This course adheres to the items listed in the College of Pharmacy Central Syllabus:
https://docs.google.com/document/d/1artQ5e1rbzxe8IETwo7BE8k8snZAEqMMz_QcW8yJ-I/edit?pli=1

Meeting Times & Locations

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Duluth Room</th>
<th>Twin Cities Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>3:30 – 5:30pm</td>
<td>LSci 144</td>
<td>WDH-7-173</td>
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</table>

Course Website: http://moodle.umn.edu

Instructional Team

If you need assistance with the course, contact one of the Teaching Assistants.

Technology Help, Duluth: 218-726-8847  itsshelp@d.umn.edu
Technology Help, Twin Cities: 612-301-4357  help@umn.edu

Faculty Office Hours: by appointment

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Email: zhan1386@umn.edu
Course Description

Course content: Pharmacoepidemiology is the study of the uses and effects of drugs in patient populations. The science of pharmacoepidemiology borrows from pharmacology and epidemiology. This course will introduce students to the field of pharmacoepidemiology including study methodology, relevant statistics, data sources, measurement of treatments and outcomes, sources of bias and control of confounding, techniques to reduce bias and confounding, survival analysis and regression techniques, interpretation of results, and drug safety surveillance and risk management.

Course format: This course is mainly lecture-based. Students are expected to prepare for each class, as debate and discussion of various concepts presented in class will take place. Near the end of the course, students will be expected to use information gained throughout the course to compose a written critique of a pharmacoepidemiology study and then orally present their critique in class.

Prerequisites

- 2nd, 3rd or 4th year pharmacy students. First year students may enroll with permission of course directors. First year students will need to show that they have had previous relevant courses in epidemiology, or public health.

Requirements

Course Materials

Required

Optional (for additional perspective)
- Epidemiology, Fifth edition (Available online from Biomed Library)
- Medical Epidemiology 2005 (Available online from Biomed Library)

Computer / Technology Requirements

- The University of Minnesota computer requirements are listed here: http://www1.umn.edu/moodle/start/technical.html
Attendance Policy
Students are expected to attend every class for which they are registered. Students are expected to attend classes on the campus where they are enrolled. Instructors may choose to take attendance. When a student is unable to attend a class for health or family reasons, the instructor must be informed in advance.

Goals & Objectives

Course Goals
Main course concepts:
- The aim of the course is to help students acquire a basic understanding of the concepts and practice of pharmacoepidemiology.

Learning Objectives
1. Discuss the concept of pharmacoepidemiology
2. Compare and contrast typical pharmacoepidemiologic study designs and explain their strengths and weaknesses
3. Discuss the roles that pharmacoepidemiology studies have had in the past regarding drug use and health outcomes and the future roles that pharmacoepidemiology can play in drug safety surveillance and comparative drug effectiveness and safety
4. Debate the threats to validity that are possible in pharmacoepidemiology studies and the variety of solutions available to avert or control for these threats
5. Using the information provided by the text, lectures, and assigned readings, compose a written critique of a recently-published pharmacoepidemiology study and orally present this critique in class
Assessments and Grading

Assignments and learning activities

Graded Assessments

- Class participation/attendance (20%)
- Midterm exam – multiple choice, short answer/essay (40%)
- End-of-semester written critique (20%)
- End-of-semester oral presentation [slides, 15-20 minutes] (20%)

The midterm exam, written critique, presentation and class participation/attendance will be graded by the course directors.

Thorough reading of assigned readings prior to class, attendance and class participation is expected. The student will take the midterm exam, select one study from recently-published pharmacoepidemiology studies, compose a written critique of the study and orally present this critique in class. You will be expected to have prepared for each class and completed any homework assignments prior to class. Class participation points will be assigned based on course director’s assessment of your preparedness for class which will be assessed through your class participation.

Course Letter Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>A</th>
<th>A-</th>
<th>B+</th>
<th>B</th>
<th>B-</th>
<th>C+</th>
<th>C</th>
<th>C-</th>
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<th>F</th>
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<tr>
<td>%</td>
<td>&gt;93</td>
<td>90-92</td>
<td>87-89</td>
<td>83-86</td>
<td>80-82</td>
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<td>73-76</td>
<td>70-72</td>
<td>60-69</td>
<td>&lt;60</td>
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Late paper or presentation material submission

Late papers or late presentation materials will be assessed a penalty. Your grade will be reduced by 5% for each day that your materials are late.

