MPHS Master of Population Health Sciences

M19-550 Randomized Controlled Trials

Fall 2019 (08/26/19 – 12/13/19)
Mondays, 1:00-4:00 pm
Location: Taylor Avenue Building
2nd floor, Richmond Room

INSTRUCTORS

Graham Colditz, MD, DrPH, colditzg@wustl.edu
Esther Lu, PhD, esther@wustl.edu
Carrie Stoll, MPH, MSW, Teaching Assistant, Carolyn.stoll@wustl.edu

OFFICE HOURS

By appointment and after class

PREREQUISITES

Introductory epidemiology and biostatistics 1 simultaneously to this course (or permission of the course master)

TARGET AUDIENCE

Clinicians interested in conducting research, clinical training program participants, students enrolled in Master of Science in Biostatistics program. Prior clinical or community research experience is helpful but not required.

COURSE DESCPRITION & OBJECTIVES

This course provides a comprehensive introduction to randomized controlled clinical trials. Topics include types of clinical trials research (efficacy and effectiveness trials), study design, treatment allocation, randomization and stratification, quality control, analysis, sample size requirements, patient consent, data safety and monitoring plans, reporting standards, and interpretation of results. The role of randomized trials in comparative effectiveness research and also the evaluation of prevention strategies is also addressed. Application of results of trials to inform practice is emphasized throughout.

Evaluation: Students design a clinical investigation protocol in their own field of interest, write a proposal for it, and critique recently published medical literature.

COMPETENCIES

1. Ability to design randomized controlled trial
   - Define research question
   - Understand efficacy and effectiveness trials, their differences and implications for clinical practice
   - Define study population and estimate sample size
   - Define approaches for recruitment strategy, randomization, and blinding
   - Apply eligibility criteria and recording of recruitment adequate for trial reports
   - Develop data collection plan for primary endpoint, secondary endpoint, covariates and adverse events and implement data quality monitoring
   - Apply strategies for monitoring trial adherence

2. Skills and experience to conduct analysis of RCT
   - Master data analysis and model fitting in context of RCT

- Conduct survival analysis
- Apply principles of interim analysis and stopping rules
- Apply principles for subgroup analysis
- Apply principles for per protocol analysis
- Understand design and implementation issues in conduct of multicenter trials

3. Master the core reporting strategies
   - Master reporting standards for RCTs following Consort and Extended Consort approaches
   - Master development of reports for data safety monitoring board
   - Understand issues pertaining to FDA standards fro reporting

4. Draw inferences from data to inform clinical and public health practices
   - Correctly use reasoning for design and methodologies employed
   - Interpret Adverse Events in context of biology and study design
   - Interpret subgroup analyses in context of biology, disease process and public health practices
   - Present oral and written reports from analyses
   - Place inference in context of clinical and public health implications for action and future research

GRADING

Your grade will be based on:

- Class participation (10%)
- HW 1: Schema (10%)
- HW 2: Primary outcome and sample size calculation (10%)
- HW 3: Data collection and analysis plan (10%)
- Final protocol presentation (10%) and paper (50%)

Grading Scale

A+: 97-100; A: 93-96; A-: 90-92; B+: 87-89; B: 83-86; B-: 80-82; C+: 77-79; C: 73-76; C-: 70-72

ATTENDANCE AND PARTICIPATION

Class attendance is required. As a courtesy to other students, you are expected to arrive on time. More than two unexcused absences from class may result in a lowered grade. Readings assigned for each class should be read ahead of the class and students should be prepared to discuss the material from readings.

POLICY ON LATE ASSIGNMENTS

Late assignments will result in a deduction of one grade point (A+ down to A) for each day late (including weekends) unless prior approval is obtained from the instructor or a compelling situation prevents prior approval (i.e. documented health issues or family emergencies).

ASSIGNMENTS & DUE DATES

Details of all assignments can be found in the Assignments folder on Canvas

- **HW 1: Schema**
  Due September 22 by 11:59 pm. Submit via Canvas.
  Presented in class on September 23.
- **HW 2: Primary outcome and sample size calculation**
  Due Oct 7 by 11:59 pm. Submit via Canvas.

- **HW 3: Data collection and analysis plan**
  Due Nov 4 by 11:59 pm. Submit via Canvas.
- **Final Presentation**
  In class on Nov 18 and Nov 25 (if needed, dependent on number of project groups). Students will sign up for a date in early October.
  Presentation slides are due the night before your assigned presentation date (Nov 17 by 11:59 pm or Nov 24 by 11:59 pm). Submit via Canvas.
- **Final Protocol**
  Due Dec 19 by 11:59 pm. Submit via Canvas.

READINGS

Text (Fundamentals of Clinical Trials: Friedman, Furberg, and DeMets. 5th edition) plus the listing that follows accessible through the library listing. The text is available as an ebook from Becker Medical Library under e-books.

