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The Use of Meta-Analysis in Economic Evaluation

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DISCUSSION PAPER 173

THE USE OF META-ANALYSIS IN ECONOMIC EVALUATION

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SUMMARY

Meta-analysis provides a family of statistical techniques for combining the results of similar studies. This paper examines the meta-analysis of clinical data in economic studies, and points to the issues and considerations that must be addressed when designing and conducting a meta-analysis of clinical data for use in an economic evaluation. We investigate whether the standard approaches employed in the meta-analysis of clinical data are satisfactory to meet the demands of economic evaluation, and assess the meta-analyses contained in a sample of economic evaluations identified from the NHS Economic Evaluation Database. Finally, we provide guidance on the appropriate use of meta-analysis for economic evaluations.

1. INTRODUCTION

In recent years, economic evaluation has become an increasingly important decision-making tool to help address resource allocation issues. Economic evaluations of health care interventions are frequently based upon prospective randomised clinical trials (RCTs) (Adams et al., 1992), but the integration of economic evaluations and clinical trials has not been without difficulties (Drummond & Davies, 1991). Furthermore, the prospective design may not be feasible, appropriate or sufficient for the needs of economic analysis in certain situations. As a consequence, a good proportion of economic evaluations are to varying extents reliant upon models, which synthesise data from different research studies, expert opinion, existing literature and databases. Some researchers have argued that modelling is an unavoidable fact of life (Buxton et al., 1997), but others have argued that analysts should be inherently aware of the limitations (Sheldon, 1996).

Meta-analysis provides a family of statistical techniques for combining the results of similar studies. This paper examines the meta-analysis of clinical data in economic studies, and points to the issues and considerations that must be addressed when designing and conducting such a meta-analysis of clinical data *for use in an economic evaluation*. An implicit question is whether the standard approaches employed in the meta-analysis of clinical data are satisfactory to meet the demands of economic evaluation.

Although this paper focuses on meta-analyses that evaluate the effectiveness of interventions across several clinical studies, it is noted that meta-analysis may also be used for components of economic evaluation that are not measurable in the clinical studies, e.g. resource use and quality of life measurements.

2. ECONOMIC EVALUATION AND THE ROLE OF META-ANALYSIS

Conceptually, economic evaluation is relatively straightforward and the methods of economic evaluation have been described extensively elsewhere (Drummond et al. 1997). However, the value and validity of the results of economic evaluation are critically dependent upon the health outcomes data available. In cost-effectiveness analysis, the estimates of effectiveness are often incorporated into the denominator.

The purpose of meta-analysis is to answer item 3 of the methodological checklist for economic evaluations (Drummond et al., 1997): '*Was the effectiveness of the programmes or services established ?*' and to address adequately sub-item 3.2: '*Was effectiveness established through an overview of clinical studies ?'*

Box 1: Checklist for Assessing Economic Evaluations

1. Was a well-defined question posed in answerable form ?
2. Was a comprehensive description of the competing alternatives given ?
3. Was the effectiveness of the programmes or services established ?
   - *3.1 Was this done through a randomized controlled trial? If so, did the protocol reflect what would happen in regular practice ?*
   - *3.2 Was effectiveness established through an overview of clinical studies ?*
   - *3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results ?*
4. Were all the important and relevant costs and consequences for each alternative identified ?
5. Were costs and consequences measured accurately in appropriate physical units?
6. Were costs and consequences valued credibly ?
7. Were costs and consequences adjusted for differential timing ?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was allowance made for uncertainty in the estimates of costs and consequences?
10. Did the presentation and discussion of study results include all issues of concern to users ?

Drummond et al., 1997

As the amount of clinical research available is daunting and unmanageable, systematic reviews are needed to efficiently integrate valid information and provide a basis for rational decision-making (Mulrow, 1994). Unlike traditional literature reviews which have been criticised for being subjective (Chalmers, 1991), systematic reviews are more objective and reliable by systematically locating, appraising and synthesising evidence from scientific studies (Deeks et al 1996). The results of primary studies may be quantitatively combined or narratively summarised in a systematic review. A meta-analysis is a systematic review in which statistical method is used to combine results of primary studies quantitatively (Der Simonian and Laird, 1986). Figure 1 shows the relationship between meta-analysis and systematic review. It should be stressed that some published meta-analyses may not be systematic in their search for literature and assessment of quality of included studies.

By combining many small studies in a meta-analysis, small but important effects that otherwise might not have been detected can be picked up and reduce the possibility of a type II error (where there seems to be no statistically significant treatment effect, when in reality such an effect exists). The enlarged sample size also generates more precise estimates and facilitates subgroup analysis, revealing patterns of correlation or variation of treatment effect across studies. As an element of meta-analysis involves the critical assessment of primary studies, weaknesses in these studies can also be highlighted. Therefore, some have advocated that meta-analysis of clinical studies provides a sound basis for economic evaluation by giving a more precise and more representative estimate of treatment effect than a single clinical trial.(Simes and Glasziou, 1992; Mugford, 1989).

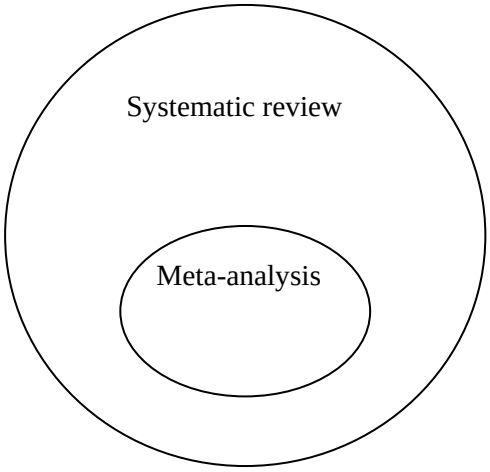

Figure 1: The Relationship Between Meta-Analysis and Systematic Review

In the next section, a checklist of the steps of meta-analysis is presented, first describing standard advice as recommended by methodologists, and second how this advice may differ in view of the needs of economic evaluation.