Re-grade Policy:

There will be no re-grades in this class.

Minimum Passing Level: C-
### Schedule

<table>
<thead>
<tr>
<th>Week 1</th>
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<tbody>
<tr>
<td><strong>Date</strong></td>
<td><strong>Sept 11</strong></td>
</tr>
<tr>
<td><strong>What is Pharmacoepidemiology?</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Wendy St. Peter</strong></td>
<td></td>
</tr>
<tr>
<td>• Distinction between pharmacoepidemiology, epidemiology, and clinical pharmacology</td>
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<tr>
<td>• Historical Background</td>
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<tr>
<td>• Potential Contributions</td>
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</table>

**Required Reading**

**Textbook of Pharmacoepidemiology**

- Chapter 1 (pages 3-16)
- Chapter 4 (pages 40-41)

**Optional Readings:**


**Basic principles of statistics and application to pharmacoepidemiology studies**

**Wendy St. Peter**

- Causality, associations and strength of evidence
- Hypothesis testing
- P-values, point estimates, confidence intervals
- Type 1 and 2 errors, power

**Required Reading (note: find a reading below that you can understand for each topic above)**

**Textbook of Pharmacoepidemiology**

- Chapter 2 (pages 17-18, 20-21-Causality, associations, strength of evidence)
- Chapter 3 (pages 30-33, Sample size, Type 1 and 2 errors, power)
- Chapter 5 (pages 57-58, Hypothesis testing)

**Essentials of Clinical Research (ECR)**

- Chapter 16 (pages 357-359-Causality)
- Chapter 2 (pages 11-21, Hypothesis testing, Type 1 and 2 errors, strength of evidence)
- Chapter 15 (pages 327-344; Hypothesis testing, statistical power, sample size, Type 1 and 2 errors, p-values, confidence interval)
- Chapter 18: pages 373-383, Hypothesis testing, estimating, p-value, Type 1 and 2 error, power)
## Week 2

**Date**
- **Sept 18**

**Interpretation of pharmacoepidemiology studies**

**Mahsa Salsabili**

- Statistical power and sample size
- Difference between OR and RR and calculations for OR and RR
- What is HR and how it is different than RR
- What is the difference between relative risk, risk ratio, and rate ratio
- Interpretation of results (RR, HR, absolute risk reduction, numbers needed to treat)
- Understanding a survival curve

**Homework:** Read required readings below and answer questions posed.

**Required Reading:**

  - Essentials of Clinical Research (ECR)
    - Chapter 16: Association, Cause, and Correlation (P345-362)
      - **Question:** What is the difference between cause and association? Come up with an example. P357-359
    - Chapter 18: It’s All About Uncertainty (P373-390)
    - Chapter 15: Statistical Power and Sample Size (P327-344)
      - **Question:** From assigned study, identify the hypothesis? What is the p-value associated with primary outcome? What is the confidence interval? What does the confidence interval mean? P 337; P379-383
      - **Question:** First identify the independent and dependent variable and the type of each variable (categorical vs. continuous), then using the statistical tool table 18.4(p389) identify what statistical test(s) is/are most appropriate? What test did the article use?
    - Chapter 16: Association, Cause, and Correlation (P345-362)
      - **Question:** From assigned study draw data table and calculate RR, RRR, ARR, & NNT. P346-357

**Optional Reading**

Textbook of Pharmacoepidemiology

- Chapter 3: Sample size; Tables 3.2 and 3.3 shows how the underlying rate of abnormal lab tests or rate of use of drug, and values chosen for α or β will change the sample size required in exposed vs control group in a cohort or case control study.

## Week 3

**Date**
- **Sept 25**

**Pharmacoepidemiologic study designs**

**Wendy St. Peter**

- Basic features, strengths and weaknesses of pharmacoepidemiology study designs
  - Case reports and case series
  - Ecological studies
  - Cross-sectional studies
  - Case-control studies
  - Nested-case control studies
Homework

1) Describe basic differences between cross-sectional study, case-control study and cohort study, with 1 strength and 1 weakness for each of these 3 study designs.
2) Which of the study designs above could be used to determine the causal association between a drug and an outcome (such as mortality)?

