Systematic Reviews and Meta-analysis: An Introduction

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Types of reviews

- Narrative (traditional)
- Systematic
- Meta-analysis
## Differences between Narrative Reviews and Systematic Reviews*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Narrative Review</th>
<th>Systematic Review</th>
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</thead>
<tbody>
<tr>
<td>Question</td>
<td>Often broad in scope</td>
<td>Focused on clinical question</td>
</tr>
<tr>
<td>Sources &amp; Search</td>
<td>Not usually specified</td>
<td>Comprehensive sources and explicit search strategy</td>
</tr>
<tr>
<td>Selection</td>
<td>Not usually specified</td>
<td>Criterion-based selection, uniformly applied</td>
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<tr>
<td>Appraisal</td>
<td>Variable</td>
<td>Rigorous critical appraisal</td>
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<tr>
<td>Synthesis</td>
<td>Often qualitative</td>
<td>Quantitative summary**</td>
</tr>
<tr>
<td>Inferences</td>
<td>Sometimes evidence-based</td>
<td>Usually evidence-based</td>
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** Statistical synthesis (meta-analysis)
All reviews

- Are retrospective & subject to bias and error
- Should address a question that is important to answer
- Identify gaps in current knowledge
- Provide information on the direction and magnitude of the effect on the outcome(s) of interest
Systematic Reviews

- What are they?
- Why are they important?
- What are their benefits?
- How do you do them?
What are they?

- A summary of the medical literature that uses explicit methods to:
  - systematically search
  - critically appraise, and
  - synthesize the world literature on a specific issue

(Sackett et al, 2000)
Why are they important?

- Health care providers, researchers, and policy makers are inundated with unmanageable amounts of information.

- e.g., ~6,000 journals (~10,000 citations) are entered weekly in MEDLINE.
Why are they important?

- Efficiently integrate existing information
- Provide data for rational decision making
- Separate the insignificant, unsound, redundant studies from the salient and critical studies
- Establish whether scientific findings are consistent and generalizable across time, different settings, populations, etc
Levels of evidence

- Systematic Reviews and Meta-analyses
- Randomized Controlled Double Blind Studies
- Cohort Studies
- Case Control Studies
- Case Series
- Case Reports
- Ideas, Editorials, Opinions
- Animal research
- In vitro ('test tube') research
What are their benefits?

- Minimizes biases (e.g., limiting to only high quality research designs such as RCTs)
- Minimizes random error (e.g., by accumulating data from large numbers of individuals from multiple smaller studies)
- Improves reliability and increases accuracy of conclusions
How do you do them?
Steps in systematic reviews

- The question
- Design the Protocol
- Search and retrieve relevant studies
- Study selection
- Data extraction
- Analysis
- Reporting
Write a clear, primary research question (PICO)

- Include:
  - Population
  - Intervention
  - Comparison
  - Outcomes
  - Some time reference (intervention timing/duration, follow-up)
Sample question

- What is the effectiveness of primary prevention strategies aimed at delaying sexual intercourse, improving use of birth control, and reducing incidence of unintended pregnancy in adolescents?

DiCenso et al, Interventions to reduce unintended pregnancies among adolescents: systematic review of randomised controlled trials, BMJ 2002
Develop the Protocol

- This is your research plan/proposal and should include:
  - The background
  - The problem
  - The methodology
Protocols should include:

- Specific question to be answered
- Strategies and sources for finding relevant studies
- Explicit and reproducible inclusion/exclusion criteria that include:
  - Population, setting
  - Problem, condition or disease
  - Exposure, intervention
  - Control
- Outcomes/end-points to be measured/assessed (what is being measured, how and by whom)
A priori inclusion/exclusion criteria

- Consider:
  - Type of intervention
  - Population
  - Time reference(s)
  - Types of study design (e.g., RCTs)
  - Language, country restrictions
Develop literature search strategy

- Data sources
  - MEDLINE, CINAHL, PsycLit, PsychInfo, EMBASE/Excerpta Medica, AMED, Cochrane Library, HealthSTAR, etc., etc…

- MEDLINE
  - OVID (institutional access) vs PubMED (widely accessible)
Other searching considerations

- PubMed’s Clinical Queries
- PubMed’s Related Articles
- Evidence-based sources (Best Evidence, Clinical Evidence, ACPJC online)
- Contacting authors, experts, drug manufacturers
- “Grey literature” (published on www)
- Secondary references (hand searches)
Pubmed

- Clinical queries
- Allows to search for systematic reviews
PubMed (Clinical Queries)

Allows to narrow down your search strategy
Searching techniques

- Boolean operators:
  - “AND”
  - “OR”
  - “NOT”
Examine initial search results

- How relevant are your search results?
- Do you need to further search the literature base?
- If your research question is broad, you may wish to conduct new search using more focused search terms.
Assess potential studies against *a priori* selection criteria

- Duplicate assessment (reduces assessor biases: e.g., duplicate assessment by clinician and methodologist pairs, followed by consensus process)
- Review abstracts against the predetermined criteria
- If in doubt include initially and retrieve the full text of the article for further assessment
- Retrieve the full text of the initially selected articles
FIGURE 1. HANDLING OF TRIALS IDENTIFIED THROUGH STUDY SEARCH.

