Clinical Research Methods (CLRES 2010) covers fundamental concepts and basic analytic methods pertaining to the 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 will last 7-9 sessions, and culminate in an examination. Section 1 will cover concepts of association and outcome, introduce standard epidemiological concepts of incidence and prevalence, define and describe relative risk, absolute risk, attributable risk and the various methods for calculating those quantities in different observational research designs. Definitions of and methods for reducing bias and confounding are major components of this section. The second session introduces of interventional trials, including the four phases of drug 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 provided. The final section of the course introduces 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.

Responsibilities

We will use both text and primary literature as reference materials for the course. All reading assignments are expected to be completed prior to the class for which they were assigned. The course comprises 3 sections. There will graded homework assignments in each section. All homework will be assigned with a due date. While group work is encouraged for in-class group exercises and homework assignments, all turned-in assignments must be written up individually. All homework is due at the beginning of class on the day indicated as its due-date in the syllabus and will not be accepted via email. Class attendance and participation is required. Most recitation sessions will be optional, although both class meetings on February 22 will be used for class lectures, and therefore attendance is required. Evaluation will be based on the exams, written homework assignments, class participation and attendance.

Course requirements

Each section will contribute to one third of the course grade. The point distribution within each section is described below:

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Class participation and attendance</td>
<td>10%</td>
</tr>
<tr>
<td>Written homework assignments</td>
<td>30%</td>
</tr>
<tr>
<td>Exams</td>
<td>60%</td>
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</table>

Attendance Policy

Students are expected to sign-in to each class (computer provided in suite lobby). If a problem is encountered with the sign-in system, please contact the course instructor(s) as well as Lauren Talotta (talottals@upmc.edu) immediately.
Course Grading Scale
For the computation of the final course grade, the following grading scale will be used:

- 90-100: A
- 80-85: B
- 70-75: C
- 60-65: D
- 86-89: B+
- 76-79: C+
- 66-69: D+
- <60: F

**NOTE:** Homework assignments, course information and communication will be available at [http://courseweb.pitt.edu](http://courseweb.pitt.edu)

**Required Textbook**

**Supplemental Textbooks**

Fundamentals of Clinical Trials, 3rd edition. Friedman, Furberg ad Dements. Spring Publisher, 1998. *(This is the best short text on clinical trials)*


**Academic Integrity**
Students in this course will be expected to comply with the University of Pittsburgh’s Policy on Academic Integrity (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.
Section 1.0: Course Section – Epidemiology

### Session 1.1 Introduction to Clinical Research Methods

**At the conclusion of this lecture, the student will be able to:**

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

**Topics:**

1. Course overview
2. Goals & components of clinical research
3. Definitions of clinical research, epidemiology, translational research, clinical epidemiology
4. Choosing a research question
5. Internal and external validity
6. Types of associations
7. Judging whether an association is causal
8. Quality of evidence

**Required Reading:**

1. Gordis textbook; Chapter 1 (*Introduction*) and 14 (*From Association to Causation: Deriving Inferences from Epidemiologic Studies*)

### Session 1.2 Quantitative Concepts in Epidemiology

**At the conclusion of this lecture, the student will be able to:**

1. Review types of variables, precision and validity.
2. Explain the difference between prevalence and incidence, including their relationship based on duration of illness.
3. Understand the complexities of these measures, including issues related to the numerator and the denominator.
4. Calculate incidence rates and prevalence given data tables with information of disease counts, population, and time.
5. Understand the difference between crude and adjusted rates.
6. Describe a confidence interval and how it applies to rates.

**Topics:**

1. Variable types, precision, validity
2. Incidence and prevalence
3. Confidence intervals

**Required Readings:**

1. Gordis textbook; Chapter 3 (*Measuring the Occurrence of Disease: I. Morbidity*) and 4 (*Measuring the Occurrence of Disease: II. Mortality*)
Homework:
Gordis Chapter 3 and 4 problems at the end of the chapter. (Do before class & check your own work)

Session 1.3
Research Study Design: Case Series and Cross Sectional Studies

At the conclusion of this lecture, the student will be able to:
1. Describe research questions that would be appropriate for a case series study.
2. 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.
3. Describe research questions that would be appropriate for a cross-sectional study.
4. 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.

