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Review

Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses

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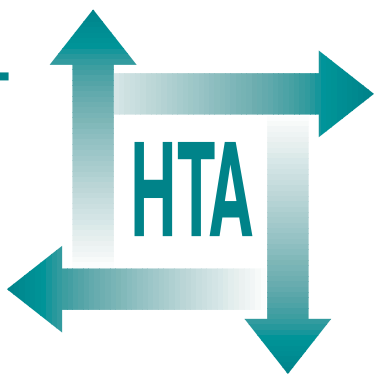

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Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Methodology Panel and funded as project number 93/52/04.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

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Contents

List of abbreviations

ACP	American College of Physicians
CDSR	Cochrane Database of Systematic Reviews
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DARE	Database of Abstracts of Reviews of Effectiveness
DVT	deep-vein thrombosis
ICC	intra-class correlation coefficient
LMWH	low-molecular-weight heparin
MA	meta-analysis*
MAPJ	meta-analysis published in peer-reviewed journal
MARCT	meta-analysis of randomised controlled trial
MeSH	Medical Subject Headings
MH	Mantel-Haenszel
NLM	US National Library of Medicine
OR	odds ratio
RCT	randomised controlled trial
ROR	ratio of odds ratios
SD	standard deviation

* Used only in tables

Executive summary

Objectives

- To examine the issue of quality assessment of randomised controlled trials (RCTs) included in meta-analyses.
- To provide empirically based recommendations on how to conduct meta-analyses with respect to quality assessment.

Five projects were carried out to achieve these objectives.

1. A database of meta-analyses was developed that provided the majority of data for the remaining projects.
2. Journal editors, methodologists and systematic reviewers associated with randomly selected articles in the database were surveyed about their views on the assessment and reporting of quality of the primary trials included in meta-analyses.
3. The frequency of quality assessment and the methods used were investigated using a sample of meta-analyses (n = 240) from the main database.
4. The effect that the quality of RCTs included in a meta-analysis has on estimates of intervention effectiveness was analysed using a sample of meta-analyses (n = 11 covering 127 RCTs) from the database.
5. Guidelines were developed on the basis of the evidence obtained in the other projects.

Data sources

A comprehensive list of studies was provided by an electronic search of databases including MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews (CDSR).

Study selection

Meta-analyses were selected. The inclusion criterion was that the study combined (pooled) the overall results of RCTs included in the meta-analysis.

Data extraction

Data extraction forms were used to extract the necessary data from the articles. Data extraction was completed in duplicate to reduce the chances of error. Inter-rater reliability was calculated before data extraction began.

Data synthesis

Quantitative analysis was difficult because of the nature of the research questions and was conducted only for the study examining the effect of RCT quality on estimates of intervention effectiveness. The data for the searching study and the survey, and the descriptive data for the quality assessment study, are discussed mostly in a qualitative manner.

Results

The overlap of articles and journals between MEDLINE and EMBASE was 80% and 87%, respectively. The database of 491 articles that was used comprised 455 meta-analyses identified by the MEDLINE search and 36 meta-analyses in the CDSR.

Response rates from the survey were 78%, 74% and 59% for reviewers (n = 121), methodologists (n = 55) and editors (n = 63), respectively. Over 90% of respondents stated that assessment and reporting of quality of RCTs included in meta-analyses was very or somewhat important. The use of RCT design features as inclusion criteria and using quality assessments to conduct sensitivity analyses were the most frequently endorsed methods of incorporating the quality assessments into meta-analyses. Most respondents believed that guidelines on the assessment and reporting of the quality of randomised trials would increase the rigour of reporting of published meta-analyses and make interpretation easier.

Of a sample of 240 meta-analyses, trial quality was assessed in 48% and in half of these data on the reproducibility of the assessments were provided. Of the meta-analyses that assessed quality, only 25% incorporated trial quality into the analyses.

Masked and unmasked quality assessments were carried out on 127 RCTs included in 11 meta-analyses in the database. The assessments were made using a validated scale (1–5, higher scores indicate superior reporting) and individual components known to affect estimates of intervention effectiveness. Masked quality assessment provided significantly higher scores (mean = 2.74;

standard deviation (SD) = 1.10) than unmasked assessments (mean = 2.55; SD = 1.20). Low-quality trials were associated with an increase of 34% in estimate of benefit (ratio of odds ratios (ROR) = 0.66; 95% confidence interval (CI): 0.52, 0.83) compared with high-quality trials. Trials using inadequate allocation concealment, compared with those using adequate methods, were also associated with an increased estimate of benefit of 37% (ROR = 0.63; 95% CI: 0.45, 0.88). The average treatment benefit across all trials was 39% (OR = 0.61; 95% CI: 0.57, 0.65). Including only trials with low quality scores increased this effect to 52% (OR = 0.48; 95% CI: 0.43, 0.54), whereas including only trials with high quality scores reduced the effect to 29% (OR = 0.71; 95% CI: 0.65, 0.77). Using all the trial scores as quality weights reduced the effect to 35% (OR = 0.65; 95% CI: 0.59, 0.71) and resulted in the least statistical heterogeneity.

Conclusions

Indexing inconsistencies within and across databases pose challenges in searching for systematic reviews or meta-analyses. Our results suggest that it is necessary to search multiple databases to identify all relevant information. Journal indexers, authors and editors should collaborate to develop and implement criteria to help users of systematic reviews and meta-analyses identify relevant publications.

The systematic reviewers, methodologists and journal editors surveyed believed that assessment of trial quality was important. This contrasts with the infrequent reporting of trial quality in published meta-analyses. Future studies should address the issue of quality assessment. Consistent reporting of the design features of RCTs may help to enhance the rigour and clinical interpretability of meta-analyses.

Among a sample of meta-analyses from the database, individual components and scales were the methods most commonly used to assess trial quality. However when quality assessments were made, in most cases they were not incorporated into the analysis. This is important because the incorporation of quality assessments can alter the estimate of the benefit of intervention, regardless of which method of assessment is used.

The results from these studies also suggest that certain characteristics of the design and execution of RCTs impact on the probability of bias, and further research is needed on this. Investigations are also needed to clarify the value of masking studies before quality assessment and to determine the advantages of the various approaches to incorporate quality assessments into the analyses. Until such empirical evidence is presented, the guidelines outlined below are a useful tool with which meta-analysts, editors, peer reviewers and readers can deal with issues pertaining to quality assessment of randomised trials included in a meta-analysis.

Guidelines

- The quality of all randomised trials included in a meta-analysis should be assessed.
- Masked quality assessment should be considered, and meta-analysts should report masking methods used or their reasons for rejecting masking.
- Primarily evidence-based components (e.g. allocation concealment, double-blinding, type of randomised trial) should be used to assess quality. Topic-specific items should be part of the quality-assessment process.
- Scales used for assessment should have been appropriately developed and evaluated. A component approach has the advantage that it can be topic-specific. However, there is no compelling evidence to recommend a component approach over a scale approach or vice versa.
- Meta-analyses should incorporate an estimate of quality assessment into the quantitative analysis as a ‘first-line’ sensitivity analysis.

Chapter 1
Introduction

Background information

The role of meta-analyses

Evidence-based health care involves the systematic collection, synthesis and application of all available scientific evidence, when available, not just the opinion of experts. Meta-analyses are a key component of evidence-based health care. Such analyses pool individual studies (either observational or randomised controlled trials (RCTs)) to provide an overall estimate of the effect of the treatment under consideration. Meta-analyses offer several potential advantages including:

- a systematic and explicit method for synthesising the evidence, providing a quantitative overall estimate derived from the individual studies
- early evidence of the effectiveness of treatments (thus reducing the need for continued study)
- an opportunity to address questions in specific sub-groups that could not be examined in individual studies because of their smaller sample size.

The development and very rapid expansion of the Cochrane Collaboration[1] attests to the positive impact meta-analyses are starting to have in health care.

A powerful example of the effectiveness of meta-analysis was the publication, in 1990, of a meta-analysis describing the efficacy of corticosteroids given to pregnant women expected to deliver prematurely.[2] The results of the meta-analysis indicated that corticosteroids significantly reduced morbidity and mortality among the infants. The analysis convincingly showed that such evidence was available at least a decade earlier (i.e. 1980). Had such evidence been recognised at that time, unnecessary suffering might have been avoided.

Assessing the quality of RCTs

The present report concerns the meta-analysis of RCTs. The first 'modern' RCT was published more than four decades ago.[3] Since then there have been substantial refinements in design.[4–6] This methodology has gained favour with healthcare researchers because of its potential to control for bias. Today, the RCT is considered the most reliable method of assessing the efficacy of healthcare interventions.[7] However, poorly conducted RCTs may yield misleading results. It is therefore important for all involved in health care to be able to assess the reliability and validity of the research evidence available.

Quality is a construct (a concept) that has been defined in a variety of ways. In this report our focus is on internal validity and here quality is defined as 'the confidence that the trial's design, conduct, analysis and presentation have minimised or avoided biases in its intervention comparisons'. We recognise however that this excludes other methodological aspects of quality – for example, those concerned with the precision and reliability of measurements, or estimation of compliance. In most instances, however, the only way to assess the quality of a trial is by relying on the information contained in the report. Therefore, it is important to recognise that an RCT with a biased design that is well reported could be judged to be of high quality, and a well-designed RCT that is poorly reported could be judged to be of low quality.

The need to assess quality stems mainly from a desire to estimate the effects of bias on the results of an RCT. Differences in quality between RCTs may indicate that some are more biased than others. Meta-analysts need to take this into account.

Three approaches to assessing the quality of reports of RCTs have been developed: component assessment, checklists, and scales. By component assessment we mean items such as randomisation and blinding. Altman and Doré[8] reviewed 80 reports of trials published in 1987 and 1988 and found that information about the type of randomisation was reported in only 32 (40%) of the trials.

To avoid selection bias in assigning patients to intervention, concealment of allocation is essential, and should be feasible in all trials. Chalmers and colleagues[9] reviewed 145 reports of RCTs concerning the treatment of acute myocardial infarction to assess whether concealment of patient assignment affected trial results. Their results indicated that trials for which concealed assignment was reported had smaller treatment effects (as defined by case-fatality rates) than trials with unconcealed assignment. Schulz and colleagues[10,11] reviewed 250 reports of RCTs and found that the odds ratios (ORs) in the

unclearly concealed trials were, on average, 30% (95% confidence interval (CI): 21%, 38%) lower than in the adequately concealed trials – that is, the unclearly concealed trials estimated the intervention to be more effective that it really was.

Colditz and colleagues have reported similar results concerning the level of blinding. In a review[12] of 113 reports of clinical trials these authors noted that trials for which a higher level of blinding was reported tended to show smaller treatment effects than trials for which lower levels of blinding were used (e.g. double-blind versus single-blind). In summary, the lower the level of blinding the greater the increase in treatment effectiveness. These results, and the results of Chalmers and colleagues[9] described above, have been corroborated by Schulz and colleagues.[13]

These studies have provided important information on the quality of reporting of individual items and highlighted how inadequate reporting should lead readers to be sceptical about the validity of trial results. Unfortunately, assessing one component of a trial report may provide only minimal information about its overall quality.

Checklists and scales provide, respectively, a qualitative and a quantitative estimate of the overall quality of an RCT. The development of checklists is a logical extension of component assessment of quality. As such, checklist items do not have numerical scores attached to them. Both checklists and scales include itemised criteria for comparing RCTs. The main difference between them is that in a scale each item is scored numerically and used to generate an overall quality score. In a systematic review of the literature, nine checklists and 25 scales were identified through computer searches of the healthcare literature and direct contact with several developers of scales and checklists.[14]

Mahon and Daniel[15] used a checklist to review 203 reports of drug trials published between 1956 and 1960 in the *Canadian Medical Association Journal*. Only 11 reports fulfilled the authors' criteria of a valid report. Several scales have been developed to assess the quality of reports of RCTs.[14] Unfortunately, the evidence suggests that the vast majority of scales have significant shortcomings and have not been developed with sufficient rigour.[14] Scales vary in size, complexity, and level of development. It might be useful to know whether different scales applied to the same trials yield similar results. Such information could guide quality assessors in their choice of scale. There would be little advantage in using a 15-item scale to assess quality if similar results could be obtained by using a three-item scale.

Powe and colleagues[16] assessed the quality of 100 contrast media trials published between 1982 and 1987 using a scale developed by Chalmers and coworkers.[17] These authors reported a mean quality score of 39% (standard deviation (SD) = 12). Andrew used his scale[18] to assess the quality of 49 contrast media trials published during the 1980s in five leading radiology journals. He reported[19] a mean quality score of 70% (SD = 14.6). Although there were some differences in the trials reviewed by the two groups, it is unlikely that these differences explain the wide variation in the quality assessments.

Additional research suggests that different scales are bound to generate discrepant results. A study was undertaken to establish whether different scales gave different quantitative and qualitative assessments of the quality of RCTs.[20] The members of the research team first trained themselves in assessing quality using six published scales. Each member of the group used at least two scales to assess each trial. During the study each group member independently assessed the quality of 12 out of 15 trials (the remaining three trials were either available only in a technical report or not published in English) used in a meta-analysis of antithrombotic therapy in acute ischaemic stroke.[21] After scoring was completed, the results were reviewed and differences were resolved through consensus and arbitration.

The results showed that overall quality scores for each trial varied greatly across scales, ranging from 23% to 74% of the maximum possible value. Similarly discrepant results were obtained using rank scores of individual trials. These results suggest that different trials might be included or excluded from a meta-analysis depending on the scale used to assess quality and the methods of including quality scores in the review. In contrast to these results, Detsky and colleagues[22] used two scales included in the study described above[20] to assess the quality of 18 trials used in a meta-analysis of parenteral nutrition. They reported only minor differences in raw scores of quality, and rankings of quality remained similar across trials.

Incorporating quality scores into meta-analyses

At least four ways[22–25] of incorporating quality scores into a meta-analysis have been suggested:

- using threshold scores for inclusion or sensitivity analyses

- using the quality score as a weight
- performing cumulative meta-analysis using quality scores as the input sequence
- visual plots.

There is little evidence supporting the validity and relative importance of any of these methods. The use of the threshold approach – perhaps the most frequently recommended method – may profoundly affect the number of trials included in a meta-analysis. This approach was used as a decision aid for the inclusion of trials in the antithrombotic meta-analysis previously discussed.[20] When the mean quality score was used as the threshold score, approximately 50% of the trials (depending on the scale used to assess quality) would not have been included in the analysis. This proportion increased dramatically, to about 75%, if the mean quality score plus one standard deviation was used as the threshold score. When the median quality score was used as the threshold score, approximately 40% of the trials would not have been included in the analysis. These results pose serious problems for the meta-analyst. If quality scores influence the number of trials included in the quantitative analysis part of a meta-analysis, they can easily affect the statistical result of the overview.

There is evidence that the quality of the trials included can affect the results of meta-analyses. Nurmohamed and colleagues[26] reviewed trials comparing low-molecular-weight heparin (LMWH) with standard heparin in proximal deep-vein thrombosis (DVT). They reported a statistically significant beneficial effect of LMWH in reducing DVT when all trials were used in the analysis. When the analysis was limited to those trials which were described as having 'strong' methodological quality, both treatments appeared to be less effective in preventing DVT and the difference between them was not statistically significant.

Results similar to these, but in the opposite direction, have also been reported. In a meta-analysis[27] of diabetic education programmes, no statistically significant beneficial effect of the programmes was found when all trials were included in the analysis. When only reports of 'good' methodological quality were analysed there was a statistically significant benefit of the programmes.

The need for more evidence

More than 10 years ago it was suggested that the quality of clinical reports should be assessed under blind conditions.[9] Empirical evidence to support this recommendation has recently been reported. A comparison of scores given to the same set of papers by two groups of judges allocated randomly to conduct the assessments under blind or open conditions showed that blind assessments of the reports produced significantly lower and more consistent scores than open assessments.[28] Over the last few years the number of published meta-analyses has grown substantially.[29] This is likely to continue as the Cochrane Collaboration matures. Even though the assessment of the validity of the primary RCTs is regarded as one of the key components of a meta-analysis, many fundamental questions remain. In this report we describe five projects that provide information to further our understanding of assessing quality in meta-analyses.

Research questions addressed in this report

Chapters 2–6 describe the methods and results of the five projects that are covered by this report. The research questions addressed in the projects are summarised below.

Chapter 2

Clinicians, practitioners, patients and policy makers are interested in the results of systematic reviews. The validity of these reviews depends on the review methodology and, in part, on the quality of the included trials. Chapter 2 describes the development of a database used to study the assessment of the quality of reports of randomised trials included in systematic reviews and meta-analyses.

Chapter 3

Meta-analytic design features and reporting styles are not standardised and therefore may be implicitly or explicitly set by those who work in this area. A survey of a broad spectrum of editors, methodologists, and meta-analysts was carried out to explore the current convictions and controversies in assessing quality in meta-analyses.

Chapter 4

The extent to which a meta-analysis could guide healthcare decisions depends, in part, on the quality of evidence available. In chapter 4 the different methods of quality assessment in masked and open conditions, and the frequency of their use, are examined. The methods used to incorporate the assessments into the results of the meta-analyses to reduce bias are also considered.

Chapter 5

There is little evidence available on which reviewers can base an assessment of whether one method of quality assessment provides a more biased estimate than any other one. To assess whether the method of quality assessment influences estimates of treatment effectiveness a method of quality assessment of RCTs using a validated scale approach is compared with one involving individual components.

Chapter 6

Many questions arise with respect to quality assessment when conducting meta-analyses. Relevant evidence is necessary for meta-analysts to make a decision on how to proceed. The purpose of the project reported in this chapter was to develop meaningful guidelines for the assessment of quality of RCTs included in meta-analyses. These guidelines are evidence-based and aimed at all those involved in the conduct of meta-analyses.

