



EPID 765

Pharmacoepidemiology

Spring 2007

Course Instructor:	Suzanne L. West, M.P.H., Ph.D., Sue_West@unc.edu 966-7129 Office hours by appointment using email
Teaching Assistant:	Huei-Ting Tsai, M.S., Ph.D. Candidate hueiting@email.unc.edu Office hours by appointment
Classroom:	McGavran-Greenberg Hall Room1304
Class time:	Friday, 11:00am -1:50pm
Course website:	BLACKBOARD site
Textbook	Strom BL and Kimmel SE (Eds). <i>Textbook of Pharmacoepidemiology</i> . First Edition. Wiley: Chichester, 2006. Strom BL, (editor). <i>Pharmacoepidemiology</i> . 4 th Edition. Wiley: Chichester, 2005.

EPID 765 - Pharmacoepidemiology Spring 2007 Course Schedule

Class	Dates for 2007	Speaker(s)	First Topic (Speaker a)	Second Topic (Speaker b)
1	January 12	a. Sue West b. Huei-Ting Tsai	Introduction to pharmaco-epidemiology	Overview of drug development
2	January 19	a. David Couper b. Sue West	Clinical trial methodology, general considerations and non-inferiority trials	Methods 1: cohort studies, conf by indication, depletion of susceptibles, examples
3	January 26	Sue West	Case control studies, time varying hazards	The availability and use of databases for epidemiologic studies of drug safety
4	February 2	a. Bill Miller b. Sara Ephross	Diagnosis and screening related to clinical issues	Birth defects claims study
5	February 9	a. Cindy Girman b. San Keller	Development and Validation of Patient Reported Outcome Measures for Clinical Trials	Incorporating existing validated QOL scales into clinical studies
6	February 16	a. Ed Pattishall b. June Almenoff	Pharmacovigilance	Data mining
7	February 23	Mary Ellen Turner	Risk Management	Risk Management
8	March 2	Bob Davis	Vaccines—efficacy	Vaccines-safety
9	March 9	a. Scott Smith b. Matt Maciejewski	Assessing adherence in pharmacoepidemiology studies	Challenges in Pharmacoepi using Secondary Data: Examples from VA
SPRING BREAK				
10	March 23	Judy Racoosin (FDA)	Pre-marketing Assessment of Drug Safety	Use of Epidemiological Methods in Pre-market Risk Assessment
11	March 30	a. Howard McLeod b. Patrick Sullivan	Pharmacogenomics	Pharmacogenetics in Schizophrenia
12	April 13	John Grabenstein	Risk Communication Applied to Vaccines & Other Drugs	Vaccine Safety Intersects with Public Policy (cardiac events after smallpox vaccination)
13	April 20	John Paul Class presentations	Health Outcomes in Pharmaceutical Companies	Class presentations
14	April 27	Class presentations	Class presentations	Class presentations

Course Description

The purpose of EPID 765 (Pharmacoepidemiology) is to introduce students to methodologic and substantive issues that are important in the design, analysis and critical appraisal of pharmacoepidemiologic studies, with a primary focus on observational studies of the effectiveness and/or safety of therapeutic drugs and vaccines in human populations. The course will cover the following topics:

- 1. The Development and Approval of New Drugs**
 - Preclinical and clinical testing for market approval
 - Role of epidemiology in drug development
- 2. Introduction to Clinical Trial Methodology**
 - Trials to show superiority (including large simple trials)
 - Trials to show equivalence or non-inferiority
- 3. The Methodology of Observational Studies of Drugs and Vaccines**
 - Basic study designs
 - Exposure definition (persons exposed, person-time, person-time within a window)
 - Outcome definition (operational definitions of disease, the utility of diagnostic codes)
 - Descriptive epidemiology of known drug-induced diseases
 - Screening issues
 - Measurement of health-related quality of life using disease-specific instruments
 - General methodology of measurement scale development and validation
- 4. Special Methodologic Issues in Observational Studies of Drugs and Vaccines**
 - Study base issues (population- vs. hospital-based studies, selecting the wrong base)
 - Misclassification (in medical records, insurance claims data, and questionnaires)
 - Confounding by indication
 - Protopathic bias, diagnostic/referral bias, duration of use bias, etc.
 - Migration of susceptibles from older drugs to newer drugs on the market
 - Variation in risk over time (defining the most appropriate window of observation)
- 5. Safety Monitoring**
 - Drug/vaccine safety surveillance activities conducted
 - Pharmacovigilance
 - Data mining
- 6. Risk Management and Risk Communication**
- 7. Information Resources for Pharmacoepidemiologic Studies**
 - Databases (administrative/claims, clinical data repositories, general practice databases)
 - Medical data privacy (issues, regulations, and future directions)

8. Adherence in Pharmacoepidemiologic Studies
9. Drug Use in Pregnancy
10. Pharmacogenetics
11. Health Outcomes: What is it and How Does it Fit in the Pharmaceutical Industry?

