreadsheet may be able to become the database, or it may be useful in organizing and decision making prior to making a database.

PERFORM THE META-ANALYSIS

We have illustrated several simple meta-analyses earlier. It is customary in meta-analyses to report effect size estimates (and confidence intervals) for all studies included, and a pooled effect size and confidence interval

INTERPRET THE RESULTS

A meta-analysis is simply evidence you may use in your attempt to integrate results from multiple studies. It is not the final word. You should evaluate how well the studies met the assumptions necessary for the meta-analysis. You should evaluate whether the studies were homogeneous or heterogeneous. Meta-analyses with heterogeneous studies are harder to interpret. We cannot emphasize sufficiently that after a meta-analysis is done, one simply has one more piece of evidence, which when integrated with other evidence, may help you decide whether you can discern something.

ISSUES IN META-ANALYSIS

1. It is a rare occurrence when all studies use the same endpoint. It is therefore necessary to examine the endpoints and determine whether they are comparable enough that it is reasonable to assume they are testing "the same" hypothesis.
2. It is a rare occurance when all studies use very similar designs. It is therefore necessary to examine the designs and determine whether they are sufficiently similar that it is reasonable to assume they are testing "the same" hypothesis. One would like to have a variety of different types of studies, all of which test similar hypotheses, so that the results of the meta-analysis are generalizable. However, if the studies are too dissimilar, the meta-analysis may be combining apples and oranges, rather than different types of oranges.
3. Studies may be dissimilar (heterogeneous).
4. Positive studies are more likely to be published. This publication bias can lead to a selection bias in the studies included in the meta-analysis. Careful searching of sources other than simply publications may reduce this selection bias, and tools such as funnel plots may aid in learning whether such bias may exist. However, this remains a difficult-to-solve issue.
5. Studies may differ widely in quality. The most obvious case of this is when studies differ grossly with respect to the number of experimental units, or subjects. All other considerations being equal, a study with more experimental units will be of higher quality, because estimates will be more precise, and hypothesis tests will be more powerful. It is possible to weight studies by sample size in a meta-analysis. However, there are many other ways in which studies can differ with respect to quality, and studies with the same sample size can range in quality from low to high. It is possible to assign quality scores to studies, and weight the meta-analysis using such quality scores, but such use is not without controversy. Restriction of the studies in a meta-analysis to only "high quality" studies may introduce bias.
6. It may be there are important confounders which could be used for stratification purposes. However, it is unlikely that all studies will use such confounders, and unlikely that sufficient information will be reported to use them in the meta-analysis. Restriction to only the studies using these confounders may introduce bias.
7. One must make a decision whether to treat the study as a fixed or random effect. Treating study as a fixed effect takes the position that these particular studies are the only studies to which you wish to generalize, and that other studies are not of interest. Treating study as a random effect assumes that these studies are a sample from all possible similar studies, and you wish to be able to generalize to the larger population. Most meta-analysis probably treat studies as a fixed effect because (a) only recently has software become available which enables treatment of study as a random effect, and (b) treatment of study as a random effect often makes it more difficult to reject the null hypothesis, and thus, more difficult to get your meta-analysis published.
8. Many clinical trials are multi-center trials, that is, the trials include a random blocking factor corresponding to the multiple sites at which the trial was conducted. Usually, each site or center contains experimental units randomized to all treatments, and thus, the study is replicated within centers. Usually, one would treat center as a random effect. Rarely do articles or other published and unpublished material include sufficient summary statistics on a per-center basis such that one could insert center as an effect in a meta-analysis of multi-center trials. This is a potential source of bias, in that center is a confounder for which the meta-analysis is thus not adjusted.
9. Meta-analysis assumes that the studies are independent of each other, although if the covariance structure among studies were known, it could be modeled. Nearly all meta-analysis software of which we're aware make that assumption. There may be hidden dependencies among studies. For example, in the medical literature, it is unfortunately not uncommon for the same data to be published multiple times. An investigator may start a study, and after a year or two have gone by recruiting subjects and collecting data, may analyze the data and publish the results. He or she may continue recruiting subjects and gathering data, and a year or two later, may analyze the data (including the data that were the basis of the previous publication) and publish that. The literature now appears to have two studies, and two sets of results, but the data in the second contain the data in the first. Another variation on the lack of independence might result if an investigator performs a study randomly assigning subjects to one of three groups: placebo, drug A, and drug B. He or she may then publish a paper comparing drug A to placebo, and publish another paper comparing drug B to placebo, with no indication that the placebo groups in both studies are in fact the same subjects. Another variation on hidden lack of independence of studies might occur if the investigator has several measures, all of which measure the same thing, imperfectly, and he or she publishes a paper on each of them. It is often difficult-to-impossible to detect these sorts of dependencies solely from the literature without being intimately familiar with the players involved.

WHEN IS A META-ANALYSIS APPROPRIATE?

A meta-analysis is appropriate whenever you have multiple studies which test the same or similar hypotheses, and the joint results of the studies do not clearly indicate the results of the test. A meta-analysis is appropriate when you have numerous contradictory studies. A meta-analysis is appropriate when trying to review a complex literature. However, the studies involved need to contain sufficient information for the meta-analysis to be meaningful, and for the meta-analyst to evaluate the assumptions properly.

WHERE ARE TOOLS AVAILABLE TO DO A META-ANALYSIS?

There is a great deal of software available for meta-analysis. We will not discuss standalone software in this paper. As illustrated

earlier, if you have the original data from multiple studies, it is straightforward to use existing SAS® procedures to analyze the combined data using Mantel-Haenszel statistics, mixed linear and nonlinear models, or generalized mixed models. If one has appropriate summary statistics, one could even analyze multiple studies by generating datasets that match the sufficient statistics, and using SAS® procedures to analylze the resulting data. There are several SAS® macros that have been written to perform meta-analysis using SAS®. Kuss and Koch (1996) have written a set of SAS macros for meta-analysis of binary data using SAS®, including both fixed and random effect models. Although these macros concentrate on binary outcome measures, several of the plotting macros can also be used for continuous measures. Wang and Bushman (1999) have written a book describing the use of SAS®for meta-analysis. Diamakos (1996) presented a flexible macro to do data analysis in SAS®, and Michael Friendly of York University has modified it to be more flexible. It can use a wide variety of effect sizes, and is appropriate for both continuous and binary data.

EXAMPLES

Examples were given in the presentation.

DISCUSSION AND CONCLUSION

Meta-analysis can be a useful tool, but it is only a tool. SAS® is well equipped to perform meta-analyses, through existing procedures and via existing macros. Perhaps it is true that meta-analysis is truly like the law and sausage

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