M19-550 Randomized Controlled Trials

Fall 2018

Time  Monday 1 to 4 PM

Location  Richmond Teaching Room (2132), 2nd Floor, Taylor Ave Building, 600 S Taylor Ave. Division of Public Health Sciences.

Instructors  Graham Colditz, MD, DrPH, Esther Lu, PhD, and guest speakers  Carrie Stoll MPH, MSW, Teaching Assistant  Sarah Humble, MS, Teaching Assistant

Office hours  By appointment and after class  
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esther@wustl.edu  
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sarah.lyons@wustl.edu

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.

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

Credits  3


https://en.wikipedia.org/wiki/Austin_Bradford_Hill
Course overview

Description: 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
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.

Assignment due dates

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

- **HW 1: Schema**
  Due September 23 by 11:59 pm. Submit via Canvas.
  Presented in class on September 24.
- **HW 2: Primary outcome and sample size calculation**
  Due Oct 8 by 11:59 pm. Submit via Canvas.
- **HW 3: Data collection and analysis plan**
  Due Nov 5 by 11:59 pm. Submit via Canvas.
- **Final Presentation**
  In class on Nov 19 and Nov 26 (if needed). Students will sign up for a date in early October. Presentation slides are due the night before your assigned presentation date (Nov 18 by 11:59 pm or Nov 25 by 11:59 pm). Submit via Canvas.
- **Final Protocol**
  Due Dec 10 by 11:59 pm. Submit via Canvas.

Grade

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).
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<th>Week</th>
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|      | Aug 27 | Overview – the role of RCTs in evaluating medical and public health interventions  
| Class 1 |        | Goals for the course  
|        |        | Homework assignments |
|      | Sept 10 | Phase III trials;  
| Class 2 |        | Efficacy vs. Effectiveness (Population definitions)  
|        |        | Trials in context of CER  
|        |        | Discuss HW assignments and final project expectations  
|        |        | Guest Speaker: Shane LaRue, MD, MPH |
|      | Sept 17 | Bias and Error  
| Class 3 |        | Randomization  
|        |        | (Biostatistics issues 1) |
|      | Sept. 24 | Homework 1: Schema Presentations |
| Class 4 |        | Sample size & stopping rules  
|        | Oct 1 | Guest Speaker: Ashley Eskew, MD |
|      | Oct 8 | Defining and enrolling patients  
| Class 6 |        | Guest Speaker: Bettina Drake, PhD, MPH  
|        |        | Ethical considerations, health literacy and participant recruitment issues.  
|        | DUE: Homework 2 Primary outcome and sample size calculation |
|      | Oct 15 | Adherence to intervention  
| Class 7 |        | RCTs for Prevention |
|      | Oct 22 | Data quality  
<p>| Class 8 |        | Intermediate endpoints/biomarker endpoints |</p>
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<td>9</td>
<td>Oct 29</td>
<td>Analysis – main hypothesis, secondary and subgroup analysis</td>
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<td>10</td>
<td>Nov 5</td>
<td>Follow-up, data monitoring, interim analysis, Adverse Events (AEs) &amp; SAEs</td>
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<td><strong>Due: Homework 3 data collection and analysis plan</strong></td>
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<td>11</td>
<td>Nov 12</td>
<td>Per protocol analysis Reporting CONSORT &amp; EXTENDED consort</td>
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<td>12</td>
<td>Nov 19</td>
<td>Final presentations</td>
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<td>13</td>
<td>Nov 26</td>
<td>Final presentations (if needed)</td>
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<td>14</td>
<td>Dec 3</td>
<td>Budgets, timelines, and feasibility</td>
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<td>Applying results of RCTs to clinical practice</td>
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<td>15</td>
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<td>Data safety and monitoring</td>
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<td><em>Guest Speaker TBA</em></td>
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<td><strong>Due: Final protocol</strong></td>
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Topics and Readings

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<td>Overview – the role of RCTs in evaluating medical and public health intervention</td>
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<td>- Chapter 1. <em>(Introduction to Clinical Trials) and Chapter 5 (Basic study design)</em></td>
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<td>- Sydes MR. Potential pitfalls in the design and reporting of clinical trials. Lancet Oncology 2010;11:694-700</td>
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<td>Classic articles</td>
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<td>- 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 and</td>
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<td>- A. Bradford Hill. The Clinical Trial. NEJM 1952</td>
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<td>Sept 10</td>
<td>Phase III trials;</td>
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<td>- COBALT investigators, NEJM 1997:337:1124-30</td>
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<td>- Ware and Antman. Equivalence trials NEJM 1997; 337:1159-61</td>
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<td>Efficacy vs. Effectiveness (Population definitions)</td>
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<td>- Chapter 5 Basic study design</td>
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- Ware J. Pragmatic trials – guides to better patient care. NEJM 2011 364:1685-7
- Glasgow R et al Use of RE-Aim to address health inequities… Trans Behav Med 2013: 3:200-2010

Sept 17 Bias and Error Randomization
Chapter 6. The randomization process

Class 3 Study Protocol
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 24 PROJECT SCHEMA PRESENTATIONS

Oct 1 Sample size & stopping rules
Chapter 8 Sample size
Class exercise on sample size estimation

Class 5 Oct 8 Ethical considerations
- Chapter 2 Ethical Issues
Health literacy and enrolment issues (read HIPAA forms, WUSTL)

Class 6 Defining and enrolling patients
Baseline data collection
Chapter 4 Study population, and
Chapter 10 Recruitment
HW 2: PRIMARY OUTCOME AND SAMPLE SIZE CALCULATION DUE

Class 7 Oct 15 Adherence to intervention
Chapter 14 Participant adherence, and 16 monitoring response variables

Class 7 RCTs for prevention
- Zelen M. Are primary cancer prevention trials feasible? JNCI 1988: 80;1442-4

Oct 22 Data quality
Chapter 11 Data collection and quality control
Intermediate endpoints
Issues in data collection and management – REDCap – J Tappenden

Oct 29 Critique RCT chosen by student interests
Analysis – main hypothesis, secondary and subgroup analysis
• Chapter 18 Issues in data analysis
• Sun,... Guyatt Is a subgroup effect... BMJ 2010, 340-

Nov 5 Follow-up, data monitoring, interim analysis, Adverse Events (AEs) & SAEs
Chapter 12 Assessing and reporting of harm
HW 3: DATA COLLECTION AND ANALYSIS PLAN DUE

Nov 12 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

Nov 19 FINAL PROTOCOL PRESENTATIONS

Dec 3 Reporting CONSORT & EXTENDED consort
Chapter 20 Reporting and interpreting of results
- Glasziou et al., *Taking interventions from trials to practice* BMJ 2010 341:c3852

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<th>Data safety and monitoring</th>
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