THE UNIVERSITY OF CALGARY

The Applicability of Meta-analyses to Guide Clinical Practice in Critical Care.

by

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ABSTRACT

The objectives of this study were to determine the quality of reports of meta-analyses addressing critical care topics, and to examine whether any features of meta-analyses may be associated with an increased probability of the results of the meta-analyses predicting the results of subsequent randomized clinical trials (RCTs).

It was found that the overall quality of meta-analyses addressing critical care topics was poor. The majority of reports were not of a standard that clinicians could have confidence that the results would be applicable in their clinical practice. Due to differences in the study questions, populations, interventions and outcomes measured, it is not common for the results of meta-analyses and large well-conducted RCTs addressing issues in acute care medicine to be truly comparable. Apart from the methodological quality of the meta-analysis, there were no features identified that would predict concordance between the results of meta-analyses and subsequent RCTs.

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DEDICATION

The ability to give 110%

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A. INTRODUCTION

One of the challenges that faces critical care physicians is that of staying up to date with the current state of knowledge, in a field that has a broad scope of practice and time dependency for many of the interventions provided. This problem is neither new nor unique to the field of critical care. In fact, the need for overviews of current knowledge was recognised as long ago as the late 18th century, when the journal *Medical and Philosophical Commentaries* was edited by Andrew Duncan[1]. However, it wasn't until the late 1970's and early 1980's that the need for scientific rigor in the performance of this type of research was widely recognised[1]. In response to the perceived need for up to date summaries of current evidence, systematic reviews and meta-analyses are becoming more prevalent, with a marked increase in the number of these types of overviews of the literature that have appeared as separate reports from the late 1980's[2].

Systematic reviews and meta-analyses are two terms used in the medical literature to describe overviews of primary studies. What is a meta-analysis and how does it differ from a systematic review? While some authors do not draw a distinction between them[3], there is an important distinction between the two types of studies. A systematic review can be defined as "the application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic" [1] or "the application of scientific strategies that limit bias to the

systematic assembly, critical appraisal, and synthesis of all relevant studies on a specific topic" by the Potsdam Consultation on Meta-analysis [4]. A systematic review then can be seen as a study that summarizes the available evidence without necessarily attempting to quantitatively combine the results of the component studies. Meta-analysis has been defined as "the statistical synthesis of the data from separate but similar, i.e. comparable studies, leading to a quantitative summary of the pooled results"[1] or again by the Potsdam Consultation on Meta-analysis as "a systematic review that employs statistical methods to combine and summarize the results of several studies" [4]. A meta-analysis takes the next step and attempts to statistically combine the results of the studies that have been found in the systematic review and produce a single summary statistic.

The need for up to date summaries of the available evidence to help guide clinicians provide optimal care for their patients is clear. It is known that the recommendations of traditional review articles, medical textbooks and the clinical opinion of experts are often at odds with the best current available evidence[5 6]. Systematic reviews in general and meta-analyses in particular have been advocated as a solution to the problem of staying up to date with the medical evidence in a particular field[7 8 9]. What remains somewhat controversial is whether the results of meta-analyses offer a reliable and reproducible estimate of the true treatment effect, a result that could be reliably followed by clinicians[10]. When a systematic review finds a large number of trials that all come to the same

conclusion there is little doubt about the correct treatment recommendations. However, there are numerous incidences of meta-analyses that have combined small trials with disparate results and produced conflicting evidence[3 11 12], as well as meta-analyses[13 14] that produced results that were in conflict with the results of subsequent large clinical trials[15 16]. When this occurs it can lead to difficulties for clinicians trying to apply the best available evidence in the care of their patients, as it is not clear which is the best evidence to follow. Grave doubts have been raised about the reliability of using meta-analyses to guide clinical practice[17 18 19].

There is another aspect to this debate that needs to be considered. There have been meta-analyses that have produced results that have been completely in keeping with the results of subsequent large clinical trials. One of the most celebrated examples deals with the use of thrombolysis for the treatment of patients with acute myocardial infarction. It has been shown that if a meta-analysis had been performed, the benefits of thrombolysis for the treatment of acute myocardial infarction could have been demonstrated as early as 1973[20]. When a meta-analysis was performed in 1982 it clearly demonstrated the efficacy of the treatment[21], however large clinical trials were still being performed up to six years later[22 23]. The results of these trials were in complete agreement with the result of the meta-analysis, serving only to reinforce and narrow the confidence intervals around the estimated treatment effect. There are consequences that arise if the results of meta-analyses reflecting the true treatment effect are not heeded. Firstly,

as did occur in this case, the treatment was not licensed in many countries for some years after the publication of the large trials, meaning that many lives were potentially lost, as the best available evidence was not used in clinical practice. Secondly there are implications for the ethical conduct of large trials, where participants are randomized to a control therapy when the active treatment is known to be beneficial. Thirdly, large clinical trials are very expensive to perform. If the results could reliably be known at lesser expense, resources could be directed to investigating other issues.

Thus there is an inconsistency in the literature with regards to the role that meta-analyses should play in guiding clinical practice. On the one hand, these reports are recommended by some highly regarded groups as constituting the highest level of published evidence[24], and in some cases that recommendation seems warranted. However, as a result of the conflicting and unreliable results that have been provided by some of these studies, there have been concerns expressed about the use of these types of reports to guide clinical practice[10 17 18 25 26]. For clinicians then the question arises, under what circumstances can the results of meta-analyses be used to guide clinical practice?

For these studies to fulfill their promise as useful summaries of the best available evidence to guide clinical practice in critical care a number of conditions will need to be met. Firstly the available reports should be of a high quality. Unless the

studies are meticulously carried out, then the results are likely to be unreliable. It is possible that the differences between the results of the discordant studies may be explained by differences in the methodological qualities of the studies. This however may not be the case, and other explanations need to be considered[27]. Therefore secondly, if there were features of the meta-analyses that predicted concordance between the results of meta-analyses and the results of subsequent high quality large clinical trials, then the reliability and robustness of the results would give confidence to clinicians, and their patients, that the correct treatment options were being followed. Meta-analyses that lack these features could then be viewed skeptically, and the results used to guide the development of further research. On the other hand, if a meta-analysis had all the features associated with concordance with the results of subsequent large, well-conducted clinical trials, then the results may be able to be used to guide clinical practice, and the expense and ethical dilemmas of conducting further large scale clinical trials could be avoided.

The aims of this study are to address these two issues. Firstly, to determine the quality of the meta-analyses that are available to critical care physicians. Secondly to attempt to determine if there is a set of features of meta-analyses, that might help in predicting the likelihood that the results of the meta-analysis will be concordant with the results of subsequent large high quality randomized clinical trials (RCTs)

B. BACKGROUND AND LITERATURE REVIEW

1. The Overview Quality Assessment Questionnaire.

In order to grade the quality of reports meta-analyses that address critical care issues, an instrument needs to be utilized. The Overview Quality Assessment Questionnaire (OQAQ)[28] is the only instrument used to grade the quality of reports review articles that has been validated as an index of the scientific quality of research overviews[29]. It is also one of the more widely used instruments, and was used to grade the quality of reports of review articles in a number of fields related to critical care[30 31], as well as to compare the quality of reports of reviews published in the Cochrane Database of Systematic Reviews compared to the quality of those published in the conventional literature[32 33].

The instrument itself consists of nine questions relating to various aspects of the scientific quality of the review article. The final question then asks the reviewer to give score on a scale of 1-7 to rate the overall scientific quality of the review. A score of five or greater should indicate that the review has minimal or minor flaws i.e. is of a high quality, and a score of 3 or less should indicate a review that has major or extensive flaws i.e. is of poor quality. It is of interest to note that the validation of this index was done according to theoretical concepts. The validity was judged according to it's face validity, construct validity and the extent to which the items measured what they purported to measure[29]. The extent to which results

of reviews that scored highly were more likely to reflect the results of other high quality studies has not been studied and was not assessed in this validation study.

2. The CONSORT and QUOROM statements.

The poor quality of reports of RCTs published in the medical literature has been a concern for some time. To address these concerns the Consolidated Standards of Reporting Trials (CONSORT) statement was published in 1996[34] and updated in 2001[35]. Subsequent observational studies have demonstrated an improvement in the quality of reporting of RCTs subsequent to the publication of the CONSORT statement[36 37]. To address similar concerns regarding the reporting of meta-analyses, a group of experts produced a consensus statement, the Quality of Reporting of Meta-analyses (QUOROM) statement in November of 1999[38]. While it may be expected that a similar improvement in the quality of reports of meta-analyses may also have occurred subsequent to the publication of the QUOROM statement, this hypothesis has yet to be investigated.

The QUOROM statement addresses the quality of the reports of meta-analyses, rather than the quality of the conduct of the actual study. While it is hoped that the quality of the reports of studies accurately reflects the methodological rigor with which the studies have been conducted, this has been shown to not always be the case for RCT's[39 40].One of the criteria used to assess the validity of the OQAQ was how well the scoring of a report of a review reflected the actual methods used to

conduct the review. It was found that the judges' assessments were consistent with what the authors stated they did in response to direct questioning[29]. Thus an improvement in the quality of the reports as measured by the OQAQ should reflect an improvement in the conduct of the meta-analysis.

3. The Quality of Meta-analyses Published in the Cochrane Database of Systematic Reviews

The Cochrane Collaboration is an international group with the specific purpose of producing and disseminating systematic reviews of health care interventions. The focus of the group on producing these reviews has led to suggestions that the reviews found in the Cochrane Database of Systematic reviews is of a higher quality than the reviews published in the regular medical journals. A number of studies have addressed this issue[32 33 41].

The first study was a comparison of 36 reviews published in the Cochrane Database of Systematic reviews in 1995 with 39 reviews that were randomly selected from a sample of reviews identified in a MEDLINE search restricted to publication in 1995[41]. It was found that the Cochrane reviews more frequently reported the criteria to include or exclude a trial (35/36 vs 18/39; $p < 0.001$) and more frequently assessed trial quality (36/36 vs 12/39; $p < 0.001$). None of the Cochrane reviews and only three of the paper-based journal reviews described the primary outcome of interest. On the basis of these results it was concluded that

Cochrane reviews appear to have greater methodological rigor. The second study evaluated aspects of the methodological and reporting rigor of systematic reviews and meta-analyses of the treatment of asthma[32]. Fifty reviews were identified, 12 in the Cochrane Database of Systematic reviews and 38 in regular journals. The OQAQ was utilised to evaluate the quality of the reports. The results of this study were that the Cochrane reviews had higher overall quality scores than the reviews published in regular journals (median 6 vs. 2 $p < 0.005$). One of the conclusions of this study was that Cochrane reviews are more rigorous and better reported than those published in peer reviewed journals. It should be noted that neither of the above studies masked the source of the reports prior to assessment and that the authors of both studies had strong connections to the Cochrane Collaboration.

The third study that addressed this issue compared the quality of 52 reports of systematic reviews published in paper-based journals with 52 reports of systematic reviews published in the Cochrane Database of Systematic Reviews[33]. The assessment of these studies was conducted in a masked fashion, and again the OQAQ was used to evaluate the quality of the reports. The results were that while the Cochrane reviews were better at reporting some items from the OQAQ the paper-based journals were better at others. Overall there was no difference between the quality of the Cochrane reviews compared to the paper-based reviews (mean overall quality score 3.35 vs 3.42). The authors concluded that the overall

quality of the reports was low, and the Cochrane reviews were not superior to the paper-based reviews. This was thought to be a serious problem as systematic reviews were advocated as “the best available evidence” to clinicians and consumers.

Finally, a study again carried out by a group of researchers from the Cochrane Collaboration evaluated the quality of 52 reviews published in issue four of the Cochrane Library in 1998[42]. The reviews were assessed in an unstructured manner by methodologists with various Cochrane affiliations and each review received a letter score from A (No problems) to D (The review might be OK but I need clarification on …). There was no score that would have indicated an unsatisfactory review. The results of the study were that overall most reviews had no problems or only minor problems, however 29% of reviews had major problems identified. There has been no evaluation of the quality of the Cochrane reviews carried out independently of the Cochrane Collaboration.

4. The Quality of Meta-analyses in Anaesthesia and Emergency Medicine.

The quality of reviews published in the emergency medicine and anaesthesia literature has been previously examined. These studies may provide a useful reference point to give some perspective of the quality of the reports in the critical care literature.