Required Reading:

Pharmacoepidemiology Text
- Chapter 2 (pages 22-29)

Essentials of Clinical Research (ECR)
- Chapter 2 (pages 21--Strength of Relationships to page 31)

Other Required Readings
- Etminan M & Samii A. Pharmacoepidemiology I: A review of pharmacoepidemologic study designs. Pharmacotherapy 2004;24:964. Read pages 964-966 (don’t read section on case-crossover studies) and 968 (confounding bias only).
- Etminan M. Pharmacoepidemiology II: the nested case-control study-a novel approach in pharmacoepidemiologic research. Pharmacotherapy 2004;1105-1109.

Bring a hardcopy to class or be able to access electronically in class for an exercise
- Block GA. Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. Kidney International 2010;78:578-89.

Week 4

Date
Oct 2

Bias, confounding and control of confounding, validity
Holly Epperly Budlong

- Types of bias
  - Selection bias
  - Indication bias
  - Measurement bias
  - Information bias
  - Misclassification (disease or exposure)
  - Immortality bias
  - Lead time bias

- Validity
  - Face validity
  - Internal validity
  - External validity
**Homework:** Choose 1 type of bias described in the required reading that is most interesting to you and use available class or online resources to further describe the type of bias and implications to study results.

**Required Reading:**

### Week 5

<table>
<thead>
<tr>
<th>Date</th>
<th>Directed Acyclic Graphs (DAG) and Analytic approaches for reduced confounding</th>
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</thead>
<tbody>
<tr>
<td>Oct 9</td>
<td>Richard Maclehose</td>
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<tr>
<td></td>
<td>• Directed Acyclic Graph Theory</td>
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<td></td>
<td>• Identifying confounders</td>
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<tr>
<td></td>
<td>• Measured vs unmeasured confounders</td>
</tr>
<tr>
<td></td>
<td>• Identifying selection bias</td>
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</table>

**Homework:** Develop a DAG for your dissertation or from Robins paper (see required readings). We will discuss in class.

**Required readings**

- Modern Epidemiology 3rd Ed – Chapter 12 Causal diagrams
- Causal Inference – Chapter 6 Graphical representation of causal effects

### Week 6

<table>
<thead>
<tr>
<th>Date</th>
<th>Analytic approaches for improved confounding control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct 16</td>
<td>Eric Weinhandl  Matching</td>
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<tr>
<td></td>
<td>• Propensity scores</td>
</tr>
<tr>
<td></td>
<td>• Instrumental variables (brief)</td>
</tr>
</tbody>
</table>

**Homework:** Read required readings below and answer the following questions

1. What types of variables should and should not be included in propensity score models?

2. Explain why p-values should not be used to diagnose the quality of matching, and describe what methodology should instead be used.

3. What is the definition of an instrumental variable? (That is, what are the conditions that define an instrumental variable?)

**Required Reading:**

- Glynn RJ et al. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic and Clinical Pharmacology and Toxicology 2006;98;253-259
### Week 7

**Sources of Data and Data Extraction**

**Cathy Starner and Pat Gleason**

- Administrative datasets (Medicare, commercial)
- Medical records (Structured data, Unstructured Data)
- Critical assessment of data sources
- Limitation of data sources

**Required Reading: Pharmacoepidemiology Text**

- Chapter 8 (Pages 118-122)
- Chapter 9 (pages 123-173)

**Measurement of treatments and outcomes**

**Cathy Starner and Pat Gleason**

- Baseline disease status
- Drug effectiveness versus efficacy
  - Treatment effect heterogeneity
- Drug exposure
  - Intent-to-treat versus as-treated
  - First fill, days’ supply, adherence, persistence
- Outcomes
  - Clinical outcomes
  - Economic outcomes

**Homework:** Use pharmacy claims data extract for sample members (see ‘Sample members for PDC calculation’ excel spreadsheet in class folder) to calculate adherence using proportions of days covered (PDC) calculation for statins for members 1 and 5. Feel free to try calculations for other members as well for extra practice.

