

Improving the conduct and reporting of Meta-analyses

Smith GD, Aveyard H, Noyes J & Penny K

In her recent *Journal of Advanced Nursing* editorial, Aveyard (2022) highlighted the increasing importance of literature reviews providing the basis for an evidence-based approach to nursing care. A systematic review is one type of review that utilises analytical methods and processes to analyse and synthesise data from primary studies. ‘Systematic review’ is also a generic label that can be applied to a reviews using a wide range of systematic methods (qualitative, quantitative and mixed-methods). Systematic reviews of interventions with similar populations, interventions and outcomes can be subject to a meta-analysis, whereby similar outcomes are pooled using appropriate software and statistical analysis. Performed correctly, meta-analysis can overcome the shortcoming of small sample sizes of individual studies and assess the heterogeneity of intervention effects. Where it is not possible to pool the outcomes of intervention studies as they are too heterogeneous, [a synthesis without meta-analysis](#) is undertaken. Systematic reviews of intervention effects commonly report a meta-analysis and synthesis without meta-analysis as not all studies can be included in the meta-analysis. Several meta-analyses (one for each outcome specified in the protocol) are usually conducted in each reported review.

At *Journal of Advanced Nursing*, we aim to publish high-quality peer reviewed systematic reviews that include meta-analyses, and all meta-analyses undergo statistical review. Well designed and conducted systematic reviews that report meta-analyses of intervention effects can provide decision-makers with important information that when combined with other information about patient values and preferences, implementation considerations and costs, can be used to

make recommendations for practice. It is the responsibility of review authors to submit a high quality and rigorously conducted review report. Nonetheless, reviews of varying quality are submitted to the journal. There are many critical integrity issues in designing, conducting, interpreting and reporting this type of systematic review that need to be scrutinised by Editors and peer reviewers in order to identify poorer quality reviews.

Across most academic disciplines, the number of published systematic review and meta-analysis studies has increased during the past decade (Fontelo & Liu 2018). However, given the exponential rise in the number of published meta-analysis studies there have been concerns raised about the quality and reproducibility of some published meta-analyses (Ioannidis 2016). Similar to organisations, such as [Cochrane](#), at the *Journal of Advanced Nursing* we were sufficiently concerned about the quality and integrity of some submitted reviews reporting meta-analyses that we have recently updated the author and peer reviewer guidelines.

In this editorial, we will examine the implications of these changes and explore other pertinent integrity issues when conducting and reporting meta-analyses. We hope review authors will take note of these issues and use the information and guidance to further improve the quality and reporting of their systematic reviews with meta-analyses.

Important prerequisites

Review authors commonly do not demonstrate in their review reports that they have the essential requisites in place to undertake a rigorously conducted and high quality review. To ensure the integrity of the review, the design and

conduct of a meta-analysis needs to fulfil several stringent requirements. An a priori protocol is required for which there is a reporting guideline (updated 2022) specifying the required structure and content. The [protocol](#) should report with sufficient justification all the methods and processes in sufficient detail to conduct the review. The review should ideally be registered before any analyses are conducted in a Systematic Reviews Registry (such as [International Prospective Register of Systematic Reviews PROSPERO](#)). Alternatively, authors have the option to register review protocols on platforms like the [Open Science Framework](#).

The right team with the appropriate range of skills and experience should be in place. All conflicts of interest should be declared and only those deemed as not having concerning conflicts of interest should be included as a team member. In addition, we encourage appropriate stakeholder engagement and patient and public involvement from the outset to help shape the review design and conduct. Ideally the review team should have an appropriate budget for conducting the review and access to all the relevant databases for searching for appropriate evidence.

Available methodological guidance

Review authors often do not fully follow methodological guidelines on the conduct of meta-analyses. Cochrane established the original method conducting a systematic review and meta-analysis, this is now internationally accepted as the gold standard (Higgins et al. 2022). The Cochrane Handbook for Systematic Reviews of Interventions provides detailed guidance that all authors should follow.

