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) Interventional and Randomized controlled trials, and 3) Clinical Epidemiology and evidence-based medicine. Each section of the course will last 8 sessions, and culminate in a short 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 interventional trials, including Phase I and Phase II 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.

Course mechanics: 3 credits; meets on Mondays, Wednesdays and Fridays from 8:30 – 10:15 and on Wednesdays from 3:30 – 5:00 for recitation (no recitation on July 7).

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

Location: Room 117 Victoria Hall.

Course requirements:
The course consists of three sections. There will be homework assignments, in-class activities/projects and an exam for each section.

Required Texts:

Optional Texts:
**Section 1.0: Course Section – Epidemiology**

<table>
<thead>
<tr>
<th>Session 1.1</th>
<th>Introduction to Clinical Research Methods</th>
<th>July 7, 2004</th>
<th>Cook</th>
</tr>
</thead>
</table>

**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

**Readings:**
1. Hulley textbook; Chapters 1 and 2.
2. Gordis textbook; Chapter 1 also pages 211-216 (Evidence for a causal relationship).

---

<table>
<thead>
<tr>
<th>Session 1.2</th>
<th>Quantitative Concepts in Epidemiology</th>
<th>July 9, 2004</th>
<th>Cook</th>
</tr>
</thead>
</table>

**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.

**Readings:**
1. Gordis textbook; Chapter 3.
2. Hulley textbook; Chapter 4.

**Homework:** Gordis Chapter 3 problems at the end of the chapter. Hulley Chapter 4 problems 1-2.

---

<table>
<thead>
<tr>
<th>Session 1.3</th>
<th>Measures of Association</th>
<th>July 12, 2004</th>
<th>McTigue</th>
</tr>
</thead>
</table>

**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.

**Readings:**
1. Gordis textbook; chapter 11
2. Epidemiology in Medicine, Chapter 4 (provided in binder)

**Homework:** Gordis textbook; Chapters 11 & Epidemiology in Medicine Chapter 4 review questions, plus supplemental questions handed out in class.
## Session 1.4 Bias, Confounding and Interaction  
**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.

**Readings:**
1. Gordis textbook; chapter 15
2. Hulley textbook; chapter 9

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

---

## Recitation Session @ 3:30  
**July 14, 2004  
Cook**

Class review session

---

## Session 1.5 Research Study Design: Cohort Studies  
**July 16, 2004  
McTigue**

**Topics:**
1. To 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. 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.

**Readings:**
1. Gordis textbook; chapter 9
2. Hulley textbook; chapter 7

**Homework:** Gordis Chapter 8 review questions, plus supplemental questions handed out in class I.

---

## Session 1.6 Case Series and Cross Sectional Studies  
**July 19, 2004  
Cook**

**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.

**Readings:**
1. Gordis textbook; chapter 10, pages 173-175
2. Hulley textbook; chapter 8, pages 107-110

**Homework:** Article discussion questions to be distributed in previous class.

**In-class small group exercise:** Design a cross-sectional study. Response to Request for Applications (RFA).

### Session 1.7 Research Study Design: Cohort Studies
July 21, 2004  
McTigue

**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).

**Readings:**
1. Gordis textbook; chapter 10  
2. Hulley textbook; chapter 8, pages 110-120  

**Homework:** Discussion questions on article to be distributed in previous class.

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

### Recitation Session @ 3:30
July 21, 2004  
Cook

Exam Review Session

### Session 1.8 Section Exam
July 23, 2004  
Cook
Section 2.0: 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 at least five types of intervention maneuvers.
5. Describe threats to blinding in an RCT and methods to overcome them.
6. Discuss the effects of dropouts and missing data on an RCT.
7. Be able to read and plan a CONSORT statement.
8. Describe the purpose and processes of phase I and II drug development trials.
9. Define, give examples, and describe the advantages and disadvantages of quasi-experimental research designs.
10. Describe the purpose, methodology, strengths and limitations of a meta-analysis.

Session 2.1 RCT I: Overview: Principles and Concepts July 26, 2004 Studenski

Topics:

1. Randomized trials as experiments.
2. Advantages and disadvantage of the RCT.
3. Four phases of intervention development.
4. Clinical vs. statistical meaningfulness.
5. Overview of trial goals (efficacy and effectiveness, internal and external validity)
6. The iterative process of RCT development; opportunities for pilot studies.
7. The CONSORT Statement

Readings:

2. Gordis textbook; pages 100-101 and 120.

Supplemental Readings (** means personal favorite):

Optional Textbook Readings (see table for readings by topic):


In Class Activity:
Plan for the three RCT small group sessions to follow. Select one of three publications on RCTs to evaluate in detail using the attached checklists. Prepare checklists in advance and discuss in small groups. Each session, two speakers from each group will present to the class.


