Appendix E. Study Quality Assessment

| **Study ID** | **Were studies selected by a census?**  **If no, how was the sample selected?** | **Did the study account for confounding or interaction among sources of bias?** | **Did the study use dichoto-mous measures for high vs. low quality?** | **If the study used dichotomous measures for high vs. low quality, how was the threshold determined?** | **IRR of risk of bias measure** | **Validity of risk of bias measure** | **How was sample size calculated?** | **Do the findings of this meta-epidemio-logical study apply to multiple clinical areas?** | **Did the study account for duplication of trials?** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Schulz 19951 | Census of Cochrane database of perinatal trials | Yes | Yes | Specific classifications were defined, e.g., if allocation sequence was of a certain type, then generation was adequate. | Not given | No justification for validity of bias measures provided. Ten trials were evaluated by two reviewers for reliability. | Not reported | No, only to pregnancy and childbirth | Yes |
| Juni 19992 | Studies were selected from a single systematic review which had 17eligible trials and all were assessed for quality using 25 different quality checklists. | Yes  All three [concealed randomization, blinding, and treatment of withdrawals] were modeled in a multivariate model | Yes | Unclear how the ratings on 25 scales were distilled into component scores. | Intraclass correlation >0.9 for 12 scales (48%), 0.8 to 0.9 for 10 scales (40%), and >0.8 for 3 scales (12%) | Unclear | The trials included in a previous systematic review. All 17 trials were included in the analysis. | Results apply to multiple types of general surgery. | Not applicable (N/A) as a single MA was used. |
| Linde 19993 | Census | Yes | Measured bias categories dichoto-mously | Reporting in article | Not given | Unknown | Census | Yes (homeopathy was applied to many different | NR |
| Moher 1998, 19994,5 | 12 meta-analyses were randomly selected (1 was subsequently excluded) from a series of MA selected from the literature. The trials within the 11 eligible meta-analyses were used for the analysis. | No | Yes | Adequate vs. inadequate based on explicit criteria | NR | Based on Jadad and Schulz’s component for biases of interests | NR | Yes (multiple interventions) and multiple clinical conditions | Yes |
| Kjaegard 19996 | Studies were selected from MA that had at least one trial with a sample size of greater than 1000 subjects during a specified time interval | Yes | Yes | Adequate vs. inadequate | Intraclass correlation for inter-observer reliability = 0.96 (95% CI, 0.92 to 0.98)  Test-retest reliability: 0.98 (95% CI 0.97-0.99) | Based on Jadad questions | NR | Yes but not disease areas were not specified. | NR |
| Balk 20027 | Census of all MAs that met their inclusion criteria available in MEDLINE (1966-2000) and Cochrane (2000; issue 3) | No | Yes | Unclear | Not given though they did pilot study and calibrated reviewers; Dual review with disagreements resolved by third reviewer | 28 items following a review of quality measures items | NR | Applicable to four clinical areas (Cardiovascular, Infectious diseases Pediatrics and General Surgery) | Not clear |
| Clifford 20028 | No | No | No | NA | No | Yes: used Jadad scale | Convenience sample | Clinical areas not specified | N/A |
| Sterne 20029 | As per Schultz | No | Yes | NR | NR | NR | NR | Unknown | NR |
| Als-Nielson, 200310 | Random sample of Cochrane reviews obtained in May 2001 | No | Yes | Based on whether study reported that it was double-blinded | Not specified | Not provided | Not calculated | Yes | Not relevant |
| Egger 200311 | Yes  Included 122 meta-analyses from 1998 issue of CDSR. From this excluded MA that did not adequate asses the bias. From this selected trials with and without bias of interest. | Yes | Yes | Presence or absence of blinding and adequate vs inadequate allocation concealment | NR | Detailed definition | NR | Yes | NR |
| Chan 200412 | Yes | No | Yes | Distinction between fully/partially and qualitatively/ unreported is whether studies provided any information on results more substantive than just P values and statements of statistical significance | NA | NA | NR | Applicability of results may be somewhat limited by the period of protocol approval (1990-1998); more recent trials may list more detailed results | N/A |
| Chan 200413 | Yes | No | Yes | Distinction between fully/partially and qualitatively/ unreported is whether studies provided any information on results more substantive than just P values and statements of statistical significance | NA | NA | NR |  | N/A |
| Kyzas 200514 | Yes | No | Yes | Blinded vs. not stated | NR | NR | NR |  | Yes |