Chapter 2

Searching for systematic reviews and meta-analyses: déjà vu

Introduction

The information age is changing the way clinicians browse the medical literature and seek research results for decision-making purposes. Although practitioners, patients and policy-makers increasingly obtain information from the Internet, the traditional source of peer-review research is biomedical journals. The clinical information needs of physicians are variable and remain ill-defined.[30] Because of the large quantity of information available, clinical informatics is becoming an increasing necessity for the timely acquisition of relevant research.[31] Searching is an important process in conducting a systematic review or a new study because the first step is to ascertain whether the research has been conducted previously. Without reliable methods for identifying all the relevant studies, it is difficult to answer this question.

In addition to their clinical uses, systematic reviews are also increasingly being used as effective sources to address important methodological questions[32] regarding the conduct and reporting of clinical trials and systematic reviews. We set out to develop a comprehensive database of systematic reviews to address several questions regarding the use of quality assessments within these reviews.

Methodology

Searching for systematic reviews: databases and search strategies

We began by conducting a MEDLINE search (Ovid Technologies, Inc.) from 1 January 1966 to 31 December 1995 to identify systematic reviews. The search strategy included search terms as Medical Subject Headings (MeSH), text words and publication types. Abstracts retrieved by the search were reviewed by one of us (ALJ). Determining whether articles were in fact systematic reviews was difficult because the methodology sections were insufficiently described in the abstracts. Furthermore, the citations were not indexed as 'systematic reviews' by the US National Library of Medicine (NLM). As a result, we decided to obtain and read the full systematic reviews. As an initial step, we retrieved hard copies of only 50 randomly selected reviews to ascertain fulfilment of eligibility criteria.

Eligibility criteria

To be considered a systematic review the article had to state:

1. the name of database(s) searched
2. the year(s) searched
3. the search terms included.

We found, however, that the majority of the articles failed to report this information in the methodology section. Consequently, we decided to focus on identifying meta-analyses of RCTs (MARCTs).

Searching for meta-analyses: databases and search strategies

To identify meta-analyses we completed an electronic search of MEDLINE (Ovid Technologies, Inc.) from 1 January 1966 to 31 December 1995 (appendix 1). The search strategy included 21 search terms as MeSH, text words and publication types. The MEDLINE search was translated using the appropriate terms to search EMBASE (SilverPlatter Information) from 1 January 1980 to 30 November 1995 (appendix 2). Both search strategies aimed to identify meta-analyses and systematic reviews published in any language.

The Cochrane Database of Systematic Reviews (CDSR) (1995, issue 2) was also searched for possible meta-analyses, as was the Database of Abstracts of Reviews of Effectiveness (DARE). Both CDSR and DARE were searched within The Cochrane Library (Update Software Ltd). DARE did not provide complete bibliographic information for each reference and we could not retrieve hard copies of the papers. We therefore elected not to include it in our search for meta-analyses. (Current versions of DARE now include appropriate sources.)

Quality control

Once the MEDLINE search strategy was refined, as a quality-control check we determined its sensitivity (i.e. the number of meta-analyses identified by a

search method expressed as a percentage of the total number of relevant articles identified) and precision (i.e. the number of meta-analyses identified by a search method expressed as a percentage of the total number of articles identified by the MEDLINE search strategy).

Citations identified by the search strategy were compared with established bibliographic lists of meta-analyses.[33,34] Systematic reviews in the American College of Physicians (ACP) Journal Club were also used as a representative collection of high-quality systematic reviews.[35] On the basis of the results of the quality-control efforts, the search strategy was modified to maximise sensitivity and precision.

Eligibility criteria for the MARCT database

A coding system was developed (*a priori*) for each article for its potential inclusion in the database. Each article identified by the MEDLINE, EMBASE or CDSR search was evaluated for inclusion based on the following four criteria (appendix 3).

1. Eligibility. (Did the article refer to meta-analyses? Yes, No, Probably.)
2. Publication type. (Was the paper a meta-analysis, editorial, or a methodological paper?)
3. Primary studies. (Did the meta-analysis include RCTs, observational studies, or mixed studies?)
4. Type of research question. (Was the article focused on treatment, diagnosis, prevention, aetiology, association, prognosis or economics?)

Two members from the research team (ALJ, DM) independently assessed each article. Disagreement was resolved by consensus.

Data extraction

To address the issues of sensitivity, precision, and overlap of articles and journals between databases, we extracted the following information from each database: number of articles identified by the search strategy, year of publication, number of journals, total number of articles coded as meta-analyses, number of articles coded as MARCTs and number of articles coded as observational studies.

Results

The MEDLINE, EMBASE and CDSR searches identified 1467, 3159 and 65 articles, respectively (*Table 1*). The articles were published between 1977 and 1995 (MEDLINE), between 1985 and 1995 (EMBASE), and in 1995 (CDSR).

TABLE 1 *Overall results of the MEDLINE, EMBASE and CDSR search for meta-analyses*

	MEDLINE	EMBASE	CDSR
No. of citations identified	1467	3159	65
No. (%) of citations retrieved	1437 (98%)	91 (3%)	65 (100%)
No. requiring translation	45	0	0
Total number coded	**1392**	**91***	**65**
No. (%†) coded as MARCTs	455 (77%)	21 (30%)	36 (92%)
No. (%†) coded as MA-Observational	38 (6%)	18 (26%)	0
No. (%†) coded as MA-Mixed	96 (16%)	30 (43%)	3 (8%)
Total no. (%‡) coded as meta-analyses	**589 (42%)**	**69 (76%)**	**39 (60%)**
No. (%†) with 'meta-analysis' in title and coded as meta-analysis	426 (72%)	39 (57%)	0
No. (%†) coded as meta-analysis but not indexed as meta-analysis in the title	163 (28%)	0¶	0
Unique number of journals	15 (13%) (n = 118)	22 (40%) (n = 55)	1 (100%) (n = 1)
Unique number of articles	41 (20%) (n = 204)	69¶ (100%) (n = 69)	65 (100%) (n = 65)
Year of publication	1977–1995	1985–1995	1995

* *Unique to EMBASE*
† *Percentage of total number coded as meta-analyses (i.e. MEDLINE, n = 589; EMBASE, n = 69; CDSR, n = 39)*
‡ *Percentage of total no. coded (i.e. MEDLINE, n = 1392; EMBASE, n = 91; CDSR, n = 65)*
¶ *The inclusion criteria for EMBASE articles were that they had 'meta-analysis' in the title and that they were unique to EMBASE*
MA, meta-analysis

The sensitivity of the MEDLINE search strategy was high: 1221 (85%) articles identified using MEDLINE were relevant. The specificity or precision of the MEDLINE search strategy when compared with established bibliographies was as follows: 34 (54%) in comparison with Jadad's pain thesis (n = 63); 17 (15%) in comparison with Dickersin's bibliography (n = 116); 63 (68%) in comparison with the ACP Journal Club (n = 93). The overall hit rate was relatively low: 114 articles (42%) were identified (*Table 2*).

The sensitivity and precision of the EMBASE search were not determined because we experienced some problems with the CD-ROM version of EMBASE and did not have the necessary technical support. Instead, we took a random sample of articles that were unique to EMBASE and had 'meta-analysis' or a variant of the word in the title. Our search identified 285 articles that met both of these criteria. We randomly selected 100 articles from the 285 identified.

TABLE 2 *Sensitivity and precision of the MEDLINE search*

	Broad search (low sensitivity)	Narrow search (high sensitivity)
Sensitivity		
Total citations	4955	1437
Likely relevant	33%	85%
Total citations × likely relevant	1635	1221
Specificity		
Journal Club therapy meta-analyses: n = 93 (1990–1995)	83 (89%)	63 (68%)
Dickersin's bibliography:		
n = 116 (1975–1988)	44 (38%)	17 (15%)
n = 40 (1985–1988)	19 (48%)	10 (25%)
Jadad pain: n = 63	58 (92%)	34 (54%)
Overall hit rate		
n = 272	185 (68%)	114 (42%)
Journal coverage		
Number of journals represented	> 500	453
Cost		
Time, cost ($2/paper)	4 months, $10,000	2 months, $3000
Time period covered		
1985–1994	1184	–
1985–1994, therapy only	3133	1043

From the articles identified, 1392 were retrieved and coded from MEDLINE and a further 91 from EMBASE and 65 from CDSR. Of these, 589 (42%), 69 (76%) and 39 (60%), from MEDLINE, EMBASE and CDSR, respectively, were coded as meta-analyses. Of the coded meta-analyses, 426 (72%), 39 (57%) and 0 had the word 'meta-analysis' or a variant of this word in the title, whereas the number of articles that were coded as meta-analyses but did not have the word 'meta-analysis' in the title was 163 (28%), 0, and 0 (*Table 1*). (For EMBASE, the inclusion criteria for these articles were that they had 'meta-analysis' or 'meta-analyses' in the title.)

Of the meta-analyses identified in the MEDLINE, EMBASE and CDSR databases, 455 (77%), 21 (30%) and 36 (93%), respectively, were MARCTs. In addition, 38 (6%), 18 (26%), and 0, respectively, were meta-analyses of observational studies and 96 (16%), 30 (43%), and 3 (8%), respectively, were meta-analyses of studies with mixed designs.

The degree of overlap of articles (MARCTs) and journals between MEDLINE and EMBASE was also examined. From MEDLINE (n = 204) to EMBASE (n = 69) the overlap of articles was 80% (*Table 2*). The overlap for journals from MEDLINE (n = 118) to EMBASE (n = 55) was 87%.

Discussion

Over the last few years there has been considerable interest in systematic reviews within medicine. More recently there has also been an interest in developing methodologies to help reduce or avoid bias in the conduct[36,37] and reporting[37,38] of systematic reviews. These efforts are likely to result in more valid reviews.

Despite such advances, there are still problems at the 'basic' level – namely, simply trying to identify systematic reviews and meta-analyses even though the search process has been simplified by more sensitive and precise search terms,[39] combination of terms,[40] and methodological filters.[41] There is a lack of consistency in indexing within and across databases.[33,42,43] Hunt and McKibbon found that even differentiating between systematic reviews and narrative reviews is complex because both are indexed as reviews.[44] We encountered considerable difficulty in identifying systematic reviews. By reviewing the title and abstract of an article we were unable to determine whether the article was a systematic review. Our decision to search for meta-analyses instead was based on these results.

An important issue concerns the question of whether or not it is justified to search EMBASE in addition to MEDLINE. We found that the overlap of MARCTs between MEDLINE and EMBASE was approximately 66%. The overlap of journals, however, was 91%. Differences in training, indexing rules, database structures and content between NLM and Elsevier may explain why the databases index similar journals but different articles.

Many of these problems are similar to those encountered in identifying RCTs. Dickersin and colleagues[45] noted that limiting a search for ophthalmology trials to MEDLINE would miss about 25% of relevant articles. Kleijnen and Knipschild[46] reported more discouraging results when trying to identify clinical trials in homeopathy, ascorbic acid and *Ginkgo biloba*. Searching one database yielded only about half of the relevant articles.[33]

To increase the sensitivity and precision of a search, standard terminology across databases should be established. It would also help if authors were asked to write a title and abstract that convey as much information as possible. Putting the word 'meta-analysis' or 'systematic review' in the title or abstract could be the most efficient way of alleviating problems that arise when searching. For clinical trials, this approach is used by journals endorsing the Consolidated Standards of Reporting Trials (CONSORT) statement[47] which requires that authors include 'randomised trial' in the title of their report.

Unless more attention is devoted to improving indexing of systematic reviews and meta-analyses we are likely to encounter similar problems to those experienced when searching for clinical trials. This problem should be addressed urgently. Systematic reviews are 'younger' (at least in medicine) than clinical trials. If action is taken now, it may be possible to minimise some of the problems that have plagued the indexing of clinical trials for so long. Several sources have noted a dramatic increase in the numbers of systematic reviews being published,[48] and this situation is unlikely to change in the future. Given the impact of evidence-based medicine on patient care, the search process should be given considerable attention. We hope that indexers, authors and journal editors will collaborate to develop and implement standards for indexing to help clinicians and researchers to identify systematic reviews.

There are limitations to our work that need to be discussed. Firstly, only a small random sample of EMBASE was used for comparisons. Secondly, a quality control check was not conducted for the EMBASE search strategy. A third limitation is that we had very few non-English language meta-analyses in our sample. Nevertheless, we used the database of 491 identified MARCTs (255 from the MEDLINE search and 36 from the CDSR search; appendix 4) as the basis from which we derived the results presented in the following four chapters.

Chapter 3

Assessing reports of RCT quality in meta-analyses: a survey of reviewers, methodologists and editors

Introduction

Systematic reviews are used by clinicians, teachers, researchers and policy makers worldwide. For clinicians, summaries of the most current relevant literature on a topic can aid decisions about the care of individual patients. Systematic reviews are useful to teach physicians in training about the best evidence available on issues of diagnosis, prognosis and treatment.[49] For researchers, the foundation of modern grant proposals is a summary and critical appraisal of previously conducted research, highlighting what is known and areas of uncertainty requiring further investigation.[50] Health-policy decisions in the USA, Canada and the UK are increasingly being informed by systematic reviews.[51–54] A controversial international health issue relevant to each of these groups was highlighted by two systematic reviews on fluid resuscitation for seriously ill patients using colloids or crystalloids.[55,56]

The validity of systematic reviews of randomised trials is grounded in the extent to which bias is minimised in the conduct of the primary studies[9,57–59] and in the review process itself.[38,60–62] The need for rigorous reporting of randomised trials has also been emphasised recently[47,63–65] to promote transparent communication of study design, and to aid readers in drawing appropriate inferences from trial results. Quantitative systematic reviews, or meta-analyses, use statistical methods to combine the results of two or more studies. Meta-analytic databases are increasingly used to explore inferences about how study design affects trial results and, by extension, the results of meta-analyses.[13,22,66–70]

However, assessment of the rigour of randomised trials included in meta-analyses is variable, and when assessments are made, different methods are used.[34] Since the reporting of meta-analyses is not standardised, design features of included trials may not be presented, even when they have been critically appraised by reviewers. Meta-analytic reporting styles may be set implicitly by example (from systematic reviewers), explicitly by expert recommendation (from methodologists) and/or by journal policy (from editors). Therefore, we surveyed all three groups to explore current convictions about the quality assessment of randomised trials included in meta-analyses.

Methods

Sampling frame

To define our sample of articles, we searched MEDLINE and the CDSR (1995, issue 2) for meta-analyses of randomised trials of preventive or therapeutic interventions. We created a database by combining 455 meta-analyses identified on MEDLINE with all 36 meta-analyses from the 65 systematic reviews comprising the CDSR. The refined MEDLINE search strategy[71] to identify the meta-analyses has been described in chapter 2.

To generate a list of respondents for our questionnaire, we randomly sampled 240 (49%) of the 491 articles. We identified the corresponding author of each meta-analysis (hereafter referred to as the systematic **reviewers**). Corresponding authors of the methodology articles represented the second set of respondents (the **methodologists**). The third group comprised editors of the journals in which the 240 randomly sampled meta-analyses were published (the **editors**).

Instrument development, format and administration

From the computerised bibliographic literature search, our personal files, and through two focus groups (each comprising five clinical epidemiologists) we generated candidate items for the questionnaire. To ensure clarity and to remove redundant or illogical items, we pre-tested the instrument by eliciting feedback from five methodologists. We mailed the modified questionnaire to all potential respondents. The first reminder was a postcard; the second reminder was sent by facsimile, accompanied by another copy of the questionnaire.

We asked respondents a set of questions to elicit their views on the assessment and reporting of the quality of randomised trials included in meta-analyses. For the purposes of this survey, we asked respondents to consider trial quality with reference to whether the design, conduct and analysis are undertaken in such as way as to minimise bias. We also provided space for commentary (appendix 5).

Analysis

We used the Pearson chi-square test to compare proportions across respondent groups.[72] We also separately compared editors with the combination of reviewers and methodologists to determine whether views on the use of reporting guidelines differed. We performed qualitative analysis of the commentary invited at the end of each item on the questionnaire, identifying emergent themes not captured by the quantitative analysis. These data were reviewed in duplicate independently by two of us (DJC, ALJ).

Results

The response rates were 121 out of 155 (78%) for reviewers, 55 out of 74 (74%) for methodologists and 63 out of 107 (59%) for editors. In total, of the 239 respondents, 145 (61%) were from North America, 80 (34%) were from Europe and 14 (6%) were from elsewhere. The overwhelming majority of reviewers, methodologists and editors reported that assessment of the quality of randomised trials included in a meta-analysis was very or somewhat important (97%, 94% and 100%, respectively).

In considering ways in which the quality of randomised trials included in a meta-analysis should be assessed, use of a series of items as in a checklist was recommended by 45% of reviewers, 57% of methodologists and 62% of editors. Assessment of a series of items that would generate an overall summary score (i.e. a scale) was recommended by 28%, 30% and 38% of reviewers, methodologists and editors, respectively. There was no significant difference in distribution of responses among the three groups ($p = 0.86$); editors gave similar responses to those of reviewers and methodologists combined ($p = 0.83$). Qualitative analysis yielded recommendations that a modest number of criteria should be used by systematic reviewers to assess and report trial quality. Reliance on universal criteria was considered inappropriate, and specific items tailored to the review question were suggested. For example, when evaluating trials comparing drug treatment with sclerotherapy for bleeding oesophageal varices, traditional blinding of patients and care givers is impossible and may not be a reasonable quality assessment item. However, evaluation of re-bleeding events using explicit, *a priori* criteria by an adjudication committee blinded to treatment may minimise the chance of a biased outcome assessment, and could be a more discriminating quality assessment item.

