Systematic reviews and Meta-analyses

• Aggregate individual studies
• Objective is to summarize evidence from multiple studies using explicit methods
• “Systematic review” or “meta-analysis”
The QUOROM Statement

- Guidance on what information should be included when reporting meta-analysis of randomized trials
- Developed in 1996
- Published in 1999

# Checklist of items

## Title
- Identify the report as a meta-analysis (or systematic review) of RCTs.
- Use a structured format.

## Abstract
- Describe the clinical question explicitly.
- Data sources: the databases (e.g., Medline) and other information sources.
- Review methods: the selection criteria (e.g., population, intervention, outcome, and study design); methods for validity assessment; data abstraction; and study characteristics.
- Results: characteristics of the RCTs included and excluded, qualitative and quantitative findings (e.g., point estimates and confidence intervals), and subgroup analyses.
- Conclusion: the main results.

## Introduction
- The explicit clinical problem, biological rationale for the intervention, and rationale for review.

## Methods
- Searching: the information sources, in detail (e.g., databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication).
- Selection: the inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design).
- Validity assessment: the criteria and process used (e.g., masked conditions, quality assessment, and their findings).
- Data abstraction: the process or processes used (e.g., comments independent, in duplicate).
- Study characteristics: the type of study design, participants’ characteristics, details of intervention, outcome definitions, and how clinical heterogeneity was assessed.
- Quantitative data synthesis: the principal measures of effect (e.g., relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data, how statistical heterogeneity was assessed, a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias.

## Results
- Trial flow: provide a meta-analysis profile summarising trial flow (see figure).
- Study characteristics: present descriptive data for each trial (e.g., age, sample size, intervention, dose, duration, follow-up period).
- Quantitative data synthesis: report agreement on the selection and validity assessment, present simple summary results for each treatment group in each trial, for each primary outcome; present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (e.g., 2×2 tables of counts, means and SDs, proportions).

## Discussion
- Summarise key findings; discuss clinical significance based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (e.g., publication bias); and suggest a future research agenda.

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*Slide 3 of 43*
Also recommended a flow diagram showing flow of studies through the review.
PRISMA: *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

- Update QUOROM
  - Emerging conceptual issues
- Systematic reviews are frequently reported
  - 2500, annually
- Not well reported
  - Wen et al, JCE, 2008
- Systematic reviews are frequently used as the starting point for practice guidelines and new primary research
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

• Reporting systematic reviews and meta-analyses that evaluate healthcare interventions

• Meeting held in 2005, Ottawa

• Published in 2009*

• Consists of a 27-item checklist

  • Open Medicine 2009; 3:123-130
  • Annals of Internal Medicine 2009;151:264-269
  • BMJ 2009 ;339:332-336
  • Journal of Clinical Epidemiology 2009; PMID: 19631508
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Checklist Item</th>
<th>Reported on Page</th>
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</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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<tr>
<td><strong>Abstract</strong></td>
<td>Provide a structured summary including, as applicable: background objectives; data sources; study eligibility criteria; participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
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<tr>
<td><strong>Introduction</strong></td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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<tr>
<td><strong>Methods</strong></td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICO5).</td>
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<tr>
<td><strong>Protocol and registration</strong></td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
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<tr>
<td><strong>Eligibility criteria</strong></td>
<td>Specify study characteristics (e.g., PICO5, length of follow-up and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<td><strong>Information sources</strong></td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<td><strong>Study selection</strong></td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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<tr>
<td><strong>Data collection process</strong></td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<tr>
<td><strong>Data items</strong></td>
<td>List and define all variables for which data were sought (e.g., PICO5, funding sources) and any assumptions and simplifications made.</td>
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<td><strong>Risk of bias in individual studies</strong></td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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<td><strong>Summary measures</strong></td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<tr>
<td><strong>Synthesis of results</strong></td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
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<tr>
<td><strong>Risk of bias across studies</strong></td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
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<td><strong>Additional analyses</strong></td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression). If done, indicating which were pre-specified.</td>
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<td><strong>Results</strong></td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
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<td><strong>Study characteristics</strong></td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICO5, follow-up period) and provide the citations.</td>
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<tr>
<td><strong>Risk of bias within studies</strong></td>
<td>Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).</td>
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<tr>
<td><strong>Results of individual studies</strong></td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
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<tr>
<td><strong>Synthesis of results</strong></td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
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<tr>
<td><strong>Risk of bias across studies</strong></td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
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<td><strong>Additional analysis</strong></td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see Item 16)).</td>
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<tr>
<td><strong>Discussion</strong></td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).</td>
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<tr>
<td><strong>Limitations</strong></td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).</td>
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<tr>
<td><strong>Conclusions</strong></td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
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<td><strong>Funding</strong></td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data) role of funders for the systematic review.</td>
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PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

