Weighing the Evidence: Critical Appraisal and Systematic Review of RCTs

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Overview

Today's session aims for you to understand:

- Importance of critical appraisal
- Questions to ask

- The importance of systematic reviews
- Key steps in conducting a systematic review
- When and how to use meta-analysis
- Sources of heterogeneity and what to do about them.

Critical appraisal

- Many published papers have serious methodological flaws

- It's not the number of flaws- it's the nature of the flaws
  - A study may have multiple minor flaws that have a negligible affect on conclusions or
  - A study may have one major flaw that means the conclusions are meaningless

- Can findings can be used to inform practice, future research and policy?

- Decide on basis of design and methodology

Critical Appraisal (steps 1 to 2)

- Key issues
  - Internal Validity
  - Generalisability

Critical Appraisal (steps 1 to 5)

- Five questions
  - Is it of interest?
  - Why was it done? (i.e. originality, uncertainty)
  - How was it done? (i.e. who is the study about, is the design appropriate, was systematic bias avoided or minimised)
  - What were the results? (how were the statistical issues dealt with?)
  - What are the implications?

Critical appraisal

- General questions to ask about study

Consideration of features specific to trials:

- Sequence generation
- Allocation concealment
- Blinding
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

Critical appraisal – a summary

- Read background
- Look specifically for stated aims and hypotheses
- **Read methods section - what is the study design**
- Re-read methods section - **bias, chance, confounding**
- Read through results - **bias, chance, confounding**
- Come up with your list of limitations and implications
- Read discussion and conclusions; compare with yours

- Lastly read abstract - is this an accurate précis of the research?

Uses of Reviews

- Summarise existing evidence
- Identify evidence gaps
- Provide the context for future studies
- Determine the effectiveness of an intervention

Problems with traditional reviews

- Articles chosen to support the author's view
- Methodology often not adequately described
- Lack of transparency about how studies were identified
- Lack of transparency about studies are included
- Process of generating conclusions often obscure
- Each study counted as an equal unit
- Potentially biased

Systematic Reviews

- Systematic reviews are prepared using a systematic approach to minimising bias and random errors, where the methods used are fully documented and which may or may not include a meta-analysis.

(Chalmers and Altman 1995)

The importance of systematic reviews – example 1

- "Advice to put infants to sleep on the front for nearly half a century was contrary to evidence available from 1970 that this was likely to be harmful. Systematic review of preventable risk factor [for Sudden Infant Death Syndrome] from 1970 would have led to earlier recognition of the risks of sleeping on the front and might have prevented over 10,000 infant deaths in the UK and at least 50,000 in Europe, the USA and Australasia."

(Gilbert et al. 2005)

Steps in a systematic review

- Prepare a review protocol
- Frame the research question
- Decide upon inclusion and exclusion criteria
- Design a robust search strategy
- Select relevant studies
- Assess the quality of studies
- Summarise the evidence
- Interpret the findings

Prepare and register a review protocol

- Write down exactly what you want to do **before** you do it.
  - Ensures the whole review team knows – and agrees – on what is being down.
  - Helps identify what resources are needed
  - Keep track of progress
  - Helps to reduce bias
  - The information can often be used in grant applications
  - Several leading journals (e.g. PLoS Med) require protocols to be provided as supplementary information when publishing a review paper.
- Register the protocol to let everyone know what you are doing

Framing the research question

- **P**atients/population/problem – important characteristics (e.g. condition, age, gender)
- **I**ntervention – what action is being considered?
- **C**omparison – what is the alternative?
- **O**utcome – what do you want to achieve?

PICOS

- P = Population- sociodemographic characteristics, setting, diagnosis- broad or narrow?
- I= Intervention package or single intervention, brief/long-term
- C= Comparison- placebo/other comparison, comparable treatment of control and treatment arms
- O= Outcome- Primary/secondary outcomes, adverse outcomes, subjective/objective measures

Inclusion and exclusion criteria

- Inclusion and exclusion criteria should follow logically from your research question
- PICO becomes PICOS
  - Patients/population/problem
  - Intervention
  - Comparison
  - Outcome
  - **Study Design**
- You may also decide to include/exclude studies based on methodological quality.
- Some systematic reviews exclude studies not published in English – but this risks introducing bias.