The majority of respondents believed that the methods used to develop a quality checklist or scale were somewhat or very important (reviewers, 92%; methodologists, 94%; editors, 95%). Several properties were considered necessary in the development and testing of a such a checklist or scale (*Figure 1*). Reviewers, methodologists and editors endorsed consideration of face validity (71%, 80%, and 64% of the three survey groups, respectively), construct validity (60%, 44% and 61%, respectively) and selection of items for which there is empirical evidence of bias (54%, 61% and 36%, respectively) in checklist or scale development. The majorities of reviewers, methodologists and editors (73%, 72% and 55%, respectively) considered that before checklists and scales were used to assess the quality of randomised trials, it

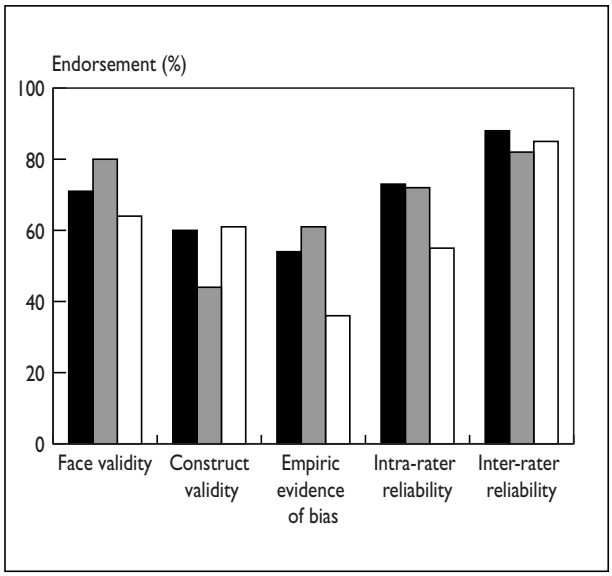

FIGURE 1 *Properties to consider in the development and testing of a checklist or scale to assess the quality of randomised trials included in meta-analyses*

The figure shows the proportions of systematic reviewers (■, n = 121), methodologists (▩, n = 55) and editors (□, n = 63) who endorsed consideration of several issues in the development and testing of a checklist or scale to assess the quality of randomised trials included in meta-analyses. For development, the issues considered were face validity, construct validity and items for which there is empiric evidence of bias. For testing, the issues of intra- and inter-rater reliability were considered.

was important to test intra-rater reliability; testing for inter-rater reliability was considered important by 88%, 82% and 85% of the three groups, respectively. There was no significant difference among respondents groups ($p = 0.23$) or between editors and reviewers and methodologists combined ($p = 0.16$). Qualitative analysis yielded suggestions that quality assessment should ideally be based on empirical evidence of bias, and that content validity should also be considered in the development of a quality checklist or scale (i.e. that the essential features of study design that minimise bias should be represented). Evaluation of 'potentially fatal flaws' of the primary trials, which may be specific to the trial design or clinical topic, was also suggested.

Several methods by which the quality assessments of randomised trials could be incorporated into meta-analyses were endorsed by various proportions of reviewers, methodologists and editors (*Figure 2*). They include trial quality features such as inclusion criteria (endorsed by 54%, 40% and 67%, of reviewers, methodologists and editors, respectively), describing the trials according to quality features (42%, 43% and 48%), statistically weighting trial results in the meta-analysis according to their quality (22%, 21% and 33%), conducting sensitivity analyses according to trial quality (63%, 66% and 43%), plotting trial results graphically according to their quality (43%, 34% and 30%), and using trial quality to order trials for cumulative meta-analyses (29%, 11% and 27%). There were no significant differences in responses among groups ($p = 0.24$), or between editors and reviewers and methodologists combined ($p = 0.06$). Other suggestions arising from the qualitative analysis emphasised a 'best evidence synthesis' approach to meta-analysis (e.g. summarising only the most rigorous randomised trials addressing a specific research question, selected according to a particular trial feature such as double-blinding).

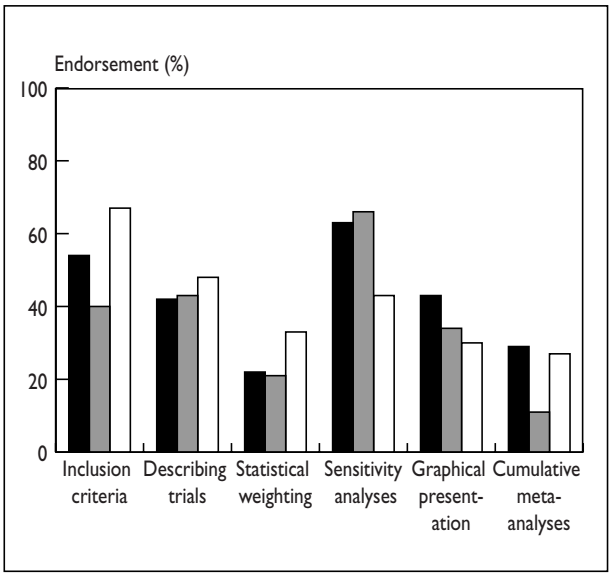

FIGURE 2 *Methods of incorporating trial quality assessments into meta-analyses*

The figure shows the proportions of systematic reviewers (■, n = 121), methodologists (▩, n = 55) and editors (□, n = 63) who endorsed several methods of incorporating trial quality assessments into meta-analyses. These included using trial quality features as inclusion criteria, describing trials according to design features, using trial quality as a statistical weight in the analysis, using quality assessments to conduct sensitivity analyses, graphically depicting trial quality in relation to trial results, and performing cumulative meta-analyses ordered by trial quality.

The majority of reviewers (88%), methodologists (84%) and editors (93%) believed that guidelines for assessing the quality of randomised trials included in a meta-analysis would be likely or very likely to increase the rigour of reporting of published meta-analyses (*Table 3*). There was no difference among the three respondent groups ($p = 0.48$), or between editors and the combined group of reviewers and methodologists ($p = 0.36$).

Most respondents also believed that such guidelines would be likely or very likely to make it easier for clinicians to interpret meta-analyses (reviewers, 60%; methodologists, 61%; editors, 76%; *Table 4*). However, a minority of respondents were concerned that instituting guidelines regarding the assessment and reporting of randomised trial quality in meta-analyses would be likely or very likely to make interpretation of meta-analyses more difficult for clinicians (reviewers, 23%; methodologists, 17%; editors, 5%). Although there was no significant difference among the three respondent groups ($p = 0.31$), editors were more convinced of the impact of such guidelines on the interpretability of meta-analyses than reviewers and methodologists combined ($p = 0.01$).

If a meta-analysis was based on the central collection and analysis of individual patient data, 75% of respondents believed that assessing the quality of these data was important; views were similar across all groups ($p = 0.20$). Several advantages were highlighted in the qualitative responses, including the opportunity to examine primary study design carefully, to conduct more precise analyses (e.g. using the intention-to-treat approach or to explore dose-responsiveness), and to evaluate the concordance of data collected with that reported in the trial publication. The merit of such a quality assurance exercise notwithstanding, concerns were advanced about the feasibility and

TABLE 3 *Guidelines for assessing the quality of randomised trials included in meta-analyses: potential impact on the rigour of reporting of published meta-analyses*

Respondent group	Number (% of total respondents) with reply:				
	Very likely to increase	Likely to increase	Neutral	Likely to decrease	Very likely to decrease
Reviewers (n = 118)	21 (18)	83 (70)	13 (11)	0	1 (1)
Methodologists (n = 50)	8 (16)	34 (68)	8 (16)	0	0
Editors (n = 61)	26 (43)	31 (51)	4 (7)	0	0

TABLE 4 *Guidelines for assessing the quality of randomised trials included in meta-analyses: potential impact on the way in which meta-analyses may be interpreted by clinicians*

Respondent group	Number (% of total respondents) with reply:				
	Very likely to increase	Likely to increase	Neutral	Likely to decrease	Very likely to decrease
Reviewers (n = 120)	11 (9)	61 (52)	20 (17)	26 (22)	2 (2)
Methodologists (n = 54)	8 (15)	25 (46)	12 (22)	9 (17)	0
Editors (n = 62)	17 (27)	30 (48)	12 (19)	3 (5)	0

effort:yield ratio of individual patient data meta-analyses.

Finally, we asked all respondents to consider how, in their role (or potential role) as editors of biomedical journals, they would deal with an otherwise rigorous meta-analysis in which the quality of randomised trials had not been assessed. Overall, 66% said they would be unenthusiastic about publishing it unless the quality of the trials was assessed, 5% were indifferent and 28% said they would be willing to publish an otherwise rigorous meta-analysis if the trial quality was not assessed. Reviewers, methodologists and editors had different views ($p = 0.04$), editors being less enthusiastic about publishing a meta-analysis in which quality had not been assessed.

Discussion

This is the first survey to explore views on the quality assessment of randomised trials included in meta-analyses. Systematic reviewers, methodologists and editors agreed that evaluation of trial quality is integral to the systematic review process. Several properties were considered important in the development and testing of an instrument, checklist or scoring system. Most respondents stated that they would be disinclined to publish a meta-analysis without inclusion of some assessment of trial quality. In addition, many different methods of quality assessment were endorsed to assess quality and incorporate these assessments into meta-analyses. This measured enthusiasm contrasts with a review of 80 meta-analyses of analgesic interventions,[34] 60% of which did not describe the methods used to assess the validity of the pooled studies, and 20% of which did not describe the design features of the primary studies. Our review of diverse interventions drawn from a large database of meta-analyses,[73] described in chapter 4, demonstrated that only 48% of meta-analyses reported one or more features of trial quality.

Thus, there appears to be discordance between what our survey respondents stated **should** happen with regards to trial quality assessment in meta-analyses, and published meta-analytic reports. Several hypotheses may explain this phenomenon, including lack of interest in or knowledge about quality reporting by reviewers, space constraints of paper publishing, or the passive dissemination and modest endorsement of previous recommendations that trial quality assessment be part of the conduct of systematic reviews. Our survey begs the question of whether assessment and reporting of trial quality in a meta-analysis really matters. Few readers would disagree that poorly designed and/or conducted trials may yield misleading results, that pooling the results of poor quality trials may create misleading

reviews, and that large variation in study quality may preclude statistical pooling in meta-analyses.[74] However, empirical evidence about how study design can affect trial results is emerging[12,75,76] and is now being catalogued by members of the Cochrane Collaboration.[32] Over-estimates of treatment effect have been demonstrated in studies that were non-randomised compared with those that were randomised, in trials with unconcealed assignment compared with those with concealed assignment, and in trials for which no double-blinding was reported compared with trials for which double-blinding was reported.[9,13,77] Debate about clinical policy implications regarding the recent systematic reviews on colloids versus crystalloids[55,56] would be usefully informed by careful examination of multiple trial quality features.

There are three basic approaches to assess the extent to which bias is minimised in primary trials. These include the component approach (one to three selected items integral to study quality such as method of treatment allocation, extent of blinding and completeness of follow-up), checklists (a series of items which produce qualitative statements about validity) and scales (which provide overall numerical scores).[19] However, the **conduct** and **reporting** of trial quality assessment in meta-analyses may be conflated in instruments such as the 100-point scale for 'quality rating of randomised trials'.[17] This tool combines items about reporting style (e.g. inclusion of trial commencement and cessation dates), sample size, items unrelated to study quality or systematic error (e.g. whether or not investigators included a power analysis), and features designed to minimise systematic error (e.g. treatment allocation, blinding, and losses to follow-up). A systematic review identified nine checklists and 25 different scales for assessing the quality of primary studies included in reviews,[14] many of which also merged issues of trial design and execution with reporting style.

This is the second survey of reviewers, methodologists and editors in which we explored views on the methodology of systematic reviews. In our first survey on publication bias affecting meta-analysis,[78] the balance of opinion supported a systematic search for unpublished material, consideration of all studies that can be subjected to uniform methodological critique, and a sensitivity analysis in which results are presented both with and without unpublished data. However, we found that three-quarters of the meta-analysts and methodologists but only half of the editors believed that unpublished material should be included in systematic reviews. In the current survey on reporting trial quality in meta-analyses, we found more uniformity of opinion among the respondents, who suggested the following:

- a parsimonious set of quality criteria focused on minimising bias in trial design and execution
- incorporation of additional items individualised according to the clinical topic
- display of this information to aid interpretation of the meta-analysis.

The strengths of this study include the sampling of three diverse international expert groups, the high response rates from reviewers and methodologists, the exploration of a variety of issues related to trial quality assessment, and the use of quantitative and qualitative methods of analysis. The weaknesses of this survey include the unexplained moderate response rate from the editors contacted. In addition, inferences from surveys of experts may bear little relation to the best approach for assessing and reporting randomised trial quality in meta-analyses. Although these survey data should not necessarily be used to determine the optimal approach, the results of this study serve as a point of departure for on-going dialogue among producers and consumers of systematic reviews regarding the quality of the randomised trials they summarise.

Chapter 4

The quality of RCTs included in meta-analyses and systematic reviews: how often and how is it assessed?

Introduction

One of the main barriers that hinder the assessment of trial quality is that quality is a complex concept or 'construct'. As for any other construct, such as anxiety, happiness or love, quality can be acknowledged without difficulty, but is not easy to define or measure. Another major barrier hindering the assessment of trial quality is that in most cases the only way a reviewer can assess quality is by relying on the information contained in the written report.[20,28] The problem is that a trial with a biased design that is well reported could be judged as having high quality, whereas a well-designed but poorly reported trial could be judged as having low quality.[20] A third major barrier is that there is an increasing number of tools available for the assessment of trial quality, but little empirical evidence to guide the selection of tools and the incorporation of the assessments into reviews.[20] There is also little empirical evidence on who should do the assessments (i.e. number, training and background of assessors), on how the assessments should be done (i.e. masked versus open conditions) or on the impact of the assessments on healthcare decisions.[28,79]

Against this background, it is possible to understand why the assessment of the quality of primary trials included in meta-analyses could be a controversial issue. Some researchers may see quality assessment as a source of bias or as uninformative, whereas others may regard it as an important strategy to identify and reduce bias. The amount of empirical evidence to inform these extreme positions, however, is insufficient. This chapter provides empirical evidence that could be used to inform the controversy. The specific objectives of this project were to estimate the proportion of published meta-analyses in which the quality of primary trials has been assessed, and to describe the methods used by meta-analysts to obtain the assessments and to incorporate them in the quantitative analysis of meta-analyses.

Methods

For this study we examined 240 meta-analyses. We randomly selected 204 meta-analyses published in peer-reviewed journals (MAPJs) from the yield of the refined MEDLINE search[56] described in chapter 2. In addition, we selected the 36 meta-analyses of RCTs included in the CDSR (1995, issue 2). We obtained hard copies of the published reports of these meta-analyses and deleted all information related to the identity and affiliation of the authors and the date of publication. For MAPJs, we also deleted the name of the journal. Using the masked copies of the meta-analyses, we extracted information from each report using eight questions that addressed aspects directly related to quality assessments (see *Box 1*). Data were also extracted, under masked conditions, on the number of trials and patients included in each report, the description of the sources of trials, inclusion and exclusion criteria, language restrictions, heterogeneity testing, and reporting of quantitative effect estimates (appendix 6). Under open conditions, a research assistant extracted information on the journal, number of authors, language and year of publication of the MAPJ. Before engaging in data extraction, we assessed inter-observer reliability by using the answers to the question 'Were the trials subjected to any quality assessment?' on a separate set of ten masked MAPJs selected at random. We decided, *a priori*, to assess inter-observer reliability by calculating intra-class correlation coefficients (ICC) and selected values > 0.5 as compatible with good agreement and values > 0.61 as compatible with substantial agreement. We chose, *a priori,* ten meta-analyses to obtain sufficient statistical power to achieve an ICC of at least 0.6. Using an SAS macro we applied established methods[80] and obtained an ICC of 0.63.

After completing the assessment of inter-observer reliability, the masked copies of all of the 240 meta-analyses were distributed in groups of 60 among all of us, ensuring that

BOX 1 Questions on quality assessment used to extract information from the meta-analyses

1. Were the trials subjected to any quality assessment? (Yes, no or cannot tell.)
2. If yes, what method of quality assessment did the author(s) report using? (This included components, checklists, scales, 'other methods' and 'not reported'.)
3. Was the reproducibility of the quality assessments assessed? (Yes, no or cannot tell.)
4. If the author(s) reported assessing quality using a component approach, which one did they use? (Six options were given including 'other'.)
5. If the author(s) reported assessing quality using a checklist, which one did they use? (Ten options were given, including 'other'.)
6. If the author(s) reported assessing quality using a scale, which one did they use? (22 options were given, including 'other'. The options were selected from a previous article.[80])
7. Were the quality scores incorporated into the quantitative analysis? (Yes, no or cannot tell/ not reported.)
8. How were the quality scores incorporated into the quantitative analysis? (Weights, thresholds, input sequence for cumulative meta-analysis, or as a visual plot.)

The questionnaire used in the study is presented in appendix 6.

information from each of the reports was extracted by a pair of individuals. After each of us completed data extraction independently, each pair met to compare the data, resolved any discordance by consensus, and sent the agreed data sets to the coordinating office in Ottawa.

Data analysis

All the data sets were stored in SAS-UNIX and converted to SPSS for Windows version 6.1 for statistical analysis by DBMS copy, Windows (v. 5.10). We calculated descriptive statistics for the answers to the eight questions by source (peer-reviewed journal or CDSR) and for all 240 meta-analyses. Differences between MAPJ and meta-analyses in CDSR were compared using chi-square tests and Fisher's exact test, where appropriate. For all comparisons, p values ≤ 0.05 were regarded as statistically significant.

Results

The 204 MAPJ were published in 118 journals, from 1977 to 1995. Of these, 199 were published in English, two in French, and one each in Spanish, Italian and Danish. All 36 CDSR meta-analyses were published in 1995 and all were published in English. Thirty-nine (19%) of the MAPJs were published in 1995.

Trial quality was assessed in 114 (48%) of the 240 meta-analyses (see *Table 5* and appendix 7). The quality of the primary trials was assessed more frequently in the CDSR meta-analyses than in the MAPJs (100% versus 38%, $p < 0.001$). Fifty-seven (50%) of the 114 meta-analyses in which trial quality was assessed provided data on the reproducibility of the assessments. CDSR meta-analyses evaluated the reproducibility of the assessments more frequently than MAPJs (56% versus 36% respectively; $p = 0.04$). Individual components and scales were the methods most frequently used (46% each) to assess trial quality. Most of the CDSR reviews used individual components to assess trial quality, while most MAPJs used scales (*Table 5*). A total of 21 quality assessment instruments were identified. None of these instruments appeared to have undergone validation following established methodological procedures and 43% were described for the first time in 1994 and 1995. Eleven of these instruments were not included in a systematic review published recently.[81]

Of the 114 meta-analyses that included assessments of trial quality, only 29 (25%) took such assessments into account during data analyses (*Table 5*). MAPJs incorporated the quality assessment in the analyses more frequently than CDSR meta-analyses (34% versus 6%, respectively; $p < 0.001$). The two CDSR meta-analyses that incorporated the quality assessments into data analysis used the quality assessments as thresholds. Of the MAPJs, one-third incorporated the quality assessments as thresholds for inclusion or exclusion from the analyses, and one-third incorporated the quality scores in the formulae as weights.

