CLRES 2010 Clinical Research Methods

<table>
<thead>
<tr>
<th>Course Information</th>
<th>Instructors</th>
<th>TAs</th>
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<tbody>
<tr>
<td>Term: Summer</td>
<td>TBD</td>
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<tr>
<td>Location: Parkvale 305</td>
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<td>Credits: 3</td>
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Class Meetings
Group A: M,W,F
Group B: M,W,F

Recitations

Course Description
Clinical Research Methods (CLRES 2010) covers fundamental concepts and basic analytic methods pertaining to design, analysis, and interpretation of clinical research studies. The course is broadly divided into three major analytic areas: (1) basic epidemiology and observational methods, (2) interventional and randomized controlled trials, and (3) clinical epidemiology and evidence-based medicine. Each section of the course includes 5-8 modules and culminates in an examination.

Section 1 covers concepts of associations and outcomes; introduces standard epidemiological concepts of incidence and prevalence; defines and describes relative risk, absolute risk, and attributable risk, as well as and the various methods for calculating these quantities in different observational research designs. Definitions of and methods for reducing bias and confounding are major components of this section.

Section 2 introduces interventional trials, the importance and effects of randomization, and the analysis and interpretation of controlled trials. Methods for comparing results across trials, as well as an introduction to non-standard trial designs, are also provided.

Section 3 describes the concepts of clinical epidemiology, including evidence-based medicine, the interpretation of diagnostic tests, the construction and use of clinical prediction rules, and the evaluation of screening for chronic disease.

Course Format
This course will be in a hybrid – or flipped – format. Rather than attending lectures in person, you will complete designated readings, video lectures, and assignments on your own time, and then come to class to discuss and apply what you’ve learned. The hybrid format allows you to:

- Engage with the content at your own pace and on your own schedule
- Rewind, rewatch, or jump ahead as necessary
- Use class time for interaction and clarification
- Spend less total time in class
The hybrid format also requires you to take more responsibility for your own learning, so please be proactive about seeking help if you have questions or are confused.

**Required Materials**

**Optional Materials**


**Course schedule**
This class is split into two groups for class sessions and recitations. Check CourseWeb to find your group. Although this course is scheduled to meet 3 times per week, 1 session per week can be completed remotely and does not require you to be physically present. You are also encouraged to check courseweb for a detailed week-by-week schedule.

**Weekly Responsibilities**
Each week, you will be responsible for completing three online modules (video lectures, readings, and quiz) and attending two class sessions.

Please complete the designated online material before coming to class, and arrive fully prepared to discuss and apply what you’ve learned. Feel free to attend the optional weekly recitation session, where your TA can answer any questions you have.

**Suggested Weekly Workflow**
Managing time in a hybrid course can be challenging. While it’s up to you how you distribute your work during the week, we suggest the following workflow:

<table>
<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
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<tbody>
<tr>
<td>Do assigned</td>
<td>Watch videos; do</td>
<td>Do assigned</td>
<td>Watch videos; do</td>
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<td>Do assignments</td>
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<td>tasks; prepare</td>
<td>readings; take</td>
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<tr>
<td>Come to class*</td>
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</table>

* Come to class*
Course Requirements

Attendance:  Class attendance and participation are required. Recitation sessions are optional.

Readings:  We will use both text and primary literature as reference materials for the course. All reading assignments should be completed prior to the class for which they are assigned. You should also complete the self-study questions at the end of each reading assignment from the textbook.

Videos:  All online lecture videos should be viewed prior to the class sessions associated with that module.

Quizzes:  Each set of online lectures will be accompanied by a brief quiz. Your quiz scores, totaled together, will count as one additional assignment per course section.

Assignments:  There will be 5 graded assignments for the course. *All assignments are due at 5 p.m. on the day indicated in the syllabus and should be turned in via CourseWeb.* While group work is encouraged for in-class group exercises, all out-of-class assignments should be completed independently.