A review of the quality of the reports of systematic reviews in the emergency medicine literature has been performed[30]. The authors of this study conducted a search using the MEDLINE and EMBASE databases, limited to five prominent emergency medicine journals, and supplemented with hand searching of four of the journals, for the eleven years from January 1988 until December 1998 and found 29 systematic reviews. Only 13% (4/29) achieved a score of ≥ 5 on the OQAQ. Of note was that the weakest areas were the failure to report validity criteria (72%), failure to report the methods used to combine studies (52%), failure to do a comprehensive search (48%) and failure to appropriately assess validity of studies (45%). No association was found between the year of publication and quality of the reviews ($r^2 = 0.02$, p=0.51). No search of the Cochrane library was conducted and subsequently no Cochrane reviews were included in this study. The authors concluded that many of the systematic reviews published in the major emergency medicine journals exhibited major methodological flaws.

A similar review of the quality of systematic reviews in the anaesthesia literature has also been conducted[31]. Studies included in this review were identified using a MEDLINE, EMBASE and CINAHL search, as well as the Cochrane library. There were no time restrictions. This was supplemented with a limited hand search of five major anaesthesia journals. Eighty-two relevant reviews were identified. In this group of studies 34/82 (41.5%) had an OQAQ score of ≥ 5. The major flaws identified were failure to refer to the validity of the studies (37/82, 41.5%), failure to report the criteria used to assess the validity of studies (34/82, 41.5%) and failure to report a comprehensive search (27/82, 32.9%). There was no comparison made between the quality of reports published in the Cochrane library and the "regular" literature, and no analysis of a temporal trend in the quality of reports was reported.

5. Concordance Between the Results of Meta-analyses and the Results of Subsequent Large Clinical Trials

The issue of concordance between the results of meta-analyses and clinical trials has been examined by a number of reports. Utilizing reports from the pregnancy and childbirth module of the Cochrane database, a study was conducted comparing the results of the largest trial (sample size > 1000) to a meta-analysis of the remaining small trials[43]. The results showed that in only 18/30 meta-analyses was the direction of treatment effect and the statistical significance of the treatment effect the same as the largest trial. There was only moderate agreement between the two forms of investigation as judged by the kappa statistic (0.46-0.53). Another

similar study, also utilizing the Cochrane Pregnancy and Childbirth Database as well as a MEDLINE search to identify meta-analyses, compared the results of meta-analyses done with fixed-effects and random effects models to the results of adequately powered clinical trials that address the same issue[44]. The conclusion from this study was that agreement between the meta-analyses and the large trials was improved by conducting meta-analyses using a random effects technique, but even when this was used discrepancies still occurred in 15/79 occasions. A third study identified large clinical trials published in major medical journals, the results of which were likely to influence medical practice, and then searched for meta-analyses that had been published prior to the clinical trial that addressed the same issue[19]. It was found that there was only a fair agreement between the two (Kappa = 0.35 95% CI: 0.06 – 0.64). The authors of this study noted that if there had been no subsequent large clinical trial, an ineffective therapy would have been recommended in 32% of cases and an effective therapy rejected in 33% of cases.

In none of these studies was the methodological quality of large clinical trials or the meta-analyses appraised raising the question as to whether methodological deficiencies in the studies may account for the discrepancy. The other point of interest is that while the studies all point out that there is discordance in the results of the two types of investigations, the reasons for the disagreement are discussed to some extent but the characteristics that predict concordance were not examined.

6. Factors that may Affect the Predictive Ability of Meta-analyses.

A number of publications have made suggestions as to when the results of a meta-analysis may give a reliable estimate of a true treatment effect. Each of these factors has been looked at in isolation, without an examination of the joint effect of each potential source of variability.

One suggestion is that it is unreliable to believe the results of meta-analyses that are based solely on small studies, and that several medium sized high quality studies need to be included to make the results reliable[45]. While no definition of a medium sized trial has been specified, a suggestion that 500 participants is a reasonable number was made. The use of funnel plots has also been suggested to be a useful tool to detect the presence of bias in a meta-analysis[46]. While there are a number of causes for asymmetrical funnel plots, the presence of symmetry may be somewhat reassuring in terms of the reliability of the results of the meta-analyses. One of the other major concerns regarding the combination of studies in a meta-analysis is the presence of heterogeneity among the component studies. While a number of methods have been proposed to detect the presence of heterogeneity amongst the studies to be included in a meta-analysis, the calculation of the I^2 statistic may be the most useful measure[47]. Again, while there is no absolute cutoff known to be associated with too much heterogeneity, an I^2 of greater than 50% can be interpreted as indicating at least a moderate amount of heterogeneity among the component studies.

These features of meta-analyses offer promise as predictors of the ability of meta-analyses to predict the results of subsequent large clinical trials. No study has looked at whether the presence of a combination of these features may determine the ability of the meta-analysis to predict the results of subsequent large clinical trials.

C. Research Questions.

1. Part One

A. Primary Question.

What is the quality of reports of meta-analyses published in the critical care literature?

B. Secondary Questions

Has the quality of reports of meta-analyses published in the critical care literature improved over time?

What is the quality of reports of meta-analyses published in the Cochrane Database of Systematic Reviews compared to the quality of reports of meta-analyses published in the conventional critical care literature?

What is the quality of reports of meta-analyses published in the critical care literature compared to the quality of reports of meta-analyses published in related fields?

2. Part Two

What, if any, features of a meta-analysis are associated with concordance between the results of the meta-analysis and the results of subsequent large, well-conducted clinical trials.

D. METHODS

1. Part One

A. Study Sample

The search for reports of meta-analyses that addressed issues pertinent to critical care medicine was conducted utilizing the MEDLINE database using the PubMed interface, as well as MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews using the OVID interface. The search terms that were used to identify studies pertinent to critical care in the PubMed MEDLINE search were; (*critical* OR intensive* OR intensive care OR intensive care units OR "intensive therapy" OR critically ill OR critical illness OR critical care).*

This was combined with a sensitive filter to identify meta-analyses[48], the search strategy for which was;

(((meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])))))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti])))) BUTNOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt])*.

The search strategy for MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews using the Ovid interface utilized the search strategy

1. intensive care.mp. or exp Intensive Care/

2. critical care.mp. or exp Critical Care/

3. critical illness.mp. or exp Critical Illness/

4. 1 or 2 or 3

combined with a sensitive filter to identify meta-analyses[49]

1. meta-analysis.pt.

2. meta-anal:.tw.

3. metaanal:.tw.

4. quantitativ: review:.tw.

5. quantitativ: overview:.tw.

6. systematic: review:.tw.

7. systematic: overview:.tw.

8. methodologic: review:.tw.

9. methodologic: overview:.tw.

10. review.pt.

11. medline:.tw.

12. 10 and 11

13. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 12

This search was supplemented by a search of Medline using the PubMed interface using the search terms;

(*cardiotonic agents OR sympathomimetic OR vasoconstrictor agents OR artificial respiration OR mechanical ventilation OR resuscitation OR shock OR multiple organ failure*) combined with the filter to identify meta-analyses[48], to find additional references that dealt with common critical care problems. A similar search was run in the EMBASE database using the search strategy;

1. exp TRAUMATIC SHOCK/ or exp HYPOVOLEMIC SHOCK/ or exp BURN SHOCK/ or shock.mp. or exp ANAPHYLACTIC SHOCK/ or exp SHOCK/ or exp HEMORRHAGIC SHOCK/ or exp SHOCK LUNG/ or exp SEPTIC SHOCK/ or exp CARDIOGENIC SHOCK/

2. resuscitation.mp. or exp RESUSCITATION/

3. multiple organ failure.mp. or exp Multiple Organ Failure/

4. exp Noradrenalin/ or exp Dobutamine/ or exp Inotropic Agent/ or inotrope.mp. or exp Adrenalin/ or exp Dopamine/

5. mechanical ventilation.mp. or exp Artificial Ventilation/

which was again combined with a sensitive filter for meta-analyses[49]. Finally a search was run in the Cochrane Database of Systematic Reviews to identify reviews that dealt with topics relevant to critical care, using the following search strategy;

1. resuscitation.mp. [mp=title, short title, abstract, full text, keywords, caption text]

2. mechanical ventilation.mp. [mp=title, short title, abstract, full text, keywords, caption text]

3. artificial respiration.mp. [mp=title, short title, abstract, full text, keywords, caption text]

4. inotrope.mp. [mp=title, short title, abstract, full text, keywords, caption text]

5. shock.mp. [mp=title, short title, abstract, full text, keywords, caption text]

6. multiple organ failure.mp. [mp=title, short title, abstract, full text, keywords, caption text]

7. 1 or 2 or 3 or 4 or 5 or 6

8. limit 7 to systematic reviews

Searches were limited to articles published in English and dealing with human subjects published between January 1, 1994 and December 31, 2003. The titles and abstracts of all the articles identified by the search were then examined to identify potentially eligible articles. Studies not potentially eligible were then excluded and the reason for exclusion recorded.

B. Study Selection

All potentially eligible studies were then retrieved and had a review of the full-text article examined to determine it met the pre-determined eligibility criteria. Assessments were conducted independently by two reviewers, with disagreements resolved by discussion, or by resort to a third reviewer if consensus could not be reached. The inclusion criteria were;

- The study addressed an issue pertinent to critical care medicine
- Study population in the included studies were adult patients
- Study population in the included studies were human participants
- The systematic review used statistical methods to produce a summary result
- The report is published in English.
- The report of the study should be first published between 1994 and 2003.

To ensure that adjudication was performed in a standardized fashion, an inclusion form (Appendix1) and a set of explanatory notes (Appendix 2) were prepared prior to the adjudication of the eligibility of the studies for inclusion. Both reviewers then agreed upon the criteria used to judge eligibility and the definitions of the various components prior to adjudication of the studies eligibility for inclusion.

C. Data Extraction

Two reviewers independently extracted data from the included studies. Again, to ensure that data was extracted in a standardized manner, a data collection form (Appendix 3) and a set of explanatory notes (Appendix 4) were prepared prior to

the data extraction and the definitions were agreed upon by both reviewers. Data were extracted from the reports regarding the individual components of the OQAQ, and summary score was then determined. Data were also collected regarding the time of publication, whether the publication was in the Cochrane Database of Systematic Reviews or in a regular journal, and if the publication was in a critical care journal or a journal that primarily dealt with another area of medical practice.

D. Analysis

The primary analysis of the data was descriptive. The proportion of reports that met each of the criteria was determined and tabulated. The estimated mean overall quality summary score was calculated.

To assess whether the overall quality of reviews had improved over time, the overall quality score of reports published prior to the publication of the QUOROM statement was compared to the overall quality score of reports published after the QUOROM statement. The QUOROM statement was first published in November 1999[38], so to allow a reasonable lag time for studies to finish and the report to be published, reports published prior to December 31, 2000 were adjudicated as the "pre-QUOROM" group and those published after January 1, 2001 as the "post-QUOROM" group. The linear trend in the overall quality score over time was also examined.

The quality of reports of meta-analyses published in the Cochrane Database of systematic reviews compared to those published in the regular literature was also examined. The proportion of reports that met each of the criteria as well as the overall quality scores were compared. Reports of Cochrane reviews that were published in regular journals were excluded from this analysis.

Finally, data from this study were compared with the data published in previous reports from the emergency medicine and anaesthesia literature using simple tabulation of the proportions of reports that met each of the criteria. The estimated mean overall quality scores and 95% confidence intervals of the reports, as well as the estimate of the proportion of reports that had minimal or minor flaws and by tabulating exact binomial confidence intervals stratified by discipline .

Agreement on the inclusion of studies was assessed using a kappa statistic. The results were summarized with means and standard deviations for normally distributed data and medians and interquartile ranges for non-normally distributed data. The means of normally distributed variables were compared using unpaired t-tests, and for non-normally distributed groups using Mann-Whitney tests. The effect of continuous variables was examined using a simple linear regression model. All statistical tests were two-sided with a p-value of <0.05 considered

significant unless otherwise stated. Statistical calculations were performed using STATA 8.2.

2. Part Two

A. Overview

A number of steps were undertaken to complete the second part of the study. Firstly, large clinical trials were identified then, a search for meta-analyses that addressed the same issue was performed. The results of the large clinical trials were compared to the results of the preceding meta-analyses to determine if the results of the meta-analysis would have predicted the result of the subsequent large clinical trials. Univariate analysis was undertaken to determine if any of the proposed factors were associated with an increased probability of concordance with the results of the RCT.

