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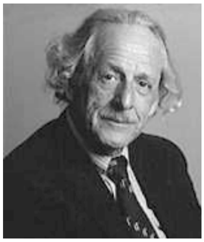

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Meta-analysis and the Metamorphosis of the Scientific Literature Review

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Diving into the subject of meta-analysis reminds me of windsurfing—one sails off on a brisk wind in one direction, but there is no guarantee you will return to your point of departure. In the last few years, particularly in the field of medicine and the social sciences, this statistical technique has been used to gather and analyze small deviations from many studies of the same subject. These small deviations, which in and of themselves may not be significant, can, when combined, reveal important scientific connections from which new research conclusions can be drawn. Thus, meta-analysis presumably advances the traditional method of assessing results in a given field—the review article.[1]

The general idea of meta-analysis dates back to at least the 1930s and perhaps even earlier. However, the word itself was first coined in 1976, by Gene Glass of the University of Arizona, to describe his studies of psychotherapy and education.[2] Since then there have been numerous books on the subject, among them Glass, B. McGaw, and M.L. Smith (1981),[3] J.E. Hunter, F.L. Schmidt, and G.B. Jackson (1982),[4] H.M. Cooper (1982),[5] R.J. Light and D.B. Pillemer (1984),[6] R. Rosenthal (1984),[7] F.M. Wolf (1986),[8] and K.W. Wachter and M.L. Straf (1990).[9]

Wave of the Future

Thomas Chalmers, a former president of Mount Sinai Hospital who is now at the Harvard School of Public Health, has called meta-analysis "the wave of the future." He asserts that "the days of the [traditional] review article are numbered."[10] Reprinted below is an article[11] by Steven N. Goodman, associate editor of the *Annals of Internal Medicine* and assistant professor of oncology and epidemiology at the Johns Hopkins School of Medicine, explaining the complexities involved in conducting a meta-analysis. He welcomes meta-analyses to his journal, but only if conducted with the necessary rigor.

Gene Glass

One example of the effects of meta-analyses is contained in a 1989 British report called *Preventive Care in Pregnancy and Childbirth*. This two-volume, 1,516-page collection reviews more than 3,000 randomly controlled clinical trials in perinatal medicine. The report's conclusions reject routine procedures such as episiotomy (cutting the tissue between the vagina and anus to facilitate delivery), restricting weight gain during pregnancy (to prevent hypertension), and repeating cesarean sections routinely after a woman has had one.[10] The study also endorses some neglected practices, such as vacuum extractions (rather than forceps), the use of corticosteroids for women delivering prematurely, and external turning for breech births.

While some hailed the work as the most important publication in obstetrics since 1752, others called its authors "an obstetrical Baader-Meinhof gang," a reference to the West German terrorist group of the Cold War era.

Any new system that challenges cherished beliefs is bound to have its detractors. Opponents of meta-analysis point to flawed online databases as a big impediment. The flaws range from biased data to significant omissions. Another objection involves choosing which studies to include in a meta-analysis. Still another is the fear of some scientists that the technique encourages further the practice of publishing only experiments reporting positive results. Thus, "no-effect," or negative studies, are excluded.

Six Major Steps to a Meta-Analysis

Joseph A. Durlak of the Psychology Department at Loyola University, Chicago, and Mark W. Lipsey of Claremont Graduate School have published recently *A practitioner's guide to meta-analysis.*[12] In this useful document, they list the six major steps necessary in a meta-analysis and also summarize the issues most important at each step (Table 1). They describe each step in a meta-analysis as a link in a chain—with the finished product only as strong as its weakest link.

The guide states:

> For example, well-formulated research questions derived from careful scrutiny of past studies are important to launch the meta-analysis, but this step can be subverted unless a representative and nonbiased literature search is conducted. Similarly, the virtues of an effective literature search are negated if coding procedures are insufficient to capture the essence of research reports or if inappropriate statistical techniques are applied to the data. Therefore, each and every aspect of the meta-analysis is important.

The authors recommend using four search strategies in any meta-analysis: manual journal searches, examination of reference lists from reviews and identified studies, computer and manual searches of abstracting and indexing databases, and contact with persons or organizations likely to have produced or to know of studies.

The authors caution:

> Computerized searches, e.g., through [online] databases, are notoriously unreliable as a means of identifying relevant literature, especially if the research topic is broad, e.g., psychotherapy, early intervention, prevention. For instance, Weisz, Weiss, Alicke, and Klotz (1987) used 21 key word terms in their computerized search for child and adolescent psychotherapy studies and obtained 1,324 citations. Ultimately, only 108 studies were included in the meta-analysis, however, and only a portion of these had been identified by the computer search procedure. We discovered (Durlak, Lampman, & Wells, 1991) that only one of three entries appearing in our computer-generated study lists was relevant and approximately two-thirds of the relevant studies were not picked up via the computer search. In short, [traditional] computer searches tend to produce high numbers of false positives (irrelevant studies found) and an untold number of false negatives (relevant studies missed) depending on the area reviewed.