Exams:  There will be one exam for each section of the course (3 total).

Grading

Evaluation will be based on the exams, written homework assignments, class participation, and attendance. Each section will contribute to one-third of the course grade. The point distribution within each section is described below:

- Class participation and attendance  10%
- Assignments  30%
- Exams  60%

For the computation of the final course grade, the following grading scale will be used:

- 90-95: A  80-85: B  70-75: C  60-65: D

Help

Please don’t hesitate to contact your TA via email if you have any questions about course content. You can generally expect an answer within 24 hours, if not sooner.
If you have any questions about scheduling or technology (CourseWeb, GoToMeeting, the sign-in system for attendance, etc.) please contact the course administrator, Juliana Tambellini at: Tambellinijm2@upmc.edu.

Course Policies
You are responsible for knowing and following these course policies. Please read them carefully.

Attendance Policy
Students are expected to sign-in to each in-person session (computer provided in suite lobby). If a problem is encountered with the sign-in system, please contact the course instructor(s) as well as Juliana Tambellini (tambellinijm2@upmc.edu) immediately.

Academic Integrity
Students in this course are expected to comply with the University of Pittsburgh’s Policy on Academic Integrity detailed here: http://www.provost.pitt.edu/info/ai1.html. Any student suspected of violating this obligation for any reason during the semester will be required to participate in the procedural process, initiated at the instructor level, as outlined in the University Guidelines on Academic Integrity. This may include, but is not limited to, the confiscation of the examination of any individual suspected of violating University Policy. Furthermore, no student may bring any unauthorized materials to an exam, including dictionaries and programmable calculators.

Recording Policy
ICRE Produced Recordings: ICRE faculty and/or staff may video and/or audio record this course (hereby referred to as "Recordings"). By enrolling in this course, you hereby give the University of Pittsburgh and the Institute for Clinical Research Education, through its faculty, employees, agents, licenses or assigns, the irrevocable and worldwide right to use your name, voice, likeness and/or image in all forms and media (to include internet websites and online course website). You waive your right to inspect or approve the finished version(s) of the Recordings, including any copy that may be created in connection therewith. You understand that you will not be paid for your participation in the Recording and that you are not entitled to your own copy of the Recording. You understand that the University of Pittsburgh is not responsible for any unauthorized use of the Recording. You have read this syllabus and have no questions about the contents and are an adult over the age of 18.

Student Produced Recordings: To ensure the free and open discussion of ideas, students may not record classroom lectures, discussion and/or activities without the advance written permission of the instructor, and any such recording properly approved in advance can be used solely for the student's own private use.

Disabilities
If you have a disability for which you are requesting an accommodation, you are encouraged to contact both your instructor and the Office of Disability Resources and Services, 216 William Pitt Union, 412-648-7890 / 412-3837355 (TTY), as early as possible in the term. Disability Resources and Services will verify your disability and determine reasonable accommodations for this course.
### Competencies addressed in this course:

#### Section I

<table>
<thead>
<tr>
<th>Competency</th>
<th>M 1</th>
<th>M 2</th>
<th>M 3</th>
<th>M 4</th>
<th>M 5</th>
<th>M 6</th>
<th>M 7</th>
<th>M 8</th>
<th>M 9</th>
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<tbody>
<tr>
<td>Research Design/Problem Formation: Propose significant and novel empirical, testable, hypothesis-driven research questions using, where appropriate, different disciplines and community engagement.</td>
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<td>Data Analysis/Applied Analytic Techniques: Describe appropriate data analysis plans for addressing specific research questions.</td>
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<td>Research Design/Methodology: Recognize the impact of diverse populations and local demography on research designs, and modify research design accordingly.</td>
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<tr>
<td>Teamwork and Leadership/Multidisciplinary Teamwork: Demonstrate behaviors that allow them to be an effective member of a multidisciplinary team, including generating multiple points of view, contributing to the development of new ideas, and demonstrating conflict management skills.</td>
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<tr>
<td>Professional Skills/Oral Communication: Prepare and deliver oral research presentations at a variety of stages to a range of audiences, and respond to constructive criticism and questions.</td>
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<tr>
<td>Professional Skills/Oral Communication: Prepare critiques of oral presentations.</td>
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<thead>
<tr>
<th>Competency</th>
<th>M10</th>
<th>M11</th>
<th>M12</th>
<th>M13</th>
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<tbody>
<tr>
<td>Research Design/Measurement: Identify basic reliability and validity issues of measuring instruments.</td>
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<tr>
<th>Competency</th>
<th>M14</th>
<th>M15</th>
<th>M16</th>
<th>M17</th>
<th>M18</th>
<th>M19</th>
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</table>
Module 1: Introduction to Clinical Research Methods