B. Identification of Randomised Clinical Trials

Large clinical trials were identified by hand searching prominent medical journals. The journals searched were The New England Journal of Medicine, Lancet, JAMA and Annals of Internal Medicine. These journals were chosen to replicate the methods of a previous comparable study[19]. To ensure that important studies not published in these journals were not missed, the ACP journal club which provides a synopsis of high quality studies from over 100 journals, was also searched. The

search for RCT's was conducted in each journal from the first issue after January1, 2000 until June 30, 2004.

The titles and abstracts of randomized clinical trials were examined and the full text articles of potentially eligible studies were retrieved. Two reviewers then examined the full text articles to determine if the study met the predetermined inclusion criteria. When multiple reports of the same study were identified, only the report that contained the primary analysis was deemed potentially eligible. Studies were considered eligible for inclusion if the report described a study that:

- Had greater than 1000 participants,
- Involved more than one centre,
- Had a procedure that maintained adequate concealment of the randomization sequence
- Had appropriate blinding of trial participants
- Presented an intention-to-treat analysis
- Considered a therapy relevant to the field of acute care medicine.

Once again, inclusion form (Appendix 5) was developed as well as a set of explanatory notes (Appendix 6) to ensure a standard interpretation of the inclusion criteria. All potentially eligible trials were reviewed independently by two reviewers, with disputes resolved by discussion, or if consensus was not possible, by resort to a third reviewer.

C. Identification of Corresponding Meta-analyses

Once the eligible large RCTs had been identified, meta-analyses that had been published prior to the RCT and addressed the same clinical issue were identified by a search of computerized medical databases. Searches were conducted in the MEDLINE database using the PubMed interface, as well as in MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews using the OVID interface. Search terms were individualized for each study, and for each database. The search terms were derived from the interventions and target condition under examination then combined with filters to identify meta-analyses[48 49]. An inclusion form was developed (Appendix 7) as well as explanatory notes (Appendix 8) to again ensure standardized adjudication of inclusion for the meta-analyses. Reports of meta-analyses were included if;

- It addressed the same clinical problem as the relevant RCT
- It was published prior to the relevant RCT
- It produced a summary statistic from the component studies
- The summary statistic was for the same outcome as the primary outcome of the corresponding RCT
- It was published within 10 years of the RCT

The inclusion criteria were applied independently by two reviewers, with disputes resolved by consensus, or if that was not possible, by resort to a third reviewer.

D. Data Extraction

Standard data forms (Appendix 9) and explanatory notes (Appendix10) were again used for data extraction. Once again, data were extracted independently by two reviewers, with disputes resolved by discussion.

The result of the RCT was first determined. If an estimate of the odds ratio was produced in the report it was taken as the result, and if an estimate of the odds ratio was not reported it was calculated along with the exact 95% confidence intervals. The result was interpreted as neutral if the 95% confidence intervals included 1, otherwise it was adjudicated to be in favor or against the therapy depending upon the direction of the estimate of the treatment effect.

Secondly the result of the meta-analysis was determined. Again, if an estimate of the odds ratio was reported, it was taken as the result. If the meta-analysis had produced a risk ratio, then the odds ratio was calculated. This was achieved by repeating the meta-analysis using a fixed or random effects model (whichever had been reported as the model used in the meta-analysis), but calculating the estimate of the odds ratio and the 95% confidence interval. The result of the meta-analysis was then determined to be in favor, neutral or against the therapy under consideration in the same fashion as described above.

The quality of the meta-analysis was graded in the same way as had been done for part one of the study. The total number of trials, total number of participants in those trials, and the number of trials that had greater then 500 participants was extracted from the reports. These numbers were taken as the numbers from the meta-analysis that corresponded to the primary outcome of the RCT. Whether RCT's alone or RCT's and observational studies were included in the meta-analysis was also recorded. It was also recorded whether the meta-analysis specifically addressed the question asked by the RCT or whether the meta-analysis addressed a broader, more 'generic' question. For example, the SAFE study[16] compared albumin solutions to normal saline in intensive care patients. A meta-analysis that examined the effect albumin solutions compared to saline in intensive care patients would be graded as specific and a meta-analysis that examined all colloid solutions compared to all crystalloid solutions would be graded as generic.

When the data in the report of the meta-analysis were presented in a fashion that allowed the reproduction of the meta-analysis, the meta-analysis was reproduced. A funnel plot was created, and then visually inspected for evidence of asymmetry. The Egger statistic was recorded, to provide a numerical assessment of the presence or absence of funnel plot asymmetry, with a p-value of <0.1 taken as evidence of asymmetry, as has been previously described[46]. The I^2 statistic was calculated using the methods described by Higgins and Thomson[47].

E. Data Analysis

Agreement on the inclusion of studies was again assessed using the kappa statistic. Descriptive statistics, boxplots and histograms were used to analyse each variable. Univariate comparisons were undertaken using unpaired t-tests for normally distributed continuous variables and Mann-Whitney tests for non-normally distributed variables. Binary variables were compared using Fisher's exact test. All tests were two-sided with a p-value of <0.05 considered significant. Due to the small numbers of studies included in the analysis, multivariate analysis was not formally attempted. Analyses were conducted using STATA 8.2.

E. ETHICAL CONCERNS

There are no human or animal subjects involved in this research. The cases will be reports of meta-analyses and clinical trials that are available in the medical literature.

F. RESULTS

1. Part One.

A. Search Results

The search for potentially eligible reports of meta-analyses was completed on August 10, 2004. A total of 7,935 articles were returned by the initial search. Of these 7723 were deemed ineligible after inspection of the titles and abstracts. 212 reports were retrieved for review. After review, 139 were considered to be eligible for inclusion[11 12 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 14 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185].

Agreement on the inclusion of articles occurred in 97.8% of cases, which gave a kappa = 0.93 ($p<0.0005$). The reasons for exclusion of reports, and the flow of studies are shown in Figure 1. Figure 2 shows the sources of publication of reports of meta-analyses that were included in this study. The reports of meta-analyses were published in a wide variety of sources, with the majority of reports being published in sources that were not classified as critical care journals.

Figure 1.

Flow Chart Showing Results of Search and Reasons for Exclusion of Reports

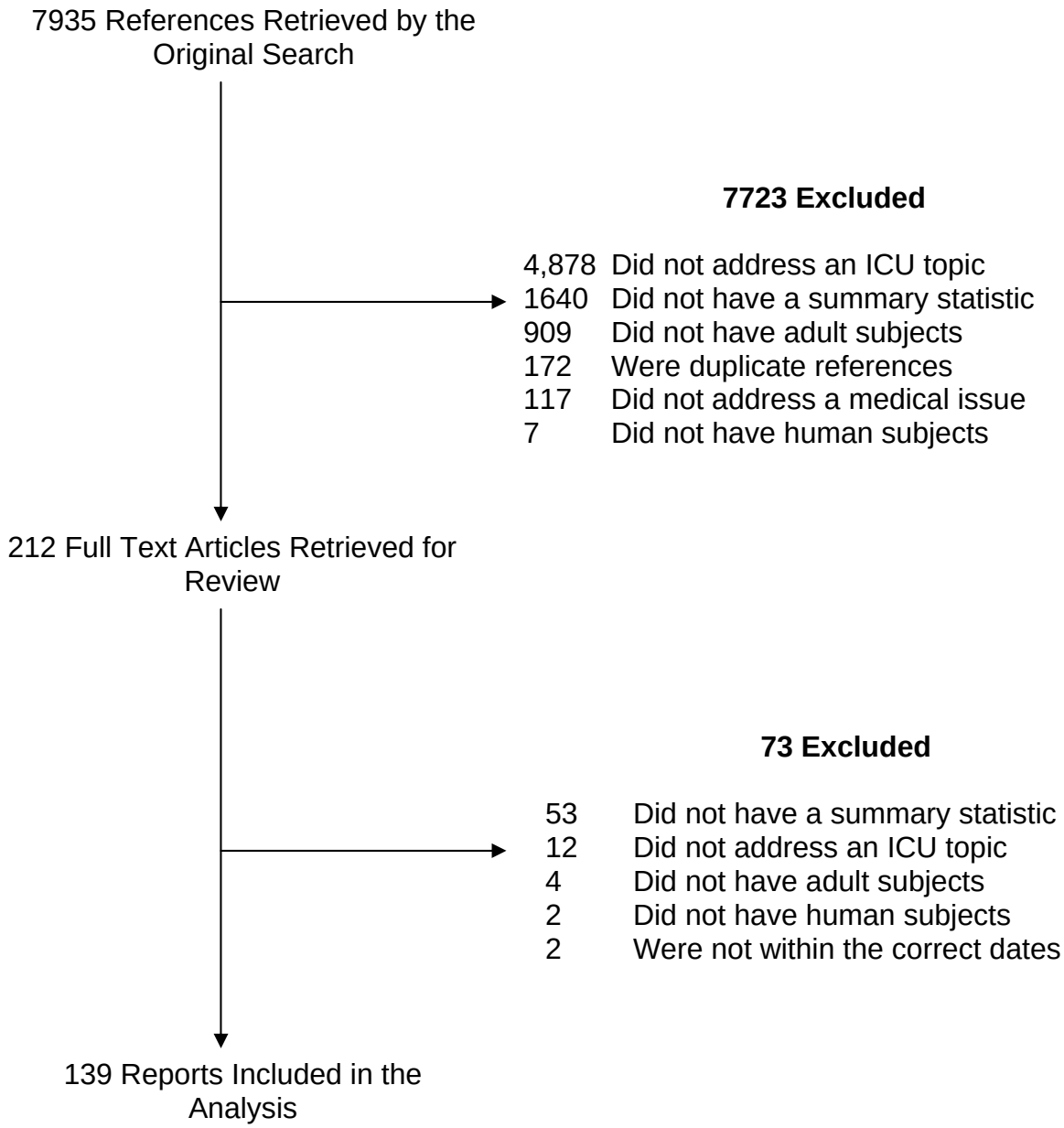
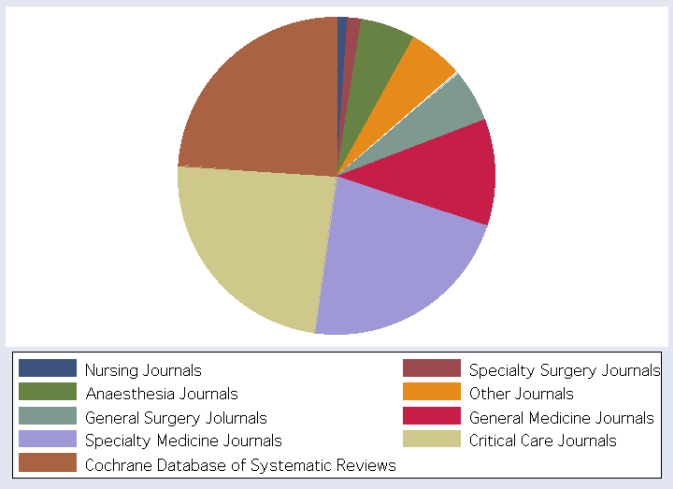


Figure 2

Source of Publication of Reports of Meta-analyses that Address Issues Pertinent to Critical Care



B. The Overall Quality Meta-analyses in the Critical Care Literature

Agreement was reached on the scoring of all component scores and the overall quality scores without the need for resort to a third reviewer. Table 1 contains the results of the quality assessment of all meta-analyses that addressed topics relevant to critical care. Of note is that the weakest areas were the failure to conduct a comprehensive search and failure to avoid bias in the inclusion of studies with only 35.3% of reports adequately fulfilling these criteria. Less than half of the reports referred to the validity of the included studies by appropriate criteria in the text.

The overall quality scores are shown in Table 2. The estimated mean overall quality score for meta-analyses published in the critical care literature from 1994 to 2003 was 3.3 (95% CI; 3.0-3.6). 43 (30.9%) reports had minimal or minor flaws as evidenced by an overall score of ≥ 5, and 96 (69.1%) reports had major or extensive flaws, scoring ≤ 4 on the overall quality summary score. The distribution of overall quality scores is shown in Figure 3. The overall distribution is approximately normally distributed.