When only the meta-analyses published in 1995 were analysed, most of the patterns outlined above persisted. Twelve of the 39 MAPJs (32%) included assessments of trial quality and most of them used scales but did not incorporate the assessments into the analyses (*Table 5*).

TABLE 5 *Assessment of trial quality in published meta-analyses*

	No. of meta-analyses (%*)			
	CDSR	**MAPJ (1995)**	**MAPJ (1977–1995)**	**Total**
Trial quality assessment	36 (100†)	12 (31†)	78 (38†)	114 (48†)
Method of quality assessment				
Components	33 (92)	1 (8)	20 (26)	53 (46)
Scales	0	9 (75)	52 (67)	52 (46)
Checklists	0	1 (8)	3 (4)	3 (3)
Other methods	1 (3)	0	0	1 (1)
Not reported	2 (6)	1 (8)	3 (4)	5 (4)
Reproducibility of the assessments	13 (36)	5 (42)	44 (56)	57 (50)
Incorporation of quality assessments into analyses	2 (6)	3 (25)	27 (34)	29 (25)
Method of incorporation				
As a threshold	2 (6)	1 (8)	9 (12)	11 (10)
As a weight	0	0	8 (10)	8 (7)
In a visual plot	0	1 (8)	3 (4)	3 (3)
Other	0	1 (8)	7 (9)	7 (6)

* *Percentage of meta-anlayses with trial quality assessment*
† *Percentage of total sample of meta-anlayses (CDSR, n = 36; MAPJ 1995, n = 39; MAPJ 1977–1995, n = 204)*

Discussion

If there is one issue around which both supporters and detractors of meta-analyses are likely to agree, it is on the dictum 'garbage in, garbage out'. This means that the extent to which a meta-analysis could guide healthcare decisions depends, at least in part, on the quality of the evidence available. This study describes, at the same time, the frequency with which the quality of primary trials is assessed in published meta-analyses, the methods used by reviewers to obtain the assessments, and the strategies to incorporate the assessments in the results of the meta-analyses.

The main strengths of this study are the inclusion of numerous systematic reviews and meta-analyses published over three decades in a wide range of journals and both in paper-based journals and in an electronic publication like the CDSR. The main weakness of the study is that it only focused on reviews identified in MEDLINE and CDSR.

Our results suggest that trial quality is not assessed in most meta-analyses. These findings are similar to those of previous studies.[14,34] What has not been shown before, however, is that when trial quality is assessed, the assessments are obtained with non-validated tools and are infrequently incorporated into the analyses. This indicates that there is a gap between what individuals say ought to be done[82] (see chapter 3) and what they do. There is also growing evidence[13,83] that the quality of reports of RCTs included in meta-analyses does influence the estimate of an intervention's effectiveness in a wide variety of settings (see chapter 5).

These results will be viewed with concern and dismay by those who regard the assessment of trial quality as an essential component of meta-analyses, particularly when the assessments are done using validated tools and are guided by empirical methodological evidence.[9,12,13,28,36,62,68,83] However, others[84] who believe that quality assessments could be one of the most important sources of bias in meta-analysis, might find relief and comfort in these results.

The use of quality assessment in all of the meta-analyses found in CDSR suggests that Cochrane reviewers and editors are following the recommendations outlined in the Cochrane Handbook.[85] The fact that only two of the 36 selected CDSR meta-analyses published in 1995 incorporated the assessments into the analyses suggests, however, that Cochrane reviewers find the assessments of little value during data analysis, or that they require more empirical evidence to incorporate them into their analyses.

The low proportion of MAPJs that include quality assessments could be explained by similar reasons

and, at least in part, by the lack of specific instructions provided by peer-review journals to authors of systematic reviews. Our findings also show that many new quality-assessment tools are being used to assess the quality of trials, but that these tools are not validated and that the assessments are rarely incorporated into the reviews. Perhaps the time is right to declare a moratorium on new tools, to concentrate our efforts on refining existing tools, and to focus on the study of the effects of different methods to incorporate quality assessments on the results of systematic reviews and meta-analyses.

The next chapter will provide empirical evidence that could help editors, peer-reviewers and authors decide whether and how to assess the quality of primary trials included in systematic reviews.

Chapter 5

Does the poor quality of reports of randomised trials exaggerate estimates of intervention effectiveness reported in meta-analyses?*

Introduction

The conduct of a meta-analysis is a retrospective scientific exercise[86] and, as such, is susceptible to several sources of biases.[87] Meta-analyses of RCTs predictably include studies of variable methodological quality. Features of randomised trials that confer the least biased estimates of treatment effect have been studied with intensity lately. Differences in quality across trials may indicate that the results of some trials are more biased than others. Meta-analysts need to take this information into consideration to minimise or avoid bias whenever possible. Similarly, there are few data to guide reviewers as to whether any one method of quality assessment provides a more biased estimate than any other one. In this study, we addressed whether the method of quality assessment of RCTs using a validated scale approach compared with one involving individual components influences estimates of treatment effectiveness.

Methods

Selection of meta-analyses

We randomly (random numbers table) selected 12 meta-analyses from our larger database of 491 meta-analyses of RCTs (see chapter 2). Three inclusion criteria were used:

- the report was published in English
- there was no formal incorporation of quality scores in the quantitative analysis
- the outcomes were presented as binary data, reported using an overall quantitative summary result.

Meta-analyses were excluded if the report did not provide references for the included trials. Nine of the meta-analyses were randomly chosen from the three most frequently reported categories of the International Classification of Disease (ICD-9), three each from digestive diseases,[88–90] circulatory diseases,[91–93] and mental health.[94–96] The remaining three meta-analyses were randomly chosen from the CDSR (1995, issue 2): one from stroke,[97] and two from pregnancy and childbirth.[98,99]

Selection of RCTs

Each meta-analysis was reviewed by two of us regarding the reported principal outcome(s). Because most of the meta-analyses did not explicitly report the primary outcomes,[71] these outcomes were selected based on the largest number of RCTs reporting data on that endpoint (e.g. mortality). One meta-analysis[99] was excluded from our study because the data from this study were provided to the principal investigator solely for the purposes of his meta-analysis (Dr A Grant, personal communication). This resulted in the selection of 22 independent outcomes (due to non-overlapping trials) across 11 meta-analyses from which 127 RCTs were identified and retrieved.

Quality assessment

The report of each RCT included in each meta-analysis was photocopied twice. On one copy a black marker pen was used to obscure the names of authors, their affiliations, any other identifiers (such as funding sources) and references. The quality of reporting of each of the resulting 254 RCTs was assessed by all of us using an incomplete randomised Latin square design (i.e. each reviewer was randomised to receive both masked and unmasked RCTs but never the same one).

Quality assessments (appendix 8) were completed using a validated scale[16] and individual components known to affect estimates of intervention effectiveness.[17] The scale consists of three items pertaining to descriptions of randomisation, masking, and drop-outs and withdrawals in the report of an RCT (see appendix 9 for definitions of terms used). The scale ranges from 0 to 5 with higher scores indicating

* A report on this project has also been published elsewhere:

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, *et al.* Does the poor quality of reports of randomized trials exaggerate estimates of intervention effectiveness reported in a meta-analysis? *Lancet* 1998;**352**:609–13.

superior reporting. The individual components assess the adequacy of reporting of randomisation, allocation concealment and double-blinding and are described in detail elsewhere[17] (see appendix 9 for definitions of terms used). We also recorded information on trial sponsorship. We pre-tested our methods by completing an inter-observer reliability study, assessed with the ICC, using a separate set of RCTs (values above 0.61 were considered as substantial agreement,[100] *a priori*).

Data extraction

In addition to the quality assessment of each RCT the following data were also extracted: the number of events and patients in the control group, and the number of events and patients in the experimental group. The data were extracted independently by two people (ALJ, DM) and consensus was achieved for any discrepancies before data entry.

Analyses

To assess mean differences in quality scores between masked and unmasked RCTs we used a paired *t*-test. To assess differences between masked and unmasked trials in the proportion with adequately reported components we used chi-square analysis and logistic regression.

The point estimate and 95% CIs from each meta-analysis were replicated using the same analytical procedures reported by the authors of the original publication (see appendix 10). To examine the impact of quality assessment on the combined point estimates we replicated the methodology used elsewhere.[13] Briefly, logistic regression models were used to explore the relationship between a binary outcome of an unwanted event (e.g. death) with several independent factors. The independent variables included an overall intervention effect, trial indicators to allow for the variation among the trials, modified treatment effects to capture variation among the meta-analyses, and an estimate of quality. Quality scores were incorporated into the analysis in a variety of ways. As a threshold (see appendix 9 for details), a quality weight (see appendix 9 for definition and usage), or individual component (e.g. double-blinding). We also performed a sensitivity analysis to explore further the relationship between a component assessment of quality compared with a scale one.

The results of these analyses are reported in terms of a ratio of odds ratios (RORs) and ORs (see appendix 9 for definitions). By our modelling convention, an OR and ROR below one indicates an effective intervention in the subgroups of trials defined in the nominator compared with those in the denominator. The mean residual deviance of the fitted models reflects the degree of heterogeneity between trials after adjusting for the independent factors. As suggested elsewhere,[13] we used an approximate *F* test for evaluating the effects of heterogeneity using the models. For all analyses $p \leq 5\%$ was considered statistically significant.

Results

The 127 RCTs included in the 11 meta-analyses involved 10,492 patients. The 11 meta-analyses were published between 1988 and 1995 in ten journals and the CDSR. The trials they contained were published between 1960 and 1995 and published in 57 journals and three books. One study was unpublished. The majority of outcomes (15 of 22, 68%) included can be defined as 'objective' (e.g. histological remission, major amputation, overall mortality, conception rate, smoking cessation assessed biochemically).

An assessment of the quality of reports of RCTs under masked and unmasked conditions using a scale and component evaluation are presented in *Table 6*. The overall quality of reporting of RCTs using a scale assessment was 2.74 (out of 5, SD = 1.1) corresponding to 55% of the maximum possible value. There were statistically significant differences in the evaluation of the quality of reporting of RCTs under masked and unmasked conditions (see *Table 6*). Masked assessment resulted in statistically higher quality scores than unmasked assessments (2.74 versus 2.55). This difference corresponds to 3.8%. We have based all further analyses presented in this paper on masked assessments only.

Using a component approach to quality assessment, we found that few RCTs reported on either the methods used to generate the randomisation schedule (15.0%) or the methods used to conceal the randomisation sequence until the point of randomisation occurred (14.3%). When assessed under masked conditions, compared with unmasked ones, allocation concealment was identified more frequently (14.3% versus 10.7%) as adequate (see *Table 6*). When we used the scale approach, we found that 121 (95.2%) trials were described as randomised and/or reported on the methods used to generate participant assignment. Of these trials only 19 (15.7%) adequately described allocation concealment.

TABLE 6 *Quality of reporting of 127 RCTs assessed using a scale[13] and individual quality components under masked and unmasked conditions[28]*

	Masked (n = 127)	Unmasked (n = 127)	Percentage difference (95% CI)
Quality rating scale	**Mean (SD)**		
Randomisation	1.09 (0.45)	1.08 (0.45)	0.02 (–0.05, 0.08)
Double-blinding	1.10 (0.84)	1.00 (0.79)	0.10 (0.02, 0.18)
Withdrawals/drop-outs	0.59 (0.49)	0.50 (0.50)	0.09 (–0.002, 0.18)
Total score*	2.74 (1.10)	2.55 (1.20)	0.19 (0.06, 0.32)
Component approach to quality assessment	**%**		
Randomisation generation	15.0	14.3	0.07 (–2.05, 3.45)
Allocation concealment†	14.3	10.7	3.60 (0.94, 6.26)
Double-blinding	66.4	64.3	2.10 (–1.60, 5.80)

* *Paired t-test for scale,* p = *0.005*
† *Adequate allocation concealment (*p = *0.004)*

We were able to replicate closely the results of the published meta-analyses for all 22 selected outcomes. The evaluation of the influence that quality assessments of the primary trials have on the results of the meta-analyses is presented in *Table 7*. Trials with a low quality score (≤ 2), compared with those with a high quality score (> 2), resulted in a significantly greater (by 34%) estimate of the treatment effect (ROR = 0.66; 95% CI: 0.52, 0.83). The effects of these results on an individual meta-analysis are presented in *Table 8*.

We conducted a threshold analysis to determine whether the exaggerated intervention effects reported above in relation to the quality scores could be explained by those RCTs in which allocation concealment was inadequately done and inadequately reported, as has been previously suggested.[13] Our analyses (see *Table 7*) did not result in any meaningful differences in terms of magnitude and direction of bias or statistical significance in comparison with those already reported here.

By incorporating estimates of quality based on individual components, we also detected exaggerated estimates of treatment effect (see *Table 7*). Clinical trials that reported allocation concealment inadequately, in comparison with those that reported it adequately, produced statistically exaggerated estimates of treatment effects of 37% (ROR = 0.63; 95% CI: 0.45, 0.88). We did not find any significant differences in treatment effects for RCTs according to whether their reports adequately described how the randomisation sequence was generated. Similarly, we did not find an exaggerated treatment effect whether or not there was adequate description of how double-blinding was achieved in a trial.

The average treatment benefit across all trials was 39% (OR = 0.61; 95% CI: 0.57, 0.65). Including only trials with low quality scores (≤ 2) in the quantitative analysis resulted in an average treatment benefit of 52% (OR = 0.48; 95% CI: 0.43, 0.54). In contrast, including only trials with high quality scores (> 2) in the analysis resulted in an average treatment benefit of 29% (OR = 0.71; 95% CI: 0.65 0.77). Using all the trial scores as quality weights resulted in an average intervention benefit of 35% (OR = 0.65; 95% CI: 0.59, 0.71). Using a quality weight, in comparison with using low or high quality scores, to incorporate estimates of quality into the quantitative analysis also produced the least statistical heterogeneity (see *Table 7*).

Discussion

Assessing the quality of reports of randomised trials included in a meta-analysis adds another layer of complexity to the reviewing process. However, our results suggest that incorporating an estimate of the quality of randomised trials is important. We found a clinically important and statistically significant 30–50% exaggeration of treatment effectiveness when results of lower quality trials are pooled. Inflated estimates of treatment effectiveness were found whether the trial quality assessments were made using a scale approach or an individual component approach.

These results are consistent with the work of Schulz and colleagues[13] who examined clinical trials in the

TABLE 7 *Relationship between different methods of incorporating quality assessment (threshold, statistical weight, and individual components) into meta-analyses and the resulting estimates (and measures of precision) of intervention effects*

Method of quality assessment	Intervention effect modifier	Assessment of heterogeneity
	ROR (95% CI)	**Ratio of heterogeneity between trials[*] (*p* value from a test of similar degree of heterogeneity between trials[†])**
Scale		
Low (≤ 2) vs. high (> 2)[‡]	0.66 (0.52, 0.83)	1.06 (*F* test with 49, 71 df, 2*p* = 0.41)
Low (≤ 2) vs. high (> 2)[¶]	0.73 (0.56, 0.94)	1.01 (*F* test with 49, 51 df, 2*p* = 0.49)
Component		
Randomisation generation[**]	0.89 (0.67, 1.20)	1.36 (*F* test with 102, 18 df, 2*p* = 0.23)
Allocation concealment[**]	0.63 (0.45, 0.88)	1.17 (*F* test with 101, 18 df, 2*p* = 0.36)
Double-blinding[**]	1.11 (0.76, 1.63)	1.02 (*F* test with 39, 81 df, 2*p* = 0.46)
	Intervention effect[††] OR (95% CI)	**Estimated heterogeneity between trials[‡‡]**
Main analysis	0.61 (0.57, 0.65)	2.99 (χ^2 with 121 df)
Sensitivity analysis		
Low quality	0.48 (0.43, 0.54)	2.88 (χ^2 with 49 df)
High quality	0.71 (0.65, 0.77)	2.73 (χ^2 with 71 df)
Quality weight	0.65 (0.59, 0.71)	1.59 (χ^2 with 121 df)

The analysis used the convention that treatment was more effective to prevent an adverse outcome. Therefore, an OR < 1 indicates an effective intervention. Furthermore, an ROR of < 1 also indicates an exaggeration of treatment effect

[*] *The residual deviance reflects the degree of heterogeneity between trials derived from a base model consisting of intervention and trial factors*

[†] *An approximate* F*-distribution was assumed for the ratio of residual deviances to compare the heterogeneity between different ways of incorporating quality. A larger degree of heterogeneity between trials results in a ratio > 1*

[‡] *Allowing for summary OR to vary according to quality (i.e. quality-by-treatment interaction) in a base model consisting of intervention, trials and modified ORs according to meta-analyses*

[¶] *Sensitivity analysis only including trials with allocation concealment reported inadequately*

[**] *Allowing for summary ORs to vary simultaneously according to the components (i.e. component-by-treatment interactions)*

[††] *Average intervention effect estimated from a base model consisting of intervention and trial factors*

[‡‡] *Expected degree of heterogeneity (i.e. residual deviance) is 1*

TABLE 8 *An illustration of the effect quality assessment (including different methods of assessment and how the resulting scores are incorporated into the quantitative data synthesis) can have on the results of a meta-analysis*

Treatment effects to prevent DVT-related death	OR (95% CI) (n = 5 RCTs)	Test for statistical heterogeneity (2*p* values)[*]
Main analysis	0.53 (0.32, 0.90)	0.7135
Sensitivity analysis		
Low-quality trials (quality score ≤ 2, n = 2 RCTs)	0.42 (0.15, 1.17)	0.5210
High-quality trials (quality score > 2, n = 3 RCTs)	0.57 (0.30, 1.10)	0.4725
Quality weight (n = 5 RCTs)	0.52 (0.27, 0.98)	0.7123

[*] *Test for heterogeneity based on Breslow-Day*[108]

Lensing and colleagues[92] *examined the effects of LMWH on several outcomes including death. Five RCTs were included in this analysis resulting in a statistically beneficial effect of LMWH reducing mortality by 47% (OR = 0.53; 95% CI: 0.32, 0.90). Two of the trials scored ≤ 2 and the other three scored > 2. When quality assessments were incorporated into the analysis the beneficial effect of LMWH disappeared. Using low-quality trials (score, ≤ 2) the OR was no longer significant (OR = 0.42; 95% CI: 0.15, 1.17) although the point estimate suggests a greater effectiveness of LMWH. Similar results were obtained if only high-quality trials (score, > 2) were used (OR = 0.57; 95% CI: 0.30, 1.10). Using a quality weight resulted in almost no exaggeration of the point estimate while maintaining the precision of the statistical result (OR = 0.52; 95% CI: 0.27, 0.98)*

field of obstetrics and childbirth and found that inadequately concealed trials, in comparison with adequately concealed ones, exaggerated treatment effectiveness by about 30–40%. Our work is based on analysis of studies from four clinical topics, and adds to the body of evidence that ignoring trial quality may introduce bias in the results of meta-analysis. This effect is likely to vary somewhat depending on how the treatment effect is summarised (e.g. relative risk, risk difference) and the control group event rate (e.g. mortality, quality of life).