At the conclusion of this module, you should be able to:

- Describe what is meant by “Clinical Epidemiology.”
- Construct specific research questions that clearly identify a population, an exposure or intervention, and an outcome.
- Explain what “association” means, and the difference between statistical error, epidemiological bias, and true cause-effect relationship.
- Identify criteria used to evaluate a cause-effect relationship, and apply those criteria to specific examples.

Before coming to class:

<table>
<thead>
<tr>
<th>Watch</th>
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<tbody>
<tr>
<td>Course Mechanics</td>
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<tr>
<td>Introduction to Clinical Research</td>
</tr>
<tr>
<td>Choosing a Research Question</td>
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<tr>
<td>Associations and Causality</td>
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<tr>
<td>The Process of Clinical Research</td>
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<tr>
<td>Study Designs and Hierarchy of Evidence</td>
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</table>

Read

- Gordis textbook: Chapters 1 (Introduction) and 14 (From Association to Causation: Deriving Inferences from Epidemiologic Studies). Do associated problems and check your own work.

Do

- Be sure to take notes on lecture videos and readings, write down any questions you have, and bring your notes and questions to class. Do this throughout the course!

Module 2: Quantitative Concepts in Epidemiology

At the conclusion of this module, you should be able to:

- Explain the difference between prevalence and incidence, including the relationship of each based on duration of illness.
- Understand the complexities of these measures, including issues related to the numerator and the denominator.
- Calculate incidence rates and prevalence given data tables with information of disease counts, population, and time.
- Calculate and interpret various measures of mortality.
- Understand the difference between crude and adjusted rates.
- Describe and apply the concept of a case definition.
- Recognize and differentiate different types of surveillance
- Set up and interpret a 2x2 table.
Before coming to class:

Watch
- Surveillance
- Introduction to Incidence and Prevalence
- More in Incidence and Prevalence
- Measures of Mortality
- Age-Adjusted Rates

Read
- Gordis textbook: Chapter 3 (*The Occurrence of Disease: I. Disease Surveillance and Measures of Morbidity*) and 4 (*The Occurrence of Disease: II. Mortality and Other Measures of Disease Impact*). Do associated problems and check your own work.

In-class exercise: 2x2 tables

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**Module 3: Research Study Design: Case Series and Cross-Sectional Studies**

At the conclusion of this module, you should be able to:
- Describe research questions that would be appropriate for a case-series study.
- Identify the most important potential sources of bias in a case-series design, and discuss methods to reduce these biases in the design phase of the study.
- Describe research questions that would be appropriate for a cross-sectional study.
- Identify the most important potential sources of bias in a cross-sectional study design, and discuss methods to reduce these biases in the design phase of the study.
- Understand strategies to improve accuracy and minimize inconsistencies in medical chart reviews.

Before coming to class:

Watch
- Case Reports and Series
- Cross-Sectional Studies
- Medical Chart Reviews

Read
- Gordis textbook: Chapter 10 (*Case-Control Studies and Other Study Designs*), pages 210-212. Do associated problems and check your own work.