Figure 3

Frequency Histogram showing the Distribution of Overall Quality Scores for Reports of Meta-analyses Published in the Critical Care Literature 1994-2003

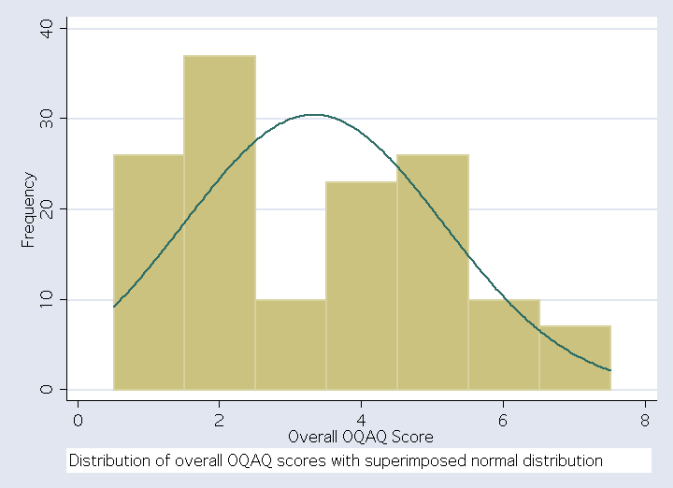


Table 1.

Overview Quality Assessment Questionnaire Component Score Results

OQAQ Question	No n(%)	Partial or Can't tell n(%)	Yes n(%)
Were the Search methods used to find evidence on the primary question(s) stated	5 (3.6)	3 (2.2)	131 (94.2)
Was the search for evidence reasonably comprehensive?	23 (16.6)	67 (48.2)	49 (35.3)
Were the criteria used for deciding which studies to include in the overview reported?	14 (10.1)	7 (5.0)	118 (84.9)
Was bias in the selection of studies avoided?	27 (19.4)	63 (45.3)	49 (35.3)
Were the criteria used for assessing the validity of the included studies reported?	38 (27.3)	8 (5.8)	93 (66.9)
Was the validity of all the studies referred to in the text assessed using appropriate criteria?	45 (32.4)	29 (20.9)	65 (46.8)
Were the methods used to combine the findings of the relevant (to reach a conclusion) reported?	12 (8.6)	17 (12.2)	110 (79.1)
Were the findings of the relevant studies combined appropriately relative to the primary question of the overview?	14 (10.1)	37 (26.6)	88 (63.3)
Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?	6 (4.3)	29 (20.9)	104 (74.8)

Data expressed as total number of reports with that score (percent)

Table 2

Overview Quality Assessment Questionnaire Summary Score Results

Overall OQAQ Score	n(%)
1	26 (18.7)
2	37 (26.6)
3	10 (7.2)
4	23 (16.6)
5	26 (18.7)
6	10 (7.2)
7	7 (5.0)

Data expressed as total number of reports receiving that score (percent)

C. Has the Quality of Meta-analyses in the Critical Care Literature Improved Over Time?

Overall, there were an increasing number of reports of meta-analyses published in the later years of the study, as shown in Figure 4. There were 59 reports of meta-analyses published on or before December 31, 2000 that were classified as “Pre-QUOROM” and 80 reports of meta-analyses published on or after January 1, 2001 which were classified as “Post-QUOROM”. Table 3 shows the number and

proportion of reports that clearly fulfilled each of the components of the OQAQ i.e. scored “yes”. The failure to refer to the validity of the included studies was a major problem pre-QUOROM with only 39% of reports adequately achieving this aspect. The proportion of reports that fulfilled this criteria had a non-significant improvement to 52.5% post-QUOROM (p=0.13 Fishers’s exact test). All other components showed a significant improvement after the publication of the QUOROM statement.

Figure 4

Frequency Histogram Showing the Number of Reports of Meta-analyses Addressing Critical Care Issues per Year, 1994-2003

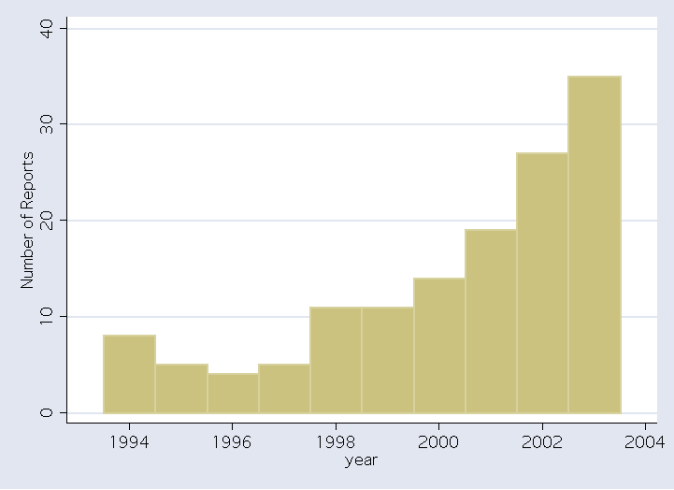


Table 3.

Comparison of Reports that Fulfilled each OQAQ Component Pre-QUOROM and Post-QUOROM

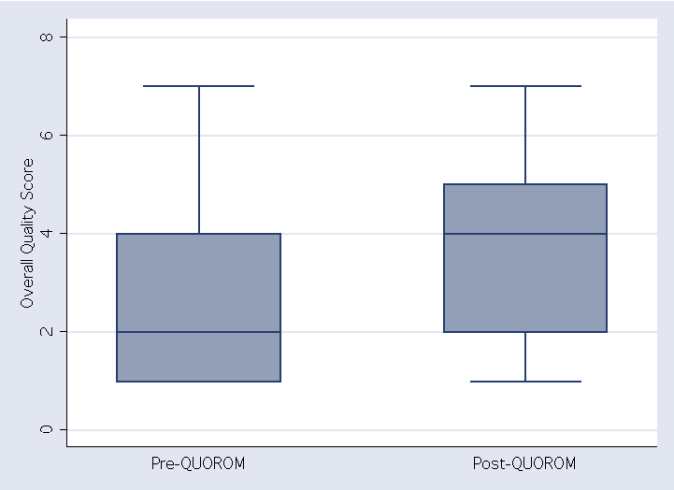
OQAQ Question	Pre-QUOROM n(%)	Post-QUOROM n(%)	p-value
Were the Search methods used to find evidence on the primary question(s) stated	52 (88.1)	79 (98.8)	0.010
Was the search for evidence reasonably comprehensive?	14 (23.7)	35 (43.8)	0.019
Were the criteria used for deciding which studies to include in the overview reported?	44 (74.6)	74 (92.5)	0.007
Was bias in the selection of studies avoided?	15 (25.4)	34 (42.5)	0.048
Were the criteria used for assessing the validity of the included studies reported?	33 (55.9)	60 (75.0)	0.028
Was the validity of all the studies referred to in the text assessed using appropriate criteria?	23 (39.0)	42 (52.5)	0.13
Were the methods used to combine the findings of the relevant (to reach a conclusion) reported?	40 (67.8)	70 (87.5)	0.006
Were the findings of the relevant studies combined appropriately relative to the primary question of the overview?	29 (49.2)	59 (73.8)	0.004
Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?	35 (59.3)	69 (86.3)0	<0.0005

Data expressed as the number of reports that scored "yes" for each component (percent). P-values derived from Fisher's exact test.

Figure 5 shows the boxplots representing the distribution of the overall quality scores for the pre and post QUOROM reports.

Figure 5

Boxplots representing the Distribution of Overall Quality Scores for the Reports Published Pre-QUOROM and Post-QUOROM



The boxplots show that the scores are approximately normally distributed and have an equal variance. The estimate of the mean quality score of the pre-QUOROM reports was 2.8 (95%CI; 2.3-3.2) and the estimate of the mean quality score of the post-QUOROM reports was 3.7 (95% CI; 3.3-4.1). This represented an estimated improvement of 0.96 (95% CI; 0.4-1.6, p=0.0018 two sided t-test).

A simple linear regression of the overall quality score over time showed that there was a significant improvement in the overall quality of reports over time. The β

coefficient of the linear regression gave an estimated improvement in the overall quality score of 0.16 per year (95% CI; 0.06-0.27, p=0.003). The trend for improvement in the overall quality scores over time is shown in Figure 6. The residual plot shown in Figure 7 shows a roughly even distribution of residuals and the boxplots of overall OQAQ score over time, shown in Figure 8 show that the variance is approximately even at all values of the independent variable, so there is no major violation of the assumptions of the linear regression.

Figure 6

Trend for Overall Quality Score for Reports of Meta-analyses Published in the Critical Care Literature over Time

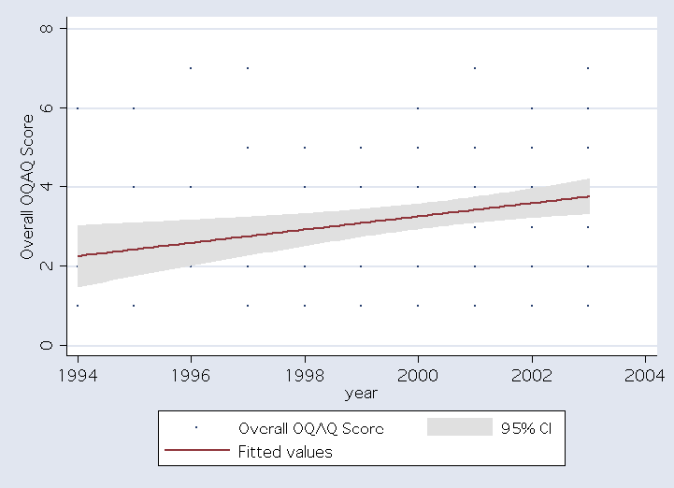


Figure 7

Residual Plot for the Regression of Overall OQAQ score on Year of Publication

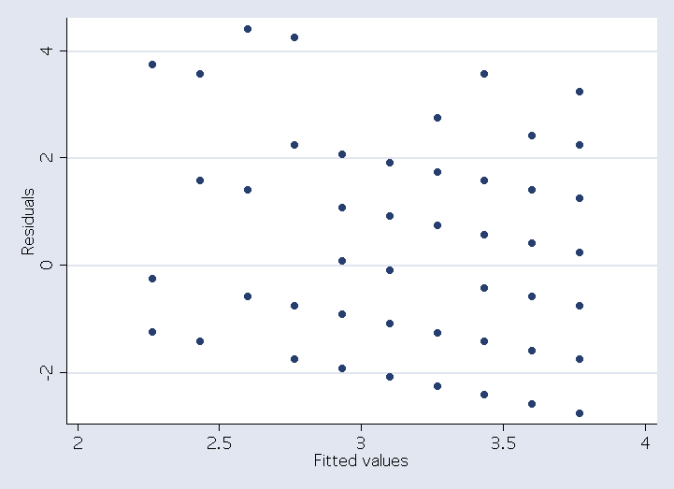
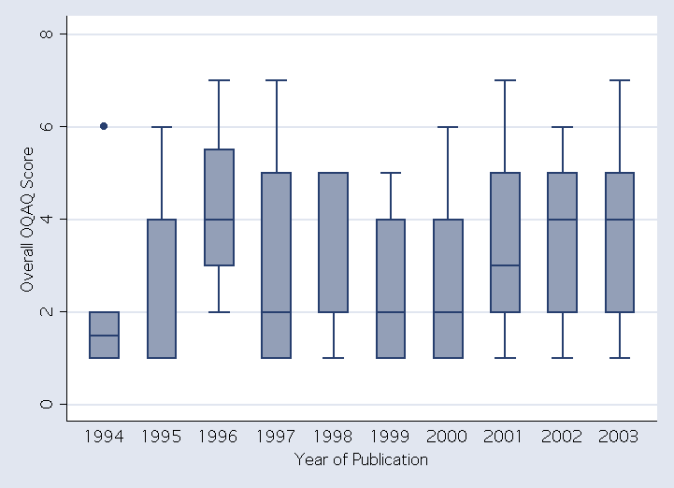


Figure 8

Boxplots Showing the Distribution of Overall OQAQ scores by Year of Publication



D. The Quality of Meta-analyses in the Cochrane Database of Systematic Reviews

There were 36 reports of meta-analyses from the Cochrane Database of Systematic Reviews and 92 reports in the regular literature that were not duplicate reports of studies already published in the Cochrane Database of Systematic Reviews. Table 4 shows a comparison of the numbers of reports that clearly fulfilled each component of the OQAQ for the reports published in the Cochrane Database of Systematic Reviews and the reports published in the regular literature, i.e. those reports that scored “yes” for that question. The reports in the Cochrane Database of Systematic Reviews were significantly better at performing a comprehensive search, reporting the criteria used to include studies, avoiding bias in the inclusion of studies, reporting the criteria for assessing the validity of studies, combining the data appropriately and drawing appropriate conclusions from the data.

