Quality in reporting adverse events and the PRISMA Harms Extension

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Su Golder
Sunita Vohra
Disclosure of conflicts of interest

• **Su Golder**
  (1) Is co-convenor of the Cochrane Adverse Effects Methods Group.
  (2) Research referred to in this workshop was undertaken as part of a MRC fellowship. The views expressed in this presentation are those of the author and not necessarily those of the MRC.

• **Sunita Vohra:**
  (1) Is co-convenor of the Cochrane Adverse Effects Methods Group.
  (2) Is an Alberta Health Institute Scholar. AHI funded portion of the development of the PRISMA Harms.
  (3) Have won $13M in funding ($10M as PI) of which <3% is from industry

AHIHS- CRIO Project: Specialty SONAR (Study of Natural health products Adverse Reaction) Focus on Cancer Subjects ($750,000); CIHR Strategic Teams in Applied Injury Research (STAIR): Safety NET: Supporting a culture of safety for spinal manipulation therapy ($1,600,000)

• **Liliane Zorzela:** nothing to declare.
Format of Workshop

1. Background on reviews of Harms and The PRISMA Harms (15 minutes)

2. Identifying pitfalls when reviewing harms (using published SRs)

3. Methods to improve reporting on reviews of harms

4. Discussion and feedback
Harms X Benefits
The number of SRs with a harm as primary outcome has increased over the years.

Although the proportion Harms/Efficacy remains the same

Why to measure:

**Benefits**
- To know if the desired effects are achieved
- To measure the size of effect
- To determine the treatment indications

**Harms**
- To identify unintended effects of an intervention
- To measure their frequency
- To identify factors associated with the unintended effects (risk factors)
Importance

• If the intended effects are small, harms may guide the decision on which therapy to use.

• The number and the seriousness of harms must be compared against the achieved benefits.

• As harms are often infrequent or rare, they are most measurable through a systematic review and meta-analysis.
Difficulties in assessing harms in a SR/MA

• Difficult to identify which studies to include

• Mixed sample population

• No standard definitions of adverse event (what is the event, how serious or severe)

• Usually reported as number of events and not number of patients

• No report of timing of event or time of data collection

• How was the event recorded (was it passive or active?)

• What were the patient risk factors or professional qualifications (if intervention is a procedure)?
Systematic reviews should

- Clearly state a set of objectives with pre-defined eligibility criteria for studies;
- Have an explicit, reproducible methodology;
- Use a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- Assess the validity of the findings of the included studies, for example through the assessment of risk of bias;
- Systematically present, and synthesise, the characteristics and findings of the included studies.

The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration

Alessandro Liberati1,2, Douglas G. Altman3, Jennifer Tetzlaff4, Cynthia Mulrow5, Peter C. Gotzsche6, John P. A. Ioannidis7, Mike Clarke8,9, P. J. Devereaux10,11, Jos Kleijnen11,12, David Moher1,13

Guidelines and Guidance

- Developed to improve clarity of reporting in SR
- Minimum set of items to be reported in SRs
- It has a focus on efficacy

<table>
<thead>
<tr>
<th>Title</th>
<th>ABSTRACT</th>
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<tbody>
<tr>
<td>Titled</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
</tr>
<tr>
<td>Structured summary</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>
</tr>
<tr>
<td>INTRODUCTION</td>
<td></td>
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<tr>
<td>Rationale</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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<tr>
<td>Objectives</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOs).</td>
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<tr>
<td>METHODS</td>
<td></td>
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<tr>
<td>Protocol and registration</td>
<td>Specify if a review protocol exists, and if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Specify study characteristics (e.g., PICOs, 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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<tr>
<td>Information sources</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 data last searched.</td>
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<tr>
<td>Search</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
</tr>
<tr>
<td>Study selection</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>Data collection process</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>Data items</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
</tr>
<tr>
<td>Risk of bias in individual studies</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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<tr>
<td>Summary measures</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<tr>
<td>Synthesis of results</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>
</tr>
<tr>
<td>Risk of bias across studies</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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<tr>
<td>Additional analyses</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.</td>
</tr>
<tr>
<td>RESULTS</td>
<td></td>
</tr>
<tr>
<td>Study selection</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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<tr>
<td>Study characteristics</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOs, follow-up period) and provide the citations.</td>
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<tr>
<td>Risk of bias within studies</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>Results of individual studies</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>Synthesis of results</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
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<tr>
<td>Risk of bias across studies</td>
<td>Present results of any assessment of risk of bias across studies (see item 15).</td>
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<tr>
<td>Additional analyses</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>DISCUSSION</td>
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<tr>
<td>Summary of evidence</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>Limitations</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>Conclusions</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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<tr>
<td>FUNDING</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data) role of funders for</td>
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SR of harms differ from SR of efficacy