The authors add that despite their limitations, however, "computer database searches do identify studies that are likely to be missed by other procedures and thus must be included in any comprehensive search strategy."

We asked Durlak to clarify his statement about online databases being "notoriously unreliable." He informed us that this statement was not an indictment of any particular database. Rather, he indicated the problem is the lack of any standardized keyword system to code studies entering a database. As a result, studies of the same topic can be coded differently not only across but also within databases. This makes it difficult for researchers relying on natural language alone to ensure they have captured all the relevant literature. I won't digress here to explain how ISI®'s databases augment searches through bibliographic coupling, etc.

Table 1: Major steps in a meta-analysis and important issues relevant at each step.

1. Formulating the research question(s)
   (a) Are specific research questions, formal hypotheses or the major variables of importance made explicit? Do such formulations rest upon prior work in the area?
   (b) Is the literature to be reviewed fully defined? Does the definition capture the important literature in the field?
   (c) Are both inclusionary and exclusionary criteria presented and are such criteria reasonable?
2. Literature search
   (a) Is a representative and unbiased sample of studies identified?
   (b) Has potential publication bias been estimated by including a sample of unpublished studies?
   (c) Have several different methods of searching the literature been used?
   (d) Is the number of relevant but nonusable studies presented?
   (e) Is a fail-safe *n* calculated to assess the robustness of obtained findings vis-a-vis the likelihood that not all relevant studies have been obtained?
   (f) Are all the sampled studies listed or available from the author?
3. Coding procedures
   (a) Are problems in coding procedures described?
   (b) Is the coding system available on request and does it contain criteria for coding potentially confusing study features?
   (c) Have proper estimations of interrater agreement been conducted and reported?
4. Index of effect
   (a) Has the pooled standard deviation been used to calculate individual effects in group difference meta-analyses?
   (b) Are all methods of calculating effect sizes described?
   (c) Is the procedure for dealing with "nonsignificant findings" made explicit? Is incidence of such findings made known? Are the implications of nonsignificant findings related to the conclusions and generalizations of the meta-analysis?
5. Statistical analyses
   (a) Are effects adjusted for small sample bias?
   (b) Are outliers identified and examined for their potential heuristic benefit?
   (c) Has an appropriate unit of analysis been used? Has one effect been calculated per construct per study per research question to avoid confounding important constructs in the analyses?
   (d) Are appropriate weighting procedures used throughout the analyses?
   (e) Has a systematic and defensible approach been taken toward analyzing differences in effect sizes?
   (f) Are *a priori* hypotheses used to explore obtained differences in effects across studies?
   (g) Is sufficient attention given to the potential influence of methodological features?
   (h) Has the meta-analyst proposed a statistical model that correctly specifies the obtained data?
6. Conclusions and interpretations
   (a) Does the meta-analyst relate the issue of power to statistical findings?
   (b) Are conclusions restricted to the literature reviewed?
   (c) Is a table presented describing the characteristics of reviewed studies so that missing information in the reporting of certain important study features is apparent?
   (d) Are appropriate qualifications offered in line with the state of the research being reviewed?

Source: Durlak J A & Lipsey M W. A practitioner's guide to meta-analysis. *Amer. J. Commun. Psychol.* 19(3):291-332, 1991. Reprinted with permission of Plenum Press.

The growing use of meta-analyses in medicine and the social sciences indicates the enthusiasm with which scientists have embraced this technique. However, many researchers are unfamiliar with what amounts to a fairly difficult concept to grasp. It is, however, an evolving research strategy. And it is difficult to keep abreast of the literature on meta-analysis itself.

As mentioned earlier, meta-analysis has the same general goals as most literature reviews—that is, to summarize the results of a particular research area, to study how findings vary as a function of key characteristics of the studies reviewed, to offer recommendations for improvement, and to draw implications for policy and practice within the research realm.

Many researchers are uncomfortable with the term meta-analysis.[13] Indeed, it has been called a "junk-word" and even termed "etymological nonsense." Other synonymous terms include "pooling," "overview" (preferred by British scientists), and "quantitative synthesis." Actually, the ancient Greek word for meta means "among" or "between." In this case, however, the modern usage of "transcending" applies, as in metaphysics.

