M19-550 Randomized Controlled Trials

Fall 2015

Time
Monday 1 to 4 PM

Location
Doll & Hill Teaching Room, 2nd Floor, Taylor Ave Building,
600 S Taylor Ave.
Division of Public Health Sciences.

Instructors
Graham Colditz, MD, DrPH, Esther Liu, PhD, Anke Winter, MD, SM,
and guest speakers
Carrie Stoll MPH, MSW, Teaching Assistant

Office hours
By appointment and after class

colditzg@wustl.edu
esther@wubios.wustl.edu
wintera@wudosis.wustl.edu
stollc@wudosis.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. 4th edition) plus the listing that follows accessible through the library listing.

Assignment due dates

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

- **HW 1: Schema**
  Presented in class on September 21. 
  Slides are due to stollc@wudosis.wustl.edu by September 20 at midnight

- **HW 2: Primary outcome and sample size calculation**
  Due Oct 5 by midnight to stollc@wudosis.wustl.edu

- **HW 3: Data collection and analysis plan**
  Due Oct 26 by midnight to stollc@wudosis.wustl.edu

- **Final Presentation**
  In class on Nov 16 and Nov 23. Students will sign up for a date in early October. 
  Presentation slides are due the night before at midnight to stollc@wudosis.wustl.edu

- **Final Protocol**
  Due Dec 7 by midnight to stollc@wudosis.wustl.edu

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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<thead>
<tr>
<th>Week</th>
<th>Date</th>
<th>Topic</th>
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|      | Aug 24  | Overview – the role of RCTs in evaluating medical and public health interventions  
Goals for the course  
Homework assignments  
  
*Guest Speaker: Jennifer Yu, MD, MPHS* |
| Class 1 |         |                                                                                                                                       |
|      | Aug 31  | Phase III trials;  
Efficacy vs. Effusiveness (Population definitions)  
Trials in context of CER  
Discuss HW assignments and final project expectations |
| Class 2 |         |                                                                                                                                       |
|      | Sept 14 | Bias and Error  
Randomization  
  
*Guest Speaker: Pam Samson, MD, MPHS* |
| Class 3 |         |                                                                                                                                       |
|      | Sept 21 | **Homework 1: Schema Presentations**                                                                                                  |
| Class 4 |         |                                                                                                                                       |
|      | Sept 28 | Sample size & stopping rules  
  
*Guest Speaker: Michael Avidan, MBBCh, Professor of Anesthesiology* |
| Class 5 |         |                                                                                                                                       |
|      | Oct 5   | Defining and enrolling patients  
Ethical considerations, health literacy and participant recruitment issues.  
  
*DUE: Homework 2 Primary outcome and sample size calculation* |
| Class 6 |         |                                                                                                                                       |
|      | Oct 12  | Adherence to intervention  
RCTs for Prevention |
| Class 7 |         |                                                                                                                                       |
|      | Oct 19  | Data quality  
Intermediate endpoints/biomarker endpoints  
  
Issues in data collection and management – REDCap - J Tappenden |
| Class 8 |         |                                                                                                                                       |
Oct 26  Follow-up, data monitoring, interim analysis, & SAEs

**Class 9**

Guest Speaker: William Powderly, MD, Director, Institute for Public Health, Co-Director of the Division of Infectious Diseases

Due: Homework 3 data collection and analysis plan

Nov 2  Analysis – main hypothesis, secondary and subgroup analysis

**Class 10**

Nov 9  Per protocol analysis

**Class 11**

Budgets, timelines, and feasibility

Nov 16  Final presentations

**Class 12**

Nov 23  Final presentations

Nov 30  Reporting CONSORT & EXTENDED consort

Applying results of RCTs to clinical practice

**Class 14**

Dec 7  Data safety and monitoring

**Class 15**

Guest Speaker TBA

Due: Final protocol
## 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)</em> and Chapter 5 <em>(Basic study design)</em></td>
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<td>- Sydes MR. <em>Potential pitfalls in the design and reporting of clinical trials.</em> 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 <em>Br J Cancer</em> 1976 34: 585-612 and</td>
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<td>- A. Bradford Hill. The Clinical Trial. <em>NEJM</em> 1952</td>
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<td>Class 1</td>
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<td>Aug. 31</td>
<td>Phase III trials;</td>
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<td>- Ware and Antman. <em>Equivalence trials</em> NEJM 1997; 337:1159-61</td>
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<td><strong>Efficacy vs. Effectiveness (Population</strong></td>
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*BMJ* = British Medical Journal  
*NEJM* = New England Journal of Medicine
• 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 Use of RE-Aim to address health inequities… Trans Behav Med 2013: 3:200-2010

Sept. 14 Biased and Error
Randomization
Chapter 6. The randomization process

Class 3 Study Protocol
See Protocol on blackboard and
Bennett et al Obesity treatment for socioeconomically disadvantaged patients in primary care practice Arch Internal Med 2012

Class 4 Sept. 21 PROJECT SCHEMA PRESENTATIONS

Sept. 28 Sample size & stopping rules
Chapter 8 Sample size
Class exercise on sample size estimation

Class 5 Lessons from Comparative effectiveness RCT at Barnes –
Michael Avidan, MB BCh,
Professor of anesthesiology
See Avidan MS, et al NEJM 2008 and 2011

Oct. 5 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. 12 Adherence to intervention
Chapter 14 Participant adherence, and 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: the place in how we understand the value of prevention strategies.* Ann Rev Public Health 2010

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<thead>
<tr>
<th>Oct. 19</th>
<th>Data quality</th>
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<tr>
<td>Class 8</td>
<td>Chapter 11 Data collection and quality control</td>
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<td>Intermediate endpoints</td>
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<td>Issues in data collection and management – REDCap – J Tappenden</td>
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Oct. 26

Class 9

Critique RCT chosen by student interests

Follow-up, data monitoring, interim analysis, & SAEs

*Chapter 12 Assessing and reporting adverse events*

**HW 3: DATA COLLECTION AND ANALYSIS PLAN DUE**

Nov. 2

Class 10

Analysis – main hypothesis, secondary and subgroup analysis
- Chapter 17 Issues in data analysis
- Sun,… Guyatt *Is a subgroup effect…* BMJ 2010, 340-

Nov. 9

Class 11

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

Class 12

Nov. 16

**FINAL PROTOCOL PRESENTATIONS**

Class 13

Nov 23

**FINAL PROTOCOL PRESENTATIONS**

Class 14

Nov. 30

Reporting CONSORT & EXTENDED consort

*Chapter 19 Reporting and interpreting*
results

- 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 15 | Dec. 7 | Data safety and monitoring | FINAL WRITTEN PROTOCOL DUE |