Beyond research papers: reviews and meta-analysis

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Definitions

- Meta-analyses are studies of studies
  - Kassirer JP, NEJM 1992

- Logical framework to a research review: similar measures from comparable studies are listed & available effect measures combined where possible
  - Dickersin, Berline, Epidemiol Rev 1992

- Meta-analysis - mathematical synthesis of results of >2 primary studies that addressed the same hypothesis in the same way
  - Greenhalgh, BMJ 1997
Definitions

- **Types of reviews**
  - Narrative review
  - Systematic review

- **Meta-analysis**
  - Statistical analysis which combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable.'
Purpose

- Avoid time and expense of conducting a clinical trial
- Make comparisons of interventions more objective and accurate
- Identify areas in which insufficient research has been performed or in which additional research may not be necessary
- Increase statistical power by combining many smaller studies.
Aims

- More information from existing data
- Pooling results of many smaller studies
- Apply one or more statistical techniques
- Evaluate therapeutic effectiveness, plan new studies, give guidelines

- Benefits or hazards not detected in small studies can be found
Information explosion

- 1940 --> 2300 biomedical journals
- 1995 --> 25000 biomedical journals
- Approx. 9000 RCTs/year
- Over 2 million articles are published annually
- More than 17,000 biomedical books are published annually

- Single studies rarely provide definitive answers to clinical questions
Systematic reviews

- Scientific investigations in themselves
- Pre-planned methods (Protocol)
- Original studies (Subjects)
- Synthesize results of multiple primary investigations by using strategies that limit bias and random error (Methods)
  - Cook DJ et al, 1998
Primary vs secondary research

- Results of a particular research study cannot be interpreted unless they are considered together with results of other studies addressing the same or similar questions.

- Research synthesis -- “science is cumulative”
Similar methodology

Primary Research
- Question / Hypothesis
- Criteria for selection of ‘subjects’
- Study population
- Sampling
- Data collection
- Data management and analysis
- Structured report

Secondary Research
- Question / Objective
- Criteria for selection of ‘studies’
- Study ‘pool’
- Study selection
- Data extraction
- Data management and analysis
- Structured report
### Narrative vs Systematic Review

<table>
<thead>
<tr>
<th>Feature</th>
<th>Narrative</th>
<th>Systematic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Broad</td>
<td>Focused</td>
</tr>
<tr>
<td>Sources/Search</td>
<td>Usually unspecified</td>
<td>Specified</td>
</tr>
<tr>
<td></td>
<td>Potentially biased</td>
<td>Explicit Criterion based</td>
</tr>
<tr>
<td>Selection</td>
<td>Unspecified</td>
<td>Uniformly applied</td>
</tr>
<tr>
<td>Appraisal</td>
<td>Variable</td>
<td>Rigorous/Critical</td>
</tr>
<tr>
<td>Synthesis</td>
<td>Usually qualitative</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Inferences</td>
<td>Sometimes evidence-based</td>
<td>Evidence-based</td>
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</tbody>
</table>
Statistical reasoning

- Limit bias
- ↑↑↑ Overall Sample Size
- ↑↑↑ Statistical Power
- ↑↑↑ Precision of the Estimate
- Provide robust estimate
- Identify crucial areas and questions that have not been adequately addressed with past research
Manuscript writing

- Similar structure as primary research
- IMRAD
  - Title
  - Abstract / Summary
  - Introduction: Why was this work undertaken?
  - Methods: How was it done?
  - Results: What did you find?
  - Discussion: what does it imply?
Introduction

- Purpose
- Rationale / Background
- Problem / Relevance / Justification / Need
- Brief Review of Literature
- Expected Implications
Aim

- Summarize a large and complex body of literature on a topic
- Resolve conflicting reports in literature
- Clarify or quantify strengths and weaknesses of studies on a topic
- Document need for a major clinical trial
Purpose

- Improve precision of an estimated treatment effect
- Detect smaller treatment effects than have been reported.
- Investigate variations in treatment effects through subgroup (or stratified) analysis.
- Improve generalizability of known treatment effects.
Methods

