J Clin Epidemiol Vol. 42, No. 10, pp. 1021-1024, 1989
Printed in Great Britain.

0895-4356/89 $3.00 + 0.00

Second Thoughts

META-ANALYSIS IN MEDICAL RESEARCH: STRONG ENCOURAGEMENT FOR HIGHER QUALITY IN INDIVIDUAL RESEARCH EFFORTS

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(*Received in revised form* 24 *February* 1989)

Abstract—In this article, we counter some criticism regarding the desirability of performing meta-analysis in clinical research. These criticisms, we argue, are based mainly on current difficulties in deriving firm conclusions based on meta-analysis, resulting from poor methodology and reporting of primary studies. This is not a fault of meta-analysis. In fact, with a better understanding of meta-analysis in the context of the full scientific research process, meta-analysis is seen as a key element for improving individual research efforts and their reporting in the literature. This in turn will further enhance the role of meta-analysis in helping clinicians and policy makers answer clinical questions.

Philosophy of science Overviews Combining studies

Various authors have set out their opinions and offered guidelines for conducting meta-analyses in clinical research [1–3]. The general view seems to be that in attempting to answer questions of interest, all past randomized clinical trials of suitable scientific quality that addressed essentially the same question must be considered. Peer reviewed publication is usually taken as evidence of suitable scientific quality and it is accepted that conclusions must only follow from a suitable explicit analysis of all of these trials.

On the other hand, the desirability of performing meta-analysis in clinical research has been disputed in the literature [4, 5]. We feel that the opposition to meta-analytic techniques may simply reflect a less than optimal view of the full scientific research process. Meta-analysis is not only desirable, but in our opinion a necessary requirement of being scientific and objective. It is desirable in that meta-analysis provides mechanisms for improving the utilization and quality of individual research efforts by identifying current inadequacies and encouraging their resolution. It is necessary in attempting to meet the scientific ideal of arriving at conclusions (and measures of uncertainty in these) only after explicit consideration and analysis of all relevant past and present research endeavors.

From the statistical point of view, there really is no escape from performing a *de facto* meta-analysis. One can either judge the effectiveness of a therapy based solely on the most recent study and ignore all previous studies, a method which is equivalent to giving the most recent study weight 1.0 and all previous studies weight 0, or try to choose the weights on some scientific basis—giving 0 only to studies that are so unrelated or conducted so poorly that no one would pay heed to them. If important differences in study findings exist they must be identified and explained. Thus meta-analysis

*Dr Detsky is supported by a National Health Research Scholar Award from Health and Welfare Canada (6606-2849-48).

might be viewed as an opportunity rather than a problem.

That most researchers realize the need for stating their results in the context of previous trials is evidenced by the literature review section in almost all scientific articles. Meta-analysis is a further development and refinement of this approach offering a more rigorous and coherent treatment of past research work. It is tempting to propose that no experimental results should be published without inclusion of an appropriate meta-analysis. In effect, one might suggest that a literature review section ought to be based on an explicitly described methodology in place of the usual *ad hoc* approach.

Most of the uncertainty surrounding the value of meta-analysis arises from concerns about the ability to arrive at firm conclusions given the varying quality of individual research efforts and their inadequate reporting. Publication bias (the tendency of authors and or editors to favour publications with statistically significant results), non-productive heterogeneity of study design, inadequate reporting of experimental protocols, and other poor research practices often do create limitations for meta-analysis. But this should not be accepted as a criticism of meta-analysis. Where there is good research and research reporting, meta-analysis presents few difficulties and no one, to our knowledge, has ever seriously questioned the advisability of its use under these circumstances.

In fact, once it is realized that meta-analysis is an ideal means of bringing out and correcting the inadequacies of previous research work, the prevalence of poor research can be seen as establishing a more pressing need for meta-analysis. If meta-analysis is unable to come adequately close to the scientific ideal mentioned earlier, then the individual research efforts themselves cannot be fully or properly interpreted. Meta-analysis is not an attempt to "make do with poor research", but rather an attempt to rigorously evaluate what we have learned (if anything at all), to uncover what we must do to learn more, and to provide mechanisms to "force" the necessary improvement. In order to do meta-analyses with a high level of certainty tomorrow, one must do meta-analyses with a certain degree of uncertainty today!

What is it about meta-analysis that will actually help bring about improvement in individual research efforts? Firstly, meta-analysis utilizes the scientific processes to identify inadequacies in the research to date. Secondly, the comprehensive, rigorous, and public peer review that a meta-analysis entails will encourage high quality participation by members of the research community in the resolution of the inadequacies. Thirdly, programs that are more likely to add to and improve on past efforts can be targeted for funding and support. If this seems surprising, perhaps we need to clarify what is involved in an appropriate meta-analysis as opposed to a simple statistical pooling of the data.

Meta-analysis is above all a scientific endeavor and therefore must be done in a manner that is explicit (both in what are considered to be facts and the proper inferences between facts) and fully replicable by other parties [6]. The facts and inferences involved should not be so contentious as to preclude the interest of peers.