3 STEPS IN THE CONDUCT OF META-ANALYSIS OF CLINICAL DATA FOR ECONOMIC EVALUATION

The conduct of a meta-analysis of clinical data for economic evaluation should follow similar rules to that of evidence-based medicine to minimise potential biases or confounding as far as possible. Guidelines have been proposed for the undertaking of meta-analysis (e.g. Cochrane Collaboration,1996; Deeks et al, 1996), and there seems to be agreement and consensus on the basic principles. The standard format as followed by the Cochrane Collaboration, an international network aimed at preparing, maintaining and disseminating systematic reviews on the effects of health care, is shown in Box 2.

Box 2: Standard Steps Involved in Conducting a Systematic Review

1. Development of a Protocol
2. Formulation of the Problem
3. Location and Selection of Studies
4. Critical Appraisal of Studies
5. Collection of data
6. Analysis and Presentation of Results
7. Interpretation of Results
8. Improving and updating Reviews

Cochrane Collaboration, 1996

3.1. Development of a protocol

It is generally recommended as with any scientific endeavour, that the methods of the meta-analysis should be established beforehand in the form of a protocol. This is to ensure a systematic and structured approach to the meta-analysis. It is desirable to make the process as rigorous and well defined as possible since reviews are essentially retrospective studies of data, and are vulnerable to many potential biases. The protocol will typically address the objectives, selection criteria, search strategy and methods, preceded with a brief summary of the biology, psychology/sociology and healthcare issues that provide the rationale for the review and place the questions in context. Although the motivations behind conducting meta-analyses are invariably different, the Cochrane Collaboration emphasises the main purpose of meta-analysis is to 'provide unbiased, up-to-date summaries of what we know and do not know about the effects of different forms of healthcare and should help people make practical decisions about healthcare'.

Similar conscientiousness applies to meta-analysis for the needs of economic evaluation. Methods of the meta-analysis should be established in advance in the form of a protocol, to ensure that the effectiveness data for the economic evaluation is derived in a systematic and unbiased manner, since selective use of effectiveness data can lead to erroneous findings for the economic analysis. As Freemantle and Maynard (1994) pointed out in their example of SSRIs, if one of the smaller trials is selected rather than drawing upon all trials as a basis of calculating health gains, the cost-effectiveness of the intervention can be made to appear more attractive.

Every effort should be made to adhere to the protocols, but it is appreciated that sometimes, this is not practically possible or appropriate as reviews are analyses of existing data which are constrained by previously-chosen study populations, settings, interventions, outcomes measures and study designs. Changes are only acceptable if they have not been performed post-hoc on the basis of results of the meta-analysis, and where changes are necessary, they should be documented and reported, and sensitivity analyses used to assess the impact of such decisions on the meta-analysis. However, in the case of economic evaluations, changes to the type of economic study performed are probably quite likely. Prior to the conduct of the meta-analysis, it is unlikely to be able to specify whether an economic evaluation would be a cost-effectiveness or cost-minimisation study. Donaldson et al. (1996) argue that it is not necessary to know at the outset whether the experimental therapy is the same, better or worse than the control therapy in terms of effectiveness, otherwise if these answers were known, there would be little point for performing the experiment.

3.2. Formulation of problem

It is generally recommended that the analyst should define and frame precisely in advance, the question(s) of the meta-analysis, since the overall framework is driven by the research question(s) and its associated hypothesises. The question(s) is also particularly important in that the readers of the meta-analysis can judge whether the meta-analysis is interesting or likely to be relevant to issues that they face.

Questions that a meta-analysis may address can be broad or narrow in scope. A broad question might be; 'Are antiplatelet agents effective in preventing thrombolytic events in humans?' whereas a narrower question might be; 'Is aspirin effective in decreasing the risks of a stroke in elderly patients with a previous history of stroke?'. The scope of the question is dependent upon multiple factors such as the question's relevance and potential impact, availability of supporting information, the potential generalisability and validity of answers to the questions, the available resources, as well as the needs and requirements of the sponsor of the study.

In terms of the needs of economic evaluation, the clinical research question of the meta-analysis should be broadly in line with the scope of the economic research question. Economic research questions can be broad or narrow. A meta-analysis designed to answer a broad research question such as 'Are antihypertensive agents effective in lowering blood-pressure?' is more suitable for a broad economic research question such as 'Does the cost-effectiveness of treatment improve with increasing pre-treatment blood pressure ?', rather than a narrower economic question such as 'Is the cost-effectiveness of β-blocker treatment for severe hypertension more cost-effective in the 50-70 age group ?'. There is a danger that clinical studies assessing broad questions can conceal different patient selections and give results that don't relate to actual patients who have known attributes of risk; e.g. age 50-70 with severe hypertension, so there may be cases when generalisations are made, when they should not.

In general, meta-analyses tend to be conducted to answer questions which are broad in nature. A background search of the clinical literature may be helpful in refining the questions of both the meta-analysis and the economic evaluation.

There are several advantages and disadvantages to framing broad or narrow questions. Narrowly focussed meta-analyses may not be generalisable to multiple settings, populations and formulations of an intervention or can lead to spurious conclusions. Alternatively broadly based reviews could be criticised for mixing apples and oranges, particularly when there is good evidence to suggest that various formulations of interventions behave very differently or that various definitions of the condition of interest or the setting are associated with markedly different courses and outcomes. On the practical side, searches for data relevant to broad questions may be more time-consuming and more expensive than narrowly defined questions, since broad questions may be addressed by large sets of heterogenous studies, and the synthesis and interpretation of data can be particularly challenging.