ISI a Useful Source for Meta-Analysis

While I did not know it when I first came to SK&F Labs in 1954 to organize Thorazine literature, I was involved in meta-analysis. In a sense, the term has become the modern metaphor for those who gave up the laboratory to work in the computer-assisted library—with the goal of producing similar results.

Or course, we also know that there are those who, in fact, maintain a balance—an equilibrium if you will—between the lab, the library, and the computer, to generate new information.

Among those information scientists whose work on integrating knowledge closely parallels the development of meta-analysis, two stand out—Don Swanson of the University of Chicago and the late Manfred Kochen of the University of Michigan.[14] Swanson has published several papers on the linkage of seemingly unrelated information.[15-17] Roy Davies of the University of Exeter, England, has written an excellent paper on *The creation of new knowledge by information retrieval and classification.*[18] It reviews previous work on producing what Swanson has called "undiscovered public knowledge." It describes techniques by which hidden knowledge may be uncovered in the literature by browsing, search strategies, and relational indexing procedures.

I've been following the literature on meta-analysis through ISI's weekly *Research Alert* ® service. If there is sufficient interest, this could be expanded so as to create a new *Focus On: Meta-analysis*, in which the information is delivered biweekly on floppy disk. We can use *KeyWords Plus* ™ [19,20] to augment the already extensive citation profile for this emerging specialty.

In the face of a continuing swell of information, senior investigators of all kinds would be well advised to employ junior assistants in the application of meta-analysis to their own research problems. The following article should serve to point you in the right direction for your voyage into meta-analysis waters.

Goodman earned his PhD in 1989 from the Johns Hopkins School of Hygiene and Public Health, Department of Epidemiology. Earlier, he received an MHS from the Department of Biostatistics (1986), an MD from New York University School of Medicine (1981), and a BA from Harvard University (1976).

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Have You Ever Meta-Analysis You Didn't Like?

By Steven N. Goodman, MD, MHS, PhD
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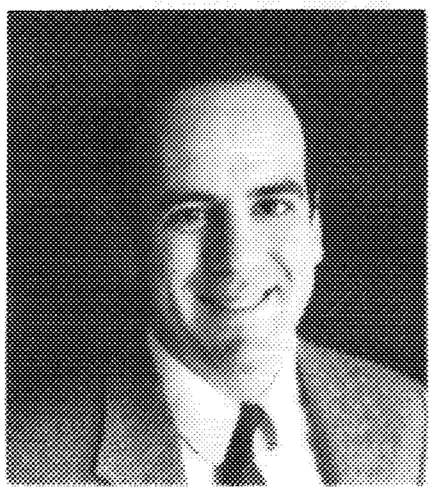
ABSTRACT

Meta-analyses and their proper place in medical literature are explained along with how they differ from traditional literature reviews. Both the qualitative and quantitative aspects of meta-analysis are considered in relation to studying the results of clinical trials.

This issue [1 February 1991] includes a meta-analysis of the use of steroids in treating chronic obstructive pulmonary disease.[1] Meta-analyses such as this one command our attention, both because they purport to provide a "definitive" answer to a clinical question that has eluded other researchers and because the work of those researchers, the grist for the meta-analytic mill, is often subject to embarrassingly intense scrutiny. They represent a new class of article, one that straddles the traditional boundaries between original research and review articles. Because meta-analysis is a relatively new and partially technical method, many physicians find themselves unable to appreciate the nuances or limitations of meta-analyses in the same way that they can appreciate those of a traditional review or original research article. Meta-analyses therefore are sometimes distrusted by physicians who do not understand the statistical techniques and resented by researchers who do not like seeing their years of effort rapidly reduced to an "effect size," with the consequent elevation of the meta-analyst to an expert in the field. These tensions have provoked controversy[2-4] as well as attention from the lay press.[5]



Steven N. Goodman

The term "meta-analysis" was coined in 1976 by Glass[6] in the psychology literature, and texts on the subject appeared in the 1980s.[7,8] The field is rapidly evolving, with the annual number of such analyses in the general medical literature increasing exponentially; the *meta*-meta-analysis, evaluating the quality of meta-analyses themselves, also has been developed.[9-11]

What are meta-analyses, and what is their proper place in medical research? This question is best answered by examining the ways in which they differ from traditional reviews. First, meta-analyses tend to be more narrowly focused than reviews—they usually examine a single clinical question, which may relate to treatment, causation, or the accuracy of a diagnostic test. Second, they have a strong quantitative component—they attempt to pool the quantitative results of several studies to give a more precise estimate of effect than would the results of any of the component studies, while still remaining clinically meaningful and statistically valid. Meta-analyses are done when there seems to be a disparity among several studies' results or when there may be an important main or subgroup effect that is too small to be measured accurately in individual trials.

