Why Synthesis?

• Evidence about an intervention or exposure taken from different studies can be conflicting.
• Methods are needed to assess all available information in an unbiased way, in order to:
  • Guide practice
    – Does an intervention work?
    – In whom does it work?
    – At what dose?
• Identify evidence gaps
• Guide further research
Synthesis of Research Data

• Systematic vs non-systematic Reviews

• Non–systematic
  • may provide an interesting overview of the literature on a topic
  • have their place in providing background but
  • do not provide unbiased answers to research questions.

• Systematic – highly structured, à priori research question/hypotheses; designed to reduce bias.

Cochrane Collaboration

• international not–for–profit organisation
• provides up–to–date information about the effects of health care by synthesising the best available evidence into systematic reviews.
• focus on quality of reviews and accessibility of information

Cochrane Library:
• http://www.cochranelibrary.com/
Cochrane Handbook:
• http://handbook.cochrane.org/
Systematic reviews

- use a predefined, explicit methodology
- methods minimise bias in all parts of the process:
  - identifying relevant studies
  - selecting them for inclusion
  - collecting and combining their data
- studies sought regardless of their results

Key Characteristics of SR

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.
Steps in Systematic Review

(1) Research question/hypotheses (PICO(S/T))
(2) Inclusion/exclusion criteria for studies, consistent with (1)
(3) Librarian advice for a systematic search strategy (aimed at getting ALL relevant studies but minimising irrelevant ones)
(4) Independent assessment of studies against (2)
(5) Assess quality of studies
(6) Extract data
(7) Data synthesis methods: narrative review & meta-analysis
   • ALL DECIDED A PRIORI AND PUT IN A PROTOCOL

Importance of à priori decisions

• Avoiding bias
• Avoiding error
• Makes you think things through
• PROSPERO – to get published!!
http://www.crd.york.ac.uk/PROSPERO/
• Deviations from à priori protocol should be explained.
The Research Question: PICO(S/T)

• **People**, patients or population - who are you asking the question about?
• **Intervention** – in what intervention (or exposure or factor) are you interested?
• **Control or comparison** - what are you comparing the intervention to?
• **Outcome** - what outcome are you interested in measuring?
• **Time** – and at what time points? &/or
• **Study design**

Steps in Systematic Review

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PRISMA

- preferred reporting items for systematic reviews and meta-analyses
- See: http://www.prisma-statement.org/

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
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<tbody>
<tr>
<td>TITLE</td>
<td>1</td>
<td>Title</td>
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<tr>
<td></td>
<td>2</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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<tr>
<td>ABSTRACT</td>
<td>2</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>INTRODUCTION</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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<td>4</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>5</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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<td>6</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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<td>7</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>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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<td>9</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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<td>10</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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<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<td>12</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>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<td>14</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>Risk of bias across studies</td>
<td>15</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>16</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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<tr>
<td>RESULTS</td>
<td></td>
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<tr>
<td>Study selection</td>
<td>17</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>18</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>19</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>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
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<tr>
<td>Synthesis of results</td>
<td>21</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>22</td>
<td>Present results of any assessment of risk of bias across studies (see item 15).</td>
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<tr>
<td>DISCUSSION</td>
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<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome, consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
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<tr>
<td>Limitations</td>
<td>25</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>26</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></td>
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<tr>
<td>Funding</td>
<td>27</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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For more information, visit: www.prisma-statement.org

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**PRISMA Flow Diagram**

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Meta-analysis

• SR may include a statistical synthesis of the results from the included studies (meta-analysis)

• This might not be possible e.g.
  • if the designs of the studies are too different for an averaging of their results to be meaningful
  • if the outcomes measured are not sufficiently similar

Alternatives to meta-analysis

• Narrative synthesis
  – Systematic describe studies and their findings
  – Caution with conclusions/interpretation as easy to be biased

• Best evidence synthesis
  – Incorporates a structured assessment of the quality, quantity and consistency of evidence for each outcome
Meta-analysis

- the statistical combination of results from two or more separate studies
- Potential advantages:
  - an increase in power
  - an improvement in precision
  - the ability to answer questions not posed by individual studies
  - the opportunity to settle controversies arising from conflicting claims.

Caveat

- also have the potential to mislead seriously, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered.
Meta-analysis

- Eg. could be done without systematic review, simply combining results ≥ 1 trial
- However, such a meta-analysis will:
  - have greater mathematical precision than any one component trial, but
  - be subject to any biases that arise from the study selection process; therefore
  - may produce a mathematically precise, but misleading, result
- Only perform a meta-analysis within a systematic review framework

Meta-analysis

- Most meta-analysis methods are variations on a weighted average of the effect estimates from the different studies.
- Variation across studies (heterogeneity) must be considered
- Methods vary with
  - types of outcome factor
  - heterogeneity
Meta-analysis – basic principles

• First stage - a summary statistic calculated for each study, to describe the observed intervention effect. Eg
  – risk ratio if data dichotomous
  – difference between means if data continuous.

• Second stage - a summary (pooled) effect estimate calculated as a weighted average of the intervention effects estimated in the individual studies.
  – weights reflect the amount of information that each study contains

Meta-analysis

• All methods of meta-analysis can assess whether variation among the results of the separate studies is compatible with random variation, or whether it is large enough to indicate inconsistency of intervention effects across studies

• Known as heterogeneity
Heterogeneity

Due to

• Clinical differences
• Study method differences

Can be

• Explored eg subgroup analyses, meta-regression (à priori)
• Taken into account with random effects meta-analysis
• A reason not to perform meta-analysis

Sensitivity Analyses and Robustness

• Many judgements are required in the process of preparing a systematic review or meta-analysis.
• Sensitivity analyses should be used to examine whether overall findings are robust to potentially influential decisions
Steps in Systematic Review

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Questions?