There are several components to a well-formulated question. A clearly defined question should specify the population, types of interventions or exposures, types of outcomes, and the types of studies that are relevant. The first component of the question is the population and setting for the disease or condition of interest. The population characteristics can be based on a series of factors such as age, sex, race, diagnosis, prognosis, educational status or presence of a particular condition such as angina or shortness of breath, whereas setting characteristics can be based on people living in the community, hospitalisation, living in nursing homes or chronic care institutions or outpatients.

The second key-component is to specify the interventions of interest and the control groups. A threat to the validity of an economic evaluation is the choice of comparator intervention. In many clinical trials, placebo is selected as the comparator as it is normally a regulatory requirement for pharmaceuticals in many countries. In economic studies, the comparator intervention should be most relevant for the policy question being addressed, and is typically usual practice. Comparators will tend to differ in different settings. Therefore there is potential for disparity to arise between the choice of comparator for the economic evaluation and the comparators in the clinical studies that are available for inclusion in the meta-analysis. Thus it is important to design the meta-analysis so that it includes clinical studies which contain relevant comparators and improve the external validity of the economic evaluations where possible.

The third component is the delineation of particular outcomes of interest. Meta-analysis may be used to derive estimates of a main outcome or outcomes such as rare events. The selection of outcome measures for the meta-analysis is a difficult one as the range of outcome measures used in clinical studies is often diverse, and this is further complicated by the fact that they are measured very differently. Outcomes may be continuous such as blood pressure or weights; categorical such as mortality or pap smear classes; dichotomous such as survival or death; and counts such as the number of live births or the number of myocardial infarctions.

The summary outcome measure calculated in a meta-analysis is usually an odds ratio or risk ratio. The odds are defined as the number of patients who fulfil the criteria for a given endpoint compared to the number of patients who do not. In any given study, there may be multiple outcome variables e.g. mortality, morbidity, and quality of life; and a given outcome variable may be expressed using more than one treatment effect measure. It is considered generally advisable to collect raw data on outcome measures e.g. numbers treated rather than derived measures such as odds ratios, since derived measures might not be of interest in the meta-analysis, calculated incorrectly by the authors, or confusing when trying to compare the results of studies that are reported using different outcome measures. If truly disease outcomes are present measuring different constructs such as mortality and clinical improvemento, then no meta-analysis should be performed. If different measures or scales such as odds ratio or risk-difference using same construct are present, then meta-analysis could be performed by using the standardised effect size. Further, economic evaluations may involve decision-analytic models which require an estimate of the conditional probability or absolute risk (rather than the relative risk). These absolute risks can be calculated directly from primary studies using common statistical methodology to combine proportions for both intervention and control groups (Laird et al., 1990).

Exclusivity can introduce the threat of bias in the reporting of outcomes. The choice of outcome(s) in clinical studies which are reported and the measurement tools which have been used to measure these outcomes, can be influenced by ex-post viewing of the results and occasionally, can be the ones with the most favourable findings**.** An example is the dichotomisation of continuous variables in pharmaceutical clinical trials. This is potentially problematic as meta-analysis can only summarise outcomes which are contained in the original studies in the first place. As the choice of outcomes can make a crucial difference to the conclusions of the meta-analysis, they should be selected with care. In

some instances, however, the outcomes for economic evaluation maybe different to those offered in the meta-analysis. Therefore it might be advisable to approach authors or sponsors for unpublished data.

Clinical studies may contain health-related quality of life scales. The different types of scales have been reviewed by Guyatt et al (1993) and can be classified into (i) specific measures; (ii) general health profiles; and (iii) preference-based measures. With respect to economic evaluation, preference-based measures can be relatively easily incorporated, but specific measures and general health profiles are not as straightforward, requiring complex mapping of health states to established preference-weighted classification or alternatively using the quality of life information from the scales to construct scenarios for health state preference evaluation. Economists should be aware of these limitations, when looking to meta-analyse data on quality of life.

The final key component is the types of study designs. Certain study designs are superior to others when answering particular questions. A hierarchy of study designs has been proposed for clinical epidemiological studies (Sackett et al. 1995), which range from large, well controlled, randomised controlled, double-blind trials to small, non-randomised studies. With differing degrees of bias inherent in each study design, Cook et al. (1992) have correspondingly proposed levels of evidence and grades of recommendation. Randomised controlled trials (RCT) are regarded in clinical circles as the gold standard research design, followed by cohort studies, case-control studies and case series. Indeed, the Cochrane Collaboration focuses on systematic reviews of RCTs for this reason. In comparisons of therapies, differences in outcome may be as a result of biases, confounding or chance rather than due to the differences between therapies under evaluation. The framework of a randomised controlled trial minimises the possibility of selection bias arising through the selection of patients for each treatment, and therefore it is not unexpected that the majority of meta-analyses performed include only randomised controlled trials. When multiple randomised controlled trials are brought together in a meta-analysis, the randomisation is preserved and hence provides a more precise estimate of treatment effect. It is particularly important to analyse the trials in terms of treatment allocated (intention-to-treat analysis).