Week	Date	Topic	Assignment Due	Readings
Class 1	Aug. 26	Overview – the role of RCTs in evaluating medical and public health interventions Goals for the course Homework assignments		Overview – the role of RCTs in evaluating medical and public health intervention • *Chapter 1. (Introduction to Clinical Trials) and Chapter 5 (Basic study design)* • Doll R. Controlled trials: the 1948 watershed BMJ 1998; 317: 1217-20 • Sydes MR. Potential pitfalls in the design and reporting of clinical trials. Lancet Oncology 2010;11:694-700 • Taylor PR, Dawsey SM, Chung JL, Guo YW, Blot WJ and the Linxian Nutrition Intervention Trial Study Group. Prevention of Esophageal Cancer: The Nutrition Intervention Trials in Linxian, China. Cancer Research (suppl..) 1994;54:2029s-2031s. • Banting FG, Best CH, Collip JB, Campbell, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. Can Med Assoc J 1991;145(10):1281-86. Classic articles • Peto R, Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design Br J Cancer 1976 34: 585-612 • Peto R, et al. II. analysis and examples. Br J cancer 1977 35:1-39 • A. Bradford Hill. The Clinical Trial. NEJM 1952

Class 2	Sept. 9	Phase III trials; Efficacy vs. Effectiveness (Population definitions) Trials in context of CER Discuss HW assignments and final project expectations Guest Speaker: Shane LaRue, MD, MPHS		Phase III trials • COBALT investigators, NEJM 1997:337:1124-30 • Ware and Antman. Equivalence trials NEJM 1997; 337:1159-61 Efficacy vs. Effectiveness (Population definitions) • *Chapter 5 Basic study design* • Tunis S, et al. Practical Clinical Trial JAMA 2003:290:1624-32 • Ware J. Pragmatic trials – guides to better patient care. NEJM 2011 364:1685-7 • Glasgow R, et al RE-AIM AJPH 1999:89:1322-7 • Glasgow R et al Use of RE-Aim to address health inequities… Trans Behav Med 2013: 3:200-2010
Class 3	Sept. 16	Bias and Error Randomization (Biostatistics issues 1)		*Chapter 6. The randomization process* See Protocol on Canvas and Bennett et al Obesity treatment for socioeconomically disadvantaged patients in primary care practice Arch Internal Med 2012
Class 4	Sept. 23	**Homework 1: Schema Presentations**	**Homework 1: Schema**	
Class 5	Sept. 30	Sample size & stopping rules		*Chapter 8 Sample size*
Class 6	Oct. 7	Defining and enrolling patients Guest Speaker: Bettina Drake, PhD, MPH Ethical considerations, health literacy and participant recruitment issues.	**Homework 2: Primary outcome and sample size calculation**	Ethical considerations • *Chapter 2 Ethical Issues* Health literacy and enrollment issues (read HIPAA forms, WUSTL) Defining and enrolling patients Baseline data collection *Chapter 4 Study population* *Chapter 10 Recruitment*
Class 7	Oct. 14	Adherence to intervention RCTs for Prevention		Adherence to intervention • *Chapter 14 Participant adherence* • *Chapter 16 Monitoring response variables* RCTs for prevention • Zelen M. Are primary cancer prevention trials feasible? JNCI 1988: 80;1442-4 • Colditz and Taylor. Prevention trials: there place in how we understand the value of prevention strategies. Ann Rev Public Health 2010

Class 8	Oct. 21	Data quality Intermediate endpoints/ biomarker endpoints Issues in data collection and management – REDCap - J Tappenden		*Chapter 11 Data collection and quality control*
Class 9	Oct. 28	Analysis – main hypothesis, secondary and subgroup analysis		• Chapter 18 Issues in data analysis • Sun,… Guyatt Is a subgroup effect… BMJ 2010, 340- • Wang et al., Statistics in Medicine – Reporting of subgroup analyses in clinical trials. NEJM 2007; 357:2189-94
Class 10	Nov. 4	Follow-up, data monitoring, interim analysis, Adverse Events (AEs) & SAEs	**Due: Homework 3 data collection and analysis plan**	• *Chapter 12 Assessing and reporting of harm*
Class 11	Nov. 11	Per protocol analysis Reporting CONSORT & EXTENDED consort		Per protocol analysis • Ware J. Interpreting incomplete data in studies of diet and weight loss NEJM 2003; 348 : 2136-7 • Williamson et al., Adherence is a multi-dimensional construct in the POUNDS LOST trial. J Behav Med 2010; 33:35-46 Reporting CONSORT & EXTENDED consort • *Chapter 20 Reporting and interpreting of results* • Schulz et al CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials BMJ 2010;340:c332 • Moher et al., CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomized trials BMJ 2010;340:c869 • Zwarenstein et al., Improving reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008;337:a2390 • Glasziou et al., Taking interventions from trials to practice BMJ 2010 341:c3852 • Ivers NM, et al. Impact of CONSORT extension for cluster randomized trials on quality of reporting and study methodology: review of random sample of 300 trials , 2000-8 BMJ 2011;343:d5886
Class 12	Nov. 18	**Final presentations**		