Design a robust search strategy

- A quick search is likely to miss studies and the studies you find are not likely to be representative of all of the studies that have been done.
- But it may not be possible to identify every relevant study that has ever been completed.
- To strike a balance, a good search strategy should:
  - Identify as many studies as possible
  - Minimise bias
  - Be efficient

Design a robust search strategy

Key components of a robust search strategy include:

- Cochrane Controlled Trials Register (CCTR)
- Multiple electronic databases and trials registers not covered by CCTR
- Screening reference lists of included studies
- Forwards citation tracking of included studies
- Hand searches of key journals
- Personal communication with experts in the field

You can ask for help from the library information specialist.

Managing your searches

- Keep records of:
  - What you searched
  - When you searched it
  - How you searched it
  - How many “hits” the search returned.
- Download/manually add citations to reference management software (e.g. EndNote, RefMan)
- Have a strategy for managing duplicates:
  - The same reference might be indexed by several databases.
  - The same study might be reported in several papers.

Selecting relevant studies quality assessment

- Reviewed by >1 person, screening for eligibility
- A priori strategy for resolving disagreements
- Record number of exclusions and reasons for these
- Risk of bias tool

What is a meta-analysis?

- **Systematic review** – process for identifying and extracting data from all relevant studies.

- **Meta-analysis** – mathematical procedure for combining results from quantitative studies (usually RCTs)
- Weighted average

- A systematic review need not include a meta-analysis, **but** a meta-analysis is not valid unless it is within a systematic review.

Meta-analysis: steps

- Extract data from each individual study
- Calculate a point estimate and confidence interval for that study
- Decide whether it appropriate to calculate a pooled average result across studies
- If so, calculate and present your pooled average result.

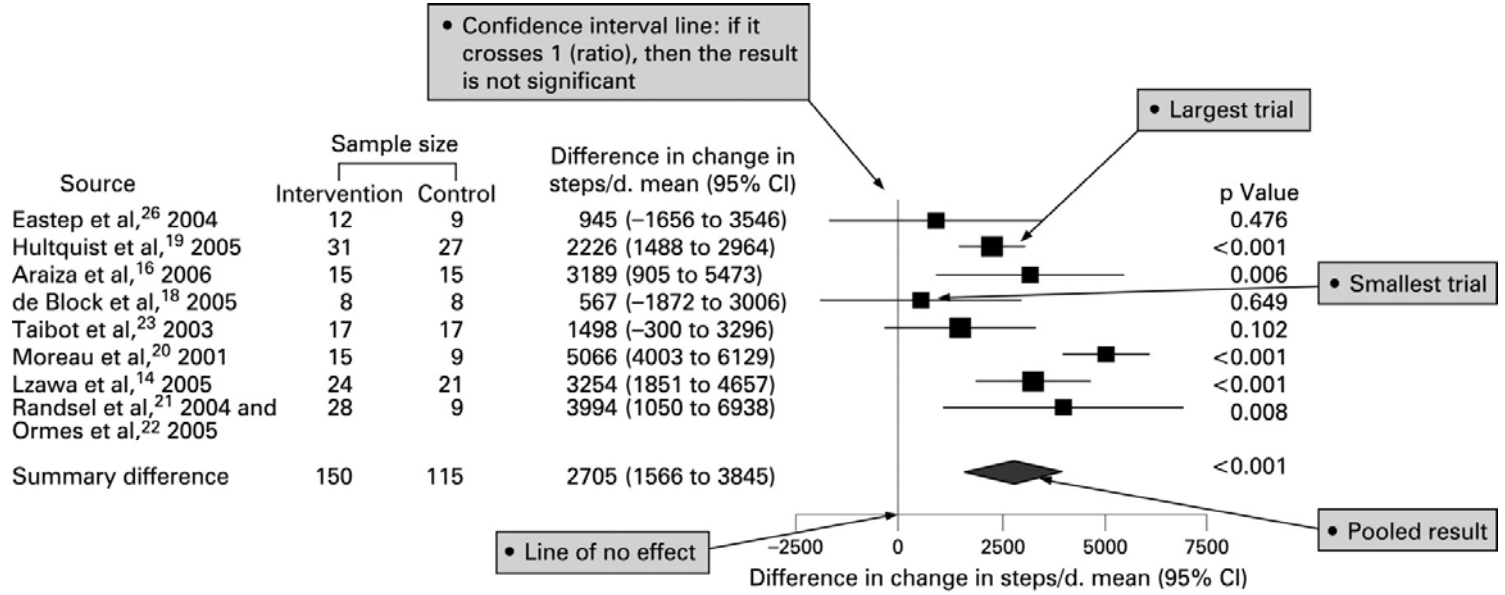
Deciding if it appropriate to calculate a pooled average