Box 3: The Relationshipt Between Levels of Evidence and Grades of Recommendation

Level of Evidence	**Grade of Recommendation**
Level 1, Large RCTs with clear cut results (low risk of error)	Grade A
Level 2, Small RCTs with uncertain results (moderate to high risk of error)	Grade B
Level 3, Non-randomised, contemporaneous controls	Grade C
Level 4, Non-randomised, historical controls	Grade D
Level 5, No controls, case series only	Grade E
	Cook et al., 1992

Economists generally support the quality criteria established by epidemiologists, but in terms of economic evaluation there arises a conflict of quality of clinical evidence with the degree of relevance. Although the randomised controlled trial is a valid vehicle for assessing outcomes, the conditions under which trials are conducted are often atypical. For example; the case-load may be highly selective, the patient and doctor may be blind to the treatment assignment, the comparator may be placebo rather than usual practice, the trial protocol may demand additional tests or procedures to be performed, patients may be more closely monitored than usual at specialist centres and the physicians and patients may be more highly motivated than usual (Drummond and Stoddart, 1984; Drummond and Davies, 1991; Adams et al., 1992). Furthermore, RCTs and even meta-analyses may be inadequate to detect certain clinical endpoints that are relevant to an economic evaluation. For example, if the economic evaluation of an intervention is based on the detection of adverse events that occur very rarely, the randomised studies may offer very imprecise information because of their short follow-up and small sample sizes. In such circumstances economic evaluation using evidence from case-control or cohort studies where very small risk differences can be detected, may be more appropriate. For example, in their economic evaluation of SSRIs versus older tricyclics, Freemantle et al. (1994) used government databases to estimate the costs, volume of prescribing and number of deaths. In general, RCTs will invariably assess efficacy rather than effectiveness, under real-world conditions. Ideally economic evaluations should incorporate clinical data on effectiveness rather than efficacy, but these may not be available especially in the case of pharmaceutical research where the majority are Phase I to III studies geared towards establishing efficacy and safety for licensing purposes.

Although combining data from studies using different designs may seem undesirable to epidemiologists for efficacy evaluation, this practice may be advantageous to maximise external validity, increasing relevance to policy and clinical practice decisions. For these reasons, in fact, economists may be satisfied to use data from the meta-analysis of non-RCT data, or in situations where no RCT data are available.

Under development is a new form of meta-analysis called cross-design synthesis which uses complementary study designs such as randomised controlled trials and observational studies, based on the underlying principle of compensating for each others inherent design weaknesses to better answer study questions (Droitcour et al., 1993). For these reasons, cross-design synthesis may have potential use for economic evaluation in the future.

3.3. Location and selection of studies

It is generally recommended that the search strategy to locate relevant studies as defined by the research question, should be as comprehensive as possible. This is a most critical and difficult step as publication bias is a major threat to the validity of a meta-analysis (Begg and Berlin,, 1989). Publication bias arises from the fact that clinically and statistically significant results are more likely to be published or presented at scientific meetings than negative ones. Thus it is possible that the subset of studies included in the meta-analysis could be unrepresentative.

Publication bias can be prevented by prospectively registering clinical trials at their inception but universal registration of all studies cannot be realised in the near future. Therefore, every effort should be made to obtain and include data from unpublished studies. The publication bias in a meta-analysis could be assessed according to identified risk factors of publication bias such as small sample size, poor study design, small or moderate effect size, and the interest of research sponsors (Song et al., 1999). The file-drawer method (Rosenthal., 1979) and funnel plot related methods (Egger et al., 1997) are often used in meta-analysis to detect the risk of publication bias.

The comprehensive of the search will invariably be dependent upon the field and the research question that the meta-analysis is designed to answer. While computerised databases such as MEDLINE (Index Medicus online), EMBASE (Excerpta Medica Online), CINAHL and SCISEARCH (the Science Citation Index) may facilitate retrieval of relevant published studies, these searches are often insufficient. Dickersin et al. (1994) found that only 30-80% of all known published randomised trials are identifiable using MEDLINE and non-English language references are seriously underrepresented. Standard advice recommends that the computerised databases should be used as an initial step and supplemented wih searches of review articles, abstracts, conference/symposia proceedings, dissertations, books, expert opinions, trial registries, communication with industry and manual searches of relevant journals. Since the comprehensiveness and efficiencies of the database searches depends upon the keywords chosen, it is advisable for the economist to enlist the help from information scientists when designing a search strategy. In some cases, a systematic review might already exist in the area of interest. Before proceeding with a meta-analysis, the economist would be wise to check databases such as the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness (DARE), the National Research Register (NRR) and MEDLINE to avoid duplication of effort.

It is within the best interests of the economist that careful consideration should be given to this stage to avoid erroneous conclusions, as in essence the results of the economic evaluation will be driven by the overview of the effectiveness data from the retrieved published and unpublished studies. An example of selection bias is a meta-analysis of paroxetine in the treatment of depression (Dunbar et al., 1991). In their study, a meta-analysis of six trials showed that there was a 12% reduction in risk in tolerability for paroxetine as compared to imipramine. However, a meta-analysis of all available studies suggested a more modest effect (Song et al., 1993).

Despite the above, meta-analyses for economic evaluation may omit clinical studies on the basis of relevance to the economic research question. For example O'Brien et al. (1994) omitted two clinical studies on the basis that they contained drugs, not being assessed in the economic evaluation on prophylatic treatments against deep vein thrombosis (DVT). Similarly, Drummond et al. (1994) omitted a study on the basis that it contained a different dosing regimen to other heparin studies. Such omissions should be explored by sensitivity analysis.

3.4. Critical appraisal of studies

It is generally recommended that studies should be critically appraised prior to inclusion in the meta-analysis, in order to understand the overall quality of the studies being combined, to detect the risk of bias, gain insight into potential comparisons and guide the interpretation of findings. Also criticial appraisal may pull out duplicate and sub-set publications**.** Furthermore one might wish to use a measure of study quality as part of the weight assigned to each study in the analysis or as a method to exclude poor quality studies. Moher et al. (1995) define quality as 'the confidence that the trial design, conduct and analyses have minimised or avoided biases in the treatment comparisons', implying that the likelihood that the results are closer to the 'truth' will be greater if the quality of the studies is higher.