Class 13	Nov. 25	**Final presentations**
Class 14	Dec. 2	Budgets, timelines, and feasibility Applying results of RCTs to clinical practice
Class 15	Dec. 9	Data safety and monitoring *Guest Speaker TBA* **Due: Final protocol**

DROP DATES

You may drop for any reason during the course of the semester. However, you may only receive a partial or no tuition reimbursement depending upon how far into the semester you drop the course. See the MPHS Student Handbook. Late withdrawals will appear on your transcript as a withdrawal.

MPHS Academic Policy Guidelines:

Guidelines regarding MPHS course registration and enrollment, grades, tuition obligation, and academic leave are consolidated in the **MPHS Student Handbook**. Please review this document.

MPHS Guidelines for Academic and Non-Academic Transgressions:

By registering for this course you have agreed to the terms of the **MPHS Academic Integrity Policy, outlined below and in more detail in the MPHS Student Handbook**. Please review this policy before submitting your first graded assignment.

Academic Integrity/Plagiarism Policy:

- Academic dishonesty is a serious offense that may lead to probation, suspension, or dismissal from the University. Academic dishonesty includes plagiarism (the use of someone else's ideas, statements, or approaches without proper citation). Academic dishonesty also includes copying information from another student, submitting work from a previous class for a new grade without prior approval from your instructor, cheating on exams, etc. You are responsible for reviewing WashU's academic integrity resources to become aware of all the actions that constitute academic dishonesty.
- All instances of academic dishonesty will be reported to the Office of the Registrar for investigation and potential disciplinary action. In addition, the instructor will make an independent decision about the student's grade on any assignment in question. The MPHS process regarding academic dishonesty is described in the MPHS Student Handbook

DISABILITY RESOURCES

It is the goal of Washington University to assist students with disabilities in removing the barriers their disabilities may pose and provide support in facing the challenge of pursuing an education at Washington University.

Washington University recognizes and accepts its professional, legal and moral responsibility to avoid discrimination in the acceptance and education of qualified students with disabilities and to provide

reasonable accommodations to such students consistent with the principles embodied in the law. These guidelines apply to students seeking admittance as well as to those who become disabled while they are enrolled.

Washington University makes every effort to insure that all qualified applicants and students can participate in and take full advantage of all programs and opportunities offered within the university. Washington University encourages and gives full consideration to all applicants for admission. Washington University does not discriminate in access to its programs and activities on the basis of age, sex, sexual orientation, race, disability, religion, color or national origin.

To learn more about services provided to students with disabilities, initiate the process of formal documentation and/or to arrange for accommodations, please review the Disability Resources for the Med School at the start of the course.

MENTAL HEALTH RESOURCES

Mental Health Services' professional staff members work with students to resolve personal and interpersonal difficulties, many of which can affect the academic experience. These include conflicts with or worry about friends or family, concerns about eating or drinking patterns, and feelings of anxiety and depression. See: shs.wustl.edu/MentalHealth.

SEXUAL ASSAULT RESOURCES

You can also speak confidentially and learn about available resources by contacting Dr. Gladys Smith, PhD, Sexual Violence Prevention Therapist and Licensed Psychologist at the Medical Campus, (314) 362-2404. Additionally, you can report incidents to the Office of Student Affairs or by contacting WUSM Protective Services 314-362-4357 or your local law enforcement agency.

BIAS RESOURCES

The University has a process through which students and staff who have experienced or witnessed bias, prejudice or discrimination against a student can report their experiences to the University's Bias Report and Support System (BRSS) team. For details see: diversityinclusion.wustl.edu/brss/.

Office of the Associate Vice Chancellor for Diversity, Equity and Inclusion (DEI)

The DEI Training Team designs, facilitates and leads diversity education programming for faculty, staff and students on a wide range of topics including: creating a climate of respect, the value of diversity and the role of biases in our day-to-day lives.
diversity.med.wustl.edu/training/

The Office of Diversity Programs promotes diversity among and prepares medical students to lead in a global society. A priority for the Office of Diversity Programs is to cultivate and foster a supportive campus climate for students of all backgrounds, cultures and identities.
mddiversity.wustl.edu/

The Diversity and Inclusion Student Council promotes an inclusive campus environment for all School of Medicine students.
sites.wustl.edu/disc/

The Office for International Students and Scholars embraces the university's mission of welcoming promising students from around the world.
wumma.wustl.edu/