- Sometimes studies are similar enough that it is useful to conduct a meta-analysis to produce a weighted average of their findings.
- Sometimes studies are too *heterogeneous* to be combined.
- Heterogeneity may be due to:
  - Clinical heterogeneity
  - Methodological heterogeneity

Fixed effects meta-analysis

- Assumes that the effect (e.g. of antidepressants in preventing postpartum depression) is the same in each study.
- Bigger studies are given more weight than smaller studies.

Fixed effects meta-analysis: forest plots



Legend:

- This square represents the individual studies effect (sometimes known as a "blob"). The size of the "blob" varies to reflect the weight a particular study has in the overall analysis (larger "blobs" have more weight).
- The black line represents the CIs of a study; the smaller "blobs," which have less weight generally have larger CIs than the larger "blobs."
- The diamond represents the overall or summary effect. The outer edges of the diamond represent the CIs.

(Perera et al. 2008)

Checking again for heterogeneity

- If you decide to combine the studies and conduct a meta-analysis, check the statistical tests of heterogeneity.
- Individual estimates of treatment effect *will* vary to some extent between studies because of chance.
- If there is excessive variation between studies (more than you would expect by chance alone) we say there is **statistical heterogeneity.**

Checking again for heterogeneity

- Check 1: look at the confidence intervals of individual studies – do they overlap? If not, there is evidence of heterogeneity.
- Check 2: look at the chi-square statistic. If the statistic is bigger than the degrees of freedom, there is evidence of heterogeneity.
- Check 3: look at the I^2 statistic – the proportion of total variation in study estimates that is due to heterogeneity. >75% indicates high heterogeneity.

Statistical heterogeneity - example

Study ID	ES	[95% CI]		% Weight
1	2.290	1.388	3.779	4.20
5	3.797	2.069	6.966	2.86
6	3.531	2.025	6.154	3.41
10	1.857	1.062	3.249	3.37
16	4.440	3.906	5.048	64.03
18	3.509	2.430	5.065	7.81
20	1.441	0.989	2.099	7.44
22	1.340	0.906	1.982	6.88
I-V pooled ES	**3.444**	**3.108**	**3.816**	**100.00**

Heterogeneity chi-squared = 65.41 (d.f. = 7) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 89.3%

Test of ES=1 : z= 23.62 p = 0.000

What to do if there is substantial heterogeneity

Three options:

- Do not pool estimates – i.e. report estimates from individual studies separately
- Allow for the heterogeneity without seeking to explain it → random effects meta-analysis
- Seek to explain the heterogeneity

Writing up

- Follow reporting guidelines for systematic reviews:
  - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org, PLoS Medicine 2009; 6(7): e1000097)
  - MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (JAMA 2000; 283:2008-2012)

Summary

- Systematic reviews have key advantages over “traditional” reviews
- Decide – and write down – in advance what you plan to do.
- Document your progress
- Remember that is not always appropriate to conduct a meta-analysis

Additional resources

- Egger M, Davey Smith G, Altman DG (eds). *Systematic Reviews in Health Care: Meta-analysis in context*. BMJ Books 2001 (available from KCL as an electronic resource)
- Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley-Blackwell 2008 (available from KCL as an electronic resource)
- Sterne J (ed). *Meta-analysis in Stata: an updated collection from the Stata Journal.* Stata Press 2009 (available from the Institute of Psychiatry Library).