In-class exercise: Design a study: Obesity and Children in Pittsburgh
Module 4: Bias, Confounding, and Interaction

At the conclusion of this module, you should be able to:

- Define bias in general and, more specifically, for different types of selection bias and information bias.
- Identify general strategies to address bias when planning a new research study.
- Define confounding and identify potential confounding variables in the study design phase and the analysis phase.
- Identify the relationships between variables that must be present in order for a variable to be a confounding variable.
- Identify general strategies to deal with confounding.

Watch

- Bias and Precision
- Confounding
- Interaction

Read

- Gordis textbook: Chapter 15 (More on Causal Inferences: Bias, Confounding and Interaction). Do associated problems and check your own work.

Module 5: Research Study Design: Cohort Studies

At the conclusion of this module, you should be able to:

- Describe key features that distinguish a cohort study from other types of observational studies.
- Describe advantages and disadvantages of a cohort study design compared with other observational study designs.
- Identify various sub-types of cohort studies.
- Apply knowledge of cohort design issues to plan a study or evaluate a published cohort study.

Before coming to class:

Watch

- Introduction to Cohort Studies
- Advantages and Disadvantages of Cohort Studies
- Design Issues

Read

- Gordis textbook: Chapter 9 (Cohort Studies). Do associated problems and check your own work.

In-class exercise: Critical review of Mozaffarian article

Module 6: Research Study Design: Case-Control Studies
At the conclusion of this module, you should be able to:

- Describe the key features that distinguish a case-control study from other types of observational research studies, and determine whether a specific study uses a case-control study design.
- Be able to identify several possible sources of “case” and “control” subjects.
- Interpret outcome measures generated from case-control studies (e.g., odds ratio).
- Recognize case-control studies based on defined cohorts, and identify situations in which these designs are appropriate.

Before coming to class:

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>- Advantages of a Case-Control Study Design</td>
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<tr>
<td>- Disadvantages of a Case-Control Study Design</td>
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<td>- Selecting Cases</td>
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<td>- Selecting Controls</td>
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<td>- Special Issues</td>
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<table>
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<tbody>
<tr>
<td>- Gordis textbook: Chapters 10 (Case-control Studies and Other Study Designs) and 13 (A Pause for Review: Comparing Cohort and Case-Control Studies). Do associated problems and check your own work.</td>
</tr>
</tbody>
</table>

Due: Assignment #1 is due at 5:00 p.m. today. Please submit via CourseWeb.

Module 7: Measures of Association I

At the conclusion of this module, you should be able to:

- Define relative risk and absolute risk.
- Recognize the same measures of association when reported in the medical literature or lay press.
- Understand the application of different measures to epidemiologic questions.
- Calculate absolute and relative risk from real-world data.

Before coming to class:

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>- Relative Risk and Absolute Risk</td>
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<td>- Estimating Relative Risk</td>
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<td>- Calculating Relative Risk in a Matched Pairs Study</td>
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<table>
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<tbody>
<tr>
<td>- Gordis textbook: Chapter 11 (<em>Estimating Risk: Is There an Association?</em>). Do associated problems and check your own work.</td>
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</table>

**In-class exercise**: MOA1 Problem Set
Module 8: Measures of Association II

At the conclusion of this module, you should be able to:
- Define measures of association, including attributable risk, population attributable risk, and number needed to treat.
- Recognize the same measures of association when reported in the medical literature or lay press.
- Calculate attributable risk, population attributable risk, and number needed to treat from real-world data.
- Interpret and apply all measures of association covered in the previous 2 sessions in policy and clinical decision making situations.

Before coming to class:

Watch
- Attribution Risk and Preventive Fraction
- Population Attributable Risk and NNT
- Indirect Estimates of AR% and PAR%

Read

In-class exercise: MOA2 Problem Set

Module 9: (Special Topic) Community-Based Participatory Research

At the conclusion of this module, you should be able to:
- Describe the principles of community-based participatory research (CBPR), and examine application of those principles into real-world projects.
- Describe the application and concerns of CBPR from community and academic investigator perspectives.
- Describe the major methodological and logistic challenges to conducting research in community settings.
- Describe application of CBPR principles to good partnerships to achieve positive outcomes and misapplication of CBPR principles that form bad partnerships.