- Searches
- Screening by report of event
- Methods of reporting
- Zero events in analysis
- Adjudication
- Patient risk factors
PRISMA Harms
Document the need for a guideline

Online Delphi

Guideline publication

In Person meeting
**Item 1- Title**

**PRISMA Statement:**
1a) Identify the report as a systematic review, meta-analysis, or both.

**PRISMA Harms:**
1b) “Specifically mention ‘harms’ or other related terms, or the harm of interest in the review.”
Item 12- Risk of bias in individual studies

PRISMA Statement: 12 a) “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.”

PRISMA Harms Extension: 12b) “Describe any assessment of possible causality in individual cases in the primary studies.”
Item 14- Synthesis of results

PRISMA Statement:
14a) “Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.”

PRISMA Harm Extension: 14b) “Specify how zero events were handled, if relevant.”
PRISMA Statement 18a) “For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.”

PRISMA Harms Extension: 18b) “For each study, present the harm addressed, how and when it was ascertained (e.g. passive report, active search, use of validated tools).”
This item is under development.
PRISMA Harms Extension steering committee:

- Sunita Vohra
  (University of Alberta)
- David Moher
  (Ottawa Hospital Research Institute)
- Doug Altman
  (University of Oxford)
- Yoon Loke
  (University of East Anglia)
- John Ioannidis
  (Stanford University)
- Pasqualina Santaguida
  (McMaster University)
- Su Golder
  (University of York)
- Jan Vandenbroucke
  (University of Leiden)
Searches

• Need a separate workshop on how to do it properly

• Suggestion: Broad searches – include different study designs: rare events are infrequently found in RCTs
Screening

• Studies are often screened by title and abstract

• Adverse Events may not be reported in title or abstract

• Full text should be searched

**Suggestion:** if adverse event is not reported, but intervention and population fit your inclusion criteria, select paper.
Definition of adverse event reporting

- Clear definition of the AEs you are looking for
- Explore differences in definitions of your main outcome
- Clear planning of how to select studies not clearly reporting on the AE definition

**Example:** you are looking for hemorrhagic stroke after use of thrombolytic drug: Studies may report hemorrhagic stroke as “neurologic adverse outcomes”, cardiovascular adverse outcomes or stroke (not dividing them into hemorrhagic or thrombotic)

**Suggestion:** plan on how to overcome it (i) contacting authors; (ii) subgroup analysis; (iii) reporting it separately; (iv) excluding papers not clearly defining the AE
Zero Events

• When measuring adverse events, zero events should be considered a valid measurement (meaning the event did not occur).

• Primary studies may report them inappropriately ("both groups had similar number of adverse events", or "no significant adverse events were reported").

• The lack of reporting may mean:
  1- the event did not occur
  2- the event occurred but was not captured
  3- the event occurred, was captured, but not reported (perhaps considered unrelated to the intervention)

Suggestions: contact authors for clarification, subgroup analysis with different study report characteristics (well reported, unsure, poorly reported)
Patient Risk factors

- Were patient risk factors measured?

- Is this patient population most susceptible to the events?

- If an procedure is evaluated, were professional qualification and skill level assessed?

- Was length of follow up assessed? Was it long enough to measure the outcome?

**Suggestion:** determine the patient risk factors that could affect the outcome measured; assess if included papers report those risk factors; report studies in separate subgroups and proceed with a subgroup analysis
Adjudication

• Could the intervention have been related to the adverse event?

• Is there a casual relationship between intervention and event?

**Suggestion:** SR author should clearly state whether the event could have been caused by the intervention, considering the qualities of the included studies and the strength of the evidence.
Worksheet

Identifying Pitfalls
Examples of how to avoid them
Benefits AND Harms