The results of our sensitivity analysis indicate that significant exaggeration of treatment effects (in terms of the selected primary outcome) remain regardless of whether or not trials in which allocation concealment are adequately reported are removed from the analysis. Unfortunately, our review indicated that few trials report on methods of allocation concealment despite its importance. We hope that new efforts to help improve the quality of reporting of RCTs will better this situation. Reviewers should not interpret our results as requiring them to make a choice between using a component or scale approach to quality assessment. Both approaches offer advantages.

We used both the individual component approach and the scale approach for quality assessment, including items derived from empirical studies, and showed that both can overestimate the effectiveness of an intervention. Whether these results remain stable when different criteria are used is uncertain. We have previously shown[20] that different scales when applied to the same randomised trial can provide markedly different estimates of quality in terms of absolute scores and rankings. It is possible that using less empirically-based criteria for quality assessment may provide different estimates regarding the exaggeration of results than those reported here.

Our results indicate that using quality as a weight appears to produce less statistical heterogeneity – a result that might have been statistically expected. It is difficult, and beyond the scope of this study, to examine statistically whether the reduction in statistical heterogeneity is an artefact or a real effect associated with quality assessment. It is unlikely that our results could be explained solely by artefact alone. Using only high-quality trials or giving more weight to trials of higher quality is likely to result in a higher signal:noise ratio, thus reducing heterogeneity. Nonetheless, there may be certain conceptual advantages to using a quality weight rather than a threshold approach. For example, by using a quality weight it is possible to include all of the trials rather than a selected sample as would be common when using a threshold approach. Our study is limited by not exploring the influence of other ways of incorporating quality weights into the quantitative analysis.[22] The component approach to quality assessment may be advantageous by being able to incorporate new evidence more quickly than it can be incorporated by those who are developing scales appropriately using accepted standards.[101] For this reason, many meta-analysts may prefer using a component approach to quality assessment.

In using a scale approach to assess quality we found that masked assessments provided statistically higher scores than unmasked assessments. It is debatable whether this small absolute difference of 3.8% is important, in terms of the additional efforts involved in masking that would be required. Many reviewers may see this difference as too small to be of importance. Several reports have examined the effects of masking on quality assessments of clinical trials.[14,28,102] There appears to be little consistency in these results in terms of their direction and magnitude. It is likely that a systematic review of this literature would shed light on this issue. Such a review is beyond the present mandate of our group.

Our study is limited in that we did not explore the relationship between unmasked quality assessments and estimates of treatment effects. In addition, the use of a quality score as a weight is based on an assumption that there is a linear relationship between the estimates of quality and the weights assigned to the response options (e.g. 1, 2 or 3). It is possible that the scaling relationship is not linear and the weighting system is more complex. If data appeared to suggest an indirect relationship our results may not be valid. Our study is also limited in that we used an abbreviated two-response option, rather than the three-response one (as reported by Schultz and colleagues[13]) to assess allocation concealment. It is possible that this resulted in the observed differences between masked and open-quality assessment in the proportion of trials reporting adequate allocation concealment. This categorisation might also explain less overlap between the component approach and the scale approach. Despite our categorisation, our results are remarkably consistent with those reported by Schultz and colleagues.[13]

Our results highlight the influence that low-quality trials have in the conduct of systematic reviews. This has not gone unnoticed. Recently considerable energies have focused on developing evidence-based methods to help improve the

quality of reporting of clinical trials.[47,63,103] Several journals have endorsed these approaches[104–107] and incorporated them into their 'instructions to authors'. It is hoped that improving the quality of reporting of randomised trials will also help reduce the bias of including such trials in systematic reviews.

The last project described in the following chapter presents a series of guides for the assessment of quality of reports of randomised trials included in meta-analyses. These guides are based on the results found in our projects and attempt to assist meta-analysts and all those involved in the conduct of meta-analyses.

Chapter 6

Guides for assessing the quality of randomised trials included in meta-analyses

Introduction

The assessment of the quality of studies included in meta-analyses has generated some heated and entertaining debate over the years. Detractors of such assessments have claimed they are an insidious form of bias and that there is no rigorous method of measuring the elusive concept of study quality.[84] On the other hand, supporters have claimed quality assessments are an essential step in any properly conducted meta-analysis.[70,109] Certainly, the rapid growth of tools to assess the quality of RCTs suggests a strong interest in this issue. By 1995 at least nine checklists and 25 scales for assessing randomised trial quality existed.[14]

Methods

The guidelines in this chapter are the result of a research programme funded by the NHS. They were formulated by the investigators during a conference held in Ottawa, Ontario, Canada in February 1997 and refined subsequently by an iterative process. We start by defining 'quality' as 'the confidence that the trial's design, conduct, analysis and presentation have minimised or avoided biases in its intervention comparisons' (see chapter 1).[20]

This chapter also includes systematically assembled evidence from the literature (i.e. *The Cochrane Library*) to help inform our recommendations.[110] We have structured the chapter as a series of pertinent questions, the answers to which will help inform meta-analysts' decisions as to how to proceed with respect to quality assessment.

Results

Should the quality of randomised trials be assessed?

In chapter 4 we reported that the quality of RCTs included in meta-analyses was assessed in only 38% of MAPJs.[73] However, the survey of methodologists, journal editors and meta-analysts (chapter 3) indicated that at least 95% of respondents believed that quality assessment of RCTs was very or somewhat important.[82] The survey also revealed that 66% of respondents would be unenthusiastic about publishing a meta-analysis unless the quality of the primary studies had been assessed.

Strong support for quality assessments comes from studies indicating that several dimensions of study quality can be used to detect bias in treatment estimates (see *Table 9*).[12,13,70,75,83] As reported in chapter 5, we have confirmed Schulz's finding[13] and demonstrated that low-quality randomised trials, in comparison with high-quality ones, exaggerated the effectiveness of the intervention by 34%, on average (*Table 9*).[83] Meta-analysis based on biased RCTs will also have a similar tendency toward bias (the 'garbage in, garbage out' phenomenon). Therefore, we recommend that the quality of all randomised trials included in a meta-analysis should be assessed.

Should the reports of randomised trials be masked when quality is being assessed?

One aspect of quality assessment that may increase the quantity of work in performing a meta-analysis is the masking of individual trials. There is direct evidence that masking does impact on the assessment of quality (*Table 9*).[28,83,101] What has not been consistent is the direction of such impact. Jadad and colleagues[28] showed that masked quality assessments scored 2.3 (out of 5) in comparison with 2.7 under open conditions ($p < 0.01$; *Table 9*). Berlin and colleagues[101] found that the mean summary quality score was 7.4 for masked assessors compared with 8.1 for unmasked assessors ($p = 0.04$; *Table 9*). As described in chapter 5, we found that significantly higher scores were obtained from masked quality assessment than from open assessments, but that the scores from masked assessments showed a more normal distribution and greater consistency (*Table 9*).[83] In all studies, although the differences were statistically significant it is not clear whether they are methodologically meaningful and whether their magnitude would be sufficient to make an important difference when quality is being incorporated into the quantitative analyses. Berlin and colleagues[101] randomised reviewers to use masked

TABLE 9 *Summary of empirical evidence relating to quality assessment of RCTs included in meta-analyses*

Reference.	Study design	No. of studies	Disease(s) of interest	Methodological item(s)	Results
Berlin *et al.*, 1997[101]	RCT	5 meta-analyses	Various	Masking of primary studies to reviewers	Masked summary OR (95% CI) = 0.63 (0.57, 0.70) and unmasked summary OR (95% CI) = 0.64 (0.5, 0.72). Mean quality score: 7.4 for masked reviewers; 8.1 for unmasked reviewers (p = 0.036).
Chalmers *et al.*, 1983[9]	Observational	145	Acute myocardial infarction	Blinding/ randomisation	Differences in case-fatality rates: 8.8% in blinded randomisation studies; 24.4% in unblinded randomisation studies; 58.1% in non-randomised studies.
Cho & Bero, 1996[117]	Observational	152	Drug studies	Pharmaceutical sponsorship	98% of drug company-sponsored trials were favourable to the drug of interest compared with 79% of those with no drug company sponsorship.
Colditz *et al*, 1989[12]	Observational	113	Studies in medical journals	Randomisation/ double-blinding	Non-randomised trials with sequential assignment had significantly better outcomes for new therapies (p = 0.004). Randomised trials that were not double-blinded favoured the new therapy significantly more often (p = 0.02) than double-blinded trials.
Detsky *et al.*, 1992[22]	Observational	8 trials (1 meta-analysis)	TPN in chemotherapy	Incorporating quality into meta-analysis	Four methods of incorporating quality into meta-analyses were demonstrated: (1) inclusion/ exclusion criteria; (2) quality scores as weights; (3) plot effect size vs. quality score; (4) sequential combination of trial results based on quality scores.
Jadad *et al.*, 1996[28]	RCT	36	Pain	Masking of primary studies for quality assessment	Mean quality score significantly (p < 0.01) higher in unmasked group (2.7) than in masked group (2.3).
Khan *et al.*, 1996[76]	Observational	34	Infertility	Crossover vs. parallel study design	Crossover trials overestimated OR by 74% compared with parallel design (95% CI: 2%, 197%).
Khan *et al.*, 1996[70]	Observational	1 meta-analysis (9 trials)	Infertility	Impact of quality assessment on treatment estimate	Summary OR: all studies 1.6 (95% CI: 0.9, 2.6); low-quality studies 2.6 (95% CI: 1.2, 5.2); high-quality studies 0.5 (95% CI: 0.2, 1.5).
Miller *et al.*, 1989[75]	Observational	221	Surgical trials	Randomisation	Significantly greater benefit in non-randomised trials compared with randomised trials.
Moher *et al.*, 1996[20]	Observational	12	Acute ischaemic stroke	Six different quality assessment scales	Significant difference in the quality score and ranking of RCT between the six quality scales.
Moher *et al.*, 1998[83*]	RCT for masking; observational for impact of quality on OR	127	Four disease areas	1. Masking 2. Impact of quality on treatment estimate. 3. Methods of incorporating quality assessment into the data analysis	1. Total score: 2.74 in masked quality assessments compared with 2.55 in unmasked quality assessment (% difference 0.19; 95% CI: 0.06, 0.32). 2. Low-quality studies overestimated benefit by 34%. Inadequately concealed trials overestimated benefit by 37%. 3. Both high quality estimates and quality-weighted estimates were not exaggerated, however, quality-weighted estimates had less heterogeneity and greater precision.
Schulz *et al.*, 1995[13]	Observational	250	Pregnancy and childbirth	Allocation concealment/ double-blinding	ORs were exaggerated by 41% for inadequately concealed trials and by 17% for trials that were not double-blinded.

[*] *See chapter 5*

trials or unmasked trials throughout the systematic review process (*Table 9*). They found that, although there were disagreements between reviewers at the various phases of the review (study selection, quality assessment and data extraction), there was no significant impact on the summary ORs for the meta-analyses included in their study. They did not, however, explore the impact of quality assessments on the overall summary estimate.

There is also indirect evidence from the peer review literature[102,111,112] that can be used to help inform any recommendation. McNutt and colleagues[102] randomised 127 manuscripts submitted for publication to be assessed under masked or open conditions. The authors reported that masked assessments, in comparison with open ones, produced statistically higher assessments of quality. Evidence of an effect in a different direction has recently been reported.[111,112] In one study, 74 pairs of peer reviewers were randomised to receive a masked or open version of a manuscript. The quality of peer review was assessed using a validated instrument and no statistical differences between the two groups were reported.[111] Similar results have been reported elsewhere.[112] Perhaps a prudent next move would be to conduct a systematic review. This is likely to provide insight into the apparently inconsistent results across the trials.

Given the currently available research evidence and the effort required to conduct masked quality assessment, strong recommendations are not warranted at present. However, we recommend that meta-analysts should at least consider this issue and explicitly justify their decision. Further research evidence is needed before a more definitive recommendation can be made.

How should the quality of reports of randomised trials be assessed?

Items for which there is empirical evidence

If quality assessment is performed, the next question becomes how should it be evaluated? Quality assessments should be based on those dimensions of RCTs that are related to bias in treatment estimates. There is increasing evidence about which dimensions of trial design and conduct affect the estimate of treatment effectiveness. Chalmers and colleagues[9] demonstrated, using 145 trials examining the treatment of myocardial infarction, that trials that were not randomised had a 58.1% difference in case-fatality rates in treatment groups relative to control groups, compared with a difference of 24.4% in trials that were randomised but not blinded, and an 8.8% difference in trials randomised and blinded (*Table 9*).

Schulz and colleagues[13] examined 250 controlled trials from 33 meta-analyses published by the Pregnancy and Childbirth Group of the Cochrane Collaboration. In comparison with trials that had adequate allocation concealment, they found the OR was exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials (*Table 9*). Trials that were not double-blinded yielded ORs exaggerated by 17%.[13] The impact of not using double-blind RCTs has been confirmed in other studies.[12,75] Our study (see chapter 5) showed that inadequately concealed trials generated a 37% increased treatment effect compared with adequately concealed trials (*Table 9*).[83] However, in that study we detected no significant difference in treatment effect between studies with adequate or inadequate description of double-blinding, or between studies with adequately or inadequately reported randomisation procedures.

Khan and colleagues[76] assessed the probability of bias in crossover trials relative to parallel trials in infertility research with pregnancy as the outcome measure. They found that crossover trials overestimated the OR by 74% (*Table 9*). The underlying reason for this bias is that crossover trials will overestimate the effectiveness of interventions when pregnancy is the outcome because once patients become pregnant they cannot be crossed over to the comparison intervention.[76]

On the basis of the evidence, we recommend that evidence-based components should be used primarily when assessing the quality of reports of randomised trials. In summary, items for which there are various degrees of empirical evidence include allocation concealment, double-blinding, and type of randomised trial. The selection and use of other items cannot be guaranteed to guard against providing erroneous and/or biased information to meta-analysts and biasing the results of meta-analyses.

The use of scales for measuring quality

One attractive feature of using a scale for measuring the quality of randomised trials is that a scale provides an overall quantitative estimate for quality. However, most scales have been developed in an arbitrary fashion with minimal attention to accepted methodological standards of validation and reliability testing.[113,114] In addition, many scales are not truly measuring quality as defined earlier, but rather focusing on extraneous factors more related to generalisability.[14,20]

In fact, through a systematic search of the literature we could find only one scale, initially used for

evaluating the pain literature,[28] which has been developed according to accepted methodological principles.[113,114] This scale has been used subsequently to compare trials in different languages and speciality areas.[36,64] It is an interval scale ranging from 0 to 5 (0 = lowest quality to 5 = highest quality) that assesses method of randomisation, double-blinding and handling of withdrawals and drop-outs. Using this scale we have shown that low-quality studies exaggerated the OR by 34% compared with high-quality ones (*Table 9*; see chapter 5).[83] Kahn and colleagues,[70] using this scale in a meta-analysis based on trials conducted in the infertility domain, have recently demonstrated that an estimate based on low-quality trials produced a statistically significant result with treatment and that this was not present in trials assessed as high quality.[70]

In our assessment of published meta-analyses (see chapter 4),[73] nine new scales were identified that had not been previously identified in a study published in 1995.[14] None of these newly identified scales had been developed using established methodological standards.[113,114] Moher and colleagues have previously shown that the results of quality assessments depend on how the scales have been developed (*Table 9*).[113] We recommend using appropriately developed scales when assessing the quality of reports of randomised trials. There is strong evidence for one scale.[22] The selection and use of less rigorously developed scales for randomised trial quality may lead to erroneous and/or biased information.

Scales versus components

Our survey of an international group of reviewers, methodologists and journal editors (chapter 3) indicated that 45%, 57% and 62%, respectively, recommended performing quality assessment through the use of a series of items.[82] The use of a scale received less support, with endorsement by 28% of reviewers, 30% of methodologists and 38% of journal editors. We have also found that 92% of systematic reviews published in the CDSR used components (e.g. allocation concealment) compared with only 26% of meta-analyses published in paper-based peer reviewed journals.[73] In contrast, scales for quality assessments were used in none of the CDSR reviews but were used in 67% of MAPJs.