The initial phase of a meta-analysis is qualitative, with an eye toward minimizing the bias arising from study design. In the report of a meta-analysis, the research question first must be posed, with no less thorough a biologic discussion than would appear in a traditional review. Meta-analysts then must comb the scientific literature comprehensively and systematically to find studies that address the question; choose an outcome variable that can be assessed from each study; pare the list to those studies that use comparable interventions and outcomes; examine the differences in patients, protocols, and confounding variables within that list; assess the "quality of information" provided by each study; and decide how to adjust for and summarize each of these many differences. Why the combination of studies with possibly different patients, interventions, and even outcomes would have clinical or biologic meaning must be clearly explained. This qualitative component of meta-analysis, usually its most useful contribution, is also the component that is most likely to be inadequate.

The quantitative part of a meta-analysis starts with an effort to ensure that the trials are similar enough so their results can be combined; that is, a statistical "test of homogeneity." The oft-repeated notion that meta-analysis can resolve "conflicting" trial results is not really true; if, with a test of homogeneity, the disparity among trial results is judged to be too great to have arisen by chance, the trial results should not be pooled. Instead, why they differ should be explained. Only fairly dramatic differences among trial outcomes, however, will result in a statistical verdict of heterogeneity if just a few trials are tested, regardless of their size. The failure to find such heterogeneity thus does not absolve the researcher from justifying biologically, by carefully examining individual trials, why the trials are combinable. As Greenland[12] noted, "...causal explanation of similarities and differences among study results is...outside the realm of statistical meta-analysis...the statistics serve as no more than a fallible pattern-recognition device, and explanation of the origin of observed patterns is beyond the scope of the device."

The next step in reporting a meta-analysis is giving a sense of what is being combined. The individual study results (with their variability) must be displayed—preferably graphically—so that even a technically unsophisticated reader can understand the essence of the studies at a glance. Callahan and associates[1] accomplish this goal by displaying effect size as a function of study sample size. Graphs showing confidence intervals for each study, perhaps with studies organized into important subgroups (for example, by study design or patient characteristics), convey this information best.

The stage is now set to do the statistical pooling, which involves not only summarizing all of the information in the studies into one number, but also examining the sensitivity of the summary result to various biologic and methodologic assumptions. Such examining is done to explore the possibility that there are identifiable subgroups of patients or studies with different responses. Callahan and colleagues[1] looked for subgroups by plotting outcome against various study characteristics. They provided one of these graphs in their report, that of treatment effect, plotted against initial forced expiratory volume in 1 second, grouped by study eligibility criteria.

Unfortunately, the ease with which pooled estimates can be calculated has resulted in a torrent of meta-analyses in which the purely quantitative components dominate. Some observers are concerned, "that the study of previous studies is being reduced to a routinized task of coding relegated to a research assistant, upping output per author-month by suppressing any role for wisdom."[2] The expectation that meta-analyses should provide "definitive results," instead of a synthesis of existing knowledge, exacerbates this problem.

A meta-analytic summary may not always be the most useful number for clinicians. When treating Ms. Jones, the clinician may want to focus on the single trial or subset of trials conducted in patients most like Ms. Jones. The initial qualitative component of a meta-analysis should present enough information about the patients and interventions in each study so that the clinician can examine the most relevant trial or trials. For example, Callahan and colleagues[1] provide such information in their Table 3. Less commonly used meta-analytic techniques focus not on pooling trial results, but on modifying individual trial estimates on the basis of the spectrum of results.[13,14] These techniques should be used more frequently.

Regardless of the summary number, meta-analysis should shed light on why trial results differ; raise research and editorial standards by calling attention to the strengths and weaknesses of the body of research in an area; and give the practitioner an objective view of the research literature, unaffected by the sometimes distorting lens of individual experience and personal preference that can affect a less structured review. The best meta-analyses knit clinical insight with quantitative results in a way that enhances both. They should combine the careful thought and synthesis of a good review with the scientific rigor of a good experiment. When a sufficient number of similar studies address a topic, a meta-analysis can move us closer to a quantitative "truth"; however, the computing of weighted averages is a comparatively small part of the process and should not be seen as its most important contribution.

With these caveats, *Annals* welcomes meta-analyses as quantitative reviews. We look for those that address important clinical questions, integrate biology and numbers in plausible and creative ways, and use statistics to clarify, not to obfuscate. These are standards that do not reside in equations and that few meta-analyses meet. We trust that our contributors will rise to the challenge.

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