Figure 9 shows the distribution of the overall quality scores for the reports published in the Cochrane Database of Systematic Reviews compared to the distribution of the overall quality scores of those reports published in regular journals. The distributions of both groups are skewed, so the groups were compared with a rank-sum test. The estimate of the median overall quality score for the reports in the Cochrane Database of Systematic Reviews was 5 (IQR 3-5.5) and the estimate of the median overall quality score for reports published in regular

journals was 2 (IQR 1.5-4). This represented a significant difference (z = 4.11, p <0.00005 Mann-Whitney test)

Figure 9.

Box plots Showing the Distribution of OQAQ Overall Summary Scores for Reports Published in the Cochrane Database of Systematic Reviews Compared to those Published in Regular Journals

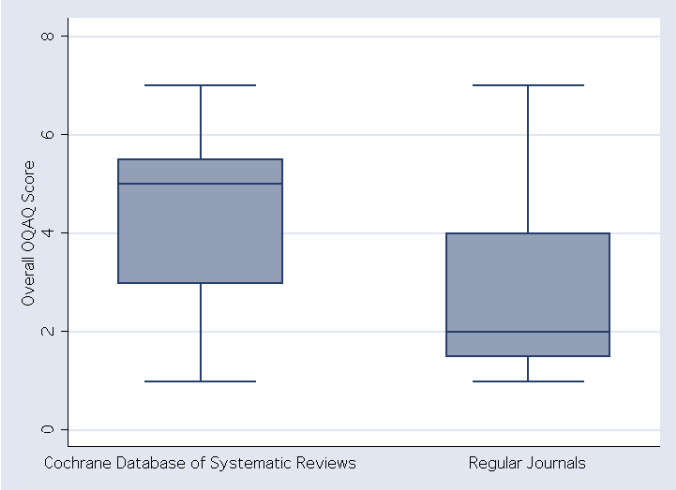


Table 4

Comparison of Reports that Fulfilled each OQAQ Component in the Cochrane Database of Systematic Reviews and Regular Journals

OQAQ Question	CDSR n(%)	Regular Journals n(%)	p-value
Were the Search methods used to find evidence on the primary question(s) stated	36 (100)	84 (91.3)	0.104
Was the search for evidence reasonably comprehensive?	23 (63.9)	20 (21.7)	<0.0005
Were the criteria used for deciding which studies to include in the overview reported?	36 (100)	72 (78.3)	0.001
Was bias in the selection of studies avoided?	22 (61.1)	23 (25.0)	<0.0005
Were the criteria used for assessing the validity of the included studies reported?	32 (88.9)	52 (56.5)	<0.0005
Was the validity of all the studies referred to in the text assessed using appropriate criteria?	20 (55.6)	41 (44.6)	0.326
Were the methods used to combine the findings of the relevant (to reach a conclusion) reported?	29 (80.6)	72 (78.3)	1.0
Were the findings of the relevant studies combined appropriately relative to the primary question of the overview?	28 (77.8)	51 (55.4)	0.026
Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?	32 (88.9)	62 (67.4)	0.014

CDSR = *Cochrane Database of Systematic Reviews. Data are represented as the number of reports that clearly fulfilled that component (percent). P-values derived from Fisher's exact test.*

E. The Quality of Meta-analyses in the Critical Care literature Compared to the Quality of Meta-analyses in the Emergency Medicine and Anaesthesia Literature

There were 29 reports of meta-analyses published in five emergency medicine journals from 1988 to 1998[30]. There were 82 reports of meta-analyses that addressed issues pertinent to anaesthesia identified up until June 1999, from a MEDLINE search not limited solely to anaesthesia journals[31]. The estimates of the mean overall quality scores for the emergency medicine, anaesthesia and critical care, as well as the estimates of the proportions of reports that had minimal or minor flaws only (i.e. had scored ≥ 5 on the OQAQ overall quality score) are shown in Table 5. The proportion of reports that clearly fulfilled (i.e. scored “yes” for that question) is shown in Table 6. It should be noted that the overall quality of reports was poor for each discipline, with the estimated mean scores being less than 5 in each discipline and less than 50% of all reports having a score of greater than or equal to 5 in each discipline.

Table 5

Comparison of the Overall Quality of Reports of Meta-analyses in the Emergency Medicine, Anaesthesia and Critical Care Literature

	Emergency Medicine	Anaesthesia	Critical Care
Mean Overall OQAQ score (95% CI)	2.7 (2.1-3.2)	4.3 (3.8-4.7)	3.3 (3.0-3.6)
Proportion of Reports with an Overall OQAQ score ≥5 (95% CI)	13.8 (3.9-31.6)	41.5 (30.7-52.9)	30.9 (23.4-39.3)

Table 6

Comparison of Reports that Fulfilled each OQAQ Component in the Emergency Medicine, Anaesthesia and Critical Care Literature

OQAQ Question	Emergency Medicine N = 29 n **(%)**	Anaesthesia N = 82 n **(%)**	Critical Care N = 139 n **(%)**
Were the Search methods used to find evidence on the primary question(s) stated	16 **(55)**	60 **(73.2)**	131 **(94.2)**
Was the search for evidence reasonably comprehensive?	5 **(17)**	49 **(60.6)**	49 **(35.3)**
Were the criteria used for deciding which studies to include in the overview reported?	20 **(69)**	66 **(80.5)**	118 **(84.9)**
Was bias in the selection of studies avoided?	6 **(21)**	46 **(56.1)**	49 **(35.3)**
Were the criteria used for assessing the validity of the included studies reported?	5 **(17)**	40 **(48.8)**	93 **(66.9)**
Was the validity of all the studies referred to in the text assessed using appropriate criteria?	7 **(24)**	39 **(47.6)**	65 **(46.8)**
Were the methods used to combine the findings of the relevant (to reach a conclusion) reported?	14 **(48)**	64 **(78.0)**	110 **(79.1)**
Were the findings of the relevant studies combined appropriately relative to the primary question of the overview?	11 **(38)**	54 **(65.9)**	88 **(63.3)**
Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?	15 **(52)**	58 **(70.7)**	104 **(74.8)**

Data expressed as the number that clearly fulfilled that component (percent).

2. Part Two

A. Search Results

There were 65 potentially eligible RCTs identified that had more than 1000 participants and addressed an issue pertinent to acute care medicine. The full text reports of these trials were retrieved for further review. Of these, 32 were excluded as ineligible after review. Agreement on the inclusion of reports of RCTs was reached in all but two cases, giving a kappa 0.94 ($p<0.00005$). Of the 33 potentially eligible RCTs[16 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216], no previously published meta-analyses were able to be identified for seven[187 191 202 203 207 209 213]. A total of 130 potentially eligible meta-analyses were identified that had been published prior to the corresponding RCT, however 102 of these were excluded after review by both reviewers. Agreement between the two reviewers on the eligibility of the meta-analyses was reached for all of these reports. Six meta-analyses[217 218 219 220 221 222] were matched to two separate RCTs [223 204], so that 22 unique meta-analyses were available for the primary analysis[164 224 217 218 219 220 221 225 226 227 228 222 13 229 230 231 232 233 234 235 236]. These were matched only to the RCT that had been completed first[223]. As the two RCTs with multiple matching meta-analyses were published in the same issue of the same journal, a sensitivity analysis was conducted with these studies matched to the later study[204]. The flow of studies and the reasons for exclusion are shown in Figures 10 and 11.

Figure 10.

Flow Chart Showing the Identification and Selection of Reports of RCT's

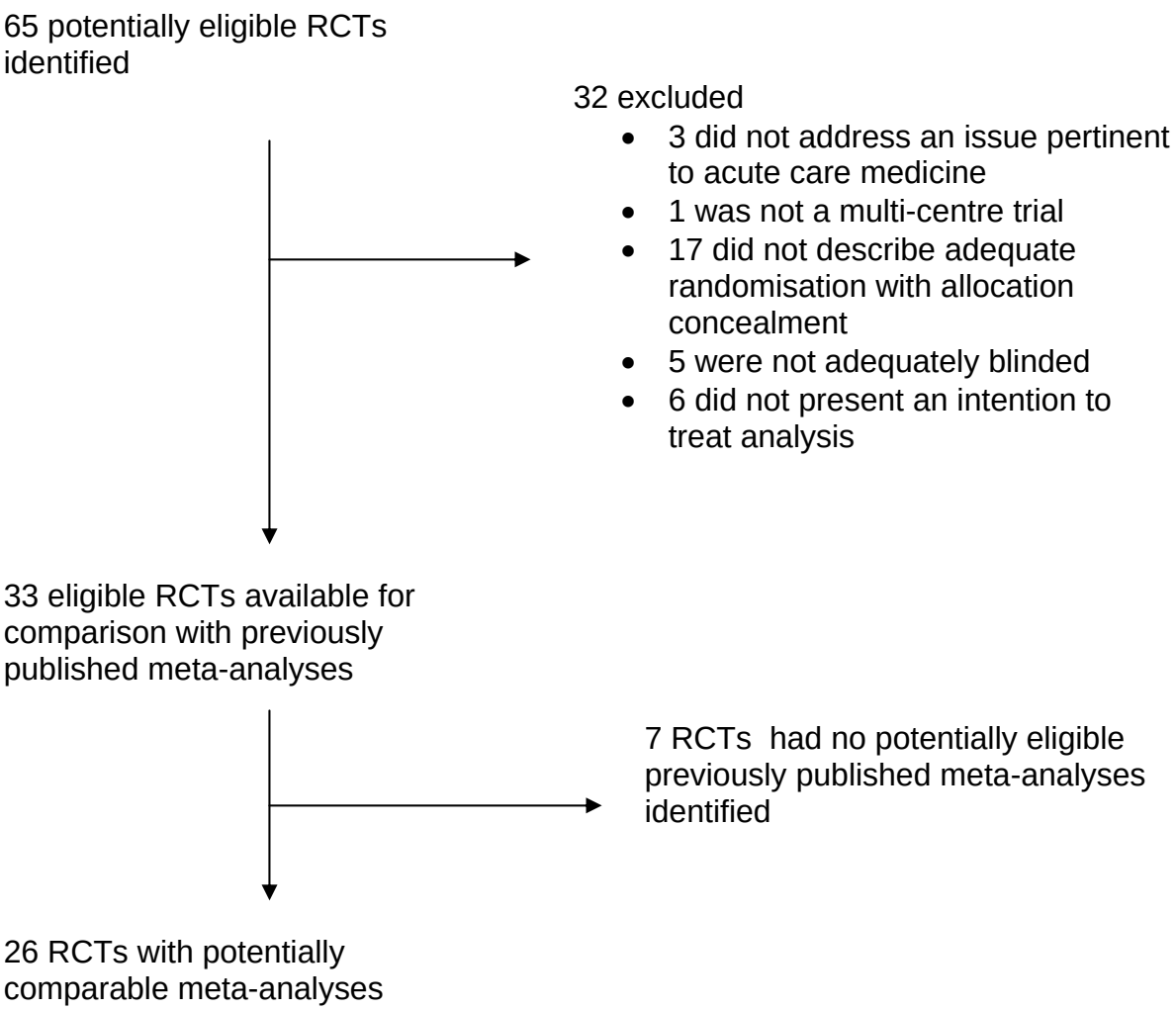
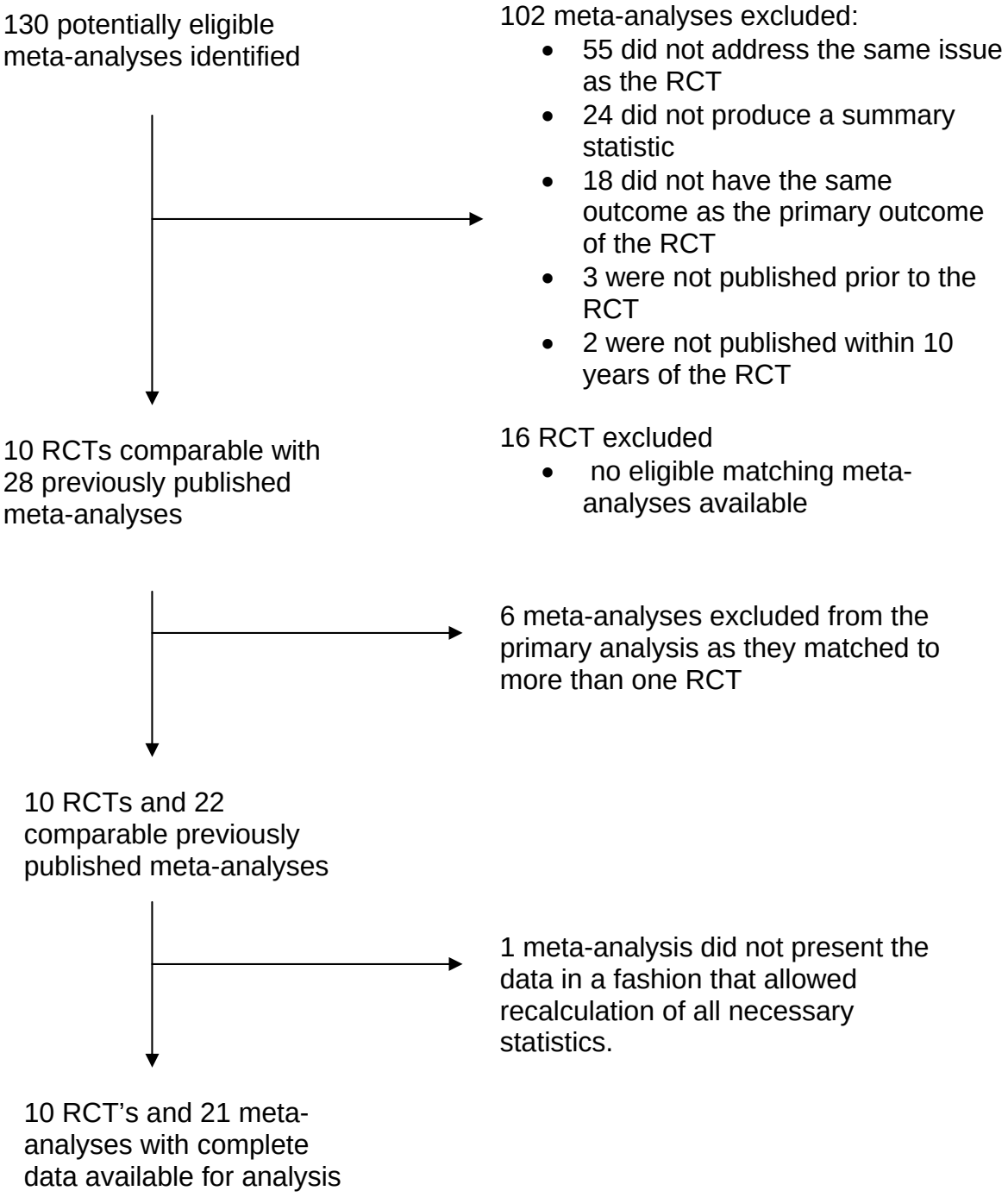