There is no evidence favouring one particular approach (i.e. component or scale) over the other as regards quality assessment. In our view using both would be complementary. This is particularly true for the components and scale we advocate using. A limitation of using the component approach alone is that only a small proportion of articles report adequate allocation concealment – 14% in our study[83] (see chapter 5) and 32% in a study by Schulz and colleagues.[13] The advantage of the component approach is that it can be tailored to the topic because appropriate and specific, relevant items can be inserted. In addition, as new items are identified through empirical evidence, they can be incorporated easily into study quality assessment. It is important to emphasise that both the scale and component approach led to exaggerated point estimates in our empirical study (chapter 5) and there is no compelling evidence to recommend one over the other.

Number and backgrounds of assessors

At least two individuals should assess the quality of each study included in the systematic review, because one reviewer or both may make random or systematic errors. We do not know much about the ideal background and number of quality assessors. When such assessments are performed we recommend using a measure of agreement, such as kappa (or weighted kappa as appropriate)[115] or intra-class correlation,[80] as appropriate. After completing the quality assessments, these individuals should meet and reach consensus on areas of disagreement; if disagreement persists a third party adjudication may be used. These recommendations are not based on empirical evidence but rather reflect our opinions.

Topic-specific quality assessment

In addition to these generic measures of quality, meta-analysts may include component assessments that are unique to the topic area being explored by the review. Such an approach allows selection of items that are most likely to capture design features important to a given set of trials, and allows omission of elements that do not distinguish among trials with respect to their quality (e.g. blinding in surgical versus medical management). A similar concept has been proposed for quality of life measurement in clinical trials.[116] Some of the respondents to our survey[82] (chapter 3) thought reliance on universal criteria was inappropriate and that specific items tailored to the meta-analysis question should be used. The major disadvantage to topic-specific quality assessment is that it may not always be evidence-based. The use of crossover trials in infertility, where pregnancy is the primary outcome, is an example of topic-specific quality assessment (*Table 9*).[76] In trials in which patients return to their baseline during a wash-out period, this finding of bias from crossover design would not be anticipated. In the area of pharmaceutical

research, Cho and Bero[117] assessed 152 studies examining pharmacotherapy reported at symposia and found that 98% of those supported by a single drug company favoured the drug of the sponsoring agency compared with only 79% of studies not supported by a single drug company ($p < 0.01$; *Table 9*). We recommend using primarily evidence-based topic-specific items as part of the quality assessment process.

How should quality of reports of randomised trials be incorporated into a meta-analysis?

Many meta-analysts incorporate quality at the level of deciding which studies to include in a systematic review. Stating that only 'randomised controlled trials' were included implies that quality has been incorporated in the meta-analysis at the eligibility phase of the review, sometimes referred to as the 'threshold approach' (*Table 9*).[22] Other markers for quality, such as blinding, may also be utilised at this stage of the meta-analysis.

One factor that will affect the incorporation of RCT quality assessments into meta-analyses is the number of studies included. If only a few studies are included then it will be very difficult to do much more than describe their quality. Another factor is whether there is significant heterogeneity based on a test for statistical heterogeneity and a visual inspection of the point estimates.

If there is significant heterogeneity among studies, then it may be helpful to use study quality to try to explore this variability.[118] We have explored two methods[83] of incorporating quality assessment into the quantitative analysis: quality weighting and performing a sensitivity analysis (*Table 9*; see chapter 5). Quality weighting is a statistical technique whereby studies with lower quality are assigned less influence on the treatment estimate than studies of higher quality (*Table 9*).[22] In our survey (chapter 3), only 22% of reviewers, 21% of methodologists and 33% of editors endorsed this quality-weighting method for incorporating quality.[82] Sensitivity analysis involves grouping the studies into different levels of quality (usually low and high) and then examining whether the point estimate differs between the two groups.[22] In the survey, this approach received more support from reviewers (63%), methodologists (66%) and editors (43%).[82]

As reported in chapter 4, only two of the 36 meta-analyses of RCTs published in the CDSR incorporated quality into the analysis, and each of these used the sensitivity analysis method.[73] Quality was incorporated into the analysis of 34% of MAPJs, and the two leading methods of incorporation were sensitivity analysis (9%) and quality weighting (8%).[73,82] Our survey revealed that often quality assessments are made but are not used to explain variability between studies. In our assessment of published meta-analyses (chapter 4), overall 48% (114 of 204) of them assessed quality but only 25% (29 of 114) incorporated quality into the analyses.

There is no strong evidence to support one method over the other. It may be that at present most meta-analysts will find threshold analyses intuitively simpler to perform and that it will be more transparent to the readers. The quality-weighting approach is based on the assumption that the scale used for quality weighting is linear and, hence, it is logical to give a study with a score of 5 out of 5 a full quality weight of 1. In our study (chapter 5) the use of quality weighting produced results that were less heterogeneous and maintained greater precision than results from threshold analysis because all studies contributed to the overall estimate (*Table 9*)[83] depending on the contribution of their quality scores. Regardless of the method selected, we recommend that all meta-analysts should incorporate an estimate of quality assessment into the quantitative analysis as a 'first-line' sensitivity analysis.

In addition to helping to explore and explain inter-study variability, study quality should assist meta-analysts in making inferences about the robustness of the results of the reviews. If study results are homogeneous but of low quality, then the reviewer should be guarded in making strong inferences based on the results of the systematic review, since these results have a higher probability of bias. If results are homogeneous and of high quality, then stronger inferences can be made. Where there is significant heterogeneity, and study quality accounts for this variability, then the point estimate of the high-quality studies should be given stronger emphasis during interpretation of the results and particularly during the application of these results in the clinical setting.

Discussion

We undertook to develop these guidelines because the overwhelming majority of meta-analysts (88%), methodologists (84%), and editors (93%) who responded to our survey (chapter 3)[82] indicated that their development would be likely or very likely to increase the potential impact on the rigour of reporting of meta-analyses.

In *Table 9* we have listed the study design used in the cited methodological studies. This table highlights the small amount of empirical evidence on these issues and the degree of uncertainty behind the proposed guidelines. The studies by Berlin,[101] Jadad[28] and Moher[83] and their colleagues are examples of randomised trials examining the impact of masking assessors to details of potentially relevant primary studies for conducting a meta-analysis. However, more experimental studies of methodological issues in meta-analyses will help to increase their rigour and thus their usefulness in practice.[119] This chapter is intended to contribute to the growing literature on the importance of RCT quality assessments for meta-analyses. *Box 2* presents a useful checklist to help meta-analysts, editors, peer reviewers and readers to assess a meta-analysis for its handling of quality assessment of randomised trials.

Most often, assessing the quality of a randomised trial means assessing the quality as stated in the report, not the quality of the actual events that occurred during the execution of the trial. With initiatives by medical journals that attempt to encourage systematic and comprehensive reporting of trials, such as the CONSORT statement,[47] it is expected that the reporting of trials will become more transparent and comprehensive over time. As evidence accumulates in favour of important design features of randomised trials that reduce the probability of bias, the quality of execution of randomised trials should improve, particularly if journal editors and funding agencies encourage investigators to conduct and report their work with this evidence in mind.

While strong evidence exists that certain characteristics of the design and execution of RCTs do impact on the probability of bias, further research is needed to identify other potential aspects influencing the results of RCTs. Further studies are also needed to clarify the role of masking studies before performing quality assessments, and the need for more than one reviewer and for reviewers of different backgrounds and levels of expertise to perform such assessments. Although several methods for the incorporation of study quality into the results of a meta-analysis have been described, further research in this area is required to determine whether there is any significant advantage of one approach over another.[22] If weighting of studies based on quality assessment proves to be an appropriate method, software will need to be developed to assist reviewers in this task.

BOX 2 Checklist for conducting and reporting of quality assessment of randomised trials included in meta-analyses

1. **Does the report include an assessment of trial quality?**
   - ❑ No.
     What was the rationale for lack of assessment?
     _____
   - ❑ Yes.
     What was the method of assessment (e.g. scale or component approach)?
     _____

2. **Was the assessment completed under masked conditions?**
   - ❑ No.
   - ❑ Yes.
     How was this achieved (e.g. black marker, computer scanning)?
     _____

3. **How many assessors completed the assessment?**
   - ❑ One.
     What was the rationale for a single assessor?
     _____
   - ❑ More than one. How many? _____

   What was the background of the assessor(s)?
   _____

   What was their area of expertise?
   _____

4. **Was any measure of inter-observer agreement reported?**
   - ❑ No.
   - ❑ Yes.
     What method was used (e.g. weighted κ or ICC)
     _____

   Was consensus sought?
   ❑ No. ❑ Yes.

5. **What instrument did the authors use to assess quality?** (If the instrument was previously developed, give a reference.)
   _____

   Was the instrument developed according to standard practice?
   ❑ No. ❑ Yes.

   Were the included items evidence-based?
   ❑ No. ❑ Yes.

   Was the instrument specifically developed for the meta-analysis?
   ❑ No. ❑ Yes.

6. **Were the quality scores incorporated into the quantitative analysis?**
   - ❑ No.
     What was the rationale for not incorporating the quality assessments?
     _____
   - ❑ Yes.
     What was the rationale for incorporating the quality assessments?
     _____

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Appendix 1

MEDLINE search strategy

MEDLINE was searched for meta-analyses from 1 January 1966 to 31 December 1995 using the following strategy.

01.	meta-analysis.pt,sh.	2866
02.	(meta-anal: or metaanal:) .tw.	2296
03.	(quantitativ: review: or quantitativ: overview:) .tw.	79
04.	(systematic: review: or systematic: overview:) .tw.	287
05.	(methodologic: review: or methodologic: overview:) .tw.	76
06.	review.pt,sh. or review: .tw. or overview: .tw.	634,672
07.	(integrative research review: or research integration:) .tw.	30
08.	7 or quantitativ: synthes: .tw.	61
09.	1 or 2 or 3 or 4 or 5 or 8	3920
10.	(medline or medlars) .ti,sh,ab. or embase.tw.	2371
11.	(scisearch or psycinfo or psychinfo) .tw.	24
12.	(hand search: or manual search:) .tw.	169
13.	(electronic database: or bibliographic database:) .tw.	88
14.	(pooling or pooled analys: or mantel haenszel) .tw.	1986
15.	(peto or der simonian or dersimonian or fixed effect:) .tw.	259
16.	(psychlit or psyclit) .tw.	15
17.	10 or 11 or 12 or 13 or 14 or 15 or 16	4663
18.	6 and 17	1447
19.	18 or 9	5109
20.	random:.tw,sh,pt. or placebo:.tw,sh.	175,571
21.	(clinical trial or controlled clinical trial) .pt.	151,285
22.	randomized controlled trial.pt.	54,762
23.	double-blind:.tw,sh.	52,249
24.	20 or 21 or 22 or 23	248,821
25.	19 and 24	1467

Appendix 2

EMBASE search strategy

EMBASE was searched for meta-analyses from 1 January 1980 to 31 December 1995 using the following strategy.

1.	1980–1995	(meta?anal*)@ (TI,AB,RWDS)	2105
2.	1980–1995	(quantitative review*)@ (TI,AB,RWDS)	54
3.	1980–1995	(quantiative overview*)@ (TI,AB,RWDS)	19
4.	1980–1995	(systematic review*)@ (TI,AB,RWDS)	179
5.	1980–1995	(systematic overview*)@ (TI,AB,RWDS)	36
6.	1980–1995	(methodologic* review*)@ (TI,AB,RWDS)	54
7.	1980–1995	(methodologic* overview*)@	9
8.	1980–1995	(review)@ (TI,AB,RWDS)@ (TI,AB,RWDS)	211,308
9.	1980–1995	(overview*)@ (TI,AB,RWDS)	11,401
10.	1980–1995	(integrative research review*)@(TI,AB,RWDS)	3
11.	1980–1995	(research integration)@ (TI,AB,RWDS)	6
12.	1980–1995	(medline)@(TI,AB,RWDS)	1316
13.	1980–1995	(medlars)@(TI,AB,RWDS)	59
14.	1980–1995	(embase)@(TI,AB,RWDS)	46
15.	1980–1995	(scisearch)@(TI,AB,RWDS)	14
16.	1980–1995	(psycinfo)@(TI,AB,RWDS)	3
17.	1980–1995	(psychinfo)@(TI,AB,RWDS)	4
18.	1980–1995	(psyclit)@(TI,AB,RWDS)	2
19.	1980–1995	(psychlit)@(TI,AB,RWDS)	13
20.	1980–1995	(hand?search*)@ (TI,AB,RWDS)	3
21.	1980–1995	(manual search*)@ (TI,AB,RWDS)	109
22.	1980–1995	(hand search*)@ (TI,AB,RWDS)	39
23.	1995	(hand-search*)@ (TI,AB,RWDS)	5990
24.	1995	(hand-search*)@ (TI,AB,RWDS)	5990
25.	1980–1995	20	3
26.	1980–1995	22	39
27.	1980–1995	(hand & search*)@ (TI,AB,RWDS)	485
28.	1980–1995	(handsearch*)@ (TI,AB,RWDS)	1
29.	1980–1995	2	54
30.	1980–1995	(manual?search*)@ (TI,AB,RWDS)	0
31.	1980–1995	(electronic database*)@ (TI,AB,RWDS)	20
32.	1980–1995	(bibliographic database*)@ (TI,AB,RWDS)	42
33.	1980–1995	(pooling)@(TI,AB,RWDS)	1163
34.	1980–1995	(pooled)@(TI,AB,RWDS)	6328
35.	1980–1995	(blood*,plasma*)@ (TI,AB,RWDS)	884,327
36.	1980–1995	(33,34) - 35	4539
37.	1980–1995	(mantel haenszel)@ (TI,AB,RWDS)	19
38.	1980–1995	(peto)@(TI,AB,RWDS)	70
39.	1980–1995	(peto + method*)@ (TI,AB,RWDS)	35
40.	1980–1995	(der simonian*)@ (TI,AB,RWDS)	5
41.	1980–1995	(dersimonin*)@ (TI,AB,RWDS)	15
42.	1980–1995	(fixed effect*)@ (TI,AB,RWDS)	63
43.	1980–1995	(random effect*)@ (TI,AB,RWDS)	166
44.	1980–1995	(meta anal*)@ (TI,AB,RWDS)	3164
45.	1980–1995	(metaanal*)@ (TI,AB,RWDS)	164
46.	1980–1995	(meta?anal*)@ (TI,AB,RWDS)	2105
47.	1980–1995	2,3,4,5,6,7	346
48.	1980–1995	10,11,12,13,14,15,16,17, 18,19	1380
49.	1980–1995	20,21,22,28,29,30,31,32, 36,37,38,39	2289
50.	1980–1995	20,21,22,28,29	204
51.	1980–1995	30,31,32,36,37,38,39	4500
52.	1980–1995	40,41,42,43,44,45,46	4545
53.	1980–1995	47,48,50,51,52	101,97

Appendix 3

Coding form used to evaluate articles defined by MEDLINE, EMBASE and CDSR searches

CODING FORM

Reference Manager no. _____ **Coder** _____

1. ELIGIBILITY

_____ NHS-Yes _____ NHS-No _____ NHS-Probable

2. PUBLICATION TYPE

_____ NHS-Meta-analysis _____ NHS-Editorial

_____ NHS-Methodological

3. PRIMARY STUDIES

_____ NHS-RCTs _____ NHS-Observational _____ NHS-Mixed

4. RESEARCH QUESTION

_____ NHS-Treatment _____ NHS-Aetiology

_____ NHS-Diagnostic _____ NHS-Association

_____ NHS-Prevention _____ NHS-Prognosis

_____ NHS-Economics

Appendix 4

Meta-analyses coded as meta-analyses of RCTs identified by the MEDLINE and CDSR search

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References are numbered as in our Reference Manager list, which should be quoted in the case of any query.

Appendix 5

Questionnaire sent to reviewers, methodologists and editors

Quality assessment of the randomised trials included in meta-analyses has been researched and debated for several years. Different opinions exist regarding whether trial quality should be assessed, and how, if at all, quality features should be incorporated in the analysis.

Enclosed is a survey for meta-analysts, methodologists and editors in which we are exploring some of these issues. We would appreciate it if you would share your views with us. Data generated by this questionnaire will help us to understand whether guidelines for assessing and reporting methodologic trial quality in meta-analyses are desirable. We hope to capture a range of opinions about these issues, and to better understand different points of view. For the purposes of this survey, please consider trial methodologic quality in light of whether the design, conduct, and analysis are undertaken in such a way as to minimise bias.

We have pilot-tested this survey and it takes about 10–15 minutes to complete. Your responses will be completely confidential. Only pooled data will be reported. To facilitate returning the completed survey, we have included a stamp-addressed envelope for your convenience. We thank you in advance for taking the time to share your perspectives.

Sincerely,

Deborah Cook *Alejandro Jadad* *Terry Klassen*
Michael Moher *David Moher* *Peter Tugwell*

This research is funded by the NHS, UK.

Quality assessment of randomized trials included in meta-analyses

1. How important is assessment of the methodologic quality of the randomized trials included in a meta-analysis?
   A. Very important.
   B. Somewhat important.
   C. No opinion.
   D. Somewhat unimportant.
   E. Not at all important
   (please go to question 6).

2. How should the quality of the randomized trials included in a meta-analysis be assessed? (Please check all that apply).
   A. By assessment of only one item (i.e., for questions of therapy, the method of treatment allocation).
   B. By assessment of only 2 or 3 items (i.e., for questions of therapy, randomization sequence generation, blinding and follow-up).
   C. By assessment of a series of items (i.e., as in a checklist).
   D. By assessment of a series of items that also provides an overall summary score (i.e., as in a scale).
   E. By some other form of assessment (Please specify):

3. When a checklist or scale is used to assess the quality of randomized trials included in a meta-analysis, how important is the way in which the checklist or scale was developed?
   A. Very important.
   B. Somewhat important.
   C. No opinion.
   D. Somewhat unimportant.
   E. Not at all important.