Watch
- CBPR: Concepts and Applications, Part 1
- CBPR: Concepts and Applications, Part 2
- CBPR: Concepts and Applications, Part 3a
- CBPR: Concepts and Applications, Part 3b
- CBPR: Concepts and Applications, Part 4a
- CBPR: Concepts and Applications, Part 4b
• CBPR: Concepts and Applications, Part 5

Read

In-class exercise: MOA role-play/interpretation
Due: Assignment #2 is due at 5:00 p.m. today. Please submit via CourseWeb.

Section 1 Exam

Module 10: RCT I: Principles & Concepts

At the conclusion of this module, you should be able to:
1. Identify advantages and disadvantages of randomized trials, as well as the importance of blinding.
2. Identify the components of high-quality trials (review the CONSORT and SPIRIT statements).
3. Appreciate various trial goals (e.g., efficacy vs. effectiveness, internal and external validity, clinical vs. statistical meaningfulness).

Before coming to class:

Watch
• What is a Clinical Trial?
• Randomization and Blinding
• Special Considerations for Randomized Trials

Read
• Gordis textbook: Chapter 7 (pages 138-154)

Do
1. Visit and become familiar with the following three websites:
2. Select one of the following papers for an online intervention session (and subsequent assignments):
   - Pharmaceutical interventions
   - Surgical interventions
   - Health-system interventions
   - Device interventions

**In-class exercise:** Principles and concepts problem set

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**Module 11: RCT II: Intervention**

**At the conclusion of this module, you should be able to:**
- Define the types of interventions used in clinical trials.
- Appreciate approaches for developing interventions.
- Identify components of a trial protocol.
- Define adherence and retention and identify strategies for improving adherence and retention in clinical trials.
- Appreciate advantages and disadvantages of combined interventions.
- Identify strategies for control-group selection.

**Before coming to class:**

**Watch**
- Introduction to Interventions
- Defining and Developing Interventions
- Trial Protocols
- Adherence and Retention
- Combined Interventions
- Control Groups
- Rules of the Game

**Read**
- Article of your choice for “Intervention” worksheet (see list in previous module).

**Do**
**In-class exercise**: Intervention problem set  
**Due**: Assignment #3 is due at the beginning of class today. Please submit via CourseWeb.

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### Module 12: Meta-Analyses  
**SPECIAL TOPIC**

**At the conclusion of this module, you should be able to:**

1. Define a systematic review.
2. Define a meta-analysis.
3. Describe the process of conducting a systematic review and meta-analysis.
4. Be aware of the Cochrane Collaboration and Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers (EPCs).
5. Describe several key issues related to meta-analysis, and their importance and impact, including:
   a. Estimates of treatment effect
   b. Between-study heterogeneity
   c. Forest plot
   d. Fixed and random effects models
   e. Publication bias
   f. Standards, guidelines, checklists for systematic reviews and meta-analyses.

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**Watch**

- UC Davis Videos 16 and 18 (17 is optional)

**Read**


**Do**

- Look over as you skim Liberati et al, above: PRISMA checklist and flowchart.

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### Module 13: RCT III: Samples and Measures

**At the conclusion of this module, you should be able to:**

- Identify how inclusion and exclusion criteria affect the internal and external validity of a trial.
- Appreciate approaches for conducting power calculations and understanding how clinical and statistical considerations are taken into account in such calculations.
- Identify strategies for successful recruitment.