Topics:
1. Case series and cross-sectional study research designs

Required Readings:
1. Gordis textbook; chapter 10 (Case-Control Studies & Other Study Designs), pages 195-198
2. Hulley textbook; chapter 8, pages 109-112

Homework:
Article discussion questions to be distributed in previous class (not to be graded).

In-class exercise:
Design a cross-sectional study. Respond to RFA.

Recitation (morning session)
Session 1.4
Bias, Confounding and Interaction

At the conclusion of this lecture, the student will be able to:
1. Define bias in general, and more specifically for different types of selection bias and information bias.
2. Identify general strategies to address bias when planning a new research study.
3. Define confounding, and be able to identify potential confounding variables in the study design phase and the analysis phase.
4. Identify the relationships between variables that must be present in order for a variable to be a confounding variable.
5. Identify general strategies to deal with confounding.
6. Define interaction, and be able to demonstrate interaction using a 2x2 table.

Topics:
1. Bias
2. Confounding
3. Interaction

Required Readings:
1. Gordis textbook; chapter 15 (*More on Causal Inferences: Bias, Confounding and Interaction*)

**Homework:**
Gordis textbook Chapter 15 review questions.

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**Session 1.5**

Research Study Design: Cohort Studies

**At the conclusion of this lecture, the student will be able to:**
1. Understand how to use longitudinal cohort data to determine whether there is an association between a factor or a characteristics and the development of a disease using longitudinal (cohort) data
2. Recognize the advantages and disadvantages of the cohort design and understand when it should be applied
3. Understand the differences between a retrospective cohort and a prospective cohort

**Topics:**
1. Using a cohort study design to examine the association between exposure & outcome
2. Different approaches to setting up a cohort study
3. Pros and cons of a cohort study design
4. Design issues
5. Critical appraisal
6. Common sources of bias in cohort studies

**Required Readings**
1. Gordis textbook; chapter 9 (*Cohort Studies*)
2. Article: Mozaffarian D. et al. Cardiac Benefits of Fish Consumption May Depend on the Type of Fish Meal Consumed: The Cardiovascular Health Study. *Circulation* 2003;107;1372-1377

**Homework:** Gordis Chapter 9 review questions (Do before class & check your own work); Critical review of Mozaffarian article (to be reviewed in class)

**In-class exercise:** Critical review of Mozaffarian article

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**Session 1.6**

Research Study Design: Case-Control Studies

**At the conclusion of this lecture, the student will be able to:**
1. Describe the key features that distinguish a case-control study from other types of observational research studies.
2. Be able to identify several possible sources of “control” subjects, and describe potential biases associated with choice of control group.
3. Interpret outcome measures generated from case control studies (e.g. odds ratio with 95% confidence interval).
4. Be able to set up and interpret a 2x2 table

**Topics:**
1. Using a case-control study design to examine the association between exposure & outcome
2. Pros and cons of a case-control study design
3. Design issues
4. Different approaches to setting up a case-control study
5. Case-control studies based in a defined cohort
6. 2x2 tables

Required Readings:
1. Gordis textbook; chapters 10 (Case-control Studies & Other Study Designs) and 13 (A Pause for Review: Comparing Cohort and Case-Control Studies)

Homework:
Review questions at the end of Gordis Chapter 10 (Do before class & check your own work).

In-class exercise: Design a case control study. Response to RFA.

Graded Homework #1 will be passed out in class today

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<tr>
<th>Recitation (morning session)</th>
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<tr>
<td>Session</td>
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At the conclusion of this lecture, the student will be able to:
1. Understand the definition and calculation of measures of association, including: Relative Risk, Absolute Risk, Attributable Risk, Odds Ratios, Number needed to treat.
2. Understand the application of the different measures to epidemiologic questions.