Session 2.2 RCT II: Intervention July 28, 2004 Studenski

Topics:
1. Types of interventions.
2. Reproducibility, intensity.
3. Randomizing.
4. Choice of control.
5. Blinding.
6. Adherence and retention, pros and cons of a run-in.
7. Factorial designs- more than one intervention.

Readings:
1. Hulley textbook; pages 147-149, 150, 152-154 and 157-160
2. Gordis textbook; pages 104-107, 109 and 118-119.

Supplemental Readings:
Optional Textbook Readings:
See RCT reference table

In class activity:

For your study:
2. Complete relevant components of the CONSORT checklist.
3. Propose feasible improvements.
4. Be prepared to discuss in your group.

Recitation Session  
July 28, 2004  Studenski

Class review session

Session 2.3  RCT III: Samples and Measures  
July 30, 2004  Studenski

Topics:
1. Participants: influence of trial goals, entry criteria, recruitment plan and sample size.
2. Baseline measures: influence of trial goals, types of measures and consistency.

Readings:
6. Hulley textbook; pages 143-146 and 146-147.

Supplemental Readings:

Optional Textbook Readings:
See RCT reference table

In Class Activity:

For your study:
1. Complete attached checklist on participants and baseline measures.
2. Complete relevant portions of the CONSORT Statement.
3. Propose feasible improvements.
4. Be prepared to discuss in your group.
Topics:
1. Outcomes: types, number, adjudication and adverse events.
2. Analysis: primary and secondary analyses, event rates and number needed to treat, intention to treat and subgroups.
3. Trial summaries: the CONSORT Statement and flow diagram.

Readings:
1. Hulley textbook; pages 160-164.
2. Gordis textbook; pages 119-120

Supplemental Readings:
2. ** L Forrow, WC Taylor, RM Arnold. Absolutely relative: how research results are summarized can affect treatment decisions. American Journal of Medicine, 1992; 92:121-124.

Optional Textbook Reading:
See RCT reference table

In class activity
For your study:
1. Complete checklist on outcome and analysis issues.
2. Complete CONSORT flow sheet and rest of the CONSORT checklist.
3. Propose feasible improvements.
4. Be prepared to discuss in your group.
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:
Be prepared to discuss whether you are convinced of the effect of the particular intervention in the article listed below.

Section 3.0: Course section – Clinical Epidemiology

<table>
<thead>
<tr>
<th>Session 3.1</th>
<th>Introduction and Evidence-Based Medicine</th>
<th>August 13, 2004</th>
<th>Williams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Introduction to the EBM Concept</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>The Practice of EBM – General Overview</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Defining the Question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Finding the Evidence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 3.2</th>
<th>Evidence-Based Medicine</th>
<th>August 16, 2004</th>
<th>Williams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Appraising the Evidence – A “thumbnail” approach to appraising evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Applying the Evidence to Patient Care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Controversies in EBM - A review of the major criticisms of Evidence Based Medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Teaching Evidence-Based Medicine in a clinical setting – A brief review of the major curricular advances</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 3.3</th>
<th>Diagnostic Tests Part I</th>
<th>August 18, 2004</th>
<th>Roberts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readings:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Gordis textbook; chapter 4.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Hully textbook chapter 12.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homework:</td>
<td>Problem set: calculating sensitivity, specificity, predictive value and likelihood ratios. Due Date: 8/20/03.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recitation Session @ 3:30</th>
<th>August 18, 2004</th>
<th>Roberts</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Session 3.4</th>
<th>Diagnostic Tests Part II</th>
<th>August 20, 2004</th>
<th>Roberts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readings:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Session 3.5</th>
<th>Evaluation of Screening</th>
<th>August 23, 2004</th>
<th>Cook</th>
</tr>
</thead>
</table>

**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.

**In-class small group exercise:** Design a screening study. Response to RFA.

<table>
<thead>
<tr>
<th>Recitation Session @ 3:30</th>
<th>August 23, 2004</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Session 3.6</th>
<th>Clinical prediction rules</th>
<th>August 25, 2004</th>
<th>Fine</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Session 3.7</th>
<th>Section Exam</th>
<th>August 27, 2004</th>
<th>Roberts</th>
</tr>
</thead>
</table>