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 DESCRIPTION & 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 for 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 ebooks.

<table>
<thead>
<tr>
<th>Week</th>
<th>Date</th>
<th>Topic</th>
<th>Assignment Due</th>
<th>Readings</th>
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| 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  
• 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  
  • A. Bradford Hill. The Clinical Trial. NEJM 1952 |
Class 2  Sept. 9  Phase III trials;  Phase III trials
Efficacy vs. Effectiveness
(Population definitions)
Trials in context of CER
Discuss HW assignments and final project expectations
Efficacy vs. Effectiveness (Population definitions)

Guest Speaker: Shane LaRue, MD, MPH5

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
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

Class 7  Oct. 14  Adherence to intervention RCTs for Prevention
Adherence to intervention

RCTs for prevention

- Zelen M. Are primary cancer prevention trials feasible? JNCI 1988; 80;1442-4

- Chapter 2 Ethical Issues
- Health literacy and enrollment issues
(read HIPAA forms, WUSTL)

- Chapter 4 Study population
- Chapter 10 Recruitment

- Chapter 14 Participant adherence
- Chapter 16 Monitoring response variables
| Class 8  | Oct. 21 | Data quality  
Intermediate endpoints/ biomarker endpoints | Chapter 11 Data collection and quality control  
Issues in data collection and management – REDCap - J Tappenden |
| 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  
• 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] |
| Class 11 | Nov. 11 | Per protocol analysis  
Reporting CONSORT & EXTENDED consort | Per protocol analysis  
• 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]  
| Class 12 | Nov. 18 | Final presentations |  |
| 12 |
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](http://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/](http://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/](http://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/](http://mddiversity.wustl.edu/)

**The Diversity and Inclusion Student Council** promotes an inclusive campus environment for all School of Medicine students. [sites.wustl.edu/disc/](http://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/](http://wumma.wustl.edu/)