Typically the quality of the study is assessed, using quality scales or checklists (Moher et al., 1995). Several such checklists and scales are available including the Department of Clinical Epidemiology and Biostatistics, McMaster University User Guides to the Medical Literature (1981). However these methods will inevitably be subjective to some extent, and care should be taken not to confuse the quality of reporting with the validity of the design and conduct of a trial. Also the relative importance of characteristics of the studies which will be assessed for quality may be different for different research topics.

3.5. Collection of data

It is generally recommended that data from primary studies are collected through the use of data extraction sheets. Data extraction sheets serve three functions; (i) as a visual representation of the review question and the critical appraisal of included studies in the meta-analysis; (ii) as a historical record of the decisions that occur throughout the review process and (iii) as a data repository form. Data extraction sheets will vary for the different reviews, but should be of suitable length to avoid omitting key data or becoming conversely tedious, boring and wasteful of time. Data extraction sheets can be electronic or paper form, the former having the advantage of being able to handle large amounts of data and eliminating the need for data entry separate from the abstraction. Typical data extracted may include items such as study design, setting, participants, interventions, outcome measures and results.

It has been suggested that studies should be read independently by two readers to minimise inter-reader variability (Begg, 1989), and hence improve reliability. Since by virtue, meta-analysis is being conducted after the data are available, meta-analysis is a form of retrospective research and is prone to potential biases inherent in such research. It is also advised that certain information such as the identity of the authors, the institutions at which the study was conducted and the sponsors of the study should be masked. Although this is ideal, however it is appreciated that this may be rather difficult to completely uphold in practice as it is difficult to attempt a review in a field without prior specialist knowledge of the field.

3.6. Analysis and presentation of results

Although statistical methods can be helpful to analyse and summarise data, it should not necessarily be regarded that a systematic review with no statistical analysis is less valuable. Statistical analysis can be more of a hindrance than a help to those who are not familiar with the statistical techniques, and statistical analysis may not be appropriate in certain cases where there is a lack of relevant valid data or where it does not make sense. For example; a summary of studies to improve prescribing could be very helpful to many different end-users, but a statistic of an average effect of interventions to improve prescribing could be meaningless and misleading.

When it is possible and appropriate, statistical methods can be very helpful to summarise research evidence. The different statistical approaches to meta-analysis share a common goal, which is to provide a more precise and generalisable estimate of treatment effect than that attainable from any individual study. The overall effect is estimated by weighting each individual effect inversely according to its variance. There are two general methods available to produce a combined estimate of effect size; one is based on the fixed effects model and the other is on the random effects model. These two methods are different in their assumptions about the true underlying effect size of each study (Sutton et al., 1998).

Heterogeneity of the results from different studies can be assessed through the use of statistical tests, but these tend to be of low power. Therefore the failure to reject the hypothesis of homogeneity of studies does not prove that the studies are estimating the same effects size. Actually, any set of studies is inevitably heterogeneous and there are many possible sources which might cause a failure of the assumptions by the fixed effects model. A remedy is the use of graphical displays to search for variable treatment effects. If heterogeneity of treatment effect is demonstrated, then the possible underlying sources of heterogeneity should be investigated and subgroup analysis applied.

The fixed effects (FE) model assumes that all the studies have identical underlying effect sizes, and different results across studies are purely due to random error. This implies that if all the studies were infinitely large, they would generate identical results. Under this assumption, the variance of the estimated summary effect size is exclusively determined by the within-study variance of each component study. The random effects (RE) model assumes that studies have different underlying effects that are normally distributed. This implies that even if all the studies were infinitely large, they would generate different results. Under this model, between-study variance needs to be taken into account as well as within-study variance in deriving the weighting factor (DerSimonian and Laird, 1986).

Economists should be careful in selecting the relevant model as occasionally, both types can generate conflicting conclusions from the same data. The random effects model will be more ‘conservative’ (Pettiti, 1994) because it provides a wider confidence interval of estimated overall effect. As the between study variance or heterogeneity becomes large, the difference in results of the two models will increase. In this situation, the random effects model will take into account the heterogeneity, which the fixed effects model tends to ignore.

Sources of heterogeneity could be investigated by subgroup analysis and meta-regression. The treatment benefit is often greater for those most at risk. For example, the segments of population with the higher levels of hypertension, may benefit most from antihypertensive drugs and in programmes of immunisation and screening, the segments of the population where the incidence is high may benefit. Inevitably the cost-effectiveness will vary according to different patient characteristics.

The robustness of a meta-analysis can be investigated through sensitivity analysis. Particularly if clinical data used in meta-analysis is limited or not reliable, the economist can undertake a sensitivity analysis based on different assumptions about the clinical evidence. For example, the long-term outcome is often not available because of inadequate follow-up as frequently witnessed in clinical trials. Alternatively the estimates from a meta-analysis may be included as part of a sensitivity analysis for testing the robustness of the estimates of the clinical data on which the economic evaluation is based. That is, if the economic evaluation is based on a single prospective study, a meta-analysis of the previously published literature could provide estimates for the sensitivity analysis.

There are several reasons why explicit reporting of the meta-analysis contained in the economic evaluation is desirable. First, it improves the transparency of the economic evaluation and makes it easier to assess whether the methods were appropriate. Secondly it facilitates comparisons between studies; that is the differences in cost-effectiveness ratios for example is due possibly to differences in study methodology rather than in the effectiveness. Thirdly, it might act as a stimulus to improve the quality of the meta-analyses undertaken. As with any research, the economic evaluation and the meta-analysis should provide sufficient information for replication of the methodology.

