



INTERMEDIATE METHODS FOR CLINICAL AND OUTCOMES RESEARCH

M88-589/M17-589

Spring, 2017

Time: Wednesday, 4:30 to 7:00 p.m.

Location: Classroom A, Division of General Medical Sciences 1th floor, Taylor Avenue Building

Instructors: Ann Marie Dale, Ph.D., OTR/L
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Office Hours: By Appointment (Contact Dr. Dale directly)

Target audience: Graduate students, trainees, or junior faculty interested in conducting clinical research, including those enrolled in the Masters of Science in Clinical Investigation program and Applied Health Behavior Research program. Prior clinical research experience is helpful but not required.

Prerequisite: Epidemiology for Clinical Research or Designing Outcomes in Clinical Research and an introductory biostatistics course.

Credits: 3

Course Overview

Introduction: This course focuses on intermediate principles of epidemiology and outcomes research as they apply to clinical research. The course provides an overview of the standard methods used in clinical research to design studies, evaluate findings, and make informed decisions in the care of patients as well as basic skills needed to evaluate the epidemiologic literature. Critical thinking and scientific/analytic competencies are emphasized throughout the course.

Purpose: This course will focus on applications of advanced epidemiologic principles and tools in clinical research and in understanding the medical literature concerning these issues. This will be accomplished via different venues that will enhance the critical thinking and scientific/analytic competencies for the students who complete the course.

Course Description

Course Format: The course format will include lectures, class discussion of exercises, supplementary reading material, critiquing the literature, a midterm exam, and a final exam.

Course Elements and Requirements for Students:

- It is very important that students attend all classes. The information needed to master the course objectives will be presented and discussed in class. Students who miss three or more classes may be asked to withdraw from the course and to re-take the course at a later time. Arrangements for exams or assignments that will be missed due to travel/conferences, etc. must be made ahead of the expected missed class.
- Students are expected to complete the assigned readings before each lecture. The readings have been selected to complement the lectures, and will provide additional examples for applying epidemiologic methods and tools in clinical research.
- Students should be prepared to discuss the exercises and any assigned readings at the start of each class and to participate in class discussion.

Course Elements and Requirements for the Instructors:

- The instructor will usually be available during normal business hours to answer any questions that you may have about the course. If your schedule precludes you from meeting during normal business hours, she will make every effort to meet with you at times that may be more convenient for you. Please feel free to contact the instructor by telephone or via email to discuss any issues concerning the course.
- The instructor retains the right to change the order of the lectures and the content of the class to meet the needs of the students who are enrolled in the course.

Readings:

- Selected chapters from a variety of epidemiologic and methodologic textbooks
- Supplementary readings

Assigned readings: All required readings (articles and/or book chapters) will be posted on Blackboard at least one week prior to the relevant class session.

Grading Determination and Policy: *The student's final grade for the course will be determined in the following way: a midterm exam (50 points), 6 homework assignments (60 points total), one article critique (30 points), and a final exam (60 points)* Late submissions will not be accepted, and critiques that are not completed independently by the student will not be graded.

The critique of the published study (30 points) will be based on the following criteria. Please use the following **separate** headings in your critique.

- 1) Study objective, setting and participants (2 point).
- 2) Description of the study design (2 point).
- 3) Brief description of the study results and its implications (2 points).
- 4) Strengths and weaknesses of the study identified by you and by the authors (2 points).
- 5) How these weaknesses of the study affected the findings (12 points).
- 6) How the authors addressed the weaknesses of the study (5 points).
- 7) How the study could be improved (5 points).

For items 4-7, focus your critique on the issues of selection bias, measurement bias, confounding, and any other methodological issues pertaining to the type of study design used in the study that were discussed during class. Please use narrative to write your critique and email it directly to Dr. Dale on or before the assigned due date. The article review is due on **April 19**.

The final grade will be based on the class distribution of 200 points from the written critique of a study (30 points), midterm exam (50 points), and 6 homework assignments (10 points each; total 60 points) and a final exam (60 points).

Grading scale

Grades/sub-grades
A+ (98% to 100%)
A (93% to 97%)
A- (90% to 92%)
B+ (88% to 89%)
B (83% to 87%)
B- (80% to 82%)
C+ (77% to 79%)
C (73% to 77%)
C- (70% to 72%)

Total points available: 200

Academic Integrity Policy

Students are expected to abide by and uphold academic integrity on all assignments and exams. If problems arise, please talk with the instructor so that the problem(s) can be remedied. Violations of academic integrity will result in notification to the Associate Dean of Academic Affairs at Washington University School of Medicine as well as to the MSCland AHBR program directors. Any hint of violation during the exams will result in a grade of 0 (zero) for that exam.

Pagers and cellular phones

Although clinicians may be expected to be available by pager or cellular phone, please limit their use as much as possible during class.

Students with disabilities

Washington University is committed to providing accommodations and/or services to students with documented disabilities. Students who are seeking support for a disability or a suspected disability should contact the Disability Resource Center (DRC) at 5-4062 on the lower level of the Women's Building (drc@dosa.wustl.edu). The DRC is responsible for approving and arranging all accommodations for University students.