Grading Policy

Students enrolled in EPID 765 are required to complete one take-home examination (midterm) and a paper discussing a topic of relevance to pharmacoepidemiology; students will present the information to the class. Class participation will be graded based on class discussions. The final grade will be computed as follows:

Midterm examination: 40%

Final paper: 30%

Class presentation: 25%

Class participation: 5%

Midterm (40%)

The midterm for EPID 765 will be **distributed on Mar 23rd and due on Mar 30th at 11am**. Students who cannot attend class on the day that the examination is being distributed must make alternative arrangements with the TA (Huei-Ting Tsai) to receive the examination in a timely manner. The limited time allotted for grading does not permit the extension of due dates under any circumstances. Therefore, *late exams will not be accepted*. Students who cannot attend class on a day that an examination is due must submit their completed examination to the TA *prior to the beginning of that class (i.e. before 11:00 am)*. It is the responsibility of the student to ensure that his/her completed examination gets to the TA before the required deadline.

Students may refer to course materials available on the web, textbooks and journal articles to complete the take-home examination. ***Collaboration with other individuals regarding any examination question is not permitted.*** In accordance with the honor code policy of the University of North Carolina at Chapel Hill, each student will be required to provide their PID to attest to the following statement: "I have completed this examination by myself without the assistance of anyone else."

Final projects (50%)

Final projects are composed of two components: final paper (30%) and class presentation (25%). Six topics are provided below to represent recent adverse events with different results.

Scenario I - Remained on the market

I: Acetaminophen and hepatotoxicity

Scenario II - Currently available through a limited-access program to ensure that only certain patients receive the medication

II-a: Propulsid and cardiac arrhythmias

II-b: Accutane (focus on birth defects)

Scenario III- Sponsor voluntarily withdrew

III-a: Vioxx and MI

III-b: Bendectin and congenital heart defects

Scenario IV- FDA requested it to be withdrawn from the market:

IV: Troglitazone and hepatotoxicity

Class presentations will be held during the final two weeks of class. There will be a group presentation on each topic. There will be 4 students for scenarios I-III and 5 students for scenario IV. Group sizes may change depending on class size. Each group presentation is expected to take 35 minutes. Suggested time allocation for each component is listed below.

Presentation for topics in scenario I to III includes following components:

- Background (7-10 mins)
- Supporting evidence that the drug should be kept on the market (7mins)
- Supporting evidence that the drug should be withdrawn from the market (7 mins)
- Moderator of students' evidence and their opinions of other choices (7 mins)

Q & A and comments from the class (4-7 mins)

Presentation for topic VI includes following components:

- Background (6 mins)
- Supporting evidence that the drug should be withdrawn from the market (6 mins)
- FDA and the company's reaction to the evidence (6 mins)
- Results from FDA and the company's actions (6 mins)
- Group's opinions about lessons learned about this adverse event (6 mins)

Q & A and comments from the class (4-7 mins)

Each student is responsible for one component of the group presentation. Student performance for the group presentation (25% of total semester grade) will be evaluated based on both the

group performance (10%) and his/her individual performance (15%). Students will be required to attend all presentation sessions to receive their full group project grade.

The final paper requires students to apply the knowledge gained from didactic instruction to summarize and critique important adverse drug reactions leading to labeling changes such as box warnings, extensive scientific debate, or removal from the US market (as is appropriate for each adverse reaction discussed). **Each student is responsible for his/her own final paper.** The written paper is limited to 10 typewritten, double-spaced pages with 1 inch margins and 12 font type; the 10 page limit EXCLUDES tables, figures, and references. References should be cited using the Uniform Requirements for Manuscripts (see N Engl J Med 1991; 324: 424-8)

A suggested outline for both the written and oral presentation is provided below:

- Pharmacology of suspect drug—provide information on the drug’s mode of action, whether the reaction would be an expected or unexpected outcome based on drug’s action and the pathogenic process involved.
- Natural history of the disease for which the drug was approved (if known) to answer the question of whether the suspected adverse drug effect could be due to a natural progression of the indication for the drug’s use.
- History of marketing for this drug—when did FDA approve the drug for marketing, provide a thorough documentation of the history of the adverse drug reaction with regard to premarketing studies, spontaneous reporting system reports, the news media, scientific research papers or case reports that suggested a problem. Discuss any regulatory actions that may have been required.
- Describe the pharmaceutical company’s responses to the potential adverse drug reaction and what studies were undertaken. What were the problems with /limitations of the studies undertaken and the company’s response to the FDA?
- Do you support the final outcome? Use appropriate evidence to support your opinion.