Statistical issues - to be aware of

Review authors commonly use the wrong statistical tests or do not conduct all the appropriate tests. Due to the availability of a wide range of meta-analytic approaches, several issues may arise when performing a systematic review and meta-analysis, effects can be multivariate rather than univariate and collecting differing causal factors together may lead to meaningless assessment of effects. Additionally, if any lower-quality studies are included in a meta-analysis, findings may be potentially biased and erroneous, producing a ‘*garbage in-garbage out*’ scenario, highlighting the importance of effective quality appraisal of studies. When individual studies are flawed, sensitivity analyses may be used to ascertain the influence of study biases. Sensitivity analysis also detects whether the overall pooled effects in the review are heavily influenced by one particular study. Whilst conducting meta-analysis, pooling of studies that have some differences may be described with the metaphor ‘mixing apples and oranges’, as such, pooling may be inappropriate if effects are not robust or consistent across studies.

Heterogeneity – is a meta-analysis feasible or desirable?

Review authors commonly do not take sufficient account of heterogeneity. In meta-analysis, heterogeneity refers to any type of variability amongst individual studies. In nursing research, different types of heterogeneity can be seen, including variations in the intervention, the study population, the design of the study, or the approach used in data analysis. It may also be due to the use of different outcome measures or measurement scales. Common approaches to investigate heterogeneity based on study characteristics include subgroup analysis and meta-regression. Examining heterogeneity is an important step in providing an accurate explanation of a study’s findings. Of course, quantifying heterogeneity is more useful than just detecting its presence. Although I^2 is a

commonly used statistic to quantify heterogeneity in meta-analysis, care must be taken to interpret the statistic correctly (Borenstein et al 2017). I^2 estimates the proportion of variation in the observed effects which is due to variation in true effects; in other words it is a measure of the proportion of variation which would remain if it was possible to eliminate sampling error. Since I^2 is a proportion and not an absolute value, it therefore does not represent a measure of the variation in effect although it is sometimes interpreted in this way. Readers of meta-analysis papers are usually interested in how much variation there is between true effects across studies, which can be estimated by multiplying the variance of observed effects by I^2 , and therefore this estimated variance of true effects should also be a useful statistic ~~to report~~ to include when reporting on heterogeneity (Borenstein et al 2017).

Risk of bias – how to assess?

Many review authors are using inappropriate, the wrong versions or obsolete tools to assess risk of bias in included studies. Authors should follow the recommendations provided in the Cochrane Handbook for Reviews of Interventions (2022) when selecting a tool. More than one tool may be required depending on the design of included studies.

Included trial integrity- how to assess integrity

Many review authors are not reporting how they assessed the integrity of included trials. Misconduct and research fraud within published studies is of [increasing concern](#). We require all review authors to take steps to establish the integrity of studies before including them in their review. Advice on doing this is outlined in the updated author guidance. Cochrane has the most detailed guidance on how to [assess trial integrity](#). Researchers have also recently developed a screening tool for identifying research integrity issues in trials that JAN authors can use when [conducting their reviews](#).

Publication bias – how to assess?

Reviews authors are commonly not including an assessment of publication bias. Even when conducted with rigour, systematic reviews and meta-analytic reviews can be subject to publication bias, this and other related forms of bias presents a potentially serious issue, which can affect the validity and generalization of findings. Egger's test is commonly used with funnel plot asymmetry, to identify publication bias in meta-analyses of continuous outcomes. This is a scatterplot of the estimate of effect from each study in the meta-analysis against a measure of its precision. Where publication bias is present, published studies are no longer a representative sample of the available evidence.

Evidence-based practice is increasingly reliant on meta-analysis to assess evidence and publication bias can distort the results of meta-analyses and systematic reviews. The tendency of authors of meta-analytic systematic reviews to select particular studies is called selection bias, this type of bias can affect the strength of the meta-analytic estimate. To avoid reviewer selection bias, studies should ideally be informed by rigorous systematic reviews that search for published and unpublished studies, seeking out individual participant data for relevant studies. Application of GRADE (see below) also includes an assessment of publication bias.

GRADE - why is it important to apply?

