Course Summary

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) Clinical epidemiology and evidence-based medicine, and 3) Interventional and randomized controlled trials. Each section of the course will last 7-8 sessions, and culminate in a short examination. Section 1 will cover concepts of association and outcomes, 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 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. The final session introduces 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.

Course mechanics: 3 credits; class meets on Mondays, Wednesdays and Fridays from 12:00 – 1:45pm (1/10-3/4) and recitation meets on Wednesdays from 8:30 – 10:00am (1/12-3/2).

Grading: Letter grade based on homework assignments, section exams, and class participation.

Location: Class will meet in 222 Parkvale Building (corners of Forbes and Meyran Avenues). Recitation will meet in 305 Parkvale.

Course requirements:
The course consists of three sections. There will be homework assignments, in-class activities/projects and an exam for each section. All homework is due at the beginning of class on the day indicated as its due-date in the syllabus.

Required Texts:
The Gordis book is a more traditional epidemiology text and is required for Section 1.0. The Hulley book is more directed toward clinical research and clinical epidemiology and is required for Section 3.0. Required reading assignments will be given from these books. Homework and problem sets also will be assigned from the Gordis book.

Section 1.0: Course Section – Epidemiology

Session 1.1   Introduction to Clinical Research Methods  January 10, 2011  Clark

Topics:
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

Required readings (to be done before class meets):
1. Gordis textbook: Chapters 1 & 14

Recommended readings:
1. Hulley textbook: Chapters 1 & 2

Session 1.2   Quantitative Concepts in Epidemiology  January 12, 2011  Unruh

Topics:
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.

Required readings (to be done before class):
1. Gordis textbook: Chapters 3 & 4

Homework: Questions at the end of Gordis Chapters 3 & 4 (Check your own work and bring questions to recitation; not to be turned in).

Session 1.3   Measures of Association  January 14, 2011  Clark

Topics:
1. To understand the definition and calculation of measures of association, including: Relative Risk, Absolute Risk, Attributable Risk, Odds Ratios, Number Needed to Treat.
2. To understand the application of the different measures to epidemiologic questions.

Required readings (to be done before class):
1. Gordis textbook: Chapters 11 & 12
2. Epidemiology in Medicine, Chapter 4 (provided in Course Readings folder)

Homework: (1) Homework problem set passed out in class will be due at the beginning of Session 1.4 (January 19, 2011).
(2) Questions at the end of Gordis Chapters 11 & 12 and Epidemiology in Medicine Chapter 4 (Check your own work and bring questions to recitation; not to be turned in).
### Session 1.4   Bias, Confounding and Interaction  January 19, 2011  Unruh

**Topics:**
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.

**Required readings (to be done before class):**
1. Gordis textbook: Chapter 15

**Recommended readings:**
1. Hulley textbook: Chapter 4

**Homework:** Questions at the end of Gordis Chapter 15 (Check your own work and bring questions to recitation; not to be turned in).

### Session 1.5   Research Study Design: Case Series and Cross-Sectional Studies  January 21, 2011  Unruh

**Topics:**
- **Case Series**
  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.

- **Cross-Sectional**
  1. Describe research questions that would be appropriate for a cross-sectional study.
  2. 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.

**Required readings (to be done before class):**
1. Gordis textbook: Chapter 10, pages 195-198

**Recommended readings:**
1. Hulley textbook: Chapter 8, pages 109-112

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

### Session 1.6   Research Study Design: Cohort Studies  January 24, 2011  Clark

**Topics:**
1. To understand how to use longitudinal cohort data to determine whether there is an association between a factor or a characteristic and the development of a disease using longitudinal (cohort) data.
2. To recognize the advantages and disadvantages of the cohort design and understand when it should be applied.
3. To understand the differences between a retrospective cohort and a prospective cohort.
Required readings (to be done before class):
1. Gordis textbook: Chapter 9
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

Recommended readings:
1. Hulley textbook: Chapter 7

Homework: (1) Homework passed out in class will be due at the beginning of Session 1.7 (January 26, 2011).
(2) Questions at the end of Gordis Chapter 9 (Check your own work and bring questions to recitation; not to be turned in).

Session 1.7 Research Study Design: Case-Control Studies January 26, 2011 Clark

Topics:
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).

Required readings (to be done before class):
1. Gordis textbook: Chapter 10

Recommended readings:
1. Hulley textbook: Chapter 8, pages 112-120

Homework: Questions at the end of Gordis Chapter 10 (Check your own work and bring questions to recitation; not to be turned in).