| Tierney 200515 | Unknown | No | NA | NA | NA | NA | NR | All data came from cancer trials. | Yes |
| Derry 200616 | Yes, -studies searched for in literature search from root to time interval. | Yes--randomization, blinding, sample size, and overall quality | NA | N/A | NR | Can’t answer | Arbitrarily specified 4 trials and/or 200 patients as a minimum for sufficient quality/validity for calculating statistical significance | Yes, multiple clinical conditions but a single intervention--acupuncture | No |
| Furukawa 200717 | No, random selection applied to census | no | Yes | Contribute to meta-analysis or not | Not specified | Not provided | "A power calculation based on their regression coefficients indicated that detecting statistically significant coefficients of this magnitude required approximately 100 reviews." | Yes | Unclear |
| Pildal 200718 | Random sample of Cochrane reviews in 2003; PubMed reviews chosen in publication order | No | Yes | See measurement of bias column | NR | Schulz approach to define adequate concealment of allocation | Convenience | Unclear, a random sample of Cochrane reviews ordered by publication sample of PubMed reviews | Only 2 trials were duplicated |
| Siersma 200719 | Random sample of Cochrane reviews | No | Yes | Based on reporting in the study | Not specified | Not provided | Not calculated | Yes | Not relevant |
| Fenwick 200820 | Census from a single database Cochrane | No | 3 categories for allocation and 2 for blinding | Commonly used criteria | No | Good | From universe of studies (Cochrane is not the universe of MA and studies) | No | Yes |
| Wood 200821 | Census from three existing meta-epidemiological databases | Yes | NA | Based on data from three previous studies (adequate vs. inadequate/ unclear | NA | Based on previous studies | Not calculated | Yes | Yes |
| Inaba et al., 200922 | The sample was not a census. Trials were selected from a wide bibliographic search of related studies. | Yes | Yes | Presence or absence of the bias | NR | NR | NR | No only some cardiac procedures | Unclear |
| Nuesch 200923,24 | Yes | Yes: Some | No: N/A | N/A | Yes  dual review reconciliation | Yes | NR | No | Yes |
| Van Tulder 200925 | Census | No | Yes | Yes vs. no or don’t know | NR | Good | used the universe of available studies | No | Yes |
| Dwan 201026 | Yes  All trials included in the systematic review 'Intravenous and nebulised magnesium sulphate for acute asthma' were assessed. | No | No | N/A for selective outcome reporting | NR | N/A | NR | No  Limited to asthma | No |
| Kirkham 201027 | Yes--all SRs in issue 4, 2006, Issue 1, 2007, and Issue 2, 2007 were searched for inclusion criteria | No | No | NA | NR | NA | NR | Yes | Yes, by conducting sensitivity analyses only for reviews that had a single M-A of the review primary outcome. |
| Hartling 201128 | Yes, census of studies meeting criteria | No | No | Low vs. high or unclear; Low or unclear vs. high | Interrater agreement for the majority of domains and overall risk of bias was moderate (k = 0.41–0.60). | Cochrane risk of bias tool | Not calculated | No | Yes |
| Herbison 201129,30 | Yes | No | Yes, in some analyses | By type of allocation approach (6 types) | Yes | Valid | NR | Yes | Yes |
| Liu 201131 | Census from review | Yes | Yes (bias measures) | Blinded, ITT | NR | Based on report in article | NR | No | No |
| Savovic 201232 | Yes, from the census of all previously published meta-epidemiological studies AND that provided data to the database | Yes, an extensive methodology was used to remove duplicates, check for completeness of the trial characteristics, and tested reliability of the rating for risk of bias | Yes | Presence, unclear, or absence of the bias | Kappa statistics ranged from 0.55 to 1.00 (median 0.87). | Data was obtained across a large number of studies and so it likely to be varied. | Not calculated | Yes | Yes |
| Hartling 201233 | Census from Hopewell study and then sample of cohort studies | Yes, it accounted for other biases through meta-regression | Yes | Yes vs. no. vs. unclear | Yes for raters and different study designs | Risk of Bias and Newcastle Ottawa scales are valid measures | Yes, but indicated these were arbitrary | Yes | Yes |
| Hróbjartsson 201234 | Census of studies that met criteria | Yes | Yes | Presence or absence of blinded assessors | No | Based on original author info | Census of available studies | Not clear, a small number of studies was used that covered a variety of treatment areas | NA |
| Mhaskar 201235 | Yes | No | yes | Presence or absence of the bias | Not specified | Not provided | Not calculated | No | Not applicable, but accounted for duplication of citations for each trial |