Blackboard

We will use Blackboard to manage the class including all readings, assignments and exercises, and any other relevant course materials. Blackboard can be accessed at <https://bb.wustl.edu/>. Readings will be posted at least one week prior to class. Slides will be posted approximately 24 hours prior to class. Assignments will be posted immediately prior to or following class.

Date	Week	Topic and Assignments
1/18	1	<p>Topic: Introduction and Review</p> <ul style="list-style-type: none"> • Course overview • Review of observational study designs • Review of main issues related to bias in observational studies <p>Readings:</p> <ol style="list-style-type: none"> 1) Altman DG and JM Bland. Uncertainty and sampling error. BMJ 2014;349-50. 2) Altman DG and JM Bland. Uncertainty beyond sampling error. BMJ 2014:349-50. 3) Schulz KF and DA Grimes. Case-control studies: research in reverse. Lancet 2002; 359:431-34. 4) Grimes DA and KF Schulz. Compared to what? Finding controls for case-control studies. 5) Lancet 2005; 365:1429-33. Grimes DA and KF Schulz. Cohort studies: marching towards outcomes. Lancet 2002; 359:341-45. 6) Text: Szkolo & Nieto- Chapter 1 <p>Assignment: Homework #1 (Due 1/25, 4:00pm)</p>
1/25	2	<p>Topic: Bias (part I)</p> <ul style="list-style-type: none"> • Selection bias • Measurement error (Misclassification) <p>Readings:</p> <ol style="list-style-type: none"> 1) Lash chapters 4, 6 (uploaded onto Blackboard) 2) Lash TL, et.al. Good practices for quantitative bias analysis. Int J Epi 2014:1969-1985. 3) Text: Szkolo & Nieto- Chapter 4 <p>Assignment: Homework #2 (Due 2/1, 4:00pm)</p>
2/1	3	<p>Topic: Bias (part II)</p> <ul style="list-style-type: none"> • Unmeasured confounding • Multiple bias modeling <p>Readings:</p> <ol style="list-style-type: none"> 1) Lash chapters 5 (uploaded onto Blackboard) <p>Assignment: Homework #3 (Due 2/8, 4:00pm)</p>

2/8	4	<p>Topic: Measurement in Epidemiology</p> <ul style="list-style-type: none"> • Developing or Evaluating Survey Measures (McQueen) • Selection of Clinical Measures <p>Readings:</p> <p>1) Kimberlin CL and AG Winterstein. Validity and reliability of measurement instruments used in research. Am J Health-Syst Pharm 2008; 65:2276-2284.</p> <p>Assignment:</p> <p>Homework #4 (Due 2/22, 4:00pm)</p>
2/15	5	<p>No class</p> <p>Homework #4 (Due 2/22, 4:00pm)</p>
2/22	6	<p>Topic: Using large data</p> <ul style="list-style-type: none"> • Bioinformatics (McIntosh) • Missing data, multiple imputation (Cooper) <p>Readings:</p> <p>1) Hersh WR, Weiner MG, Embi PJ, et al. Caveats for the Use of Operational Electronic Health Record Data in Comparative Effectiveness Research. Med Care. 2013;51 (8 0 3):S30-S37.</p> <p>2) Rombach I, Rivero-Arias O, Gray. The current practice of handling and reporting missing outcome data in eight widely used PROMs in RCT publications: a review of the current literature. Qual Life Res Jan. 2016, online.</p> <p>3) Graham JW. Missing Data Analysis: Making It Work in the Real World. Ann Rev Psychol 2009;60:549-576.</p> <p>4) Janssen KJM, Donders ART, Harrell FE, et al. Missing covariate data in medical research: To impute is better than to ignore. J Clin Epi 2010; 63:721-727.</p>
3/1	7	<p>Topic: Treatment trials I (Schechtman) and II (Gillespie)</p> <ul style="list-style-type: none"> • Review of randomized clinical trial design • Testing hypotheses for superiority and non-inferiority trials • Challenges in clinical trials—why do we get the wrong answer so frequently? • Economic evaluation alongside clinical trials <p>Readings:</p> <p>1) Petrou S and A Gray. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. BMJ</p>