- Includes long explanatory document*
  - Example of good reporting
  - Explanation and rationale for reporting this information (item)
  - Relevant data about how this information is reported presently

- Flow diagram

*Annals of Internal Medicine 2009;151:w65-w94
*Journal of Clinical Epidemiology 2009; PMID: 19631507

BMJ 2001;323:1-8
Any general comments on the paper?

• Wait for my last slide!
PRISMA – item 5, protocol and registration

• “Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number”

– Can you locate any text about this issue in the report?
Rationale for reporting protocol and registration

• A protocol is important because it pre-specifies the objectives and methods of the systematic review
• Having a protocol can help restrict the likelihood of biased post hoc decisions in review methods, such as selective outcome reporting.
• Possibly reduce publication bias
• Although worthwhile protocol amendments are common, one must consider the effects that protocol modifications may have on the results of a systematic review, especially if the primary outcome is changed. Bias from selective outcome reporting in randomized trials has been well documented.
Reporting protocol and registration

• Authors may modify protocols during the research, and readers should not automatically consider such modifications inappropriate. Authors should, however, describe the modifications and explain their rationale.
More than 5500 systematic reviews, at various stages of completion, are currently available in the Cochrane Library (www.cochrane.org) and 9000 systematic reviews are critically appraised for validity in the Database of Abstracts of Reviews of Effectiveness, or DARE (www.crd.york.ac.uk). Funding agencies such as the United Kingdom Medical Research Council and the Canadian Institutes of Health Research require systematic reviews as part of the rationale to fund randomized trials. Systematic reviews form the starting point of well-developed practice guidelines. Graduate students are often encouraged to complete a systematic review as part of their thesis and clinical trainees often perform such reviews during research-related elective courses.¹

Although the development of systematic reviews has grown exponentially over the last 30 years, no consistent strategy exists for registering protocols or results. Slightly less than half of reports from systematic reviews indicate the existence of a protocol for their development.² We believe it is time to consider creating a registry of protocols for systematic reviews and of completed reviews.

Why is a registry needed?

A registry of systematic reviews may reduce publication bias, enhance transparency and avoid duplication of effort.

Such a registry should be part of an existing clinical trial registry.

cal research of about a third of a million participants annually might be unused in a systematic review.⁴

Many agencies and organizations are considering how to prioritize the completion of systematic reviews and are trying to balance the needs of patients, clinicians and other decision-makers with the resources available.⁵ Given that many organizations need reviews on the same topics (such as assessment of medications and technologies), avoiding unnecessary duplication would free resources from these agencies to tackle other topics of research. A registry of reviews would allow decision-makers and researchers to determine more easily which reviews are in development by other groups. We anticipate that this information could facilitate collaboration by bringing together research groups with common interests and perhaps making the process of developing reviews more efficient by increasing the number of team members involved.
Rationale for registering systematic reviews

• Not all systematic reviews are published
  – 12.4% non publication rate
• Excessive duplication of systematic reviews
• Possibly facilitate updating of systematic reviews
How many journal editors would be interested in helping to enable registration of systematic reviews?
PRISMA – item8, search

• “Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated”

  – Can you locate any text about this issue in the report?
“MeSH terms used were premenstrual syndrome, progesterone, and progestogen, as well as the individual drug names, together with title and abstract searches for keywords progesterone, pro-gestogen, premenstrual syndrome, premenstrual ten-sion (PMT), late luteal phase dysphoric disorder (LLPDD), premenstrual dysphoria (PMD), and pre-menstrual dysphoric disorder (PMDD).”
Does this information enable replication?
Databases searched for systematic review