3.7. Interpretation of results

The strength of evidence and the extent of the applicability of results should be discussed to aid decision-makers in interpreting the results. The strength of evidence might involve a consideration of the methodological limitations of the included studies in the meta-analysis and the methods used that might affect practical decisions about healthcare or future research. The extent of applicability of the results is very important because the circumstances of the studies included in the meta-analysis are not necessarily the same as others. Discussion should focus on the spectrum of circumstances to which the evidence is likely to be applicable or not applicable and predictable variation in effects across different circumstances. Examples include biological and cultural variation, variation in compliance and variation in baseline risk.

The issue whether to adjust the clinical results from the meta-analysis is a complicated one. For example, should adjustments be made for the likelihood of lower compliance in actual clinical use? Poor compliance reduces the apparent effectiveness, but also the costs. Alternatively should adjustments be made for the possibility that the trial protocol affect cost or benefits? (e.g. less depressed people are less likely to comply with a/d therapy and are most likely to spontaneously recover and how would average effectiveness change in a different compliance pool).

O'Brien et al. (1995) wanted to assess the cost-effectiveness of H. Pylori eradication relative to alternative pharmacologic strategies in the long-term management of persons with confirmed duodenal ulcer (D.U.). A key factor was the probability of ulcer recurrence (at six months and 12 months) under the various regimens. Given the large number of randomised trials, they performed a meta-analysis to estimate the probabilities. However, in the ulcer trials, the rates of recurrence are estimated by endoscopic examination. This is problematic as economic evaluation seeks to estimate costs and consequences as they would occur in normal clinical practice, in which patients would not be endoscoped unless they had bothersome symptoms and consulted their physicians. Therefore it is likely that some of the ulcers detected by endoscopy would be asymptomatic or silent. In order to account for this O'Brien et al.(1995) reviewed the trials that reported symptomatic and asymptomatic recurrence separately and estimated that about 75% of recurrences determined by endoscopy are symptomatic (See box 4). The adjusted rates of ulcer recurrence were used in their cost-effectiveness model. The issue is whether effectiveness estimates of each study to be included in the meta-analysis should be adjusted a priori with the meta-analysis, or ex ante.

Box 4: Adjustment to Trial-Based Data in a Study of Ulcer Therapy

	Ulcer Recurrences Per 1000 Patients		
Strategy	Total	Symptomatic	Expected one-year cost per patient
1. Heal and wait; treat DU recurrence with:			
(a) ranitidine	108 (100%)	81 (75%)	329
(b) Omeprazole	108 (100%)	81 (75%)	341
2. Heal and H. Pylori eradication immediately with:			
(a) omeprazole and amoxicillin	20 (100%)	15 (75%)	272
(b) triple therapy	20 (100%)	15 (75%)	253

Adapted from O'Brien et al. (1995)

3.8. Improving and updating reviews

Cumulative meta-analysis entails repeating at periodic intervals, the steps in the original meta-analysis. From a technical viewpoint, the establishment of databases to allow the prompt updating of meta-analyses presents many opportunities. As these databases become more developed, it will become easier for economists to update the clinical evidence on which their economic evaluations are based. Clinical practice is subject to rapid change, but equally policy makers need to make the best decisions they can today, recognising that the data is not (may never) be perfect. The importance of updating a meta-analysis is also highlighted by the fact that studies with positive or significant results are often published ealier than those with negative or non-significant results (Song et al., 1999). The treatment effect may therefore be overestimated if studies that become available sebsequently are not included.

4. ISSUES SURROUNDING THE META-ANALYSIS OF ECONOMIC EVALUATIONS

Intuitively, health economists have a number of reservations towards combining economic data. Firstly, there has been substantial discussion on the reliability of cost-effectiveness 'league tables' and the degree of comparability between individual economic studies owing to different technical specifications (Mason et al. 1994). It is also not immediately evident which technical components of economic evaluation can be summarised. Secondly, doubts have been expressed on the transferability of economic data from setting to setting as resource usage or costs may be specific to countries or regions (Drummond et al. 1992).

Despite these concerns, there are several reasons why health economists might be interested in conducting a meta-analysis of existing economic evaluations. In practical terms, performing a meta-analysis could be potentially less costly and less time-consuming than performing further primary economic studies (Mulrow 1995) though this merits further investigation. For example, the alternative to a meta-analysis might be to conduct a much larger economic study than those already in existence. Universally, but especially apparent in developing countries, there are healthcare providers, researchers and policy makers with access to severely limited financial resources for obtaining research-based information.

Also, there are situations when decisions need to be made based on limited information. Meta-analysis may give decision-makers confidence that they are making the best use of what economic evidence is available at the time. The use of meta-analysis in the reimbursement approval process of drugs represents a potential application. Currently two jursidictions, the Commonwealth of Australia and the Province of Ontario, Canada have cost-effectiveness as a criterion in order to secure reimbursement. Currently assessments are based on one or more primary economic evaluations. However, as more studies are published, meta-analysis could potentially assist the reimbursement authorities in their decisions through summarising the best available economic evidence at the time alongside the clinical evidence.

From a technical point of view, meta-analysis may provide a solution to the issue of generalisability. Economic evaluations have often been critiqued as being specifically restricted to particular contexts or settings. Furthermore, a structured assembly of results from previous studies allows for the exploration of reasons for inconsistencies and variability. Finally, meta-analysis may provide a stimulus for updating knowledge in a particular disease area and providing guidance concerning the design of future economic studies.

