

## Conducting a Systematic Review and Meta-Analysis: A Project Course

Systematic reviews and meta-analyses are considered by many investigators to be the highest level of evidence for answering clinical questions. Well-conducted, methodologically rigorous systematic reviews can resolve uncertainties about therapeutic or diagnostic interventions and be helpful for the practicing physician. Despite this, researchers, intimidated by the numerous steps and the complex statistics involved in conducting a systematic review and meta-analysis, may be reluctant to undertake this type of study. In this course, we aim to help investigators perform a comprehensive systematic review and meta-analysis by providing: 1) assistance in the formulation of the research protocol; 2) access to research librarians and other resources essential for conducting a comprehensive literature search; 3) collaboration with statisticians experienced in meta-analysis; 4) assistance in interpretation of results and manuscript development; and 5) mentoring from a team of physicians and research scientists experienced in systematic reviews and meta-analysis. Participants in this course will perform a systematic review and meta-analysis in their area of interest, with the goal of publishing a manuscript in a timely fashion.

### ***Course Instructors:***

- Mentors: Smita Nayak, Jim Bost, Meg Cunnane
- Research librarian: Charles Wessel
- Statisticians: Jim Bost, DC Statistician

### ***Course Information:***

2.0 credits, project course, anticipated duration 12-15 months

### ***Course Objectives:***

By the end of this course, participants will have:

1. Developed a systematic review/meta-analysis research protocol
2. Implemented the research protocol
3. Interpreted the research results
4. Drafted a manuscript for publication

### ***Course Pre-requisites:***

Prior to enrolling, investigators must:

1. Demonstrate understanding of the methodology of systematic reviews and meta-analyses by:
  - a. Taking the “Introduction to Systematic Reviews and Meta-Analysis” course offered through the CRTP *or*
  - b. Reading the required textbook: Egger M, Davey Smith g, Altman A (eds). Systematic Reviews in Health Care: Meta-analysis in Context. 2<sup>nd</sup> Edition. BMJ books. London, England, 2001.
2. Form a core investigative team, consisting of two primary researchers and a content expert
  - a. The two primary researchers (or one primary researcher and an additional data abstractor) will be responsible for writing the research protocol, conducting the systematic review and meta-analysis, and writing the manuscript.
  - b. The content expert will be a clinician or investigator who is very familiar with the research topic and the current literature that has been published on that topic – this person should be available to answer content-related questions as needed.
3. Formulate a specific clinical question that can be answered with a systematic review and meta-analysis (this may require a preliminary literature search to ensure there are multiple studies concerning the question of interest.)
4. Be willing to complete an evaluation of the course at the completion of their participation.

### Course Structure and Schedule

The goal of this course is to help investigators develop, implement, and publish a systematic review and meta-analysis. The course will be divided into “blocks” dedicated to the components of these tasks. During the first block, each investigative group will meet individually with the team mentors and the research librarian to develop the research protocol. This research protocol will be reviewed, revised as appropriate, and approved by the team mentors and research librarian prior to study commencement. During the second block, the investigators will perform the systematic review outlined in the research protocol. Communication between the team mentors and the study investigators will occur largely over email (during “office hours”) in this block, with individual meetings scheduled on an as-needed basis. The third block will be devoted to the meta-analysis. At the beginning of this block, study investigators will meet with team mentors to review the meta-analysis methods outlined in the research protocol. Results of the analysis will be communicated via email or meetings, as needed. The last block will focus on interpretation of results and manuscript development. The research investigators will meet with the team mentors and the research librarian to develop the manuscript outline and discuss issues relevant to presentation of results. Investigators will submit drafts to the team mentors and research librarian for review and feedback via email, with meetings scheduled as necessary. We estimate that the entire course will last 1 to 1.5 years.

**Group meetings with team mentors**  
 Email communications: feedback and trouble-shooting

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
<b>Block 1: Develop the research protocol</b>												
<i>Develop systematic review protocol</i>												
<i>Develop systematic review protocol (cont'd); determine meta-analytic methods</i>												
<i>Submit protocol</i>												
<b>Block 2: Perform the systematic review</b>												
<b>Block 3: Perform the meta-analysis</b>												
<b>Block 4: Interpret the results, develop the manuscript</b>												