**Required Reading TBD: Pharmacoepidemiology Text**

- Chapter 6 (Pages 65-67)
- Chapter 20 (Pages 314-322)
- PQA Adherence Measure Specifications on Proportion of Days Covered (PDC)
- PDC Measure Calculation
### Week 8

**Date**
Oct 30

**Drug Safety Surveillance and Risk Management and Pharmacovigilance**

**Holly Epperly Budlong**

- Drug Safety
  - Drug-drug interactions
  - Adverse drug events
  - Classification criteria
  - Errors of omission
  - Errors of commission
- Signal sources and generation
- Signal identification
- Signal detection algorithms
- Dis-proportionality Analysis

**Homework:** After reading required reading, please answer the following question:

- In your own words and based on your own experience, explain reasons why drug safety surveillance and risk management and pharmacovigilance are important?

**Required Reading:** Pharmacoepidemiology Text

- Chapter 22 (pages 370-378, 384-392)

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### Week 9

**Date**
Nov 6

**Midterm Exam**

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### Week 10

**Date**
Nov 13

**Selected Pharmacoepidemiology Applications**

**Wendy St. Peter**

- Drug utilization studies
- Comparative effectiveness and safety research (observational studies)
- Comparative effectiveness (meta-analyses)

**Homework:** Read Coding Systems by Optum, RxNorm Overview, Generic Product Identifier

**Q1:** Why are hierarchical numerical coding systems used to categorize drugs within databases?

**Q2:** What are the similarities and differences between NDC, GPI and RXNorm drug coding?

**Required Reading:**

- Textbook of Pharmacoepidemiology
  - Chapter 22 (pages 339-346, 393-401)
  - Chapter 19 (pages 300-312).
- Coding Systems. OPTUM White Paper 2017 (pages 1-4)
### Week 11

**Date**  
Nov 20

**Principles of survival analysis and other regression techniques**  
**Rui Zhang**

- Kaplan-Meier
- Cox Regression

**Homework:** Read the Kadra A article and VassarStats tutorial (below) and answer the questions.

Q1: Why do we need Kaplan-Meier estimate?
Q2: Use the tool from the VassarStats website to calculate the example in Figure 1 in the Kalra A. article.

**Required Reading:**

- Tutorial_Kaplan-Meier Survival Probability. [http://vassarstats.net/survival.html](http://vassarstats.net/survival.html) or PDF on course website.

### Week 12

**Date**  
Nov 27

**Miscellaneous topics**  
**Eric Weinhandl and Wendy St. Peter**

Topics may include some or all of the following

- Data presentation
  - Patient Characteristic tables: Means (SD), medians (25th-75th percentiles) and standardized differences
- Difference in difference approach for confounding control
- New user designs
- Sensitivity analyses

**Homework:**

1) Review the ‘Pharmacoepidemiology Article Review and Presentation Evaluation Form’ and come to class with questions.

2) Using required reading and other information learned in class, critique patient characteristic tables from Yusuf A. Comparative Effectiveness...Am J Kidney Dis 2014;64:95-103, Block GA. Cinacalcet hydrochloride..Kidney Int 2010;78:578-589, and Arnold ME. Impact of pharmacist intervention...Am J Health-Syst Pharm 2015;72(suppl 1);S36-42.
   
   a. Should p-values be used to compare intervention and control groups?
   b. When should mean +/- SD be used, when should median and IQR (25th-75th percentile) be used to represent central patient characteristics?
   c. Explain value of using standardized differences to evaluate differences in patient characteristics.

3) Using required reading, describe the advantage of using a “new user” study design over analysis of current or existing phosphate binder users in the article Yusuf A. Am J Kidney Dis 2014;64:95-103.
4) Explain how difference-in-difference analyses resolve the problem inherent in before-after studies using Chertow GM. Epoetin alfa and outcomes in dialysis amid regulatory reform. JASN 2016;27.

Required Reading:
- Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Communications in Statistics-Simulation and Computation, 2009;38:1228-34.
- Textbook of Pharmacoepidemiology
  - Page 325: New Users

<table>
<thead>
<tr>
<th>Week 13</th>
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<tbody>
<tr>
<td>Date: Dec 4</td>
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<td><strong>Oral Presentations</strong></td>
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<th>Week 14</th>
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<tr>
<td>Date: Dec 11</td>
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<tr>
<td><strong>Oral Presentations and Course Evaluation</strong></td>
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