- ABI/Inform (ProQuest)
- ProQuest Digital Dissertations & Theses
- CINAHL (1982 to present) (hosted by EBSCOhost)
- Clinical Evidence (BMJ Publishing Group)
- Evidence-Based Medicine Reviews (hosted by Ovid; incorporates ACP Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessments, NHS Economic Evaluation Database)
- EconLit (1969 to present) (hosted by EBSCOhost)
- EMBASE (1980 to present) (hosted by Ovid)
- International Pharmaceutical Abstracts (IPA) (hosted by Ovid)
- MEDLINE (1966 to present with daily update) (hosted by Ovid)
- PAIS International and PAIS Archive (hosted by CSA)
- Web of Science (hosted by ISI)
Search strategy and terms

• “Our search strategy was to combine searches of terms clustered around the concepts of prescription drugs, intervention types and study methodologies (not applicable for some databases), as detailed below. Each of these term clusters was “translated” into the syntax and vocabulary of each database we searched. Wherever possible, we used subject headings, exploded to include all relevant subheadings. We also employed key word synonyms for the concepts of drugs and our interventions of interest. In databases where it was possible and useful, search filters for methodologies were applied or key words for impact, assessment, and outcomes were added.”
• **Concept A: Drugs:**
  (Pharmaceutical* OR Prescription OR Prescription Drug* OR Drug* OR Medicine* OR Medication*)

• **Concept B: Intervention type**
  (Hierarchical OR Multilevel OR tiered OR differential) AND/SAME/ADJ (copay* OR copay* OR user charge* OR user-charge* OR charge* or fee* OR formular* or subsid* OR benefit*)

  (Hierarchical copay* OR Hierarchical co-pay* OR Hierarchical user charge* OR Hierarchical user-charge* OR Hierarchical charge* OR Hierarchical fee* OR Hierarchical formulary* OR Hierarchical subsid* OR Hierarchical benefit* OR multilevel copay* OR multilevel co-pay* OR multilevel user charge* OR multilevel user-charge* OR multilevel charge* OR multilevel fee* OR multilevel formulary* OR multilevel subsid* OR multilevel benefit* OR multi-level copay* OR multi-level co-pay* OR multi-level user charge* OR multi-level user-charge* OR multi-level charge* OR multi-level fee* OR multi-level formulary* OR multi-level subsid* OR multi-level benefit* OR tiered copay* OR tiered co-pay* OR tiered user charge* OR tiered user-charge* OR tiered charge* OR tiered fee* OR tiered formulary* OR tiered subsid* OR tiered benefit* OR differential copay* OR differential co-pay* OR differential user charge* OR differential user-charge* OR differential charge* OR differential fee* OR differential formulary* OR differential subsid* OR differential benefit*)

  (Reference drug* OR Reference pric* OR Reference based pric* OR Reference-based Pric*)

  (Therapeutic interchange* OR therapeutic substitut* OR drug interchange* OR drug substitut* OR product interchange* OR product substitut* OR generic interchange* OR generic substitut*)

• During the process of brainstorming and collecting search terms, we initially excluded or did not think of a few search terms that are used in the US context of predominantly private health care, including the following terms:
  • cost sharing
  • formularies*
  • health benefit plans/employee
  • insurance, pharmaceutical services
  • prescription fees
Rationale for reporting search

• Perusing the search strategy allows interested readers to assess the comprehensiveness and completeness of the search, and to replicate it
  – Essential for updating (i.e., keeping systematic reviews up-to-date)
Reporting guidance

• We realize that journal restrictions vary and that having the search strategy in the text of the report is not always feasible
  – Expensive real estate
• We strongly encourage all journals, however, to find ways, such as a “Web extra,” appendix, or electronic link to an archive, to make search strategies accessible to readers
• We also advise all authors to archive their searches so that:
  – others may access and review them (e.g., replicate them or understand why their review of a similar topic did not identify the same reports)
  – future updates of their review are facilitated
PRISMA – item 12, Risk of bias in individual studies

• “Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis”

– Can you locate any text about this issue in the report?
“We assessed trial quality using a scale developed by Jadad et al,11 which assesses the randomisation, double blinding, reports of drop outs, and withdrawals for the trials.