		<p>2011: 342.</p> <p>2) Ramsey SD, et al. Cost-Effectiveness Analysis Alongside Clinical Trials II—An ISPOR Good Research Practices Task Force Report. <i>Value In Health</i> 2015;18:161-172.</p>
3/8	8	Midterm Exam (in class)
3/15	9	Spring Break- no class
3/22	10	<p>Topic: Intervention Effects in Observational Studies I (Olsen)</p> <ul style="list-style-type: none"> • Overview • Propensity Scores <p>Readings:</p> <p>1) Newgard GD, Hedges JR, Arthur M, Mullins RJ. Advanced statistics: The propensity score—A method for estimating treatment effect in observational research. <i>Acad Emerg Med</i> 11, 953-961, 2004.</p> <p>2) Haukoos JS and RJ Lewis. The Propensity Score. <i>JAMA Guide to Statistics and Methods</i> 2015;314:1637-1638.</p> <p>3) Raghunathan K, Shaw A, Nathanson B., et al. Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis. <i>Crit Care Med.</i> 2014; 42:1585-1591.</p>
3/29	11	<p>Topic: Predictive and Prognostic Models (Dale)</p> <p>Readings:</p> <p>1) Steyerberg EW, AJ Vickers, NR Cook, T Gerds, M Gonen, N Obuchowski, MJ Pencina and MW Kattan. Assessing the performance of prediction models: a framework for some traditional and novel measures. <i>Epidemiology</i> 2010; 21:128- 138.</p> <p>2) Croft P, Altman DG, Deeks JJ et al. The science of clinical practice: disease diagnosis or patient prognosis? Evidence about “what is likely to happen” should shape clinical practice. <i>BMC Med.</i> 2015; 13:20.</p> <p>3) Hemingway H, Croft P, Perel P et al. Prognosis research strategy (PROGRESS) 1: A framework for researching clinical outcomes. <i>BMJ</i> 2013; 346:e5595.</p> <p>4) Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. <i>BMJ</i> 2009;338.</p> <p>5) Steyerberg EW & Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. <i>European Heart Journal</i> 2014; 35:1925-1931.</p> <p>6) Steyerberg EW, Veville BA, Koppert LB et al. Surgical Mortality in Patients With Esophageal Cancer: Development and Validation of a Simple Risk Score. <i>J Clin Onc</i> 2006; 24(26):4277-4284.</p> <p>Assignment:</p>

		<p>Homework #5 (Due 4/5)</p> <p>Pflug N, et al., Development of a comprehensive prognostic index for patients with chronic lymphocytic leukemia, <i>Blood</i> 2014;124(1):49-62.</p> <p>Lipsky BA, et al., Developing and validating a risk score for lower-extremity amputation in patients hospitalized for a diabetic foot infection, <i>Diabetes Care</i> 2011;34:1695-1700.</p>
4/5	12	<p>Topic: Intervention Effects in Observational Studies II (TBD)</p> <p>Readings:</p> <p>Assignment:</p> <p>Homework #6 (Due 4/12)</p> <p>Federspiel JJ, et al., Evaluating the effectiveness of a rapidly-adopted cardiovascular technology with administrative data: the case of drug-eluting stents for acute coronary syndromes, <i>Am Heart J</i> 2012; 164 (2):207-214.</p>
4/12	13	<p>Topic: Statistical methods for longitudinal data I (Rowlands)</p> <ul style="list-style-type: none"> • Time-dependent confounders • Marginal Structural Models • Competing risks analysis <p>Readings:</p> <ol style="list-style-type: none"> 1) Robins JM, MA Hernan and B Brumback. Marginal Structural Models and Causal Inference in Epidemiology. <i>Epidemiology</i> 2000; 11:550-560. 2) Wolbers M, MT Koller, JCM Witteman and EW Steyerberg. Prognostic Models with Competing Risks Methods and Application to Coronary Risk Prediction. <i>Epidemiology</i> 2009; 20:555-561. <p>Assignment:</p> <p>Article Review (Due 4/19, 4:00pm)</p>
4/19	14	<p>Topic: Statistical methods for longitudinal data II</p> <ul style="list-style-type: none"> • Identifying Trajectories and latent class models (TBD) • Mediation models and SEM (McQueen) <p>Readings:</p> <ol style="list-style-type: none"> 1) Xie Y, Bowe B, Xian H et al. Estimated GFR Trajectories of People Entering CKD Stage 4 and Subsequent Kidney Disease Outcomes and Mortality. <i>Am J Kidney Dis</i> 2016. 2) Xie Y, Bowe B, Xian H et al. Rate of Kidney Function Decline and Risk of

		<p>Hospitalizations in Stage 3A CKD. Clin J AmSoc Nephrol 2015: 1-10.</p> <p>3) Xie Y, Bowe B, Xian H et al. Renal Function Trajectories in Patients with Prior Improved eGFR Slopes and Risk of Death. PLOS ONE Feb. 2016, DOI:10.1371/journal.pone.0149283</p>
4/26	15	<p>Topic: Studying context in epidemiology (Dale)</p> <ul style="list-style-type: none"> • Social determinants of health, geographic variation in outcomes • Multilevel models <p>Readings:</p> <ol style="list-style-type: none"> 1) Diez-Roux AV. Multilevel analysis in public health research. Annu Rev Public Health 2000; 21: 171-192. 2) Turk-Adawi KI, NB Oldridge, SS Tarima, WB Stason, DS Shepard. Cardiac Rehabilitation Patient and Organizational Factors: What Keeps Patients in Programs? J Am Heart Assoc 2013. 3) Crump C. Birth History Is Forever: Implications for Family Medicine. J Am Board Fam Med 2015; 28:121-123.
5/3	16	Final Exam (In Class)