- Sources of Relevant Studies
- Search Strategies
- Selection of Studies
- Appraisal of Studies
- Data Extraction
- Statistical Analysis - Strategy
Sources

- Electronic Databases
- Online Journals
- Manual Search
- Reference Lists
- Study Registries
- Current Awareness Publications
- Text Books and Reference Books
- Monograms and Recent Advances
- Dissertations and Thesis
Sources

- Pharmaceutical & Appliance Companies
- Funding Agencies
- Professional Organizations
- Personal Contact
- Personal Knowledge
- E Journals
- Foreign Language Literature
- Unpublished Studies?
- Abstracts?
Selection and appraisal

- Relevance of studies to review question
- Judge features of design and analysis
### Differences in inclusion

#### Papers included and excluded in meta-analysis of RCTs relating peptic ulcer to steroid therapy by Conn & Blitzer and Messer et al

<table>
<thead>
<tr>
<th></th>
<th>Conn &amp; Blitzer</th>
<th>Messer</th>
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<tbody>
<tr>
<td></td>
<td>Included</td>
<td>Excluded</td>
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<tr>
<td><strong>Messer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Included</td>
<td>25</td>
<td>46</td>
</tr>
<tr>
<td>Excluded</td>
<td>17</td>
<td>113</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>159</td>
</tr>
</tbody>
</table>
Duplicate publication

- Data access vs data excess
- Example
  - Single trial of risperidone for chronic schizophrenia was reported in seven different publications with different authorship
Flip side of publication bias

- Negative trials less likely to be published
- Consequences are similar in both cases
  - Excessively precise and inflated effect size estimates
Quantitative methods

- Statistical methods to combine results (Effect Measures) of multiple studies
- Statistical methods involved appear to be mathematically complex
Quantitative Methods

• Four basic questions
  • Are results of different studies similar?
  • To the extent that they are similar, what is the best overall estimate?
  • How precise and robust is this estimate?
  • Can dissimilarities be explained?
Quantitative Methods

- Stepwise tasks
  - Deciding whether to combine data and defining what to combine
  - Evaluating statistical heterogeneity of data
  - Estimating a common effect
  - Exploring and explaining heterogeneity
  - Assessing the potential for bias
Results

- Typical presentation: graphic form
- Tables
- Effect measures: point estimates and 95% CI
- Data in 2x2 table format
- Study characteristics
- Co-variates (Codes)
- Summary Estimates (5 % CI)
- Heterogeneity statistics
Types of analyses

- Subgroup Analysis
- Quality Assessment (Scores)
- Cumulative Meta-Analysis, Stepwise Deletion
- Meta-Regression Results
- Sensitivity Analysis
- Cross Design Synthesis
- Publication Bias (Funnel Plot)
Publication Bias

- Selection bias
  - Publication bias
  - Location bias
  - English language bias
  - Citation bias
  - Multiple publication bias
- **True heterogeneity**
  - Size of effect differs according to study size
  - Intensity of intervention
  - Differences in underlying risk

- **Data irregularities**
  - Poor methodological design of small studies
  - Inadequate analysis
  - Fraud
Arrange studies

- Publication date
- Sample size
- Quality of study
- Duration of treatment
- Size of treatment dose
- Study design
- Effect measures
Beta-carotene and cardiovascular mortality

Cohorts
- Male health workers
- Social insurance, men
- Social insurance, women
- Male chemical workers
- Hyperlipidaemic men
- Nursing home residents

Trials
- Male smokers
- Skin cancer patients
- (Ex)-smokers, asbestos workers
- Male physicians

Cohorts combined
Trials combined
Egger et al BMJ 1998
Mortality results from 33 trials of beta-blockers in secondary prevention after myocardial infarction
Adapted from Freemantle et al *BMJ* 1999
Discussion

- Summary estimates (implications)
- Results of large trials and MA
- Results of earlier MA vs current MA
- Selection and appraisal criteria
- Analytical strategy
- Heterogeneity
- Biases (Selection bias, data extraction bias, source of support, ecologic bias, publication bias)
- Strengths and limitations
Conclusion

- Meta analyses and systematics reviews
- Best available evidence
- Influence decision making in clinical practice and public health