... our own quality scale, which assesses the quality of the trials for study design, reproducibility, and statistical analysis. This eight point scale comprised the following: confirmation that no other medications or oral contraceptives were being taken; a power calculation to justify patient numbers or more than 65 participants in each arm (enabling detection of a small effect size of 0.3, see below); a single, clearly stated dose of drug; reproducible measurement of premenstrual symptoms; clear presentation of results; a description of the number and reason for trial withdrawals; exclusion of, or a separate analysis of, participants with a major psychiatric disorder; and whether or not the trial was supported by independent funding.”
Rationale for reporting risk of bias

• “Risk of bias” rather than “quality assessment”
  – Box 4, of e&e

• The likelihood that the treatment effect reported in a systematic review approximates the truth depends on the validity of the included studies, as certain methodological characteristics may be associated with effect sizes.
  – For example, trials without reported adequate allocation concealment exaggerate treatment effects on average compared to those with adequate concealment.

• Therefore, it is important for authors to describe any methods that they used to gauge the risk of bias in the included studies and how that information was used.

• Additionally, authors should provide a rationale if no assessment of risk of bias was undertaken.
“Authors should report how they assessed risk of bias; whether it was in a blind manner; and if assessments were completed by more than one person, and if so, whether they were completed independently. Similarly, we encourage authors to report any calibration exercises among review team members that were done. Finally, authors need to report how their assessments of risk of bias are used subsequently in the data synthesis (see Item 16).”
• “We awarded one point for each category present in the trial.
• Each trial was independently scored by two investigators and the third investigator arbitrated on any disagreements.
• We used predetermined criteria for the recognition of the highest quality trials. A score of 3 or more was required in the Jadad score for the trial to be designated “high quality” and included in the meta-analysis; a score of less than 3 meant that the trial was designated “low quality.”
PRISMA – item 15,
Risk of bias across studies

• Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
  – Can you locate any text about this issue in the report?
“We used the method of Egger et al to detect bias (such as publication and location bias) in the included trials with a funnel plot. We assessed the asymmetry of the funnel plot quantitatively by plotting a linear regression of the standard normal deviate (standardised mean difference divided by SE) against precision (inverse of SE). A regression line that passes through the origin of the plot (within error limits) indicates symmetry and hence the absence of bias.”
Rationale for reporting assessment of bias across studies

• Reviewers should explore the possibility that the available data are biased.
• They may examine results from the available studies for clues that suggest there may be:
  – missing studies (publication bias)
  – missing data from the included studies (selective reporting bias)
PRISMA – item 17, study selection

• “Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram”
  – Can you locate any text about this issue in the report?
• “We identified 14 published trials that assessed the efficacy of progesterone in the management of premenstrual syndrome. We excluded four: two because of their low quality score on the Jadad scale, one because the data could not be extracted, and one because the trial failed to make a prospective diagnosis of premenstrual syndrome before randomisation. Ten trials remained .......”
Rationale for reporting study selection

• The X-Files factor!
• “Authors should report, ideally with a flow diagram, the total number of records identified from electronic bibliographic sources (including specialized database or registry searches), hand searches of various sources, reference lists, citation indices, and experts.
• It is useful if authors delineate for readers the number of selected articles that were identified from the different sources so that they can see, for example, whether most articles were identified through electronic bibliographic sources or from references or experts.”
PRISMA – item27, funding

- Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review
  - Can you locate any text about this issue in the report?
• “Funding: No external funding.
• Competing interests: SO’B has been reimbursed for lectures and conferences by Hoechst Marion Roussel, Shire Pharmaceuticals, SmithKline Beecham, Eli Lilly, Searle, Sanofi Winthrop, Zeneca, Galen Laboratories, Solvay Pharmaceuticals, and Novo Nordisk. He has also received funds for research staff from Searle, SmithKline Beecham, Eli Lilly, and Sanofi Winthrop. He is married to a member of the research department of Zeneca Pharmaceuticals.”
Rationale for reporting funding

• Given the potential role of systematic reviews in decision making, we believe authors should be transparent about the funding and the role of funders, if any.

• Lexchin and colleagues observed that outcomes of reports of randomized trials and meta-analyses of clinical trials funded by the pharmaceutical industry are more likely to favor the sponsor’s product compared to studies with other sources of funding.
  – Similar results have been reported elsewhere.

• Analogous data suggest that similar biases may affect the conclusions of systematic reviews.
Guidance for reporting funding

• Sometimes the funders will provide services, such as those of a librarian to complete the searches for relevant literature or access to commercial databases not available to the reviewers.
  – Any level of funding or services provided to the systematic review team should be reported.

• Authors should also report whether the funder had any role in the conduct or report of the review.
• Series of rapid responses
  – 5 rapid responses
  – 1 about methods
• Interesting read
• All on-line @ BMJ.com