Class participation

Class participation is a mandatory and will be judged by discussion during the lecture.

Summary of important Date

Event	Distributed	Due (beginning of class)
Mid-Term	Take-home: March 23	March 30
Final paper		
- Topics and list of group members		January 26
- Background draft and list of references		March 9
- Final paper		April 20
- Class presentation		April 20, April 27

Other Resources

Users' Guides to the Medical Literature – an educational series published by the Journal of the American Medical Association. Hyperlinks to all of the articles in this series are posted on the EPID 765 website under Course Documents.

Recommended Websites:

(Hyperlinks to these sites are posted on the EPID 765 website under Course Documents)

Around UNC:

Cecil G. Sheps Center for Health Services Research

<http://www.shepscenter.unc.edu/>

The UNC Program on Health Outcomes and the
Center for Education and Research in Therapeutics (CERT)

<http://certs.unc.edu/>

The Cochrane Library

<http://www.cochrane.org/index.htm>

The best source for reliable, up-to-date, systematic reviews of randomized controlled trials on the effects of hundreds of different health care interventions.

[login=hc005377; password= white7]

International Conference on Harmonization

<http://www.ich.org/cache/compo/276-254-1.html>

Guidance on all matters related to the preclinical and clinical development of new medicines for regulatory approval in Europe, Japan, and the United States. Although the ICH guidelines do not address epidemiologic issues to any extent, persons working in pharmacoepidemiology still should be familiar with these international guidelines.

International Society for Pharmacoepidemiology

<http://www.pharmacoepi.org/>

The International Society for Pharmacoepidemiology (ISPE) is a non-profit international professional membership organization dedicated to promoting pharmacoepidemiology. The [Public Policy/Links](#) page has hyperlinks to ISPE policy statements, other professional associations, data privacy sites, government agencies, research organizations, and online resources (CDC publications, Merck Manual, PDR).

The UK Committee on Safety of Medicines

<http://www.open.gov.uk/mca/csmhome.htm>

The independent advisory committee which advises the UK Licensing Authority on the quality, efficacy and safety of medicines. It is among the most respected advisory bodies in the field of drug regulation.

The University of York's NHS Center for Reviews and Dissemination

<http://www.york.ac.uk/inst/crd/>

Links to systematic reviews, health technology assessment and evidence-based health care resources.

Instructions about Readings

Students should note that some of the lecture outlines in the weekly folders were not complete at the start of the course but they will be complete at least one week prior to the lecture. They should check the EPID 765 Blackboard site each week to confirm the list of readings for the upcoming class. Students are expected to read all of the *recommended readings* before each lecture. In addition to the recommended readings, some lectures outlines also include *optional readings* and *relevant websites*. These supplemental readings are intended for students who want to enrich their understanding of a particular topic.

The following information can be used to access the Blackboard site for EPID 765
The Blackboard site can be accessed using Netscape or Microsoft Internet Explorer but is more easily accessed using Microsoft Internet Explorer.

Go to <https://blackboard.unc.edu>

Click LOGIN task bar on the left hand side.

Login using your ONYEN user name and password. This is the same user name and password used for email.

This will bring up a screen saying welcome!

Under "My Courses", It will say 'Courses in which you are participating' and Spring 2007 will be listed

Click on Spring 2007 Pharmacoepid

This will bring up the announcements page. On the left there will be a series of task bars entitled: announcements, course information, staff information, course documents, assignments, communication, external links and tools. **Course documents** contains all of the readings for the lectures.

Click on Course Documents.

A folder with each lecture will appear. If you click on a lecture folder, it will open and show a list of readings for each lecturer that day. Some of the lectures may have 2 lecturers but the readings for each lecturer will be listed in this folder under the lecture title.

Most of the readings are listed by author and year and number of bytes and can be accessed

by clicking on the author and year. As an example, Lecture 5 has 2 speakers, Drs. Cynthia Girman and San Keller. Dr. Girman's first reading is

Chassany (2002) (1274548 Bytes)

When you click on Chassany (2002), a new window will open. From here the reading can be viewed, printed or saved. Some of the readings are very large, but they may only require that you read the first 15 pages. Check which pages to read before printing the whole document.

The full reading list will be below the speaker's name and will contain the required and recommended readings. You will be able to download most of the required and recommended readings from the website. There may also be a list of relevant websites under the required readings that will pertain to the lecture.

NOTE: All of these readings are in PDF format so for downloading, you will have to have Adobe Acrobat Reader. Make sure this is installed on the computer you are working on before trying to download a reading. If you do not have this program it can be downloaded from www.adobe.com

To log out there is an icon on the top right hand side labeled log out.