**Before coming to class:**
Watch
- Selecting Patients for Clinical Trials
- Power Calculations
- Practical Aspects of Recruitment
- More Practical Aspects of Recruitment

Read
- Gordis textbook: Chapter 8

In-class exercise: Samples and measures problem set

Module 14: RCT IV: Outcomes and Analyses

At the conclusion of this module, you should be able to:
- Identify characteristics of good primary and secondary outcome measures for clinical trials.
- Appreciate why composite and surrogate outcome measures are used for clinical trials and limitations of these outcome types.
- Identify types of adverse outcomes in clinical trials and how they are monitored.
- Appreciate types of analyses used in clinical trials (e.g., intention-to-treat, per protocol) and how missing data is handled in analyses.

Before coming to class:

Watch
- Primary and Secondary Outcomes
- Composite Outcomes
- Surrogate Outcomes
- Adverse Events and Trial Monitoring
- Analysis
- Equivalence

Read
- Gordis textbook: Do the exercises for Chapters 7 and 8 (they are after chapter 8) and check your own work.

In-class exercise: Outcomes and analysis problem set

Module 15: Quasi-Experimental Designs

At the conclusion of this module, you should be able to:
- Define, give examples, and describe the advantages and disadvantages of quasi-experimental research designs.
- Introduction to Quasi Experimental Designs
- Pre-Post Studies
- Crossover and N-of-1 Studies

**Read**


**Due:** Assignment #4 is due at 9:00 a.m. today. Please submit via CourseWeb.

**Section 2 Exam**

**Module 17: Introduction and Evidence-Based Medicine I**

At the conclusion of this session, you should be able to:

- Understand the role of evidence-based medicine in clinical practice.
- List the 5 A’s of evidence-based medicine.
- Develop an appropriate research question.
- Search databases for literature and find the evidence.

**Watch**

- Introduction to Evidence-Based Medicine
- PICO Questions and Acquiring Evidence
- Appraisal

**Read**


**Do**

- Develop a preliminary research question based on your own interests.

**In-class exercise:** Computer lab exercise/demonstration

**Module 18: Evidence-Based Medicine II**

At the conclusion of this module, you should be able to:

- Appraise the content of articles.
- Identify the parts of a scientific article.
- Apply evidence to a clinical or research scenario.

**Before coming to class:**
Due: Assignment #5 is due at 5:00 p.m. today. Please submit via CourseWeb.

Module 19: Evaluation of Screening

At the conclusion of this module, you should be able to:
- Identify possible biases in screening studies and how to address them in the design phase.
- Describe how the natural history of disease and the characteristics of available testing may influence screening intervention decisions.
- Identify the strengths and weaknesses of various study design options as they apply to screening studies.

Before coming to class:

Watch
- Effects of Disease and Test Characteristics on Screening Policy Decisions
- Bias in Screening Studies
- Epidemiological Evaluation of Screening Interventions

Read
- Gordis textbook: Chapter 18 (The Epidemiologic Approach to Evaluating Screening Programs). Do associated problems and check your own work.

In-class exercise: In-person, small-group exercise: Screening

Module 20: Clinical Prediction Rules

At the conclusion of this module, you should be able to:
- Explain how to derive and apply a clinical prediction rule
- Appreciate methodological standards for clinical prediction rules

Before coming to class:

Watch
- Introduction to Clinical Prediction Rules
- Development Methodology
### Module 21: Decision Analysis: Role in Clinical Epidemiology

**At the conclusion of this module, you should be able to:**
- Discuss rationales for decision analysis use in clinical research.
- Describe use of decision-analysis techniques in generating and exploring research hypotheses.
- Demonstrate the importance of sensitivity analysis in decision analysis modeling.

### Watch
- Introduction to Decision Analysis and Potential Roles
- Demonstration of Concepts
- Modeling Techniques
- Use of Decision Analysis in Clinical Research

### Read
- Richardson WS, Detsky AS. Users' Guides to the Medical literature. VII. How to Use a Clinical Decision Analysis. A. Are the Results of the Study Valid? *JAMA.* 1995;273:1292-1295

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**In-class exercise:** Evaluating clinical prediction rules