*Meeting Schedule and Faculty Responsibilities*

Course Topic	Faculty
<b>Block 1: Develop the research protocol</b>	
<i>Month 1: Meeting #1</i>	Team mentors: Meg, Smita, Jim
Developing the systematic review protocol	Research librarian: Charlie Wessel
<i>Month 1: Meeting #2</i>	Team mentors: Meg, Smita, Jim
Developing the systematic review protocol (continued)	Research librarian: Charlie Wessel
<i>Month 2: Meeting #3</i>	Team mentors: Meg, Smita, Jim
Developing/revising the systematic review/meta-analysis protocol	DC Statistician
<i>Month 2: Meeting #4</i>	Team mentors: Meg, Smita, Jim
Reviewing the protocol	
<i>Months 2-3: Email communications</i>	Team mentors: Meg, Smita, Jim
Finalizing the protocol - submit protocol for review by team mentors	Research librarian: Charlie Wessel
<b>Block 2: Perform the systematic review</b>	
<i>Months 3 – 8: Email communications during “office hours”</i>	Team mentors: Meg, Smita
Trouble-shooting	
<i>Meetings as necessary</i>	Team mentors: Meg, Smita
	Research librarian: Charlie Wessel
<b>Block 3: Perform the meta-analysis</b>	
<i>Month 9: Meeting #5</i>	Team mentors: Meg, Smita, Jim
Review the retrieved literature, abstracted data, and meta-analysis protocol	DC Statistician
<i>Month 9: Meeting #6</i>	Team mentors: Meg, Smita, Jim
Review results of analysis, discuss further analysis	DC Statistician
<i>Months 9-10: Email communications</i>	Team mentor: Jim
Reviewing and interpreting the results	DC Statistician
<b>Block 4: Develop the manuscript</b>	
<i>Month 11 Meeting #7</i>	Team mentors: Meg, Smita, Jim
Outline the manuscript draft	
<i>Months 11-12: Email communications</i>	Team mentors: Meg, Smita
Reviewing and revising the manuscript draft	

Block I	Discussion Topics
<b>Meeting I Developing the Systematic Review Protocol</b> <b>Faculty: Smita, Jim, Meg, Charlie Time: 2 hours</b>	
<i>Development of the Research Protocol</i>	
➤ Review of essential steps in study design	Importance of the research protocol
➤ Refinement of clinical question	PICO format
➤ Definition of eligibility criteria <ul style="list-style-type: none"> <li>▪ Participants, interventions, comparisons, outcomes</li> <li>▪ Study designs, methodological quality</li> </ul>	Defining inclusion/exclusion criteria Creating an inclusion/exclusion criteria form ➤ Example inclusion/exclusion criteria form
➤ Development of search strategy <ul style="list-style-type: none"> <li>▪ Databases to be searched (CCTR and other databases of interest)</li> <li>▪ Methods for identifying ongoing/unpublished studies and grey literature</li> <li>▪ MEDLINE search strategy</li> </ul>	Research librarian to review various databases, pros/cons of each Discuss ways of finding grey literature ➤ Example MEDLINE search strategy
➤ Study selection strategy <ul style="list-style-type: none"> <li>▪ Identifying relevant articles (one or two investigators, title/abstract v. full text)</li> <li>▪ Method for keeping track of excluded studies</li> <li>▪ Strategy for resolving disagreements</li> </ul>	Using inclusion/exclusion criteria form to select studies Strategies for resolving disagreements Recordkeeping of excluded studies ➤ Example “excluded study” form
➤ Assessment of study quality <ul style="list-style-type: none"> <li>▪ Quality scale v. assessment of key components</li> <li>▪ One or two investigators</li> <li>▪ Blinding of investigators to journal, authors</li> </ul>	Discussion of pros/cons of quality scales and key component assessments Pros/cons and methods for blinding ➤ Example quality assessment scale
➤ Data extraction <ul style="list-style-type: none"> <li>▪ Designing data extraction form</li> <li>▪ Piloting data extraction form</li> <li>▪ One or two investigators</li> <li>▪ Consider blinding</li> </ul>	Developing the data extraction form Piloting the data extraction form Methods for blinding, resolving disagreements ➤ Example data extraction form

➤ *“Tools” provided to team investigators (can be modified for use in their own study protocol)*

**Assignment:** The investigative team will define the clinical question, inclusion/exclusion criteria, search strategy, and methods for quality assessment; they will develop and pilot a data extraction form. The team will write a draft systematic review protocol and bring this written draft to meeting #2 for review.

