OBSERVATIONAL STUDY DESIGN
PART II

SYSTEMATIC REVIEW AND META-
ANALYSIS: METHODS

Welcome to the second session in the three-part series focused on observational study design. In this module, we will introduce topics related to systematic review and meta-analysis.

Outline

- Definitions
  - Systematic Reviews
  - Meta-analysis
- Methods: identifying articles, abstracting data
- Methods: statistical analysis
- Reporting
- Guidelines

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In this module I will cover methods of systematic review, focusing on features and methods of systematic review that differ from a typical, more descriptive literature review. We will define systematic reviews and meta-analysis, will discuss methods for identifying articles and abstracting data, will discuss statistical analysis methods, and finally, will discuss reporting and guidelines.

Definitions

Let's first start with some definitions.

Definition

- Systematic Review
    - "The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Meta-analysis may be, but is not necessarily, used as part of this process. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardized methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results."
    Last, *A Dictionary of Epidemiology*. Oxford University Press, 2001.

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Last, in A Dictionary of Epidemiology, defines a systematic review as "The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Meta-analysis may be, but is not necessarily, used as part of this process. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardized methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results."

Definition

- Systematic Review
  - "A review that has been prepared using a systematic approach to minimizing biases and random errors which is documented in a materials and methods section. A systematic review may, or may not, include a meta-analysis: a statistical analysis of the results from independent studies, which generally aims to produce a single estimate of a treatment effect."

  Systematic Reviews in Health Care: Meta-analysis in context. Edited by Egger, M. Smith, G.D., Altman, D.G., London: BMJ Books, 2nd edition, 2001.

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Egger et al. define a systematic review as "A review that has been prepared using a systematic approach to minimizing biases and random errors which is documented in a materials and methods section. A systematic review may, or may not, include a meta-analysis: a statistical analysis of the results from independent studies, which generally aims to produce a single estimate of a treatment effect."

Definition

- Meta-analysis
  - "A statistical synthesis of the data from separate but similar, i.e., comparable, studies, leading to a quantitative summary of the pooled results."

    Last, *A Dictionary of Epidemiology*. Oxford University Press, 2001.

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Last, in his Dictionary of Epidemiology, defines a meta-analysis as "a statistical synthesis of the data from separate but similar, i.e., comparable, studies, leading to a quantitative summary of the pooled results". The primary objective is to derive a pooled estimate of the intervention effect from clinical trials, or the pooled estimate of an association between exposure and outcome in observational studies. In other types of meta-analyses, you may be interested in deriving a pooled estimate of diagnostic test accuracy based on a collection of studies investigating a particular diagnostic testing approach.

Objectives

- Derive pooled estimates of prevalence, incidence, diagnostic performance, or association
- Example: Estimate the pooled difference in mean outcome between interventions
  - Increased precision
  - Increased power to detect small, but clinically-meaningful, intervention effects
  - Assess consistency of differences across studies

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With meta-analysis, we are pooling data from multiple studies, resulting in a larger overall sample size, increased precision and improved power. Based on the pooled data, we will increase the probability of detecting small but clinically-important intervention effects or associations. In addition, the pooled data provide information about the consistency of intervention effects across multiple studies and provide insights into factors that may be associated with differential intervention effects.

Why meta-analyses?

- Many studies provide inadequate power to detect important clinical differences in treatment outcome
- Information contained in a series of trials may provide definitive results not contained in any one trial

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Why is meta-analysis important? Individual studies may be underpowered, particularly relative to secondary endpoints or adverse events. While a single study may not provide sufficient information, a series of trials, analyzed using meta-analysis methods, can be informative.

Heterogeneity

- Treatment effects may vary across studies
  - Variations in
    - Interventions
    - Study population
    - Length of follow-up
    - Response assessment
    - Quality of study conduct and data
  - Random variability

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Reported intervention effects vary from study to study. Why does such variation occur? It may be due to differences across studies in the interventions, for example, dose or formulation; differences in patient populations, for example, differences in age, gender or clinical characteristics; differences in duration of follow-up; difference in response assessment methods; and differences in study conduct and quality of data collection, to name a few possible sources of variation. In addition, intervention effects may vary due to random variability (i.e., variation due to chance). With meta-analysis methods, we can explore these sources of variation.

Potential problems with meta-analyses

- Publication bias: "Positive" studies more likely to be published
- Bias in reporting:
  - Negative endpoints may not be reported
  - Secondary endpoints may be summarized without giving data

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A potential problem with systematic reviews and meta-analysis is publication bias. We are only able to summarize and analyze information that we are able to retrieve. Therefore, if negative trials, meaning, those in which no association or no difference is found, or results do not support the investigators' hypotheses, are not published, our review will not reflect those results. As another example, while primary endpoints from a trial may be reported, secondary endpoints may presented in less detail or not at all depending on the results relative to the initial hypotheses.