Figure 11.

Flow Chart Showing the Identification and Selection of Corresponding Meta-analyses



B. Primary Analysis

Of the ten RCTs, three presented their primary results as risk ratios, four as odds ratios and three as hazard ratios. The 22 corresponding meta-analyses produced a summary statistic that was an odds ratio in twelve cases, a risk ratio in eight cases, and in two cases it was unclear which summary statistic was calculated. In only eight of the pairs of RCTs and corresponding meta-analyses were comparable metrics used.

Table 7 shows the results of the RCTs and the corresponding meta-analyses as well as the ratio of odds ratios. According to the predetermined definition of agreement, there were eleven meta-analyses that produced results that reflected both the direction and magnitude of the result of the subsequent RCT, and eleven meta-analyses that produced discordant results. Table 8 shows the characteristics of the meta-analyses that produced results concordant with and discordant with the respective subsequent RCTs. There were no significant differences between the two groups in univariate analysis. There were only four meta-analyses that were graded as having minimal or minor flaws. All four produced results that were concordant with the results of the matching subsequent RCT.

Table 7.

Results of RCTs and Corresponding Meta-analyses

RCT	**RCT Result** OR (95% CI)	**MA**	**MA result** OR (95% CI)	**Ratio of OR**
Abraham	1.02 (0.89-1.24) Neutral	Freeman	0.87 (0.75-1.01) Neutral	1.17
BEST	0.88 (0.74-1.03) Neutral	Avezum	0.72 (0.55-0.91) In favour	1.22
BEST	0.88(0.74-1.03) Neutral	Bonet	0.64 (0.54-0.75) In favour	1.38
BEST	0.88 (0.74-1.03) Neutral	Brophy	0.65 (0.53-0.80) In favour	1.35
BEST	0.88 (0.74-1.03) Neutral	Doughty	0.69 (0.54-0.89) In favour	1.28
BEST	0.88 (0.74-1.03) Neutral	Heidenreich	0.69 (0.54-0.83) In favour	1.28
BEST	0.88 (0.74-1.03) Neutral	Landry	0.69 (0.69-1.02) Neutral	1.28
BEST	0.88 (0.74-1.03) Neutral	Lechat	0.68 (0.53-0.88) In favour	1.29
Dargie	0.74 (0.57-0.97) In favour	Freemantle	0.77 (0.69-0.85) In favour	0.96
Dargie	0.74 (0.57-0.97) In favour	Houghton	0.77 (0.68-0.89) In favour	0.96
Dargie	0.74 (0.57-0.97) In favour	Soriano	0.87 (0.82-0.92) In favour	0.85
Finfer	0.99 (0.88-1.11) Neutral	Cochrane	1.84 (1.26-1.86) Against	0.54
Finfer	0.99 (0.88-1.11) Neutral	Scheirhout	1.3 (0.97-1.74) Neutral	0.76
Finfer	0.99 (0.88-1.11) Neutral	Wilkes	1.1 (0.9-1.36) Neutral	0.90
MAGIC	1.0 (0.9-1.2) Neutral	Woods	0.61 (0.43-0.87) In favour	1.64
MAGPIE	0.41 (0.28-0.6) In favour	Witlin	0.36 (0.15-0.89) In favour	1.14
Muir	0.95 (0.8-1.13) Neutral	Muir	0.67 (0.35-1.26) Neutral	1.4

Table 7 continued

RCT	**RCT Result** OR (95% CI)	**MA**	**MA result** OR (95% CI)	**Ratio of OR**
Packer	0.63 (0.49-0.8) In favour	McMurray	0.62 (0.53-0.72) In favour	1.02
Packer	0.63 (0.49-0.8) In favour	Schmidt	0.55 (0.33-0.92) In favour	1.15
Packer	0.63 (0.49-0.8) In favour	Whorlow	0.65 (0.44-0.96) In favour	0.97
Pepine	0.97(0.89-1.06) Neutral	Pahor	1.1 (1.02-1.18) Against	0.88
Simoons	1.0 (0.83-1.24) Neutral	Kong	0.88 (0.79-0.97) In favour	1.14

RCTs identified by Surname of first author or by acronym, meta-analyses (MA) identified by surname of first author. Results of RCTs and meta-analyses shown as Odds Ratios (95% confidence Intervals) and the overall direction of treatment effect. The ratio of Odds ratios calculated as the OR of the RCT/ the OR of the meta-analysis.

Table 8.

Characteristics of the Meta-analyses that Produced Results Concordant with and Discordant with the Results of Subsequent Large RCTs:

Primary Analysis

	Concordant N=11	**Discordant** N=11	P=value
Included only RCTs	10 (90.9%)	11 (100%)	1.0*
Number of trials	11 IQR 4-31	18 IQR 9-22	0.55**
Number of Participants	2958 IQR 1608-20333	3141 IQR 2841-18969	0.76**
Number of trials with > 500 participants	2 IQR 0-12	2 IQR 1-3	0.84**
Specifically addressed the same issue as the RCT	2 (18.2%)	4 (36.4%)	0.64*
Symmetrical Funnel plot	7 (63.6%)	9 (81.8%)	0.64*
I^2 statistic	26.7 IQR 0-45.3	0 IQR 0-8.5	0.07**
Overall OQAQ score	1 IQR 1-5	2 IQR 1-3	0.70**

Data shown as number (percent) or median (IQR). P-values from Fisher's exact test or Mann-Whitney test***

C. Sensitivity analysis.

To examine the effect of matching of the meta-analyses to the RCT that was completed first[223], the univariate analysis was repeated using the RCT that was completed second[204] as the reference standard to compare the results. There were 17 meta-analyses that produced results that were concordant with the results of the subsequent meta-analyses. The features of the concordant and discordant meta-analyses are shown in Table 9.

The estimate of the proportion of meta-analyses that specifically addressed the same issue was significantly greater in the meta-analyses that produced discordant results, however with such a small number of meta-analyses producing discordant results in the sensitivity analysis, the true significance of this result is questionable. There were otherwise no significant differences between the two groups.

Table 9

Characteristics of the Meta-analyses that Produced Results Concordant with and Discordant with the Results of Subsequent Large RCTs: Sensitivity Analysis

	Concordant N=17	**Discordant** N=5	P=value
Included only RCTs	16 (94.1%)	5 (100%)	1.0*
Number of trials	18 IQR 5-22	9 IQR 6-12	0.46**
Number of Participants	3039 IQR 2533-7732	18969 IQR 1204-27743	0.67**
Number of trials with > 500 participants	2 IQR 1-3	2 IQR 0-4	0.90**
Specifically addressed the same issue as the RCT	2 (11.8%)	4 (80%)	0.009*
Symmetrical Funnel plot	13 (76.5%)	3 (60%)	0.59*
I^2 statistic	8.5 IQR 0-31.7	15.8 IQR 0-50.5	0.78**
Overall OQAQ score	2 IQR 1-3	1 IQR 1-2	0.53**

Data shown as number (percent) or median (IQR). P-values from Fisher's exact test or Mann-Whitney test***

H. DISCUSSION

The aim of this study was to investigate the usefulness of meta-analyses to guide clinical practice in critical care. For these meta-analyses to be useful, the reports that are available to clinicians need to be of a high quality, and for the results to be robust and believable, they should concur with the results of other high quality evidence that addresses the same clinical question. This study found that there are major deficiencies in the quality of the reports of meta-analyses that address critical care issues. However the quality of reports is improving over time, and there is some evidence that the quality of the reports in the Cochrane Database of Systematic Reviews is better than the quality of reports in regular journals. The quality of the reports of meta-analyses in the anaesthesia and emergency medicine literature is similar to the quality of the reports in the critical care literature. It was also found that the issue of the comparing the results of meta-analyses and subsequent large, high quality clinical trials was difficult. It was infrequent for the studies we selected to address the same issue, have the same outcome, or use the same outcome measurement. Therefore, the comparison of these results was problematic. The independent variables that were identified in this study did not explain any of the variance between the discordant findings between the meta-analyses and the results of subsequent large RCTs.

1. Part One.

There are a large number of reports of meta-analyses that address topics pertinent to critical care available to physicians. The number of reports is increasing with time, as has been demonstrated in a number of other studies[2 31]. If critical care physicians are to use these reports to guide their clinical practice they cannot rely on browsing solely from critical care journals. The majority of reports of meta-analyses are not published critical care journals, in fact only 25.9% of the reports identified in this sample, were found in critical care journals. However, the result of this study raises questions about the quality of those reports and therefore whether they can be recommended without qualification as the best evidence to guide clinical practice at the present time.

It was found that the overall quality of reports of meta-analyses in the addressing critical care topics is poor. Studies with an overall OQAQ score of five or more are regarded as having minimal or minor flaws, this score being the minimal for a report to have believable results. The average score of the reports in the critical care literature was only 3.3, so clearly the majority of reports are of an inferior quality. Less than one third of reports had a score of five or more. This places an important caveat on the recommendation that these reports are the highest quality evidence available. Clinicians must still critically appraise the reports prior to consideration of the recommendations made in the report of the meta-analysis[24].