Topics:
1. 2x2 Tables
2. Defining Absolute & Relative Risk
3. Calculating Relative Risk
4. Risk Ratio
5. Odds Ratio ("regular" & "matched pairs")

Required Readings:
1. Gordis textbook; chapter 11 (Estimating Risk: Is There an Association?)
2. Epidemiology in Medicine, Chapter 4 (provided on Courseweb)

Homework:
Graded Homework #1
Questions at the end of Gordis Chapter 11 and Epidemiology in Medicine Chapter 4 (Do before class & check your own work)

Due today: Graded Homework #1

In-class exercise: Problem set to be handed out in class

Graded Homework #2 will be passed out in class today (due 1/30)

<table>
<thead>
<tr>
<th>Session</th>
<th>Measures of Association II</th>
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<td>1.8</td>
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</table>

At the conclusion of this lecture, the student will be able to:
1. Understand the definition and calculation of measures of association, including: Relative Risk, Absolute Risk, Attributable Risk, Odds Ratios, Number needed to treat.
2. Understand the application of the different measures to epidemiologic questions.

**Topics:**

1. Defining, calculating and interpreting several additional measures of association
   - Attributable Risk
   - Preventive Fraction
   - Population Attributable Risk
   - Number Needed to Treat

**Required Readings**

1. Gordis textbook; chapter 12 (*More on Risk: Estimating the Potential for Prevention*)
2. Epidemiology in Medicine, Chapter 4 (provided on Courseweb)

**Homework:**

- Measures of Association Self-study Problem Set 1 (any problems not finished in class)
- Questions at the end of Gordis Chapter 12 (Do before class & check your own work)

**In-class exercise:** Measures of Association Unknowns Debate

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**Section 2.0: Course Section - Clinical Trials**

**Recitation (morning session): Exam Discussion**

**Session** 2.1 **Meta-analyses**

**At the conclusion of this lecture, the student will be able to:**

1. Describe the purpose, methodology, strengths and limitations of a meta-analysis.

**Topics:**

This lecture will provide an introduction to systematic review and meta-analysis of RCTs. It will cover:

1. Rationale for systematic reviews and meta-analysis of RCTs
2. How to conduct a good systematic review; when to consider doing a meta-analysis
3. The Cochrane collaboration
4. Statistical methods for meta-analysis. These include
   - Choosing a fixed effect or random effects model
   - Assessing for heterogeneity
   - Evaluating your studies for publication bias
   - Exploring heterogeneity: sensitivity and subgroup analyses

**Required readings:**


Supplemental readings:


Homework:
Complete the Meta analysis exercise chart to compare and contrast the inclusion/exclusion criteria from one of the articles below (you need only read one of the articles below). We will provide the completed table once these are submitted.

**Paper 1:**

**Paper 2:**

**Paper 3:**

Session 2.2 Background to Clinical Trials

**At the conclusion of this lecture, the student will be able to:**
1. Describe the purpose, phases, pros and cons of the RT.
2. Describe and use basic design concepts important to the validity of a randomized trial.
3. Describe the purpose and processes of phase I and II drug development trials.
4. Be able to read and plan a CONSORT statement.

**Topics:**
1. Brief history
2. Advantages and disadvantages
3. When are clinical trials necessary
4. Intervention development
5. Efficacy, effectiveness, validity, safety, and ethics
6. The Consolidated Standards of Reporting Trials (CONSORT) Statement

**Required readings:**


**Supplemental readings:**
1. Hulley textbook; review Chapter 1, and pages 147 and 169.

**Homework:**
Based on your the last digit of your birth date, complete the CONSORT checklist for one of the following papers before class. Then, break into groups to review and discuss your CONSORT checklist in small groups.

**Group 1:** Birth *day* ends in 1-15 (e.g., February 4):

**Group 2:** Birth *day*: 16-31:

**In-class exercise:**
Review and discuss your CONSORT checklist in small groups organized by birthday.

**Due today:**
Turn-in your individual CONSORT checklists at the end of class.

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### Session 2.3 Interventions

**At the conclusion of this lecture, the student will be able to:**
1. Describe how design decisions affect the feasibility and generalizability of a randomized trial.
2. Describe threats to blinding in an RCT and methods to overcome them.
3. Discuss the effects of dropouts and missing data on an RCT.

**Topics:**
1. Types of interventions
2. Types of controls
3. Randomizing
4. Factorial designs
5. Blinding
6. Adherence and retention

**Required readings:**
1. Gordis textbook; pages 133-146.

**Supplemental readings:**


Homework:
We will distribute homework exercises for completion prior to class and in classroom discussion. A representative from each group will then present their trial designs to the class.