Block I	Tasks Accomplished
<b>Meeting II Developing the Systematic Review Protocol</b> <b>Faculty: Smita, Jim, Meg, Charlie Time: 1- 2 hours</b>	
<i>Development of the Research Protocol</i>	
➤ Review of clinical question	Focused, important question
➤ Review of eligibility criteria	Defined inclusion/exclusion criteria Inclusion/exclusion criteria form
➤ Review of search strategy	Clearly articulated search strategy Timeline for search
➤ Review of study selection strategy	Methods for identifying relevant articles “Excluded study” form Strategy for resolving disagreements
➤ Review of methods for assessing study quality	Methods for assessing quality Quality assessment form Strategy for resolving disagreements

**Assignment:** The investigative team will refine the written systematic review protocol based on feedback from the team mentors and research librarian.

Block I	Discussion Topics
<b>Meeting III Developing the Systematic Review Protocol, Determining Meta-Analytic Methods</b> <b>Faculty: Smita, Jim, Meg, DC Statistician      Time: 2 hours</b>	
<i>Development of the Research Protocol</i>	
➤ Choice of outcome measure	Pros/cons of various outcome measures Outcome measure appropriate for question
➤ Methods for assessing heterogeneity	Discussion of graphical, statistical methods
➤ Possible sources of heterogeneity	Discuss possible sources of heterogeneity for this question Strategies for handling heterogeneity
➤ Choice of method for estimating combined effect <ul style="list-style-type: none"> <li>▪ Fixed effects</li> <li>▪ Random effects</li> </ul>	Discussion of pros/cons of each
➤ Sensitivity analysis to investigate influence, robustness, and bias <ul style="list-style-type: none"> <li>▪ To methodological quality</li> <li>▪ To length of follow-up</li> <li>▪ To possible publication bias</li> <li>▪ Other considerations?</li> </ul>	Methods for assessing publication bias Strategies for performing sensitivity analysis
➤ Subgroup analysis	<i>A priori</i> determination of subgroups and plans for analysis

**Assignment:** The investigative team will define the outcome measure, possible sources of heterogeneity, and subgroups of interest. The team will draft a written meta-analysis protocol and bring this draft to meeting #4 for review.

Block I	Tasks Accomplished
<b>Meeting IV Developing the Systematic Review Protocol, Determining Meta-Analytic Methods</b> <b>Faculty: Smita, Jim, Meg, DC Statistician Time: 2 hours</b>	
<i>Development of the Research Protocol – Part II</i>	
➤ Review of outcome measure	Outcome measure appropriate for research question
➤ Review of methods for assessing heterogeneity	Statistical method for assessing heterogeneity
➤ Possible sources of heterogeneity	Strategy for handling heterogeneity if identified
➤ Choice of method for estimating combined effect	Fixed effect v. Random effect model
➤ Sensitivity analysis to investigate influence, robustness, and bias	Methods for assessing publication bias Strategies for performing sensitivity analysis
➤ Subgroup analysis	Identified subgroups

**Assignment:** The investigative team will refine the systematic review and meta-analysis protocol based on feedback from the team mentors and faculty. The team will then submit the completed protocol via email to the team mentors for review and approval.

### Block III

#### Meeting V Review of Systematic Review Results and Meta-Analysis Protocol

**Faculty:** Smita, Jim, Meg, DC Statistician      **Time:** 2 hours

##### *Discussion topics*

- Review of identified and excluded studies, recordkeeping
- Review of extracted data
- Review meta-analysis protocol
  - Discuss possible heterogeneity
  - Discuss timeline

**Assignment:** The investigative team will work with the primary statistician to review summary statistics, heterogeneity, publication bias, and the results of sensitivity analysis and subgroup analysis prior to meeting #6.

### Block III

#### Meeting VI Review and Interpretation of Meta-Analysis Results

**Faculty:** Smita, Jim, Meg, DC Statistician      **Time:** 1-2 hours

##### *Discussion topics*

- Review results of meta-analysis
- Consider strength of results
- Discuss limitations of results, including publication bias
- Discuss applicability of results
- Consider numbers-needed-to-treat to benefit/harm

**Assignment:** The investigative team will review and interpret the strength and applicability of results, and consider implications for future research.

## Block IV

### Meeting VII Developing the Manuscript Outline

**Faculty:** Smita, Jim, Meg, Charlie Wessel

**Time:** 1-2 hours

#### *Discussion topics*

- Discussion of typical format for systematic review/meta-analysis manuscript, reporting recommendations (as per QUORUM, MOOSE guidelines)
- Division of writing responsibilities
- Development of timeline for writing
- Review of Jim's role, Charlie's role in writing sections of manuscript

**Assignment:** The investigative team will begin writing a draft of the manuscript, and will submit it to the team mentors and research librarian for comments and feedback.