Steps

- Well-defined question
  - Which treatments and patients will be investigated?
  - Specify inclusion and exclusion criteria
    - Patient population (disease of interest, age, comorbidities, etc.)
    - Treatment
    - Study design (clinical trials, comparison arms, etc.)
    - Report data of interest
    - Report original research findings (not reviews, etc.)

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The systematic review is driven by the question of interest. The question should indicate, at a minimum, the patient population of interest, which may be defined by disease status, the intervention and control or comparison. Then, inclusion and exclusion criteria are developed around the question of interest and will be used to screen identified articles for inclusion in the systematic review.

Steps (continued)

- Define search terms
  - Help from a librarian!
- Identify sources
  - Published literature: Medline, Embase, Cochrane reviews
  - Clinical trial registries
  - Professional meeting abstracts
  - Industry
  - Bibliographies of identified manuscripts
- Implement search and track results

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In order for the search to be exhaustive, specialized skills are needed for the literature search. You should enlist the assistance of a professional librarian who is familiar with medical literature databases and the process by which medical literature is indexed. Note that when specifying search terms, you cannot rely solely on MeSH heading terms, but also need to include searches for terms in more general locations including titles, the abstract, and other headings.

To be exhaustive, the search must include multiple sources of publications including publication databases, clinical trial registries, professional meeting abstracts, and other sources.

When searching the literature, it is important to track our results and to report the flow of identified manuscripts from identification to inclusion in the analysis.

Example: Enteral tube feeding for older people with advanced dementia

Objective:

- To evaluate the outcome of enteral tube nutrition for older people with advanced dementia who develop problems with eating and swallowing and/or have poor nutritional intake.

Reference: Enteral tube feeding for older people with advanced dementia (Review), 2009 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.

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Throughout this module, we will refer to an example of a systematic review and meta-analysis focused on the evaluation of outcomes of enteral tube nutrition for older people with advanced dementia who develop problems with eating and swallowing and/or have poor nutritional intake. This was a systematic review and meta-analysis that was conducted through the Cochrane Collaboration, which is a non-profit organization focused on gathering and summarizing evidence related to healthcare interventions. The Cochrane Collaboration is known for high quality systematic review and meta-analyses.

Example: selection criteria

- Randomized controlled trials (RCTs), controlled clinical trials, controlled before and after studies and interrupted time series studies that evaluated the effectiveness of enteral feeding via a nasogastric tube or via a tube passed by percutaneous endoscopic gastrostomy(PEG) were planned to be included.
- In addition, controlled observational studies were included.
- The study population comprised adults aged 50 and over (either sex), with a diagnosis of primary degenerative dementia made according to validated diagnostic criteria such as DSM-IV or ICD-10 (APA 1994; WHO 1993) and with advanced cognitive impairment defined by a recognized and validated tool or by clinical assessment and had poor nutrition intake and/or develop problems with eating and swallowing.
- Where data were limited we also considered studies in which the majority of participants had dementia.

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After defining the question of interest, the investigators then need to define inclusion and exclusion criteria to determine which studies are eligible to be included in the review and which are not.

In this specific example, we see that the investigators were interested in particular study designs, including randomized controlled trials. They also clearly defined the patient population of interest.

Example: search terms

- What search terms would you propose?
  - See table 1 (pages 5-9) from Cochrane Review
  - Search terms related to dementia, artificial feeding, and study design
  - MESH headings: defined and classified by US National Library of Medicine
  - .mp. field (title, original title, abstract, name of substance word, subject heading word)

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Now, given the question of interest and the eligibility criteria, what search terms should be specified? Again the search terms should result in a comprehensive, exhaustive search of the literature.   We want to identify all publications that are related to a given question of interest.

When you review the search terms, you will note that there are multiple terms for each construct: patient population, treatment, and study design.

Note that search terms are of two main types, (1) MESH headings, which are main categories that are defined and classified by US National Library of Medicine and (2) .mp fields, which are more general terms that are captured through the search engine such as OVID or PubMed.

Example: Sources

- Many sources are required
  - Published literature: Medline, Embase, Cochrane reviews
  - Clinical trial registries
  - Professional meeting abstracts
  - Industry
  - Bibliographies of identified manuscripts
- Cochrane review pages 9-11

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After identifying the search terms, the investigators then implemented the search using multiple literature databases, such as Medline and Embase, and other sources such as clinical trial registries and professional meeting abstracts.

Refer to pages 9-11 of the Cochrane review to see an example of a thorough literature search.