Many review authors are not applying GRADE when it is appropriate to do so. We require all meta-analyses and syntheses without meta-analysis to be assessed using GRADE, Grading of Recommendations Assessment, Development and Evaluation (GRADE) can be used to assess the quality/certainty of evidence for each outcome. The GRADE website provides a repository of guidance on how to apply GRADE (www.gradeworkinggroup.org/). There is also a chapter on how to apply GRADE in the Cochrane Handbook for Systematic Reviews of Interventions (2022). Within GRADE, there are five domains (risk of bias, consistency of effect, imprecision, indirectness and publication bias). Using GRADE, evidence can be classified as high, moderate, low, or very low certainty. When evidence is graded as high for a particular outcome, further research is unlikely to change confidence in the estimate of effect. When evidence is rated as very low the researcher may have found a knowledge gap that can be filled by new research. Authors should include a Summary of Findings table reporting their GRADE assessments in their review report.

Reporting guidelines

Many review authors are not adhering to the appropriate reporting guideline. Review authors of meta-analyses should familiarise themselves with and adhere to the updated PRISMA 2020 guidelines and reporting checklist and the recent Synthesis without Meta-analysis reporting guideline. PRISMA P is also the extension for protocols. The PRISMA 2020 statement for the conduct and reporting of systematic reviews and meta-analysis studies appears on the [EQUATOR-network website](https://www.equator-network.org/), it includes a 27-item reporting checklist, a study flow diagram, and an explanation and elaboration document. It provides an expanded checklist that stipulates the requirements for the title, abstract, introduction, rationale, and objectives in a publication (Page et al 2021). It also

includes guidance on the subsections required within the methods section of the publication, including: the eligibility criteria of the selected studies; information sources; search strategy; selection process; data collection process; data items; assessment of the risk of bias; effect measures; synthesis methods; assessment of reporting bias; and certainty assessment. The checklist also includes main subsections required in the results section of a publication, which includes: study selection; study characteristics; risk of bias in the selected studies; results of individual studies; results of study synthesis; reporting bias; and certainty of evidence. Statistical reviewers, when assessing the suitability of systematic review submissions to the journal, will ensure that PRISMA 2020 guidelines are closely adhered to. These guidelines offer a valuable resource in ensuring thorough and logical reporting of any form of systematic review.

Can you add a sentence here to highlight how reviews have changed a lot and that writing reviews really is a dynamic space. We hope that by updating the author and peer reviewer guidance we will see an improvement in the quality and integrity and a reduction in the rejection rate of systematic reviews of interventions with and without meta-analysis.

Professor Graeme D. Smith (Helen, Jane and Kay to be added)

Caritas Institute of Higher Education

Hong Kong

E: gsmith@cihe.edu.hk *add information on co-authors*

References

Aveyard H (2022) The future direction for the publication of literature reviews in the Journal of Advanced Nursing. *J Adv Nurs*. 2022 Jun;78(6):e82-e83.

Aveyard H, Bradbury-Jones C (2019) An analysis of current practices in undertaking literature reviews in nursing: findings from a focused mapping review and synthesis. *BMC Med Res Methodol.*;19(1):105.

Borenstein, M., Higgins, J. P. T., Hedges, L. V., and Rothstein, H. R. (2017) Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res. Syn. Meth.*, 8: 5– 18. doi: [10.1002/jrsm.1230](https://doi.org/10.1002/jrsm.1230).

Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, **372**, n71.

Fontelo P, Liu F (2018) A review of recent publication trends from top publishing countries. *Syst Rev.*;7(1):147.

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, & Welch VA (2022) Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). *Cochrane*, 2022.

Ioannidis JP (2016) The mass production of redundant, misleading, and conflict- ed systematic reviews and meta-analyses. *Milbank Q.*;94(3):485-514.

Patsopoulos NA, Analatos AA, Ioannidis JP (2005) Relative citation impact of various study designs in the health sciences. *JAMA*. 2005;293(19):2362-66

Smith GD, Ho KHM (2022) Systematic reviews: When should they be updated? *Journal of Clinical Nursing* 2022 Sep 25.