Abbreviations: ITT = intent to treat; MA = meta-analysis; NA = not applicable; NR = not reported; SR = systematic review;

References for Appendix E

1. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995;273(5):408-12. PMID: 7823387.

2. Juni P, Witschi A, Bloch R, et al. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282(11):1054-60. PMID: 10493204.

3. Linde K, Scholz M, Ramirez G, et al. Impact of study quality on outcome in placebo-controlled trials of homeopathy. J Clin Epidemiol. 1999;52(7):631-6.

4. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998;352(9128):609-13. PMID: 9746022.

5. Moher D, Cook DJ, Jadad AR, et al. Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses. Health Technol Assess. 1999;3(12):i-iv, 1-98. PMID: 10374081.

6. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med. 2001;135(11):982-9. PMID: 11730399.

7. Balk EM, Bonis PA, Moskowitz H, et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. JAMA. 2002;287(22):2973-82. PMID: 12052127.

8. Clifford TJ, Barrowman NJ, Moher D. Funding source, trial outcome and reporting quality: are they related? Results of a pilot study. BMC Health Services Research. 2002;2(1):18. PMID: 12213183.

9. Sterne JA, Juni P, Schulz KF, et al. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Stat Med. 2002;21(11):1513-24. PMID: 12111917.

10. Als-Nielsen B, Chen W, Gluud C, et al. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? JAMA. 2003;290(7):921-8. PMID: 12928469.

11. Egger M, Juni P, Bartlett C, et al. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. Health Technol Assess. 2003;7(1):1-76.

12. Chan AW, Krleza-Jeric K, Schmid I, et al. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. CMAJ. 2004;171(7):735-40. PMID: 15451835.

13. Chan AW, Hrobjartsson A, Haahr MT, et al. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA. 2004;291(20):2457-65. PMID: 15161896.

14. Kyzas PA, Loizou KT, Ioannidis JP. Selective reporting biases in cancer prognostic factor studies. J Natl Cancer Inst. 2005;97(14):1043-55. PMID: 16030302.

15. Tierney JF, Stewart LA. Investigating patient exclusion bias in meta-analysis. Int J Epidemiol. 2005;34(1):79-87. PMID: 15561753.

16. Derry CJ, Derry S, McQuay HJ, et al. Systematic review of systematic reviews of acupuncture published 1996-2005. Clin Med. 2006;6(4):381-6. PMID: 16956145.

17. Furukawa TA, Watanabe N, Omori IM, et al. Association between unreported outcomes and effect size estimates in Cochrane meta-analyses. JAMA. 2007;297(5):468-70.

18. Pildal J, Hrobjartsson A, Jorgensen KJ, et al. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol. 2007;36(4):847-57. PMID: 17517809.

19. Siersma V, Als-Nielsen B, Chen W, et al. Multivariable modelling for meta-epidemiological assessment of the association between trial quality and treatment effects estimated in randomized clinical trials. Stat.Med. 2007;26(14):2745-58.

20. Fenwick J, Needleman IG, Moles DR. The effect of bias on the magnitude of clinical outcomes in periodontology: a pilot study. J Clin Periodontol. 2008;35(9):775-82. PMID: 18840153.

21. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ. 2008;336(7644):601-5. PMID: 18316340.

22. Inaba Y, Chen JA, Mehta N, et al. Impact of single or multicentre study design on the results of trials examining the efficacy of adjunctive devices to prevent distal embolisation during acute myocardial infarction. Eurointervention. 2009;5(3):375-83. PMID: 19736164.

23. Nuesch E, Reichenbach S, Trelle S, et al. The importance of allocation concealment and patient blinding in osteoarthritis trials: a meta-epidemiologic study. Arthritis Rheum. 2009;61(12):1633-41. PMID: 19950329.

24. Nuesch E, Trelle S, Reichenbach S, et al. The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. BMJ. 2009;339:b3244. PMID: 19736281.

25. van Tulder MW, Suttorp M, Morton S, et al. Empirical evidence of an association between internal validity and effect size in randomized controlled trials of low-back pain. Spine (Phila Pa 1976). 2009 Jul 15;34(16):1685-92. PMID: 19770609.

26. Dwan K, Gamble C, Kolamunnage-Dona R, et al. Assessing the potential for outcome reporting bias in a review: a tutorial. Trials [Electronic Resource]. 2010;11:52. PMID: 20462436.

27. Kirkham JJ, Dwan KM, Altman DG, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. BMJ. 2010;340:c365. PMID: 20156912.

28. Hartling L, Bond K, Vandermeer B, et al. Applying the risk of bias tool in a systematic review of combination long-acting beta-agonists and inhaled corticosteroids for persistent asthma. [Review]. PLoS ONE [Electronic Resource]. 2011;6(2):e17242. PMID: 21390219.

29. Herbison P, Hay-Smith J, Gillespie WJ. Different methods of allocation to groups in randomized trials are associated with different levels of bias. A meta-epidemiological study. J Clin Epidemiol. 2011;64(10):1070-5. PMID: 21474279.

30. Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. [Review] [60 refs]. J Clin Epidemiol. 2006;59(12):1249-56. PMID: 17098567.

31. Liu CJ, LaValley M, Latham NK. Do unblinded assessors bias muscle strength outcomes in randomized controlled trials of progressive resistance strength training in older adults? Am J Phys Med Rehabil. 2011 Mar;90(3):190-6. PMID: 21173683.

32. Savovic J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Ann Intern Med. 2012 Sep 18;157(6):429-38. PMID: 22945832.

33. Hartling L, Hamm M, Milne A, et al. Validity and inter-rater reliability testing of quality assessment instruments. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2007-10021-I.) AHRQ Publication No. 12-EHC039-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

34. Hróbjartsson A, Thomsen AS, Emanuelsson F, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. BMJ. 2012;344:e1119. PMID: 22371859.

35. Mhaskar R, Djulbegovic B, Magazin A, et al. Published methodological quality of randomized controlled trials does not reflect the actual quality assessed in protocols. J Clin Epidemiol. 2012 Jun;65(6):602-9. PMID: 22424985