4. In your opinion, which properties should be evaluated in the development and testing of a checklist or scale to assess the quality of randomized trials to be included in a meta-analysis? (Please check all that apply).
   A. Face validity – (does the instrument appear sensible to individuals who will use it?).
   B. Intra-rater reliability – (are the results similar when the instrument is used on the same study on different occasions by the same rater?).
   C. Inter-rater reliability – (are the results similar when different raters use it on the same study?).
   D. Construct validity – (does the instrument correspond to conceptual frameworks concerning quality assessment?).
   E. Empirical evidence showing that the items in the checklist or scale modify the effect size in a trial or meta-analysis.
   F. Other properties (Please specify):

5. How should the assessment of the quality of the randomized trials be incorporated into a meta-analysis? (Please check all that apply).
   A. By using the quality assessments as a screening threshold when examining the titles and abstracts of trials.
   B. By applying the quality assessments to the full manuscripts of the trials as an inclusion criterion for the meta-analysis.
   C. By using the quality assessments to describe the validity of the results of the primary trials.
   D. By using the quality assessments as a statistical weight in the meta-analysis.
   E. By using quality assessments to conduct sensitivity analyses (e.g., stratifying studies to conduct subgroup analyses based on trial features).
   F. By plotting trial results according to ascending or descending quality.
   G. By performing cumulative meta-analyses using quality assessments to sequence trial results.
   H. By some other method (Please specify):

6. It has been suggested that guidelines be developed for assessing the quality of randomized trials included in a meta-analysis. What impact do you think such guidelines would have <u>on the rigor and reporting of published meta-analyses</u>?
   A. Very likely to increase the rigor of reporting of published meta-analyses.
   B. Likely to increase the rigor of reporting of published meta-analyses.
   C. No input on the rigor of reporting of published meta-analyses.
   D. Likely to decrease the rigor of reporting of published meta-analyses.
   E. Very likely to decrease the rigor of reporting of published meta-analyses.

7. What impact do you think such guidelines would have <u>on the way in which meta-analyses might be interpreted by clinicians</u>?
   A. Very likely to make interpretation of meta-analyses easier.
   B. Likely to make interpretation of meta-analyses easier.
   C. No interpretation.
   D. Likely to make interpretation of meta-analyses more difficult.
   E. Very likely to make interpretation of meta-analyses more difficult.

8. If a meta-analysis is based on the central collection and analysis of individual patient data, should there be a quality assessment of this data?
   A. Yes.
   B. No opinion.
   C. No.
   Please describe the reason for your answer.

9. If you were an editor of a bio-medical journal, how would you deal with an otherwise rigorous meta-analysis in which the quality of the randomised trials had not been assessed?
   A. I would be very enthusiastic about publishing it if the quality of the trials was not assessed.
   B. I would be somewhat willing to publish it if the quality of the trials was not assessed.
   C. No opinion.
   D. I would be somewhat unwilling to publish it unless the quality of the trials was assessed.
   E. I would be very unenthusiastic about publishing it unless the quality of the trials was assessed.

10. Do you have any comments about assessing or reporting trial quality for meta-analyses:

Basic demographic information

This information will be used to help us interpret the results of this survey.

1. How would you **primarily** define yourself professionally? Please check only one.
   A. Clinician
   B. Editor
   C. Epidemiologist
   D. Methodologist
   E. Statistician
   F. Other (Please specify):

2. How long have you been an editor, methodologist, statistician or clinician?
   A. < 1 year
   B. 1–5 years
   C. 6–10 years
   D. 11–15 years
   E. > 15 years

3. Are you:
   A. Female
   B. Male

4. In what age range are you?
   A. < 35 years of age
   B. 35–44 years of age
   C. 45–54 years of age
   D. 55–64 years of age
   E. > 65 years of age

Thank you!

Would you be interested in receiving a copy of the results of this survey? Yes No

Please provide your name and address (postal or electronic).

Appendix 6

Data extraction form for assessing the quality of RCTs

NHS Project 1: Data Extraction Form

❑ Cook	❑ Jones	❑ Moher, M
❑ Jadad	❑ Klassen	❑ Moher, D
❑ Tugwell		

---

1. What database was the meta-analysis identified in ?

   ❑ MEDLINE ❑ CDSR

2. What journal was the meta-analysis published in? (i.e. for example, JAMA).
   _____

3. What year was the meta-analysis published in ? _____

4. What is the language of the published meta-analysis? _____

5. No. of authors(s)_____

6. How were the trials identified?

❑ MEDLINE	❑ EMBASE	❑ Other
❑ Hand-searching	❑ Content experts	❑ Reference lists
❑ Corresponding authors	❑ Abstracts	❑ Conference proceedings
❑ Industry source		

❑ Some other way, please specify _____

continued

continued

7. How many trials were considered for inclusion?

   No. _____ ❑ Can't tell

8. How many trials were excluded?

   No. _____ ❑ Can't tell

9. Did the authors report the list of inclusion and exclusion criteria?

   ❑ Yes ❑ No ❑ Can't tell

10. Did the authors measure the reproducibility criteria?

    ❑ Yes ❑ No ❑ Can't tell

11. How many trials were included in the meta-analysis?

    No. _____ ❑ Can't tell

12. How many patients were included in the meta-analysis?

    No. _____ ❑ Can't tell

13. Were any trials excluded because of the language in which they were published/reported?

    ❑ Yes ❑ No ❑ Can't tell

14. If yes, how many?

    No. _____ ❑ Can't tell

15. Were the trials subjected to any quality assessment?

    ❑ Yes ❑ No ❑ Can't tell

16. If yes, what method of quality assessment did the author(s) report using? (To be considered a scale, there needs to be an overall quantitative score.)

    ❑ Component ❑ Checklist ❑ Scale

    ❑ Some other method ❑ Not reported

17. Was the reproducibility of the quality assessed?

❑ Yes ❑ No ❑ Can't tell

18. If the author(s) reported assessing quality using a component approach, which one did they assess? ***Check all that apply***

❑ Randomisation – generation ❑ Randomisation – allocation concealment

❑ Withdrawals/dropouts ❑ Blinding of analysts ❑ Blinding of patients

❑ Blinding of caregivers ❑ Blinding of outcome adjudicators

❑ Other, please specify _____

19. If the author(s) reported assessing quality using a checklist, which one did they use?

❑ Badgley ❑ Bland ❑ Dersimonian ❑ Gardner

❑ Grant ❑ Lionel ❑ Mahon ❑ Thomson

❑ Weintraub

❑ Other, please specify (this may include a modification of the aforementioned checklist)

_____

20. If the author(s) reported assessing quality using a scale, which one did they use? ***Check all that apply***

❑ Andrew ❑ Annals ❑ Beckerman ❑ Brown

❑ Chalmers, I ❑ Chalmers, TC ❑ Cho ❑ Colditz

❑ Criteria based ❑ Detsky ❑ Evans ❑ Gotzche

❑ Imperiale ❑ Jadad ❑ Jonas ❑ Kleijnen

❑ Koes ❑ Linde ❑ Nurmohamed ❑ Onghena

❑ Poynard ❑ Reisch

❑ Other, please specify (this may include a modification of the aforementioned scale)

_____

continued

continued

21. Were the quality scores incorporated into the quantitative analysis?

❑ Yes ❑ No ❑ Can't tell

22. What were the quality scores used as?

❑ Sensitivity analysis: ❑ *A priori* ❑ *A posteriori*

❑ Subgroup analysis: ❑ *A priori* ❑ *A posteriori*

23. If yes, how were the quality scores incorporated into the quantitative analysis?

❑ As a weight ❑ As a threshold score for inclusion in analysis

❑ As the input sequence in a cumulative meta-analysis

❑ As a visual plot

24. Was there a primary outcome stated?

❑ Yes ❑ No ❑ Can't tell

25. What was the statistical result of the meta-analysis?

❑ Positive ❑ Equivalent ❑ Negative

Positive – upper end of the confidence limits is below unity

Equivalent – confidence intervals cross unity

Negative – lower end of the confidence limits is above unity

26. What was the overall quantitative estimate of the meta-analysis?

		Point estimate	95% CI	
			Lower	Upper
OR (e.g. OR = 1.87)	=	_____	_____	_____
Risk difference	=	_____	_____	_____
Relative risk	=	_____	_____	_____
WMN	=	_____	_____	_____
ES	=	_____	_____	_____
Other method	=	_____	_____	_____

27. Was there any formal evaluation of between trials heterogeneity reported?

❑ Yes ❑ No ❑ Can't tell

Appendix 7

Summary of results of extraction of data on quality assessment in 240 meta-analyses

TABLE 10 *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
366	No	na	na	na	na	na	na	na
824	No	na	na	na	na	na	na	na
655	Yes	Scale	Yes	na	na	Thomas	No	na
635	Yes	Scale	No	na	na	Imperiale	Yes	Weight
377	No	na	na	na	na	na	na	na
622	No	na	na	na	na	na	na	na
616	No	na	na	na	na	na	na	na
597	Yes	Scale	No	na	na	Thomas Chalmers	Yes	Threshold
582	No	na	na	na	na	na	na	na
565	No	na	na	na	na	na	na	na
564	No	na	na	na	na	na	na	na
540	Yes	Scale	Yes	na	na	Ian Chalmers	No	na
529	No	na	na	na	na	na	na	na
509	No	na	na	na	na	na	na	na
503	No	na	na	na	na	na	na	na
495	No	na	na	na	na	na	na	na
473	No	na	na	na	na	na	na	na
480	No	na	na	na	na	na	na	na
436	No	na	na	na	na	na	na	na
468	No	na	na	na	na	na	na	na
440	Yes	Can't tell	No	na	na	na	No	na
437	No	na	na	na	na	na	na	na
403	No	na	na	na	na	na	na	na
429	Yes	Scale	No	na	na	Marshall	No	na
400	No	na	na	na	na	na	na	na
391	No	na	na	na	na	na	na	na
859	No	na	na	na	na	na	na	na
373	No	na	na	na	na	na	na	na

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
879	No	na	na	na	na	na	na	na
487	No	na	na	na	na	na	na	na
1055	No	na	na	na	na	na	na	na
789	Yes	Scale	No	na	na	Thomas Chalmers	Yes	Threshold
505	Yes	Scale	No	na	na	Glasziou	Yes	Visual Plot
498	Yes	Scale	Yes	na	na	Soloman	No	na
567	No	na	na	na	na	na	na	na
756	No	na	na	na	na	na	na	na
748	Yes	Scale	Yes	na	na	Collins	No	na
743	No	na	na	na	na	na	na	na
719	No	na	na	na	na	na	na	na
714	Yes	Not reported	No	na	na	na	No	na
652	No	na	na	na	na	na	na	na
650	No	na	na	na	na	na	na	na
627	No	na	na	na	na	na	na	na
629	Yes	Scale	Yes	na	na	Thomas Chalmers	No	na
634	No	na	na	na	na	na	na	na
521	No	na	na	na	na	na	na	na
550	No	na	na	na	na	na	na	na
776	No	na	na	na	na	na	na	na
763	No	na	na	na	na	na	na	na
746	Yes	Scale	Yes	na	na	Detsky	Yes	Threshold
745	Yes	Scale	No	na	na	Thomas Chalmers	No	na
1850	Yes	Component	Yes	Randomisation generation Withdrawals/ drop-outs Other	na	na	No	na
1834	Yes	Component	No	Randomisation generation Other	na	na	No	na
1849	Yes	Component	Yes	Randomisation generation Withdrawals/ drop-outs Other	na	na	No	na
1833	Yes	Component	No	Other	na	na	No	na
1838	Yes	Component	Yes	Randomisation generation Other	na	na	Yes	Threshold

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
1843	Yes	Component	No	Randomisation generation Other	na	na	Yes	Threshold
1844	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs Other	na	na	No	na
1839	Yes	Component	No	Randomisation generation Allocation concealment Withdrawals/ drop-outs Blinding of patients Other	na	na	No	na
1845	Yes	Component	No	Randomisation generation Other	na	na	No	na
1024	No	na	na	na	na	na	na	na
1296	No	na	na	na	na	na	na	na
1418	No	na	na	na	na	na	na	na
1472	No	na	na	na	na	na	na	na
1479	No	na	na	na	na	na	na	na
1482	Yes	Component	No	Randomisation generation	na	na	No	na
1518	Yes	Component	Yes	Randomisation generation Other	na	na	No	na
1529	No	na	na	na	na	na	na	na
1543	No	na	na	na	na	na	na	na
1568	No	na	na	na	na	na	na	na
1578	Yes	Scale	No	na	na	Thomas Chalmers	Yes	Weight
1589	Yes	Scale	No	na	na	Ian Chalmers	Yes	Weight
1628	No	na	na	na	na	na	na	na
1637	No	na	na	na	na	na	na	na
1642	No	na	na	na	na	na	na	na
1655	Yes	Component	No	Blinding of patients, care givers	na	na	Yes	Weight
1656	No	na	na	na	na	na	na	na
1668	Yes	Checklist	No	na	Dersimonian	na	No	na
1669	No	na	na	na	na	na	na	na
1697	No	na	na	na	na	na	na	na

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
1699	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs Blinding of patients, care givers	na	na	No	na
1707	No	na	na	na	na	na	na	na
1709	Yes	Scale	Yes	na	na	Ian Chalmers	Yes	Weight
1718	Yes	Scale	Yes	na	na	Dersimonian	Yes	Not reported
1757	Yes	Scale	No	na	na	Thomas Chalmers	No	na
1771	No	na	na	na	na	na	na	na
1773	Yes	Scale	No	na	na	Poynard	No	na
1731	No	na	na	na	na	na	na	na
1778	Yes	Scale	Can't tell	na	na	Can't tell	Yes	Weight
1795	No	na	na	na	na	na	na	na
1803	No	na	na	na	na	na	na	na
1804	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs	na	na	No	na
1893	Yes	Component	No	Randomisation generation	na	na	No	na
1892	Yes	Component	No	Randomisation generation	na	na	No	na
1888	Yes	Component	Yes	Randomisation generation Withdrawals/ drop-outs Other	na	na	No	na
1886	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs Blinding of analysts, patients, care givers	na	na	No	na
1881	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs Blinding of patients, care givers	na	na	No	na
1880	Yes	Component	No	Randomisation generation	na	na	No	na

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
1879	Yes	Component	No	Randomisation generation Blinding of analysts, patients, care givers	na	na	No	na
1875	Yes	Component	Yes	Randomisation generation Blinding of patients, care givers	na	na	No	na
1828	No	na	na	na	na	na	na	na
367	No	na	na	na	na	na	na	na
415	No	na	na	na	na	na	na	na
451	Yes	Scale	Yes	na	na	Cronin & Cook	Yes	Threshold
508	Yes	Scale	No	na	na	Evans	No	na
609	Yes	Component	No	Randomisation generation Blinding of patients, care givers	na	na	Yes	Not reported
623	No	na	na	na	na	na	na	na
689	No	na	na	na	na	na	na	na
735	Yes	Scale	No	na	na	Not stated	Yes	Not reported
762	No	na	na	na	na	na	na	na
811	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs	na	na	No	na
821	Yes	Scale	No	na	na	Thomas Chalmers	No	na
902	No	na	na	na	na	na	na	na
963	Yes	Component	No	Randomisation generation Allocation concealment Withdrawals/ drop-outs	na	na	Yes	Not reported
970	Yes	Scale	Yes	na	na	Thomas Chalmers	No	na
1019	No	na	na	na	na	na	na	na
943	No	na	na	na	na	na	na	na
1021	No	na	na	na	na	na	na	na
1025	No	na	na	na	na	na	na	na
927	Yes	Scale	No	na	na	Marchand	No	na
878	No	na	na	na	na	na	na	na

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
876	No	na	na	na	na	na	na	na
866	No	na	na	na	na	na	na	na
786	No	na	na	na	na	na	na	na
697	Can't tell	na	na	na	na	na	na	na
1470	Yes	Checklist	Can't tell	New scale with items from Chalmers, Poynard, Greenberg	na	na	No	na
1444	No	na	na	na	na	na	No	na
1443	No	na	na	na	na	na	na	na
1434	Yes	Scale	Yes	na	na	Cook	No	na
1401	No	na	na	na	na	na	na	na
1368	No	na	na	na	na	na	na	na
1353	Yes	Scale	Yes	na	na	Cook	Yes	Weight
1351	Yes	Scale	Yes	na	na	Thomas Chalmers	Yes	Threshold
1323	No	na	na	na	na	na	Yes	na
1317	Yes	Scale	No	na	na	Gotzsche	No	na
1292	Yes	Component	No	Blinding of care givers	na	na	Yes	Not reported
1291	No	na	na	na	na	na	na	na
1267	Yes	Scale	No	na	na	Can't tell	No	na
1230	No	na	na	na	na	na	na	na
1216	No	na	na	na	na	na	na	na
1213	Yes	Component	No	Withdrawals/ drop-outs Blinding of patients, care givers	na	na	No	na
1198	No	na	na	na	na	na	na	na
667	Yes	Scale	No	na	na	Poynard	Can't tell	na
603	No	na	na	na	na	na	na	na
1187	Yes	Component	No	Withdrawals/ drop-outs Other	na	na	Yes	Threshold
1186	Yes	Scale	No	na	na	Thomas Chalmers	Yes	Threshold
1185	No	na	na	na	na	na	na	na
1166	Yes	Component	Yes	Allocation concealment Other	na	na	Yes	Not reported
1158	Yes	Scale	No	na	na	Thomas Chalmers	No	na
1153	No	na	na	na	na	na	na	na

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
1135	Yes	Scale	No	na	na	Thomas Chalmers	No	na
1132	Yes	Scale	Yes	na	na	Thomas Chalmers	No	na
1118	No	na	na	na	na	na	na	na
1078	Yes	Component	No	Randomisation generation Allocation concealment Withdrawals/ drop-outs Blinding of patients Other	na	na	No	na
1039	Yes	Component	No	Randomisation generation Allocation concealment	na	na	No	na
1873	Yes	Component	No	Randomisation generation Allocation concealment Withdrawals/ drop-outs Other	na	na	No	na
1874	Yes	Component	No	Randomisation generation Blinding of patients, care givers	na	na	No	na
1870	Yes	Component	No	Randomisation generation Allocation concealment	na	na	No	na
1857	Yes	Component	No	Randomisation generation Allocation concealment Withdrawals/ drop-outs	na	na	No	na
1887	Yes	Component	No	Allocation concealment	na	na	No	na
1851	Yes	Component	No	Randomisation generation Allocation concealment Withdrawals/ drop-outs Blinding of care givers	na	na	No	na
1853	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs Blinding of patients, care givers	na	na	No	na

