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INTRODUCTION TO SYSTEMATIC REVIEWS & META-ANALYSES

Joel J. Gagnier MSc, PhD

Course Description

- Overview of methods for completing systematic reviews
- 5 lectures, 3.5 hours each (1.5 hours, break, 1.5 hours)
- For credit students must complete a protocol for a systematic review on a topic of their interest
  - Due in 1 week
  - Must attend 4 of the 5 lectures and complete the assignment
- Protocol completion is recommended for non-credit students as well

Topics to be covered

- Introduction to synthesis research
- Formulating a topic and developing a protocol
- Searching and screening the literature
- Data extraction and evaluating the quality of studies
- Analyzing and integrating the outcomes of studies
- Qualitative and quantitative methods of data integration
- Assessing bias and variations in effect
- Interpreting the evidence
- Presenting the results
- Critical appraisal of systematic reviews

Course texts

- **Course text A:** Littell JH, Corcoran J, Pillai V. *Systematic Reviews and Meta-analysis*. Oxford: Oxford University Press, 2008.
- **Course text B:** *Introduction to Meta-Analysis*. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. New Jersey: A John Wiley and Sons, 2009.

Assignment

- Complete a protocol for a systematic review (SR) of your interest
- Following Cochrane Collaboration format
- Will complete a section each day in the last hour of each class
  - I will help with all proposals
- It is hoped that each of you will complete the SR

Lecture 1

- Introduction to synthesis research
- Formulating a topic and developing a protocol

Overview

Introduction to Synthesis Research

- History of use of Systematic reviews
- Narrative reviews VS systematic reviews
- Steps in a systematic review

Formulating a topic

- The research team
- The research question

Developing a protocol

- Parts of the Manuscript

The Problem

Where is the knowledge we have lost in information?

T.S. Eliot, "The Rock"

Great Chain of Evidence

- Many thousands of new scientific studies completed each day
  - Many are published
  - Many are not
- Evidence-based decision making is taking hold
- But often we have limited time to use the literature; to:
  - Find
  - Evaluate
  - Apply

A solution

- Several mechanisms are evolving which will help us out:
  - Evidence-based guidelines
  - Evidence-based Journals
  - Synthesis research / data integration

Data Integration Research

Original research which combines other original research

Examples

- Clinical practice guidelines
- Economic evaluations
- Clinical decision analyses
- Systematic reviews

Clinical Practice Guidelines/Evidence Based Guidelines

- Systematically developed statements
- Intended to assist end users (practitioners, patients, funders, public health officials)
- On decisions about appropriate health-care for example
  - For specific clinical circumstances
- Evidence based guidelines use systematic reviews of the literature

Economic Evaluations

- Compare costs and consequences of different course of action
- Use systematic reviews of primary studies

Decision analyses

- Quantify likelihood and valuation of the expected outcomes associated with competing alternatives

Systematic Reviews

- Use explicit and rigorous methods to:
  - Identify
  - Critically appraise
  - Synthesize
- Look for the whole "truth" (not just a part…a single or few studies)
  - Assemble **all** available evidence (e.g., all controlled studies)

History

- James Lind, 18th century
  - Critically reviewed a number of reports on the prevention and treatment of scurvy

History

- Archie Cochrane, an epidemiologist, published an influential book in 1972 (Effectiveness and Efficiency)
  - criticized our collective ignorance about the effects of health-care.

"It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, updated periodically, of all relevant randomized controlled trials"

History

- In 1987 Cochrane referred to a systematic review of corticosteroid treatment in pre-term births
  - showed that a short-inexpensive course of corticosteroid treatement substantially reduced the risk of premature deaths due to complications
  - evidence showed that had a systematic review been done 10 years earlier we could have prevented many premature deaths

History

- Statistical basis
  - 17th century, astronomy and geodesy
  - Leplace used probability models to combine and quantify the uncertainty of a set of observations that was caused by measurement errors
  - Gauss, normal distribution
  - Leplace, central limit theorem
  - Pearson, Tippet, Fisher, Yates and Cochran provided methods for combining statistics

Now

- Cochrane Collaboration
  - 12,000 researchers
  - 90 countries
  - 5000+ Cochrane Systematic Reviews
- 7000+ other Systematic Reviews