Potentially relevant trials identified in electronic databases:
- PubMed: n = 278
- Embase: n = 247
- LILACS: n = 238
- CIAHL: n = 253

Articles screened for retrieval: n = 206

Trials excluded because they were not on SLIT in allergic asthma in children: n = 313

Potentially relevant trials on SLIT use in patients with allergic asthma: n = 73

Trials excluded from meta-analyses:
- Non-randomised: n = 20
- Designed for safety: n = 9
- Outcomes not validated for this review: n = 8
- Open studies: n = 8
- Studies not placebo controlled: n = 5
- Studies designed for adults: n = 4
- Duplication detected: n = 2
- Not available data: n = 1
- Evaluation post challenge test: n = 1

Randomised, placebo-controlled, double-blind trials with SLIT in allergic asthma in children: n = 9
Managing search results

- Bibliographic software
  - Reference Manager
  - EndNote
  - Procite
  - RefWorks (web based)
- Searchable, can add notes and produce formatted reference lists and bibliographies
Quality assessment (methodology)

- It’s important to include studies of good quality because including poor quality studies can have an impact on the results.
- There are three main types of quality assessment tools:
  - A list of components of quality
  - A comprehensive checklists
  - Quality scales which allow scores to be applied to a study
Quality assessment (methodology)

- Important to have two or more reviewers with process for resolving disagreements
- Consult an expert in study design to ensure you use important indicators in your criteria
- Use a predesigned and piloted form to apply criteria and keep a record of decisions
Quality assessment (methodology)

- Assess methodologic quality of studies (in duplicate + consensus)
  - Appropriateness of randomization
  - Blinding
  - Allocation concealment
  - Follow-up rates
  - Description of drop-outs/withdrawals
  - Intention-to-treat analysis
  - A priori power calculations
  - Outcome collection (objective vs subjective)
Jadad scale (RCTs)

- Was the study designed as randomized? (+1) and was method to generate sequence of randomization described /appropriate (+1) or was it inappropriate (-1)

- Was the study designed as double blind? (+1) and was method of double blinding described appropriate (+1) or was it inappropriate (-1)

- Was there a description of withdrawals and drop outs? (+1)

- Total Jadad score: 5 = very adequate ; 1 = inadequate
Quality assessment: randomization (CONSORT)

- Sequence generation: Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)

- Allocation concealment: Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned

- Implementation: Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups
Data extraction

- The data extraction is based on the predetermined Population, Intervention(s), Comparison, and Outcomes
- Use a data extraction form that has been piloted
- Consider how the data will be coded and incorporate this into the design of the form
- Have this done by two or more reviewers and cross-check the information because the process of data extraction is prone to error
- If data is missing consider how you will handle this – for example, contact the authors
Sample data extraction form

Systematic review of cluster randomized trial in primary care
Analyzing results

- Prepare tabular summaries of data
- Determine the magnitude and direction of the effects of the intervention(s)
- Are there subgroup analysis (looking at a specific category of data)
- Sensitivity analysis (looking at whether changes to the methods changes the results, for example, including a different type of study design)
Data synthesis/summary

- If heterogeneity of studies exist (varying patient populations, different interventions, diverse outcomes, etc), statistical pooling of data (“meta-analysis”) may not be possible
- Therefore, summarize data qualitatively in systematic fashion
Meta-analysis (forest plot)

Data synthesis/summary

- How clinically relevant are outcomes?
- How valid are individual study results?
- Are results consistent from study to study?
- In individual studies, what is the magnitude of the treatment effects, and, how precise are these effects?
Assessing publication bias (funnel plots)

**Figure 1.** A fictitious funnel plot with no publication bias

**Figure 2.** The same plot showing publication bias.
Data synthesis/summary

- How different were patient populations from study to study?
- Are treatments feasible in your setting? (consider your reference population)
- What are the potential benefits and harms of the treatments?
Reporting

- Have your audience in mind
- Are you planning to publish your results? Where?
- Are you writing for a journal? Which one?
Conclusions

- Because of the vast amount of available information, systematic reviews are invaluable.
- Systematic reviews use explicit methods to limit bias and random error, improving the reliability and accuracy of conclusions.
- Systematic reviews efficiently integrate existing information to enable rational decision making.
- Often used to formulate evidence-based guidelines and legislation around treatment practices.