Author(s): Joel J. Gagnier M.Sc., Ph.D., 2011

License: Unless otherwise noted, this material is made available under the terms of the Creative Commons Attribution–Noncommercial–Share Alike 3.0 License: http://creativecommons.org/licenses/by-nc-sa/3.0/

We have reviewed this material in accordance with U.S. Copyright Law and have tried to maximize your ability to use, share, and adapt it. The citation key on the following slide provides information about how you may share and adapt this material.

Copyright holders of content included in this material should contact open.michigan@umich.edu with any questions, corrections, or clarification regarding the use of content.

For more information about how to cite these materials visit http://open.umich.edu/education/about/terms-of-use.

Any medical information in this material is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. Please speak to your physician if you have questions about your medical condition.

Viewer discretion is advised: Some medical content is graphic and may not be suitable for all viewers.
Attribution Key
for more information see: http://open.umich.edu/wiki/AttributionPolicy

Use + Share + Adapt
{ Content the copyright holder, author, or law permits you to use, share and adapt. }

- **Public Domain – Government**: Works that are produced by the U.S. Government. (USC 17 § 105)
- **Public Domain – Expired**: Works that are no longer protected due to an expired copyright term.
- **Public Domain – Self Dedicated**: Works that a copyright holder has dedicated to the public domain.
- **Creative Commons – Zero Waiver**
- **Creative Commons – Attribution License**
- **Creative Commons – Attribution Share Alike License**
- **Creative Commons – Attribution Noncommercial License**
- **Creative Commons – Attribution Noncommercial Share Alike License**
- **GNU – Free Documentation License**

Make Your Own Assessment
{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

- **Public Domain – Ineligible**: Works that are ineligible for copyright protection in the U.S. (USC 17 § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

- **Fair Use**: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (USC 17 § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.
INTRODUCTION TO SYSTEMATIC REVIEWS & META-ANALYSES
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.

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
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 treatment 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
  - 17\textsuperscript{th} 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)

Terminology

- **Overview** = sometimes used to denote a systematic review
- **Narrative reviews** = summaries of research that lack explicit descriptions of systematic methods
<table>
<thead>
<tr>
<th>Feature</th>
<th>Narrative review</th>
<th>Systematic Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Broad in scope</td>
<td>Focused question</td>
</tr>
<tr>
<td>Sources and Search</td>
<td>Not usually specified, potentially biased</td>
<td>Comprehensive sources and explicit search strategy</td>
</tr>
<tr>
<td>Selection</td>
<td>Not usually specified, potentially biased</td>
<td>Criterion-based selection, uniformly applied</td>
</tr>
<tr>
<td>Appraisal</td>
<td>Variable</td>
<td>Rigorous critical appraisal</td>
</tr>
<tr>
<td>Synthesis</td>
<td>Often a qualitative summary</td>
<td>Qualitative or Quantitative summary</td>
</tr>
<tr>
<td>Inferences</td>
<td>Sometimes evidence-based</td>
<td>Usually evidence-based</td>
</tr>
</tbody>
</table>
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 cooperation
- 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
Meta-analyses of observational studies in epidemiology

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 (someone 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](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
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!!