Systematic reviews

- The assembly, critical appraisal, and synthesis of all relevant studies that address a specific question.
- Application of scientific strategies
  - In ways that limit bias
  - The review process itself (like any other type of research) is subject to bias
    - Good reviews have rigorous methods and clear reporting (PRISMA)

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

Terminology

- Overview = sometimes used to denote a systematic review
- Narrative reviews = summaries of research that lack explicit descriptions of systematic methods

Systematic VS Narrative reviews

Feature	Narrative review	Systematic Review
Question	Broad in scope	Focused question
Sources and Search	Not usually specified, potentially biased	Comprehensive sources and explicit search strategy
Selection	Not usually specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal
Synthesis	Often a qualitative summary	Qualitative or Quantitative summary
Inferences	Sometimes evidence-based	Usually evidence-based

How to tell quickly!

- If the question is not clear from the title, abstract, or introduction, or
- If no methods section is included the paper

More likely to be a narrative review than a systematic review

Systematic reviews: Benefits

- Can detect small but clinically significant treatment effects
- Save us time (quicker than a new large RCT or observational study)
- Have clear methods and results
- Define the boundaries of what is known and not known
- Systematic reviews can help clinicians/scientists keep abreast of the literature by:
  - summarizing large bodies of evidence
  - helping to explain differences among studies on the same question

Systematic reviews: Benefits

- Save time and money for researchers, clinicians, policy makers, funding bodies, reviewers
- Considered a very high level of evidence
- Influences decision makers
- Influences the design of future trials
- Notes the limitations of current research
- Appraises the quality of existing information
- Costs very little, if anything

Systematic Review: Examples

- Protein restriction decreases the progression of renal disease
- Bed rest is not effective for low back pain
- Supplemental Vitamin D prevents cancer and cardiovascular disease in women

Costs

- The major costs associated with a sys review are labour:
  - Yours
  - Statistician (if required)
  - Collaborating reviewer(s)
- Additional costs are related to obtaining articles
  - Ordering, Copying, translating etc

Types of Systematic Reviews: Qualitative VS Qualitative

Qualitative systematic review (best evidence synthesis)

- The results of primary studies are summarized
- Not statistically combined
- Described narratively
- Still use other methods to limit bias

Quantitative systematic review (meta-analysis)

- The results of two or more primary studies are combined
- Statistically combined
  - Individual patient data (IPD) / Pooled analysis
  - Aggregate patient data (APD)
- Use methods to limit bias

Types of Meta-analyses

IPD (pooled analysis)

Advantages:

- Data updated
- Can perform valid subgroup analyses on individual pt and trial levels
- Increased power to detect differences
- Accurate summary effects and variances

Disadvantages:

- Time consuming
- Costly
- Require much cooporation
- Simpson's paradox…baseline or group differences may confound effects; reverse the direction of effect even when each trial shows the other direction

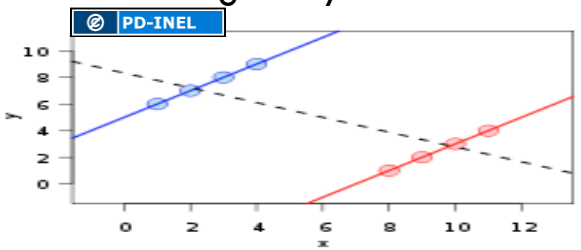
APD

Advantages:

- Easier
- Inexpensive
- Examine trial level covariates with accuracy

Disadvantages:

- Less power
- Subgroup analyses of patient level covariates suffer from ecologic bias
  - where a variable associated with a group appears to have an influence on the treatment effect; this effect may not show up on the individual level; this is due to inherent heterogeneity at the individual level



Error/bias

- All reviews (narrative & systematic) are retrospective, observational studies & are subject to
  - systematic error
  - random error
- The quality of a review
  - depends on the extent to which scientific review methods minimize error and bias

Systematic reviews change minds

- Systematic reviews have been found to influence clinical practice and change minds
- E.G. Vitamin D supplementation prevent cancer and cardiovascular disease in women
  - Clinicians now regularly test vitamin D levels in women
  - Many women are now taking 1000-2000 IU of vitamin D per day

PRISMA Statement

- Developed to improve the quality of reporting of systematic reviews.
- List of criteria for reporting your systematic review
- It is available at http://www.prisma-statement.org/statement.htm

MOOSE statement

- Meta-analyses of observational studies in epidemiology

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283(15):2008-2012.

