HOW TO APPROACH A META-ANALYSIS

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Introduction

Although there has always been some controversy about its validity, meta-analysis has become popular as the number of studies with similar protocols has grown. By systematically combining studies, one attempts to overcome limits of size or scope in individual studies to obtain more reliable information about treatment effects.

A meta-analysis goes beyond a literature review, in which the results of the various studies are discussed and compared. Meta-analysis synthesises the results of the individual studies into a new result. A meta-analysis also differs from a 'pooled data' analysis because the summary results of the previous studies, not the results on individual subjects, are combined for analysis.

Because a meta-analysis does not involve human subjects or experimental animals directly, it is often considered an easy study that can be done with a minimum of effort and little attention is sometimes paid to details of design. A valid meta-analysis, however, requires the same careful planning as any other research study.

Methods

Defining the Objectives of the Study

The first step is to identify the problem. This includes specifying the disease or condition of interest, the population of interest, the specific treatments or exposures being studied and the outcome measurements (efficacy, adverse reactions or both) being studied.

The goals of the study should be defined at this stage. Meta-analyses attempt to meet one or both of two goals: summarising the available data or explaining the variability between different studies.

When the objective is to summarize the effects of an intervention, all studies compared should have similar patient characteristics and the outcome measures should be consistent. Thus, the summary measure resulting from the meta-analysis would reflect the effect of the treatment being studied. In practice, however, there is always variability between studies both in patient characteristics and in outcome measures, which is the primary motivation for performing a formal meta-analysis.

Alternatively, one might attempt to model the variability between studies to understand why different studies had different results. This would suggest that as wide a range of studies should be included as possible. Frequently both objectives can be served in the same meta-analysis, by providing summary statistics of treatment or exposure effects in sub-groups, often referred to as a sensitivity analysis, and modelling the difference across studies as a function of patient characteristics.

Defining the Population of Studies Included in the Meta-Analysis

Inclusion and exclusion criteria for studies are as necessary in a meta-analysis as they are in clinical studies to safeguard against selection bias. These criteria need to be specified in the meta-analysis protocol, just as inclusion/exclusion criteria are specified in a clinical protocol.

The inclusion criteria should address at least the following:

1. Type of study
2. Patient characteristics
3. Treatment modalities
4. Outcome measures

Locating Studies

Comprehensively locating studies is by far the most difficult step of any meta-analysis but it is the most important step. A structured plan is necessary to manage the frequently large number of papers. Most meta-analyses begin with a search using the Medline system. This should be supplemented by the use of other computerised indices, such as in-house research listings and reports from professional organisations.

Options for finding unpublished studies include peer consultation, i.e. networking among your professional colleagues and contacting specific investigators, and manually reviewing special meeting issues of journals from the major professional organisations in the field. In addition, one might publish a request for information at meetings and in newsletters.

In meta-analysis, one is particularly concerned with publication bias, i.e. the effect of failing to detect unpublished trials. A common reason for not publishing is nonsignificant or uninteresting results. Clearly, leaving out negative studies in any meta-analysis will substantially bias the result so that treatment may appear more effective than it actually is.

Screening and Evaluation

A quick review of the abstracts of the papers will eliminate those that are clearly not relevant to the meta-analysis or do not meet other criteria, such as study design, specific population, duration of treatment, or date of the study. If the published material is just an abstract, there must be sufficient information to evaluate its quality. There must also be summary statistics to put into the meta-analysis, available either from the written material or in writing from the investigator. It is essential that when the available written information is insufficient for the meta-analysis that strenuous efforts be made to contact the principal investigator to obtain the needed information in order to reduce the effect of publication bias. This becomes even more important for material that has not been formally published.

Assuming adequate information is available, each study should then be subjected to a structured review of the quality of the study.

Data Abstraction

Data should be abstracted onto structured forms designed to capture relevant information in a concise, focused fashion. The protocol should specify the items, the information to be collected for each item and the format for collecting the items.

Data Analysis

Specific methods for data analysis in meta-analysis have been developed and are available in many texts and articles. The simplest method is to use a weighted average of the effects of each study. The analysis is usually based on a summary statistic derived from the study, often referred to as the effect size and a weight, which in most cases is the inverse of the variance of the effect size and is usually related to the sample size. The Q statistic is a test of homogeneity between studies. A large value of Q indicates that there is significant heterogeneity between studies. The choice of analytic methods usually requires input from a statistician experienced in meta-analysis.

Reporting and Interpretation

The protocol should indicate how the results of the meta-analysis will be presented. Like the data analysis, this preliminary plan may be modified during the implementation of the study. The published meta-analysis should include a table containing all relevant descriptive information about each of the papers that are included in the analysis in a table. Ideally, all articles reviewed would be described, but this is not always practical, particularly if the number is large and many of them are irrelevant

Conclusion

In summary, a meta-analysis is an important and valuable tool for summarising data from multiple studies. However, it is not an easy task and requires careful thought and planning to provide accurate and useful information.