Steps (continued)

- Review titles and abstracts for inclusion and identify papers that must be reviewed in full
- Process performed by at least 2 investigators to avoid bias

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Frequently, an exhaustive search results in hundreds of potentially eligible papers. While the search terms could be made more restrictive, you would increase your chance of missing relevant literature. We typically use a 2-stage screening approach where we first screen the titles and abstracts relative to our inclusion and exclusion criteria. Any paper that clearly does not satisfy the eligibility criteria will be excluded from the review. Any paper that either meets the eligibility criteria or if it is unclear if the criteria are met, due to lack of methodological detail, will be reviewed in full. The process should be conducted by at least 2 investigators, with discussion or consensus review by a third reviewer if differences cannot be resolved.
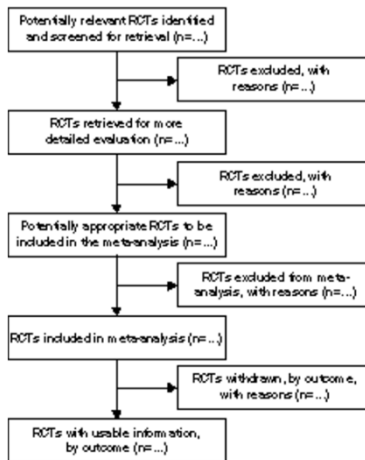
While screening the papers for inclusion, you should track the flow of the eligible papers. A set of guidelines for reporting of systematic reviews and meta-analyses have been developed. PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

In summarizing the selection of papers, you will identify the number of papers per source, the number of unique papers, the number of eligible papers, and the reasons for exclusion.

Steps (continued)

- Careful data collection
  - Multiple reviewers to extract data
    - Patient population
    - Treatments
    - Follow-up: length, completeness
    - Design: blinding, randomization
    - Study quality: potential for bias
    - Outcomes: data, assessment methods/definitions
      - Ideally simple, unambiguous outcome variables

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You will begin the data abstraction process by developing a general data capture form. The form must be general in the sense that the data of interest will be reported in varying ways across the studies. Not all papers will report information about all data points of interest. As an example, if tracking infection rates, comparisons between an intervention and control arm may be presented as a difference in proportions, a rate ratio, an odds ratio, or a hazard ratio. It is best to record all available data and then after data abstraction is complete, determine how best to summarize the information.

Is a formal Meta-analysis appropriate?

- In some cases, a formal, meta-analysis may be inappropriate or misleading:
  - Differences in patient populations, treatment or control approaches, study conduct
- A systematic review, without a formal meta-analysis, is performed
- Results from studies individually presented
- Example: Patel et al., Am J Cardiol, 2009

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Before continuing from a systematic review to a formal meta-analysis, we need to consider whether the pooled analysis will result in meaningful estimates. If there are notable differences in patient populations, intervention or control approaches, study conduct or methods, it may not be appropriate to derive a pooled estimate. The pooled estimate, in such cases, would not correspond to a well defined clinical setting or intervention. In such cases, a descriptive, study-level summary would be more appropriate instead of a formal meta-analysis.

Formal Meta-analysis

- Analysis
    - Combine estimates across studies
        - **Fixed effects method**: Peto-Yusuf (Cochran-Mantel-Haenszel)
            - Assume all studies are estimating the same true (but unknown) fixed effect of an intervention
            - The true effect of treatment is the same value in each study
            - Differences in the treatment effect across studies is due solely to chance

When pooling intervention effects, there are two main methods of analysis: a fixed effects method and a random effects method. Under the fixed effects method, we assume that all studies are estimating the same true (but unknown) fixed effect of an intervention. Also, we assume that the true effect of treatment is the same value in each study and that differences in the treatment effect across studies are due solely to chance variation.

Formal Meta-analysis

- Analysis
  - Combine estimates across studies
    - **Random effects method**: Der Simonian and Laird
      - Assume that the studies are inherently different
      - The treatment effects for the individual studies are assumed to vary around some overall average treatment effect
      - The treatment effects are assumed to be normally distributed with a mean and variance, where the variance is assumed to be non-zero for random effects models
      - Confidence intervals for pooled estimates from random effects analyses will typically be wider than from fixed effects analyses

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In contrast, with a random effects analysis method, we assume that the studies are inherently different and the analysis method account for study-to-study variation. Under a random effects analysis approach, we assume that the treatment effects for the individual studies vary around some overall average treatment effect. The treatment effects are assumed to be normally distributed with a mean and variance, where the variance is assumed to be non-zero for random effects models.

Note that as a result of allowing for study-to-study variation, given the extra source of variance included in the estimation, confidence intervals for pooled estimates from random effects analyses will typically be wider than from fixed effects analyses.