   Group 1:
   Birthday 1-15

   Group 2:
   Birthday: 16-31

In-class exercise:
Review and discuss your individual homework worksheet in small groups organized by birthday.

Due today:
Everybody is expected to turn-in their individual homework worksheet at the end of class.

Recitation (morning session)

<table>
<thead>
<tr>
<th>Session</th>
<th>Recruitment, Sample Sizes, and Measures</th>
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At the conclusion of this lecture, the student will be able to:
1. Describe the importance of and strategies to achieve recruitment goals.
2. Appreciate some patients’ motivation for participation in clinical research.
3. Discuss the effects of dropouts and missing data on an RCT.
4. Appreciate the decision making involved with selection of the primary and secondary outcome measures.

Topics:
1. Recruitment and validity
2. Sample sizes
3. Selecting assessment measures

Required readings:
1. Gordis textbook; pages 147-152.

Supplemental readings:
**Homework:**
Today's homework exercises will focus on challenges and strategies to overcome subject enrollment challenges in a variety of environments. Depending on your research interests, select one of the articles below to read prior to class.

**Paper 1:**

**Paper 2:**

**Paper 3:**

**Paper 4:**

**In-class exercise:**
We will form two groups in class to discuss each article (the number of people who have read each article will vary within each group).

**Due today:**
At the end of class, everybody will be expected to turn-in a *typewritten* 1-2 paragraph (but no more than 1 page) lesson(s) he or she learned from the article they read prior to class.

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<table>
<thead>
<tr>
<th>Session</th>
<th>Quasi-Experimental Designs</th>
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**At the conclusion of this lecture, the student will be able to:**
1. Define, give examples, and describe the advantages and disadvantages of quasi-experimental research designs.

**Topics:**
Not all experimental designs fit well into the rubric of observational or interventional randomized controlled trials. There are a series of study design types that have elements of one or both, and are called quasi-experimental designs. The major attribute that quasi-experimental designs usually lack is the random assignment of patients to a therapy. Pre-post interventions, N of one trials, crossover designs, and several other modifications of standard experimental designs are often more practical to institute, but their interpretation requires substantial care to avoid bias and confounding.

**Required readings:**


Homework:
We will split into two groups (Group 1: birthday 1-15; Group 2: birthday 16-31). Depending on your research interests, select one of the articles below to read prior to class.


Due today:
At the end of class, everybody will be expected to turn-in a typewritten 1-2 paragraph (but no more than 1 page) lesson(s) he or she learned from the article they read prior to class.

In-class exercise:
We will form two groups in class to discuss each article. After a discussion period, a representative from each group will present “lessons learned” from each paper to the rest of the class for discussion.

Session 2.6 Outcomes and Analyses

At the conclusion of this lecture, the student will be able to:
1. Discuss the effects of dropouts and missing data on an RCT.
2. Appreciate the advantages and disadvantages of using surrogate and composite endpoints.

Topics:
1. Selecting outcome measures
2. Composite outcome measures.
3. Primary and secondary analyses
4. Final thoughts

Required readings:
2. Gordis textbook; pages 152-153.

Homework:
The homework exercises will focus on composite and surrogate clinical endpoints in clinical trials.


**In-class exercise:**
We will form two groups in class to discuss each article according to birthdate (Group 1: birthday 1-15; Group 2: birthday 16-31).

**Due today:**
At the end of class, everybody will be expected to turn-in a *typewritten* 1-2 paragraph (but no more than 1 page) lesson(s) he or she learned from one the two articles they read prior to class.