While the overall quality of reports is of some interest, the results of the component scores of the OQAQ may offer insight into the areas that should be improved. The areas that were most poorly attended to were the conduct of a comprehensive search, the avoidance of bias in the selection of studies and the assessment of the validity of all the included studies. These are crucial elements in the conduct of a meta-analysis, without which the results of the study will be questionable. Authors contemplating conducting meta-analyses and reviewers assessing studies for publication may be able to focus on these aspects of the conduct and reporting of meta-analyses, in order to have the greatest impact on improving their overall quality.

There is some cause for optimism however. Clearly the quality of reports of meta-analyses has improved over time. While it is hard to pinpoint the exact cause for the improvement, it may be that the dissemination of guidelines such as the QUOROM statement[38] has been associated with an improvement in the quality of reports. A similar improvement in the quality of reports has been found with regards to the quality of reports of RCTs following the publication of the CONSORT statement[37]. Authors should be encouraged to follow these guidelines in the hope that a more standard, high quality report of this type of study will become the norm, and clinicians can spend more time considering the results of the meta-analysis, rather than the methodological quality of the report.

The Cochrane collaboration was founded with the specific purpose of producing high quality, up to date summaries of medical evidence, so that physicians could apply the best available evidence in caring for their patients. Previous assessments of the quality of the reports of meta-analyses in the Cochrane Database of Systematic Reviews have been all been conducted by reviewers with strong links to the Cochrane collaboration. These reviews have generally found that the Cochrane reviews were of a higher quality than the reviews published in regular journals[32 41]. When the reviews were conducted in a blinded fashion this advantage was not apparent[237]. This study is the first to assess the quality of the reviews published in the Cochrane Database of Systematic Reviews independently of the Cochrane Collaboration. It was found that while the reports of Cochrane reviews were of a higher quality than the reports of reviews published in regular journals, there is room for significant improvement in both. In particular the reports of Cochrane reviews did not report a reasonably comprehensive search in one third of reviews and one third did not report methods that would have avoided bias in the selection of studies.

Of particular note was that almost half of the reports of meta-analyses published in the Cochrane Database of Systematic review were adjudicated as failing to refer to the validity of the included studies using appropriate criteria. This was most often because a single criterion was used, the presence or absence of adequate allocation concealment. This was judged to be inadequate, as there are other

aspects of the conduct of RCTs that are important in the avoidance of bias[238 239 240]. Improved reporting of the validity of the included studies would give physicians greater confidence that the reports of the meta-analyses published in the Cochrane Database of Systematic Reviews are of a standard that would warrant basing clinical decisions on the results of these reviews.

It was found that the quality of the meta-analyses in the critical care literature was comparable to the quality of reviews published in the emergency medicine[30] and the anaesthetic literature[31]. There were some differences in the conduct of this study compared to the conduct of the previous studies that makes comparing the results somewhat problematic. This study looked solely at meta-analyses and the previous reviews included all systematic reviews. The time difference between the studies is also significant. These factors make it difficult to draw strong conclusions regarding the comparative quality of the reviews in the different fields. It should suffice to note that there is ample room for improvement in the quality of the reviews in each of the fields.

There are a number of limitations to this study. Critical care is a field of medicine that covers a wide variety of fields. As such sampling the meta-analyses that address critical care topics is difficult. While attempts were made to include a diverse range of search terms, it is possible that there are a significant number of studies that were not identified by the search strategy employed in this study. The

studies not included could have different characteristics to those included, although it is difficult to imagine that they could be systematically different. It is also important to note that while the OQAQ is the instrument most widely used to grade the quality of meta-analyses and systematic reviews, its validity rests only on theoretical concepts. High quality reviews should produce results that are concordant with the results of other high quality evidence that examines the same question. This issue has yet to be addressed.

2. Part Two

Discordant results of meta-analyses and RCTs that address the same issue can lead to confusion for clinicians when they are caring for their patients. This issue has been addressed in a number of previous studies that found a variable level of agreement between the results of meta-analyses and the results of large RCTs[19 43 44]. These studies have not considered the methodological quality of the meta-analyses and RCTs. The result of this study suggest that when only RCTs that have characteristics associated with an absence of bias; a method of randomization that maintains allocation concealment, adequate blinding and an intention to treat analysis, and high quality meta-analyses are compared, the results may be more likely to concordant. In fact, all four of the meta-analyses that were graded to have only minor flaws produced results that were confirmed by the subsequent RCT. Obviously with such small numbers of studies to compare, this result should be interpreted with considerable caution.

One of the major findings of this study is that when strict, predefined rules are used to judge the comparability of the two types of investigations, the issue of comparability becomes somewhat less significant. There are relatively few instances where meta-analyses and RCTs are actually addressing the same issue. Differences in the study question, populations, therapies under investigation and outcomes measured, mean that the results of these studies are rarely truly comparable. Clinicians may need to carefully consider the issue at hand to determine which study most accurately addresses the issue confronting them, rather than using a predefined hierarchy.

One of the features of meta-analyses that has been purported to be associated with concordance between the results of meta-analyses and the results of RCTs is the presence of a symmetrical funnel plot. A previous study found asymmetrical funnel plots in three out of four discordant pairs of meta-analyses and corresponding RCTs and no asymmetrical funnel plots in four out of four concordant pairs[46]. In contrast, this study did not find any association between the presence of a symmetrical funnel plot and the level of concordance between the results of a meta-analysis and the corresponding RCT.

In fact, in the primary analysis, none of the features that might be expected to be associated with concordance between the results of the meta-analyses and the results of the RCTs were found to predict agreement between the results of the studies. It would reasonably be expected that meta-analyses that contained more participants, more trials, had less heterogeneity between the included studies, addressed the question at hand specifically and had symmetrical funnel plots would be more likely to come to the same conclusion as the corresponding RCT. However, this was not found to be the case in this study. None of these factors were found to be significantly associated with the level of agreement.

Why might this be the case? Certainly the fact that only four high quality meta-analyses were identified in this study is a significant issue. If meta-analyses are not meticulously performed then the results are not likely to be believable. The sampling in this study may also be an issue. The fact that there were two large RCTs that addressed the same question, coming to different conclusions, that were published in the same issue of the same journal and had multiple meta-analyses matched to them made the analysis problematic. Fifty percent of the meta-analyses in the primary analysis agreed with the result of the subsequent RCT and 77.3 percent of the meta-analyses in the secondary analysis agreed with the result of the corresponding RCT. This means that the results of this part of the study are not at all robust to the assumptions used and so the results should be interpreted cautiously.

There are two further issues regarding the underlying assumptions in this study that warrant further discussion. The first is the assumption that the result of the large RCT represents “the truth”. Whether this assumption is valid or not is impossible to test, but the randomized experiment is held in high regard scientifically and has been responsible for advances in many scientific disciplines.

Secondly, there is some controversy about how to define agreement between the two types of studies. This study used a definition that might be useful to clinicians, dividing the results into being in favor, neutral or against the experimental therapy under investigation. It may be possible to define agreement more simply, for example as being in favor of the therapy when the estimate of the treatment effect is less than one with confidence intervals that do not include one, and not in favor when the confidence intervals include one or the estimate and the confidence intervals indicate a benefit to the control therapy. Such a definition lacks a degree of precision, but using a more simplified approach may be necessary in future studies. Another method for determining agreement between the results of meta-analyses and comparable RCTs has been suggested[241]. This method involves a calculation of the difference between the two results, and the calculation of the standard error of this difference. This method may offer some statistical advantages but is more difficult to interpret for most clinicians.

The difficulties that have been encountered in this study may provide useful pointers for future studies in this field. If there was a set of features of a meta-analysis that when present meant that it was very likely to predict the results of subsequent large RCTs, then knowledge of these features would be useful. There appears to be insurmountable problems in attempting to identify these features in a retrospective fashion. A prospective study may be a more appropriate study design to attempt to identify these features. Large RCTs could be identified from the electronic databases that now exist that publish the protocols for RCTs that are being undertaken. Protocols that describe studies that have the methodological features associated with a lack of bias could be identified, prior to the results of these studies being available. Meta-analyses could then be undertaken, that addressed the specific question at hand and were meticulously carried out, to remove these variables as confounding factors in the association under examination. The funnel plots, degree of heterogeneity and numbers of trials and participants could be used as independent variables in a logistic regression analysis to determine if there was a combination of features that allowed the prediction of the results of the RCT.

I. CONCLUSIONS

There are a large number of reports of meta-analyses that address issues pertinent to critical care, and these numbers are increasing over time. These reports appear in a wide variety of sources, so that physicians who would like to use the results of these studies to guide their clinical practice would need to employ strategies other than browsing critical care journals in order to access all of the relevant reports. The overall quality of the reports is low, and the majority of reports of meta-analyses are not of a methodological quality whereby the results of the study could reliably be used to guide clinical practice. The components of the meta-analyses that are most in need of improvement are the search for studies to be included in the meta-analysis, the avoidance of bias in the inclusion of studies, the assessment of the validity of the included studies using appropriate criteria.

The quality of reports of meta-analyses does seem to be improving over time, and the dissemination of guidelines for the reporting of meta-analyses, such as the QUOROM statement may be responsible this improvement. The reviews that are published in the Cochrane Database of Systematic Reviews do appear to be of a higher quality than those published in regular journals. However, an independent assessment of the quality of reports of meta-analyses published in the Cochrane Database of Systematic Reviews indicates that there is ample room for improvement in the quality of these reviews as well. The quality of the reports of

meta-analyses that address issues pertinent to critical care is similar to the quality of reports in the emergency medicine and anesthesia literature.

Attempting to find a set of features of meta-analyses that predict concordance with subsequent large RCTs is difficult in a retrospective study. When only high quality RCTs are considered for comparison, there were only ten RCTs that had meta-analyses available for comparison. There were only four meta-analyses that were of an acceptable methodological quality that were identified for comparison. All four of these meta-analyses had results that were concordant with the result of the corresponding RCT. When all available meta-analyses were considered, the number of trials included in the meta-analysis, the number of trials with greater than 500 participants, the total number of participants in the meta-analysis, the presence of a symmetrical funnel plot, whether the meta-analysis addressed the exact issue as the RCT, and the degree of heterogeneity as gauged by the I^2 statistic, were not significantly associated with the result of the meta-analysis predicting the result of the subsequent RCT in univariate analysis. Due to the methodological problems encountered in attempting to investigate this relationship in a retrospective fashion, a prospective study may be more appropriate to further investigate this question.

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APPENDIX 1.

Inclusion Form for Potentially Eligible Articles For Part One

Reference:

Inclusion Criteria

		Yes/No
1.	Does this study address an issue pertinent to critical care medicine?	
2.	Do the included studies have an adult population?	
3.	Do the included studies have a human population?	
4.	Does the study produce a combined or summary statistic from the results of the included studies?	
5.	Is the report in English?	
6.	Was the review first published between 1994 and 2003?	

Does this study meet all of the inclusion criteria for the study? Yes No

Should this study be included in this study? Yes No

If not, why not?

APPENDIX 2.

Explanatory Notes for the Inclusion Form for Potentially Eligible Articles for Part One

Does this study address an issue pertinent to critical care medicine?

- An issue pertinent to critical care medicine would be:
    - A therapy that is normally delivered in an intensive care unit, e.g. mechanical ventilation, etc
    - A condition that normally requires most patients to be cared for in an intensive care unit, e.g. multiple organ failure, severe pancreatitis, etc.
- The issue addressed by the study is one that is directly pertinent to critical care physicians. For example if the study dealt with a comparison of two surgical procedures, then it would not be eligible.
- If the study dealt solely with an issue that was not relevant to medical practice then it was not eligible, e.g. studies that dealt solely with nursing, physiotherapy or respiratory therapy issues.

Do the included studies have an adult population?

- Meta-analyses could be included if they present the results for adults, even if they also present the results for children or infants, as long as they results relating to adults are clearly presented.

Do the included studies have a human population?

- Meta-analyses can only be included if the included studies were reports of studies on human populations.

Does the study produce a combined or summary statistic from the results of the included studies?

- Meta-analyses can only be included if the report combines the results of the included studies to produce a summary statistic regardless of how the studies are combined.

Was the review first published between 1994 and 2003?

- For reviews which have been updated and only the most recent report is available, if the initial report was published between 1993 and 2004 then study is eligible for inclusion.

If the study is to be excluded, the reason that the study did not fulfill the inclusion criteria should be written as the reason for exclusion.

APPENDIX 3.