Formal Meta-analysis

- Investigate heterogeneity
  - Breslow-Day test
  - Q statistic: a formal test of homogeneity (Egger 2001)
    - Often under-powered
  - I-squared index and corresponding 95% confidence interval: used to summarize the proportion of the total variability in effect sizes due to between-study variation (Huedo-Medina et al. 2006).
  - Meta-regression
  - Subgroup/sensitivity/influence analyses

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The final set of analysis methods relate to formal approaches for investigating heterogeneity. These methods can be used to determine whether a fixed effects modeling approach is reasonable or if a random effects modeling approach, which allows for study-to-study variation, should be used. Common methods include the Breslow-Day test of homogeneity for odds ratios, the Q statistic, and the I-squared index. In addition, meta-regression can be used to determine how intervention effects differ depending on study-level characteristics, such as the proportion of male participants or the proportion of patients with severe disease. Finally, subgroup, sensitivity, and influence analyses can be performed to understand heterogeneity and the influence of a given study or set of studies on the results.

Statistical Methods References

- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-88.
- M Egger, G Davey Smith, Doug Altman (eds). *Systematic Reviews in Health Care. Meta-analysis in Context*. London: BMJ Books, 2001
- Huedo-Medina, T.B., Sa´nchez-Meca, J., Marı´n-Martı´nez, F., and Botella, J. Assessing Heterogeneity in Meta-Analysis: *Q* Statistic or *I*2 Index? *Psychological Methods* 2006, Vol. 11, No. 2, 193–206.
- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22(4):719-48.

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This slide includes citations for some key references in meta-analysis and systematic review. The edited book Systematic Reviews in Health Care. Meta-analysis in Context provides an excellent overview of related methods.

Data Summaries

- Tables of study characteristics and results
- Graphical summaries
  - Forest plot: summarize individual and pooled estimates
  - Funnel plot: assess potential for publication bias
- Analyses of data quality
  - Jadad score
  - Descriptive summaries of potential for bias

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Commonly reported data summaries include tables of study design characteristics, patient characteristics, and results; a table 1 of all meta-analyses and systematic reviews. Next, you will find Forest plots that display the individual study results and overall pooled estimates for meta-analyses. Funnel plots can be used to assess the potential for publication bias. Finally, papers typically include a summary of study quality, either reported in terms of a numeric quality score for each study or a descriptive summary of factors associated with potential bias and rigor.

Resources and References

The following slides include a listing of useful references and guideline documents. It is helpful to review these guidelines prior to initiating a systematic review or meta-analysis to ensure that your methodology is sound and that you are tracking all of the information required for complete reporting.

Methods Reference

Systematic Reviews in Health Care: Meta-analysis in context.

Edited by Egger, M. Smith, G.D., Altman, D.G., London: BMJ Books, 2nd edition, 2001.

The Systematic Reviews in Health Care: Meta-analysis in Context book provides a very nice overview of systematic review and meta-analysis.

Cochrane Collaboration

- http://www.cochrane.org/
  - Cochrane reviews
  - Cochrane handbook for systematic reviews of interventions: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

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The Cochrane collaboration is an excellent resource for guidelines and best practices in terms of systematic review and meta-analysis methodology. The collaboration also publishes topic-specific systematic reviews and meta-analyses. This is a good place to check before initiating a project of your own to ensure that your project has not already been completed.

Guidelines: Meta-analysis of clinical trials

- PRISMA guidelines (replace QUORUM guidelines)
- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. Ann Intern Med, 151(4);
- http://www.prisma-statement.org/statement.htm

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The PRISMA guidelines should be followed when reporting systematic reviews and meta-analyses of clinical trials. The paper and website include useful checklists and example flow diagrams that should accompany publications of meta-analyses and systematic reviews.

Guidelines: Meta-analysis of observational studies

- 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 Apr 19;283(15):2008-12.

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The MOOSE guidelines reflect best practices for meta-analysis of observational studies.

Guidelines: Meta-analysis of diagnostic accuracy studies

- Health Technol Assess. 2004 Jun;8(25):iii, 1-234. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003 Nov 10;3:25.

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QUADAS reflects best practices in systematic review and meta-analysis of diagnostic accuracy studies.

Guidelines: Meta-analysis of Individual Participant Data

- Riley RD, Lambert PC, bo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221. PMID: [20139215](20139215)

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Finally, recent work has focused on meta-analysis of individual participant data across multiple studies.

Summary

- Systematic reviews are exhaustive searches addressing focused questions
- Search methods are designed to limit bias
- Procedures and results should be reproducible
- Meta-analysis is a formal statistical approach for deriving pooled estimates of associations and sources of variability

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In summary, there are important features of systematic reviews that distinguish them from more descriptive, narrative summaries. Systematic reviews are based on exhaustive searches of available literature and follow search methods that limit bias and are reproducible. Finally, when treatment approaches and patient populations are fairly consistent, it may be appropriate to derive overall, pooled estimates using meta-analysis methods. In the next module, we will discuss an example of a meta-analysis and focus on interpretation of the results.