5. REVIEW OF ECONOMIC EVALUATIONS CONTAINING META-ANALYSES

To date, relatively few economic studies have employed data from meta-analysis as a source of estimates of treatment effectiveness. Mugford et al. (1989) conducted a cost-effectiveness study of antibiotic prophylaxsis in caesarian section, based on data from a meta-analysis of 58 controlled trials, which estimated that the odds of wound infection reduced by 50-70%. Mugford et al. (1991) also employed a meta-analysis of trials to estimate the effects of corticosteroids and surfactants for

reducing respiratory distress syndrome and death before discharge. In their comparison of anti-fungal agents in terms of cost-effectiveness for the treatment of onychomycosis of fingernails and toenails in 13 countries, Arikian et al. (1994) conducted a worldwide meta-analysis of randomised controlled trials to derive clinical success rates, relapse rates and side-effect rates. Similarly meta-analysis has been applied to estimate outcome probabilities in decision analytical models. Einarson et al. (1995) employed a meta-analysis of 34 studies to derive success rates, relapse rates and adverse events for their decision analysis model in the examination of oral antidepressants in the management of major depressive disorders. Jefferson and Demichelli (1994) have undertaken a meta-analysis of both the epidemiological and economic variables pertaining to vaccination against hepatitis B. The meta-analysis of economic data is, however, at an early stage of development.

The conduct of meta-analyses for the purposes of economic evaluation has been far from adequate. In a search of the NHS Economic Evaluation Database, 28 economic evaluations (see table 1) were retrieved which had derived their measure of effectiveness based on a meta-analysis of clinical studies. Yet in many cases the authors failed to satisfy some of the requirements for a sound meta-analysis (box 5).

Box 5: Limitations of Meta-Analyses of Clinical Data in 28 Economic Evaluations

Limitation	**Number of studies**
Failure to state source of studies	15
Small number of studies or number of studies not stated	10
Mixing of experimental and observational study designs	12
No quality assessment of studies	22
No weighting of studies	20
Heterogeneity not investigated	21

6. DISCUSSION

Meta-analysis provides a family of statistical techniques for combining the results of similar studies. It is a useful tool for economists to explore estimates of effectiveness of interventions. This paper has attempted to highlight the issues and considerations that must be addressed when designing and conducting a meta-analysis of clinical data for use in an economic evaluation.

To address a specific resource question, an economic evaluation should be based on reliable information about the relative effect of treatments that are compared. For the purpose of economic evaluation, a meta-analysis of clinical data should address a specific clinical question, determine which studies and data are valid, and how they are synthesised. It is appreciated that meta-analyses are retrospective in that they are potentially subject to many of the same biases which affect other retrospective studies. Therefore a meta-analysis is reliant upon good clinical study methodology as well as good review methodology.

Although more and more economic evaluations are being performed alongside clinical trials, it is unlikely that economists will ever dispense with modelling. In fact, modelling is ‘an unavoidable fact of life’ and the need for the meta-analysis of clinical data will remain with us for many years to come. Obviously there still exists much potential for development. Performing economic evaluations based on effectiveness data from meta-analysis makes a lot of sense because meta-analysis can provide reasonable effectiveness estimates for economic evaluations when no large trial has been performed.

The next step? In the summing up of the Potsdam Consultation on meta-analysis in March 1994, Cook et al. recommended that economists and epidemiologists should collaborate to determine how to incorporate economic evaluation into systematic reviews. However before this next step can be a possiblity, economists should seek to strengthen the methodology of economic evaluation as far as possible, and one of these facets is to improve the quality of clinical effectiveness data on which economic evaluation is based.

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Table 1 Studies Containing 'Meta-Analyses' From the NHS Economic Evaluation Database

	Authors	Health care intervention	Outcomes	Method of combination						Results
				Source	No	Study Design	Quality assessment	Weighting	Heterogeneity investigated	
1	Avruch S, Cackley AP 1995	Special supplementary food programme	Low birthweight rates Very low birthweight rates	Not stated	17	Not Stated	No	Yes (sample size)	No	Reduction of low birthweight babies by 3.01% Reduction of very low birthweight babies by 1.13%
2	Blaufox MD et al. 1996	Captopril technology, Doppler, captopril test and arteriography	Sensitivity, specificity, positive predictive value	MEDLINE	47	Not stated	No	Yes (sample size)	Yes	e.g. Diagnostic test captopril renogram sensitivity = 89% specificity = 92% positive predictive value = 83%
3	Chancellor JV et al. 1997	Lamivudine (3TC) and zidovudine (ZDV) combinayion therapy	Risk of disease progression, risk of AIDs and risk of death	Not stated	6	RCTs	No	No	No	Relative risk = 0.509
4	Chang RW et al. 1996	Total hip arthroplasty (THA) for the osteoarthritis of the hip	Efficacy of primary and revision THA, operative mortality, long-term infection failure rates, long-term asceptic failure rates and natural progression of functional class III osteorthritis	MEDLINE	25	Not stated	Yes	No	No	Not stated

Table 1 cont'd

5	Cummings SR et al. 1989	Physician advice to stop smoking	Quit rate of 1 year	MEDLINE +review bibliographies	7	RCTs	No	No	No	Quit rate at 1 year = 2.7%
6	Edelson JT et al. 1990	Monotherapies to reduce hypertension	Reduction in blood pressure	Databases+ bibliographies	153	RCTs	Yes	Yes (inverse of variance)	No	Change in DBP = -9.8 (propranolol hydrochloride), -7.4% (hydrochlorothiazide), -10.0 (nifedipine), -8.1% (prazosin hydrochloride), -4.9 (captopril)
7	Einarson TR et al. 1995	Oral antidepressant therapies	Success rates, relapse rates and adverse events	Not stated	34	RCTs	Yes	No	Yes (random effects)	Success rate=50.9% (TCA), 49.2% (HCA) 30.3% (SSRI)
8	Gabriel SE 1995	Misoprostol prophylaxis in the prevention of gastric ulcers	Probabalities of endoscopically proven ulcer, hospitalisation, effectiveness, relative risk, proportion aged 60+	Not stated	Not stated	Not stated	No	No	No	Probability of endoscopically proven ulcer = 0.216, effectiveness = 0.74, relative risk = 3.0, proportion aged 60+ = 0.5
9	Gifford DS et al. 1995	Peripartum management of term breech pregnancy	Caesarian rates, proportion of cephalic presentations in labour, maternal & infant mortality and morbidity	MEDLINE+ other databases	4	RCT	No	No	No	Caesarian rate = 24.5%
10	Goel et al. 1989	Total parenteral nutrition	Surgical complication rate, TPN complication rate	Litarature searches + investigators	18	RCT	Yes	Yes (quality)	No	Risk of iatrogenic complication=6.7% (TPN)