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

Session 1.8 Section Exam January 28, 2011 ALL
### Section 2.0: Course section – Clinical Epidemiology

#### Session 2.1  Introduction and Evidence-Based Medicine-I  January 31, 2011  Zgibor/Saleh

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

*Computer lab exercise*

#### Session 2.2  Evidence Based Medicine-II  February 2, 2011  Zgibor/Saleh

**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

*Computer lab exercise*

#### Session 2.3  Diagnostic Tests Part I  February 4, 2011  Zgibor

**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.

**Readings:**
1. Gordis textbook; chapter 5.
2. Hully textbook chapter 12.

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

#### Session 2.4  Diagnostic tests Part II  February 7, 2011  Zgibor

**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) curses will be described and calculated for several types of test.

**Readings:**

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

#### Session 2.5  Evaluation of Screening  February 9, 2011  Zgibor
**Topics:**

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.

**Readings:**

1. Gordis textbook; chapter 18.

**Homework:**  Review questions, chapter 18.

**Class exercise:**  Design a screening study.  Response to RFA.

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<th>Session 2.6</th>
<th>Clinical Prediction Rules</th>
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**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.

**Readings:**


**Homework:**  none

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<tr>
<th>Session 2.7</th>
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| Session 2.8  | Section Examination | February16, 2011 | Zgibor |
Section 3.0: Course Section - Clinical Trials

Section objectives:

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 how design decisions affect feasibility and generalizability of a randomized trial.
4. Describe threats to blinding in an RCT and methods to overcome them.
5. Discuss the effects of dropouts and missing data on an RCT.
6. Be able to read and plan a CONSORT statement.
7. Describe the purpose and processes of phase I and II drug development trials.
8. Define, give examples, and describe the advantages and disadvantages of quasi-experimental research designs.
9. Describe the purpose, methodology, strengths and limitations of a meta-analysis.

OVERVIEW OF READING ASSIGNMENTS:
Clinical trials are covered in only a very brief way in our two main textbooks, but are covered at too much depth specific texts devoted to clinical trials only (e.g., our optional textbook below). Over the next six sessions, you should at a minimum review the assigned readings before class from either Hulley or Gordis (or both), and read the supplemental reading materials depending upon your personal and career interests.

OVERVIEW OF GRADING
25% Homework (5 assignments x 10 points each)
75% Final Exam

OPTIONAL TEXTBOOK READING:
   “A concise overview of the essential aspects of clinical research and trial design. Presents the principles and practical details needed to design, conduct, and interpret the results on clinical trials” (Amazon.com). Plus, the book is co-authored by the ICRE’s own Dr. Lee.
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

Readings:
1. Hulley textbook; review Chapter 1, and pages 147 and 169.
2. Gordis textbook; pages 131-132.

Home Activity for Review in Class:
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. You will turn-in your individual checklist at the end of class.

Group 1: Birthday ends in 1-10 (e.g., February 4):

Group 2: Birthday: 11-20:

Group 3: Birthday 21-31:
Topics:
1. Types of interventions
2. Types of controls
3. Randomizing
4. Factorial designs and clustering
5. Blinding
6. Adherence and retention

Readings:
2. Gordis textbook; pages 133-46.

Supplemental Readings:

Home Activity for Review in Class:
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. Everybody will be expected to turn-in their individual worksheets at the end of class.

Group 1: Birthday 1-15
Group 2: Birthday: 11-31
Topics:
1. Recruitment and validity
2. Sample sizes
3. Selecting assessment measures

Readings:
2. Gordis textbook; pages 147-152.

Supplemental Readings:

Home Activity for Review in Class:
The homework exercises will focus on challenges and strategies to overcome enrollment challenges in a variety of environments.

Depending on your research interests, select one of the articles below to read prior to class. We will form four groups in class to discuss each article (groups will vary in size). After a discussion period, a representative from each group will present “lessons learned” from each paper to the rest of the class for discussion. 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.

Paper 1:

Paper 2:

Paper 3:

Paper 4:
Topics:
Topic:
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.

Readings:

Home Activity for Review in Class:
The homework exercises will focus on challenges and strategies to overcome enrollment challenges in a variety of environments.

Depending on your research interests, select one of the articles below to read prior to class. 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. 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.

Paper 1:

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

Readings:
2. Gordis textbook; pages 152-153.

Supplemental Readings:


Home Activity for Review in Class:
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. Everybody will be expected to turn-in their individual worksheets at the end of class.

Group 1: Birthday 1-15
Group 2: Birthday: 11-31
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 reading:

Supplemental readings:

Home Activity for Review in Class:
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.