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### Section 3.0: Course section – Clinical Epidemiology

[Recitation (morning session)]

<table>
<thead>
<tr>
<th>Session</th>
<th>Section</th>
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<tr>
<td>2.7</td>
<td>Section Examination</td>
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</table>

### Session 3.1: Introduction and Evidence-Based Medicine-I

**At the conclusion of this lecture, the student will be able to:**
1. Understand the role of EBM in clinical practice
2. List the 5 A's of EBM
3. Develop an appropriate research question
4. Search databases for literature and finding the evidence

**Topics:**
1. Introduction to the EBM Concept
2. The Practice of EBM – General Overview
3. Defining the Question
4. Finding the Evidence

**Required Readings:** None

**Homework:** Homework 1: Writing a Research Question

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

<table>
<thead>
<tr>
<th>Session</th>
<th>Section</th>
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<tr>
<td>3.2</td>
<td>Evidence Based Medicine-II</td>
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</table>

**At the conclusion of this lecture, the student will be able to:**
1. Appraise the content of articles
2. Identify the parts of a scientific article
3. Apply evidence to the clinical scenario

**Topics:**
1. Appraising the Evidence – A “thumbnail” approach to appraising evidence
2. Applying the Evidence to Patient Care
3. Controversies in EBM - A review of the major criticisms of Evidence Based Medicine
4. Teaching Evidence-Based Medicine in a clinical setting – A brief review of the major curricular Advances
**Required Readings:** none

**Due today:** Homework 1

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

<table>
<thead>
<tr>
<th>Session</th>
<th>Diagnostic Tests Part I</th>
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**At the conclusion of this lecture, the student will be able to:**
1. Describe the difference between diagnosis and screening
2. Evaluate diagnostic test performance
3. Understand the relationship between sensitivity and specificity
4. Understand the relationship between marginal and joint probabilities
5. Relate a 2x2 table and a decision tree
6. Construct a ROC curve

**Topics:**
Diagnostic tests are one of the most common mechanisms for obtaining clinical information about the presence or absence of disease. In this session, the basic characteristics of diagnostic tests will be explored, sensitivity, specificity, predictive value will be defined. Characteristics that are necessary for a good screening tests and diagnostic test are reviewed.

**Required Readings:**
1. Gordis textbook; chapter 4.

**Homework:** Homework 2 calculating sensitivity, specificity, predictive value and likelihood ratios.

<table>
<thead>
<tr>
<th>Session</th>
<th>Diagnostic Tests Part II/Community-based</th>
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<tr>
<td>3.3</td>
<td>Participatory Research</td>
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</table>

**At the conclusion of this lecture, the student will be able to:**

**Topics:**
Many diagnostic tests have positivity criteria that are “set”: there is no absolute positive or negative. This includes tests such as the Troponin cutoff for the diagnosis of a myocardial infarction and the size of a mediastinal node on CT to be considered pathological adenopathy. This session will examine methods for understanding the tradeoffs between different cut offs for a diagnostic test, and explore the tradeoff between sensitivity and specificity. Receiver Operating Curves (ROC) curves will be described and calculated for several types of test.

**Required Readings:**

**Homework:** ROC curve construction: examine the CA-19-9 spreadsheet data and construct an ROC curve.

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<thead>
<tr>
<th>Session</th>
<th>Evaluation of Screening</th>
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</table>

**At the conclusion of this lecture, the student will be able to:**
1. Identify possible biases in screening studies and how to address them in the design phase.
2. Describe how the natural history of disease may influence the type of screening intervention that
may be needed,
3. Identify the strengths and weaknesses of various study design options as they apply to screening studies.

**Required Readings:**
1. Gordis textbook; chapter 18.

**Homework:** ROC curve construction: Homework 3 Problem set: evaluation diagnostic screening

**Due today:** Homework 2

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### Session 3.5  Clinical Prediction Rules

**At the conclusion of this lecture, the student will be able to:**
1. Explain how to derive and apply a clinical prediction rule
2. Appreciate methodological standards for clinical prediction rules

**Topics:**
The purpose of a clinical prediction rule is to make assessments of the risk of a future event based on characteristics of the patient. There is a wide array of clinical prediction rules, from simple scores such as the Ranson criteria in pancreatitis, to the Pneumonia Severity Index which predicts the likelihood of bad outcomes in community acquired pneumonia or the APPACHE (Acute physiology score) which predicts the likelihood of death for patients admitted to the Intensive care unit. This section will describe the development, testing and validation and clinical application of clinical prediction rules.

**Required Readings:**

**Due today:** Homework 3

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### Session 3.7  Section Examination