More specifically, as recently related in the literature [1], there should be adequate compliance with the following requirements:

(a) An explicit and detailed working protocol.
(b) A literature search strategy that can be replicated.
(c) Inclusion and exclusion criteria for research reports and list of exclusions with reasons given.
(d) Verification of independence of published studies (use of separate groups of patients in each study.)
(e) A careful exploration of differences in treatment effect estimates with the aim of explaining them on the basis of relevant clinical differences, differences in quality of research or simply sampling variation with appropriate combination of treatment effect estimates *where* indicated. In order that this analysis can be easily replicated, a listing of individual study treatment estimates, a listing of what is believed to be the most relevant clinical differences between studies and a rating of each study on the basis of quality of research with reasons given will be required. The relevant clinical differences that are investigated should be motivated by theory. Differences that are discovered by "data dredging" may misdirect further research if, as is very likely, they are due to chance alone. In areas where all of the

research is of exceptionally high quality, quality ratings may be unnecessary.

(f) A careful consideration of the potential effects of publication bias, including the probability of such censoring of research endeavors—given the particular question and the community that is addressing it.

(g) A set of conclusions which includes a summary of what was believed to be done adequately and what was done inadequately along with suggestions and directions for future research. If new study results are being presented, the motivation for the present study should be given.

If no quantitative estimates are available, requirement (e) is inapplicable, but a rigorous "non-quantitative" meta-analysis should still comply with the other requirements. If this sounds demanding—it is. But then as was once said, "pleading hardship is no defence in science!" The research community will have to find the means to meet these demands if it wishes to strive for the scientific ideal we mentioned earlier. Perhaps funding agencies should become more aware of the need for meta-analytic input into funding decisions and the need for financial support of meta-analytic work.

Meta-analysis to date has not only been able to identify some very general inadequacies in research practices but has also led to corrective action being taken in some areas of clinical research. For instance, as we pointed out earlier, research findings should not be interpreted in isolation—we need to consider all relevant efforts. This problem became highlighted with the publication of meta-analyses, and efforts to overcome it have likewise been supported by meta-analysis proponents. We would venture that today most editors of medical journals and major funding agencies are well aware of the utmost importance of publishing well-conducted experiments that arrived at null conclusions. In some areas the problem is being more fully addressed by the establishment of study registries [7].

As for encouraging the resolution of inadequacies, the scientific, comprehensive, and public peer review that a meta-analysis provides for researchers will help ensure high quality participation by members of the research community. Meta-analysis provides scientific feedback to investigators who addressed a similar question. Who did well compared to whom? Who was able to blind the outcome assessor and who was not? Did this make a difference in the treatment effect estimate? Feedback is necessary for learning and improving skills as well as helpful in attracting the interest of highly motivated up-and-coming researchers.

In the meta-analysis field, in order to increase the likelihood and value of feedback, we insist that the outcome results for each study be reported individually so that anyone interested can re-analyse the data for themselves. In our own endeavors, this has heightened our awareness and concerns about entering data twice (and having the computer check for differences), and checking other aspects twice and thrice and performing other very important, albeit not exciting, tasks. This alone has lead us to hope that meta-analysis will become a field where replication is almost effortless for any interested and capable reader. It is not unusual for a journal's reviewer to be able to challenge and contribute to the actual numerical analysis in a meta-analysis submitted for publication. Someday this may be the case for all published clinical experiments (via optical scanning of the few pages of raw data that all studies could be required to provide for this).

Often studies that are reviewed in meta-analyses make similar errors such as inadequate patient selection, improper followup, failing to blind outcome assessors, etc. Very little is likely to be learned by the addition of a similarly flawed study. This suggests that as a minimum, anyone proposing to do research (especially on human subjects) should be required to supply a meta-analysis so as to be able to coherently argue that a further study is likely to be productive. If such a meta-analysis has not been done or is of questionable quality this is probably where the greatest opportunity for gaining insight lies. Why repeat others' mistakes or attempt to do what others could not do without first having a reason to believe that it is possible to do better?

In conclusion, we must take research and research reporting seriously enough to bring it up to the level where the performance of meta-analysis is not limited by difficulties (such as having to combine experimental results from individual studies of poor quality or being unable to get a good estimate of the likely number of non-significant studies that were not published). Meta-analysis is in itself an important vehicle for accomplishing this. The most

common conclusions of early meta-analyses with regard only to why the question has not been answered and what needs to be done to answer it (along with some judgement on how likely it is that further research is warranted) should not be regarded as a failing. After all, the ultimate objective is to be able to answer the question or in some cases go on to another question we may be better able to answer. To do otherwise, is to ensure inefficient use of the scarce resources available for research [8].

Acknowledgements—The authors wish to express appreciation for the insight, encouragement and assistance given by David F. Andrews, David Brenner, Kristan A. L'Abbe, Allison D. McGeer, Gary Naglie and C. David Naylor especially in regard to meta-analytic methodology.

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