Data Collection Form For the Quality of Meta-analyses in the Critical Care Literature

Reference:

	Quality Features	1	2	3
1	Were the Search methods used to find evidence on the primary question(s) stated			
2	Was the search for evidence reasonably comprehensive?			
3	Were the criteria used for deciding which studies to include in the overview reported?			
4	Was bias in the selection of studies avoided?			
5	Were the criteria used for assessing the validity of the included studies reported?			
6	Was the validity of all the studies referred to in the text assessed using appropriate criteria?			
7	Were the methods used to combine the findings of the relevant (to reach a conclusion) reported?			
8	Were the findings of the relevant studies combined appropriately relative to the primary question of the overview?			
9	Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?			

10. How would you rate the quality of this overview?

Flaws						
Extensive				Minor		
	Major				Minimal	
1	2	3	4	5	6	7

Publication date:

Dec 31, 2000 or before (0)

Jan 1, 2001 or later (1)

Was this review published in the Cochrane Database of Systematic Reviews?

Yes (0)

Regular journal publication of a Cochrane review (1)

No (2)

How would you categorise the primary focus of the journal that published this review?

Critical Care (0)

Anaesthesia (1)

General Medicine (2)

Specialty Medicine (3)

General Surgery (4)

Specialty Surgery (5)

Nursing (6)

Cochrane Database of Systematic Reviews (7)

Other (8)

APPENDIX 4.

Explanatory Notes for the Data Collection Form for the Quality of Meta-analyses in the Critical Care Literature

Quality Features:

1 = No

2 = Partially or Can't tell

3 = Yes

If the methods that were used are reported incompletely relative to a specific item, score that item as "partially." Similarly, if there is no information provided regarding what was done relative to a particular question, score it as "can't tell," unless there is information in the overview to suggest either that the criterion was or was not met.

For Question 2, for a search to be considered comprehensive the methods used to perform the search should include searching for unpublished material as well as multiple medical databases (EMBASE as well as MEDLINE). If only published material was searched for the search should be marked "partially"

For Question 4, for bias to have been avoided in the selection of studies, the report should indicate that explicit criteria were used to define studies eligible for inclusion.

For question 6, to determine whether the validity was assessed using appropriate criteria, all the studies in the text must have had their validity assessed and explicit criteria which were appropriate for the type of research question that was being addressed must have been used.

For Question 8, if no attempt has been made to combine findings, and no statement is made regarding the inappropriateness of combining findings, check “no.” If a summary (general) estimate is given anywhere in the abstract, the discussion, or the summary section of the paper, and it is not reported how that estimate was derived, mark “no,” even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, mark “can’t tell.”

For an overview to be scored as “yes” on Question 9, data (not just citations) must be reported that support the main conclusions regarding the primary question(s) that the overview addresses.

10. How would you rate the quality of this overview?

The score for Question 10, the overall scientific quality, should be based on your answers to the first 9 questions. The following guidelines can be used to assist with deriving a summary score: if the “can’t tell” option is used one or more times on the preceding questions, a review is likely to have minor flaws at best, and it is difficult to rule out major flows (ie, a score ≤4). If the “no” option is used on Questions 2, 4, 6, or 8, the review is likely to have major flaws (ie, a score of ≤3, depending on the number and degree of the flaws).

Publication date:

Check the box that reflects the date that the review was published, not the date that the review was accepted for publication. For reviews published in the Cochrane Database of Systematic Reviews, check the date corresponding to the date of the most recent substantive update.

Was this review published in the Cochrane Database of Systematic Reviews?

Check yes for this item if the review was actually published in the Cochrane Database of Systematic Reviews. If the review was performed by the Cochrane review group, but published in a regular journal, check that item.

How would you categorise the primary focus of the journal that published this review?

Examples:

- Critical Care: *Critical Care Medicine, Intensive Care Medicine*…
- Anaesthesia: *Anaesthesia, British Journal of Anaesthesia*…..
- General Medicine: *Lancet, BMJ….*
- Specialty Medicine: *Chest, Hepatology…*
- General Surgery: *Surgery, British Journal of Surgery….*
- Specialty Surgery: *Journal of Neurosurgery, Journal of Trauma….*
- Nursing: *American Journal of Critical Care, Heart and Lung….*
- Other: *Annals of Pharmacotherapy, xenotransplantation…..*

Appendix 5.

Inclusion Form for Randomized Controlled Trials.

Reference:

Inclusion Criteria

		Yes/No
1.	Does this study address a therapy pertinent to acute care medicine?	
2.	Does the study have an adult, human population?	
3.	Does the study have >1000 total participants?	
4.	Does the study involve more than one centre?	
5.	Does the report describe a randomization procedure that maintains allocation concealment?	
6.	Does the report describe an adequate blinding?	
7.	Does the report present an intention-to treat analysis?	
8.	Is the report in English?	

Does this study meet all of the inclusion criteria for the study? Yes No

Should this study be included in this study? Yes No

If not, why not?

Appendix 6.

Explanatory Notes for the Inclusion Form for Randomized Controlled Trials

1. Does this study address a therapy pertinent to acute care medicine?

A therapy that is pertinent to acute care medicine would be any treatment that a physician might offer to a patient in an acute care hospital. For example, studies that examine treatments for acute or severe heart failure should be included, but treatments for chronic heart failure should not be. The treatment in question may be primarily a treatment for any medical condition, not limited to any particular specialty.

2. Does the study have an adult, human population?

The study population should be predominately adults >18 years of age.

3. Does the study have >1000 total participants?

At least 1000 participants should be initially enrolled in the study.

4. Does the study involve more than one centre?

There should be at least 2 centres where participants were enrolled and study interventions were conducted.

5.Does the report describe a randomisation procedure that maintains allocation concealment?

Randomization is concealed if the person who is making the decision about enrolling a patient is unaware of whether the next patient enrolled will be entered in the treatment or control group (using techniques such as central randomization, sequentially numbered opaque, sealed envelopes). If randomization wasn’t concealed, patients with better prognoses may tend to be preferentially enrolled in the active treatment arm resulting in exaggeration of the apparent benefit of the intervention (or even falsely concluding that the intervention is efficacious.

When the method of randomisation is not explicitly stated, either in the report or a previously published report of the methods of the trial, then the method of randomisation should be adjudicated to be unclear and inadequate.

6.Does the report describe an adequate blinding?

Patients, clinicians, those monitoring outcomes, judicial assessors of outcomes, data analysts, and/or those writing the paper are unaware of whether patients have been assigned to the experimental or control group. To avoid confusion the term "masked" is preferred in studies in which vision

loss of patients is an outcome of interest.

A determination as to whether blinding is adequate will have to be made on an individual basis depending on the nature of the trial, taking into account which members of the trial structure were blinded and the outcomes measure. An outcomes adjudication committee, masked to the treatment allocation, and with “hard” end-points such as mortality or with a-priori defined outcomes may be adequate blinding for interventions where it is not possible or ethical to blind the participants or health-care providers.

7.Does the report present an intention-to treat analysis?

Analyzing study participant outcomes based on the group to which they were randomized even if they dropped out of the study or for other reasons, did not actually receive the planned intervention. This analysis preserves the power of randomization, thus maintaining that important unknown factors that influence outcome are likely equally distributed across comparison group.

Appendix 7.

Inclusion Form for the Corresponding Meta-analyses

RCT reference

Meta-analysis

		Yes	No
1	Does this study address the same issue as the RCT?		
2	Does this study produce a summary statistic?		
3	Does this study have the same primary outcome as the RCT?		
4	Is this study published prior to the RCT?		
5	Is this study published within 10 years of the RCT?		
6	Is this study in English?		

Does this study meet all of the inclusion criteria for the study? Yes No

Should this study be included in this study? Yes No

If not, why not?

Appendix 8.

Explanatory Notes for the Inclusion Form for the Corresponding Meta-analyses

1. **Does this study address the same issue as the RCT?**

   The meta-analysis would be considered to be addressing the same issue as the RCT if the RCT met the inclusion criteria for the met-analysis. In other words, if the RCT had been completed prior to the meta-analysis it would have been included in the meta-analysis.

2. **Does this study produce a summary statistic?**

   For a positive response, the meta-analysis in question should be a report of a stud that reviews previous primary studies and combines the results to produce a summary statistic of the estimated treatment effect for the therapy.

3. **Does this study have the same primary outcome as the RCT?**

   For a positive response, the meta-analysis should produce a summary statistic equivalent to the primary outcome of the RCT to which it is being compared.

4. **Is this study published prior to the RCT?**

   The publication dates should be used to determine whether the meta-analysis was published prior to the RCT. For reviews published in the Cochrane Database of Systematic Reviews, the date of the most recent substantial update should be used. If the RCT is included in the MA, then it is not eligible.

5. **Is this study published within 10 years of the RCT?**

   The publication dates should be used to determine whether the meta-analysis was published within 10 years of the RCT. For reviews published in the Cochrane Database of Systematic Reviews, the date of the most recent substantial update should be used.

6. **Is this study in English?**

   The report of the meta-analysis should be published in the English language.

Appendix 9.

Data Collection Form for Part Two RCT reference

MA reference

1. What was the result of the RCT?

In Favour Neutral Against

What was the summary statistic (CI):

2. What was the result of the MA?

In Favour Neutral Against

What was the summary statistic (CI):

Quality of the MA.

	Quality Features	1	2	3
1	Were the Search methods used to find evidence on the primary question(s) stated			
2	Was the search for evidence reasonably comprehensive?			
3	Were the criteria used for deciding which studies to include in the overview reported?			
4	Was bias in the selection of studies avoided?			
5	Were the criteria used for assessing the validity of the included studies reported?			
6	Was the validity of all the studies referred to in the text assessed using appropriate criteria?			
7	Were the methods used to combine the findings of the relevant (to reach a conclusion) reported?			
8	Were the findings of the relevant studies combined appropriately relative to the primary question of the overview?			
9	Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?			

10. How would you rate the quality of this overview?

Flaws						
Extensive			Minor			
	Major				Minimal	
1	2	3	4	5	6	7

Features of the MA

	Features		
1	What types of trials were included in the MA?	0	1
2	How many trials were included in the MA?		
3	How many participants were included in the MA?		
4	How trials with >500 participants were included in the MA?		
5	Is the MA specific or generic?	0	1
6	Is the funnel plot for this MA symmetrical?	0	1
7	What is the Egger statistic for the MA?		
8	What is the I^2 statistic?		

Appendix 10.

Explanatory Notes for the Data Collection Form for Part Two

a). What was the result of the study?

Record “In favour” if the result of the RCT or MA is significantly in favour of the experimental therapy, “neutral” if a non-significant result and “against” if a statistically significant result in favour of the control therapy. The result of the RCT should be recorded as the primary outcome of the RCT, and the result from the MA that corresponds to the RCT.

Record the actual result as the OR (and CI) as reported in the RCT or MA, or the OR should be calculated from the data in the report of the study.

b). Quality of the MA.

The same criteria used to grade the quality of the MA’s in the previous analysis will be used to grade the quality of the MA’s here.

c). Features of the MA.

1. What types of trials were included in the MA?

Record 0 if both observational studies and RCT’s were included and 1 if only RCT’s were included in the quantitative synthesis.

2. How many trials were included in the MA?

Record the number of trials that were included in the analysis that produced the result that is comparable to the RCT.

3. How many participants were included in the MA?

Record the total number of participants that were included in the analysis that produced the result that is comparable to the RCT.

4. How many trials with >500 participants were included in the MA?

Record the number of trials with >500 participants that were included in the MA that corresponded to the RCT.

5. Is the MA specific or generic?

Record 0 (generic) if the MA addresses a similar topic but not exactly the same as the RCT, e.g., if the RCT examines the effect of metoprolol in heart failure and the MA examines the effect of b-blockers in heart failure. Record 1 (specific) if the MA and RCT examine the same issue e.g., both examine the effect of metoprolol in heart failure.

6. Is the funnel plot for this MA symmetrical?

Record 0 if the funnel plot appears asymmetrical to simple visual inspection and 1 if the funnel plot appears symmetrical.

7. What is the Egger statistic for the MA?

This statistic will be calculated using the “metabias” command in Stata.

8. What is the I^2 statistic?

This will be calculated using the formula $I^2 = 100\% \times (Q - df) / Q$

Where Q is Cochran’s heterogeneity statistic and df is the degrees of freedom.