Table 1 cont'd

11	Goldman L et al. 1988	Beta-adrenergic therapy	Mortality rates	Review articles+ citations from original publications	21	RCT	Yes	No	No	Mortality = 23.7% (1st yr), 20.4% (2nd year), 30.9% (3rd year)
12	Johannesson M. 1994	New antihypertensive drugs	Reduction in CHD and stroke	Not stated	Not stated	Not stated	No	No	No	Reduction in CHD = 16%, reduction in stroke = 38%
13	Johannesson M. 1995	Antihypertensive drugs	Reduction in CHD and stroke	Not stated	Not stated	Not stated	No	No	No	Reduction in CHD = 38%, reduction in stroke = 16%
14	Johannesson M. 1996	Antihypertensive drugs	Reduction in DBP, reduction in CHD and stroke risks	Databases, bibliographies, meeting abstracts, personal communication	17	RCT	No	Yes	Yes	Mean decrease in DBP =5-6mmHg; CHD risk reduction=16%, stroke risk reduction=40%
15	Jonsson BG 1994	Antihypertensive drugs	Reduction in CHD and stroke	Not stated	Not stated	Not stated	No	No	No	Reduction in CHD = 38%, reduction in stroke = 16%
16	Marchetti et al. 1996	Oral pharmacologic therapies	Mycologic cure rate	Review article bibliography	14	6 RCT, 8 unknown	No	No	Yes (random effects)	Mycologic cure rate=41%(GRI), 79%(ITR), 16%(KET), 87% (TER).
17	Nease RF et al. 1994	Preference-fixed protocols versus preference-flexible protocols in the treatment of mild hypertension	Reduction in rate of myocardial infarction and stroke	Not stated	8	RCT	No	No	No	Reduction in myocardial infarction = 9%, reduction in stoke = 40%
18	Nuijten MJC et al. 1995	Behavioural and mental disorder drugs	Time without depression	Not stated	Not stated	Not stated	No	Yes (proportion of market share)	Yes	Time without depression = 8.2 months (standard therapy), 7.6 months (citalopram)

Table 1 cont'd

19	O'Brien B et al. 1994	Prevention of DVT after total hip replacement using LMW heparin	Deep-vein thrombosis risk	Not stated	10	RCT	No	No	Yes	Risk differenceo f DVT = -7.1 (overall, -8.2 (distal)
20	O'Brien B et al. 1995	Eradication of H. pylori for confirmed, but uncomplicated duodenal ulcer	Ulcer recurrence rates	MEDLINE	12	RCT	No	Yes (inverse of variance)	No	Pooled rate of recurence = 65.4% (placebo), 12.8% (rantidine)
21	Oster et al. 1986	Nicotine gum to facilitate smoking cessation	1 year cessation rate	Not stated	Not stated	RCT	No	No	No	Cessation rate = 4/5% (advice & counselling), 35% (gum)
22	Oster et al. 1987	Stockings, intermittent pneumatic compression, heparin and dihydroergotamine for the prevention of DVT after surgery	Rate of DVT, pulmonary embolism and death	Not stated	Not stated	RCT	No	No	No	Signifiant difference in clinical outcomes for stockings vs prophylaxis
23	Sintonen H, Alander V. 1990	Omeprazole	Healthy days	Not stated	Not stated	RCT	No	No	No	Healthy days= 121.5(Omeprazole), 88.2 (ranitidine), 89.6 (Sucralfate)
24	Sonnenberg A et al. 1995	Duodenal ulcer management by H2 anatagonists, selective vagotomy and antibiotics	Healing rates and recureence rates	Not stated	Not stated	Not stated	No	No	No	Healing rate = 77%(H2 anaag onists), 95% (anti secretory+antibiotics); recurrence rate=2.5% (H2 antagonists), 25% (vagotomy)

Table 1 cont'd

25	Tasch R et al. 1996	Histamine H2 Receptor Antagonist (H2RA) famotidine	Symptom relief obtained with treatment	MEDLINE	19	2 RCT, 17 unspecified	No	No	No	Symptom relief=0.68 (antacids), 0.63 (placebo), 0.75(H2RA), 0.80 (PPI)
26	Van den Boom et al. 1996	Omeprazole and reflux surgery	Ability to cure, remission, reduction in hospitalisation	MEDLINE	25	Not stated	Yes	Yes (RCT design criteria)	No	Effectiveness (healing stage) = 91% (omprezole 40mg); = 88% (maintenance stage)
27	Walan et al. 1994	Treatment of duodenal ulcer with omeprazole or ranitidine	Healing rates, relapse rates, risk of death	Not stated	15	RCT	No	No	No	Healing rate=93% (omeprazole); 83& (ranitidine); relapse risk=6.5% (without txt), =2.0% (with txt). Risk of death=20%
28	Wong et al. 1995	Treatment of hepatitis B e antigen positive chronic hepatitis B with interferon-alpha-2b	Disapperance of HBeAg and HBsAg and the relative risk for developing cirrhosis	MEDLINE	9	RCT	No	No	Yes	Pooled odds for interferon-alpha-2b for HBeAg disappearance =7.4%. Relative risk for developing cirrhosis=2.39