Systematic Review (SR) Methods

How do you do one??

The team

- SRs can be done by one person, but are then subject to bias.
- At least two people on a review; may need the influence of a third.
- But, too many cooks….
- Consider:
  - Methodologist
  - Someone with clinical expertise
  - Statistician (some-one who has been trained to do or has done systematic reviews)

The Team

- Meet to discuss interests
- Decide on roles and responsibilities
- Consider funding
  - Internal (academic institutions)
  - NIH (comparative effectiveness; RFPs)
  - CIHR (knowledge synthesis)
  - Other?

Parts in the Manuscript

- Abstract
  - Background, methods, results, discussion, conclusions
- Background
- Methods
- Results
- Discussion
- Conclusions

Protocol

- Should start with writing a complete protocol
- Required by Cochrane and Campbell collaborations
  - Submit for review by relative review groups
    - http://www2.cochrane.org/contact/entities.htm
  - May take 3-6 months to approve
- Helps to clearly organize your rationale and methods

Steps

1. Formulate a question
2. Define inclusion/exclusion criteria
3. Locate studies
4. Select studies
5. Assess study quality
6. Extract data
7. Analyze and present results
8. Interpret results

1. Question

- Start broad then narrow it.
- Broadly search the literature to become familiar with what types of studies exist
  - What has and hasn't been done
  - Is a new SR needed?
- Ideally, you will want to summarize top level evidence
  - Randomized trials, cohort studies, case control studies
    - Depends on your question

1. The question

Involve every potential collaborator on the question: Don't rush it!

- P.I.C.O.T.
- P) Patients
- I) Intervention
- C) Control Group
- O) Outcomes of Interest
- T) Timing element for all ??

Examples of Questions of Interest

Do this…….

- P) Patients
- I) Intervention
- C) Control Group
- O) Outcomes of Interest

Requirements for Protocol

- Title:
  - Intervention for condition/problem in population
  - Consider adding the term systematic review or meta-analysis if publishing in peer-reviewed journal

Protocol

- Background:
  - Description of the condition/problem and its significance
    - Biology, diagnosis, prognosis, epidemiology
    - Impact (financial, economic etc)
  - Describe intervention/exposure
    - What is it?
    - Place in context of competing alternatives

Background

- How the intervention/exposure may work
  - Components, mechanism, delivery methods etc
  - Create rationale for how connected to the specific condition
- Why is it important to do this review
  - Why this question is important; this should be clearly established from above
  - Might be an update of an older review

Objectives

- Precise statement of the primary objective of the review
- Single sentence
- Format
  - "to assess the effects of [intervention/exposure or comparison] for [health problem/condition] for/in [types of people, disease or problem and setting if specified]"
- Can be followed by a series of specific objectives
  - relating to different participant groups, different comparisons of interventions, or different outcome measures
- Hypotheses are not necessary
  - SRs are observational in nature

Conflicts of Interest

- State conflicts of interest and sponsorship statements
  - Involvement in included studies, other reviews
  - Working for a private company that manufactures the intervention
- Could bias the SR

Plans may change

- In the context of the review you may want to change some methods
- This is fine
- State what you changed and why
- Transparency!!

Define Inclusion/exclusion criteria

- Decide a priori what your inclusion and exclusion criteria will be.
  - just as you wouldn't include just anyone in a trial, you won't include just any information into a SR.
  - What to consider
    - Derives from your question (PICO)
      - have the type of patients with a particular characteristics (condition/ exposure) and outcomes we are interested in
    - Study design
    - published since a specific date
  - Note: excluding studies due to methodological flaws is inappropriate; biases the SR; must include ALL

Inclusion/Exclusion

- Exclusion criteria:
  - any other study design
  - other examples?
- Defining the criteria for inclusion and exclusion a priori reduces the likelihood of bias.
  - Decide what studies to include based on their methods, not on their results

Inclusion/Exclusion

- Typically done by two individuals
  - Separately and independently
  - Use checklist of inclusion/exclusion criteria
    - Use excel spreadsheet
  - Useful to pilot the checklist on a small number of included papers
    - Then revise and assess all trials
  - Meet for consensus
    - Include 3rd party of consensus not met

Protocol Development

- Work on
  - Individual questions
  - Background
  - Objectives
  - Inclusion exclusion

Thank-you!!