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
1894	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs Blinding of patients, care givers	na	na	No	na
1895	Yes	Not reported	No	na	na	na	No	na
1521	No	na	na	na	na	na	na	na
991	No	na	na	na	na	na	na	na
1110	Yes	Scale	Yes	na	na	Sanderson	Yes	Threshold
1124	No	na	na	na	na	na	na	na
1476	No	na	na	na	na	na	na	na
1086	Yes	Scale	No	na	na	Thomas Chalmers	No	na
1089	No	na	na	na	na	na	na	na
1107	Yes	Scale	Yes	na	na	Warshafsky	No	na
1184	No	na	na	na	na	na	na	na
1210	Yes	Scale	Yes	na	na	Thomas Chalmers	No	na
1193	Yes	Component	No	Randomisation generation Other	na	na	Yes	Threshold
1182	No	na	na	na	na	na	na	na
1160	No	na	na	na	na	na	na	na
1152	Yes	Scale	No	na	na	Thomas Chalmers	No	na
1252	No	na	na	na	na	na	na	na
1220	No	na	na	na	na	na	na	na
1350	No	na	na	na	na	na	na	na
1402	Yes	Scale	No	na	na	Boissel	No	na
1424	Yes	Scale	No	na	na	Poynard	No	na
1430	No	na	na	na	na	na	na	na
1390	No	na	na	na	na	na	na	na
1392	No	na	na	na	na	na	na	na
1391	No	na	na	na	na	na	na	na
1400	No	na	na	na	na	na	na	na
1429	No	na	na	na	na	na	na	na
1435	No	na	na	na	na	na	na	na
1457	No	na	na	na	na	na	na	na

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
1890	Yes	Component	No	Randomisation generation Blinding of outcome adjudicators	na	na	No	na
1872	Yes	Other	No	na	na	na	No	na
1708	Yes	Scale	No	na	na	Thomas Chalmers	No	na
1869	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs Other	na	na	No	na
1330	Yes	Scale	No	na	na	Anderson	Yes	Weight
1388	No	na	na	na	na	na	na	na
559	No	na	na	na	na	na	na	na
1739	No	na	na	na	na	na	na	na
1194	No	na	na	na	na	na	na	na
1575	No	na	na	na	na	na	na	na
1441	Yes	Not reported	No	Can't tell	Can't tell	Can't tell	No	na
1591	No	na	na	na	na	na	na	na
1662	No	na	na	na	na	na	na	na
1556	Yes	Scale	No	na	na	Thomas Chalmers	No	na
935	Yes	Scale	No	na	na	Ian Chalmers	No	na
1670	Yes	Component	No	Withdrawals/ drop-outs	na	na	No	na
1689	No	na	na	na	na	na	na	na
1820	No	na	na	na	na	na	na	na
1632	Yes	Component	Yes	Randomisation generation Other	na	na	No	na
1626	No	na	na	na	na	na	na	na
1756	Yes	Scale	No	na	na	Mulrow	No	na
1077	No	na	na	na	na	na	na	na
649	Yes	Scale	No	na	na	Thomas Chalmers	No	na
1680	No	na	na	na	na	na	na	na
1588	Yes	Scale	No	na	na	Ian Chalmers	No	na
1693	No	na	na	na	na	na	na	na
1515	No	na	na	na	na	na	na	na
1815	No	na	na	na	na	na	na	na
1891	Yes	Component	No	Randomisation generation	na	na	No	na

* *Number in our larger database of meta-analyses*
na, not applicable

continued

TABLE 10 contd *How often and how is quality assessed: results of each meta-analysis*

Meta-analysis number*	Was quality assessment performed?	Method of quality assessment	Was reproducibility assessed?	Component approach used	Checklist used	Scale used	Was quality incorporated into the analysis?	Method of incorporation
1836	Yes	Component	No	Randomisation generation Withdrawals/ drop-outs Blinding of outcome adjudicators Other	na	na	No	na
1862	Yes	Component	No	Allocation concealment Blinding of patients, care givers Other	na	na	No	na
1866	Yes	Component	No	Randomisation generation Allocation concealment	na	na	No	na
1858	Yes	Not reported	No	na	na	na	No	na
1861	Yes	Component	No	Randomisation generation Other	na	na	No	na
1197	Yes	Scale	No	na	na	Thomas Chalmers	Yes	Weight
1042	No	na	na	na	na	na	na	na
1468	Yes	Component	No	Randomisation generation Other	na	na	No	na
1415	Yes	Component	No	Randomisation generation Other	na	na	No	na
1141	No	na	na	na	na	na	na	na
918	Yes	Component	No	Allocation concealment Other	na	na	No	na
1062	No	na	na	na	na	na	na	na
1031	No	na	na	na	na	na	na	na
1043	No	na	na	na	na	na	na	na
990	No	na	na	na	na	na	na	na
1408	No	na	na	na	na	na	na	na
759	Yes	Scale	No	na	na	Thomas Chalmers	Yes	Visual Plot
1898	Yes	Component	No	Withdrawals/ drop-outs Other	na	na	No	na

* *Number in our larger database of meta-analyses*
na, not applicable

Appendix 8

Data extraction form for completing quality assessment of RCTs

QUALITY ASSESSMENT OF RCTs

1. a) Reviewer _____ **b) Trial no.** _____

2. Funding source

- ❑ Single drug company
- ❑ Multiple drug company
- ❑ Drug company plus non-drug sponsor
- ❑ Non-drug company
- ❑ None listed
- ❑ Can't tell – masked

Single drug company	***– single pharmaceutical company***
Multiple drug company	***– more than one such company***
Drug company plus non-drug sponsor	***– one or more pharmaceutical companies plus a non-pharmaceutical organisation***
Non-drug company	***– another, non-pharmaceutical, sponsor or sponsors, including universities, medical societies, government and foundations***
None listed	***– no sponsors mentioned***

3. Level of support

- ❑ Study intervention
- ❑ More than study drugs
- ❑ Can't tell

4. What are the following quality scores based on?

- ❑ Masked assessment
- ❑ Open assessment

continued

continued

Jadad's scale

5. Randomisation

❑ Yes ❑ No

(extra point) ❑ Yes ❑ No

Randomisation – trials that report using the following methods are to receive a point: reporting that the trial was a 'randomised' one. Trials that describe (and was appropriate) the method of randomisation, such as table of random numbers, computer generated, receive an additional point. However, if the report described the trial as randomised and it was inappropriate, such as date of birth, hospital numbers, a point is deducted.

6. Double-blinding

❑ Yes ❑ No

(extra point) ❑ Yes ❑ No

Double-blinding – trials that report using the following methods are to receive a point: reporting that a trial was 'double-blind'. Trials that describe (and was appropriate) the method of double-blinding, such as identical placebo, active placebo, receive an additional point. However, if the report described the trial as double-blind and it was inappropriate, such as comparison of tablets versus injection with no double dummy, a point is deducted.

7. Withdrawals and drop-outs

❑ Yes ❑ No

Withdrawals and drop-outs – trials that report using the following methods are to receive a point: the number and reasons for dropouts and withdrawals in each group must be stated. However, if there is no statement on withdrawals, this item must be given no point.

Schulz's components

8. Randomisation generation

Adequately stated? ❑ Yes ❑ No

Randomisation generation – trials that report using the following methods are to receive a point: trials that report using either a random-numbers table, computer random number, coin tossing, dice throwing, and shuffling.

9. Allocation concealment

Adequately stated? ❑ Yes ❑ No

Allocation concealment – trials that report using either central randomisation, numbered or coded bottles or containers, or a statement indicating that drugs were prepared by a pharmacy. Serially numbered, opaque, sealed envelopes is another example of adequate allocation concealment. Reports of using 'sealed envelopes' without mention of 'opaque' are not to receive a point.

10. Double-blinding

Adequately stated? ❑ Yes ❑ No

Double-blinding – trials that report using the following methods are to receive a point: trials purporting to be accounts of double-blind trials.

Thank you for your help!

Appendix 9

Definition of terms used

The definitions below were used in quality assessment described in chapter 5.

Allocation concealment	Adequately concealed trials were trials in which concealment up to the point of treatment (e.g. central randomisation) was reported.
Double-blinding	Was the study described as double-blind? An additional point is given if the method of double-blinding was described and it was appropriate (e.g. identical placebo). However, a point was deducted if the method of blinding was described and it was inappropriate (e.g. comparison of tablet versus injection with no double dummy).
Generation of random numbers	Clinical trials that reported the following methods for generation of their allocation sequence were considered adequate: computer, random number table, shuffled cards or tossed coins, and minimisation. Inadequate methods included alternate assignment and assignment by odd/even birth date or hospital number.
High-quality trials	Using a scale approach to quality assessment, high-quality trials were those ones scoring > 2 (out of maximum possible score of 5). This assignment was made before beginning the study.
Low-quality trials	Using a scale approach to quality assessment, low-quality trials were those ones scoring ≤ 2 (out of maximum possible score of 5). This assignment was made before beginning the study.
Quality	The confidence that the study design, conduct, analysis, and presentation have limited biased comparisons of the intervention under consideration.
Quality weight	In the main meta-analysis, one combines the study estimates weighting proportionally to their precision to derive the pooled estimate. In the corresponding sensitivity analysis, we advocated the use of a quality weight that was a product of precision and the quality of reporting score. By weighting on precision and trial quality (in this study scaled by the quality score), we can assess the effect of various bias-induced aspects of the trial design and reporting on the pooled estimates of treatment effectiveness.
Randomisation	Using a scale approach to the assessment of randomisation involved the following. Was the study described as randomised (this includes the use of words such as randomly, random, and randomisation)? An additional point was given if the method to generate the sequence of randomisation was described and it was appropriate (e.g. table of random numbers, computer generated). However, a point was deducted if the method to generate the sequence of randomisation was described and it was inappropriate (e.g. date of birth).
Ratio of odds ratios	Typically, clinical trials are conducted such that the experimental intervention, compared with the standard intervention, prevents an unwanted outcome (e.g. mortality). Therefore, an OR < 1 favours the intervention under consideration. In the

	context of this study an ROR (e.g. low-quality trials versus high-quality trials) can be interpreted as providing an estimate of the effects of quality on the point estimate and precision of the result. An ROR can be interpreted in much the same way as an OR.
Replication	For each meta-analysis, we extracted the statistical methods used to derive the combined treatment estimates and faithfully replicated these pooled estimates in the main analysis.
Sensitivity analysis	For trials assessed using individual components two data syntheses are completed: analysing the results for those trials in which the item is adequately reported, and also presenting the results for those trials that inadequately report the characteristic. Using a scale approach two analyses are also completed: analysing the results for those trials in which the item scores above a pre-specified score, and presenting the results for those trials scoring below the pre-specified score.
Statistical heterogeneity	In the logistic regression analysis, the variation in a clinical outcome was related to its systematic sources such as trials and treatment through logistic regression models. For each model, the deviance divided by its degrees of freedom was regarded as an approximate measure of over dispersion, reflecting the degree of heterogeneity between trials. We used approximate *F* ratio tests to compare the heterogeneity of trials with low quality, high quality and quality weight.
Threshold analysis	For trials assessed using individual components only those trials that adequately report the characteristic are included in the analysis. Using a scale approach only those trials scoring above a pre-specified score are included in the analysis.

Appendix 10

Statistical approaches used to generate empirical evidence

Suppose that K independent studies give data as in *Table 11*, each compares a treatment and control groups on a binary outcome with an assessed quality score q_k.

TABLE 11 *Observed counts for study k among K 2 x 2 contingency tables*

Treatment group	Success	Failure	Total
Treated	a_k	b_k	m_k
Control	c_k	d_k	n_k
Total	t_k	$N_k - t_k$	N_k

Mantel–Haenszel (MH) method

We define notations that use the counts shown in *Table 11*. Let

$$R_k = a_k d_k / N_k,\ R_+ = \sum_k R_k \text{ and } S_k = b_k c_k / N_k$$

and $S_+ = \sum_k S_k$

$$P_k = (a_k + d_k)/N_k \text{ and } Q_k = (b_k + c_k)/N_k$$

The MH estimate $\hat{\theta}_{MH} = R_+/S_+$ is a weighted average of the study specific estimate of the OR $\hat{\theta}_k$, with weight equal to S_k. To account for quality assessment, define

$$S'_k = q_k S_k \text{ and } S'_+ = \sum_k S'_k$$

The weighted average scheme imposes that

$$R'_k = q_k R_k \text{ and } R'_+ = \sum_k \mathrm{R}'_k$$

hence the quality-adjusted estimate $\hat{\theta}'_{MH} = R'_+/S'_+$.

As a consequence, an appropriate variance for $\hat{\theta}'_{MH}$ on a log scale[120] is

$$\mathrm{var}(\log \hat{\theta}'_{MH}) = 0.5 \sum_k ((P_k R'_k/R'^2_+) + (P_k S'_k + Q_k R'_k)/ (R'_+ S'_+) + (Q_k S_k S'^2_+))$$

Peto method

Define

$$E_k = (a_k + b_k)(a_k + c_k)/N_k \quad (1)$$

and

$$V_k = (a_k + c_k)(b_k + d_k)(a_k + b_k)(c_k + d_k)/ N_k^2(N_k - 1) \quad (2)$$

Under the null hypothesis of no treatment effect and fixed marginal totals of *Table 11*, E_k and V_k is respectively the mean and variance of a hypergeometric random variable A_k (with instance a_k). Each study observation a_k can be weighted by its quality score q_k in the combined estimate $A_+ = \sum_k q_k a_k$, expectation $E_+ = \sum_k q_k E_k$ and variance $V_+ = \sum_k q_k^2 V_k$. A quality-adjusted estimate of the common OR θ (log scale) is $(A_+ - E_+)/V_+$ with variance $1/V_+$.

Inverse-variance weighted method

This method of combining results is generally applicable to all endpoints (e.g. absolute risk difference, relative risk (RR), and treatment group rates). Let G_k be a generic outcome estimate (e.g. RR) from study k and $W_k = 1/\mathrm{var}(G_k)$. The inverse-variance weighted estimate for the K studies is G where $G = (\sum_k W_k G_k)/(\sum_k W_k)$ with variance $\mathrm{var}(G) = 1/(\sum_k W_k)$. With the additional adjustment by quality assessment, define $W'_k = q_k W_k$ then the combined estimate G' becomes

$$G' = (\sum_k W'_k G_k / (\sum_k W'_k)$$

with variance

$$\mathrm{var}(G') = (\sum_k q_k W'_k)/(\sum_k W'_k)^2$$

Test of no treatment effect

Under the null hypothesis, the mean E_k and variance V_k of A_k is given in (1) and (2), respectively.

Let the quality adjusted $A_+ = \sum_k q_k a_k$, expectation $E_+ = \sum_k q_k E_k$ and variance $V_+ = \sum_k q_k^2 V_k$, then null hypothesis can be tested[121] by the chi-square statistic:

$$\chi^2 = (A_+ - E_+)^2 / V_+$$

with 1 degree of freedom.

Test of homogeneity of the ORs

The chi-square test of constant OR sums up the squared deviations of observed a_k and its expectation $E(A_k|\hat{\theta})$, each standardised by its variance[108]

$$\chi^2 = \sum_k ((a_k - E(A_k|\hat{\theta}))^2 / \mathrm{var}(A_k|\hat{\theta}) \qquad (5)$$

($K-1$ degree of freedom). This test is affected by the quality adjustment only through the quality adjusted estimate $\hat{\theta}$. In our calculations, we use the MH estimate $\hat{\theta}'_{MH}$, the asymptotic estimate $E(A_k|\hat{\theta}_{MH})$ and $V(a_k|t_k; \hat{\theta}_{MH})$ given in (3) and (4), respectively.

With respect to quality adjustment, the global statistic in (5) may lack power against the alternative of a systematic increase or decrease in the observed a_k with an increase in quality q_k.[122] In such a situation, a chi-square test (one degree of freedom) for a trend between the observed a_k and trial quality q_k can be calculated as follows:

$$\chi^2 = (\sum_k q_k(a_k - E(A_k|\hat{\theta})))^2 / (\sum_k q_k^2 \mathrm{var}(A_k|\hat{\theta}) - (\sum_k q_k \mathrm{var}(A_k|\hat{\theta}))^2 / (\sum_k \mathrm{var}(A_k|\hat{\theta})))$$

Dersimonian–Laird method for random effect model

We refer back to the generic notations used previously in the inverse-variance weighted method. The Breslow–Day chi-square statistic for homogeneity test (5) can be calculated for any outcome G[122]

$$Q_b = \sum_k \upsilon_k (G_k - \hat{G})^2$$

where $\hat{G}$ is the weighted estimate $\hat{G} = (\sum_k \upsilon_k G_k) / \sum_k \upsilon_k)$ and υ_k the inverse of the k within-trial variance. The weighted estimate $\hat{k}$ can be adjusted for quality assessment through $\upsilon'_k = q_k \upsilon_k$ to $\hat{G}' = (\sum_k \upsilon'_k G_k) / (\sum_k \upsilon'_k)$. However, quality assessment only affects the statistic Q_b and the subsequent estimate Δ_b^2 of the between-trial variation through the quality-adjusted estimate $\hat{G}'$. When homogeneity is present, one non-iterative estimate of Δ_b^2 is

$$\Delta_b^2 = \max(0, (Q_b - (K-1)) / (\sum_k \upsilon_k - (\sum_k \upsilon_k^2 / \sum_k \upsilon_k)))$$

Under a random effect model, a combined estimate G_{RD} can be weighted both on quality score q_k and the sum of within- and between-trial variations $W_k = 1/(1/\upsilon_k + \Delta_b^2)$

$$G_{RD} = (\sum_k W'_k G_k) / (\sum_k W'_k)$$

where

$$W'_k = q_k W_k$$

and variance

$$\mathrm{var}(G_{RD}) = (\Sigma_k q_k W'_k) / (\Sigma_k W'_k)^2$$

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