Washington University in St. Louis
SCHOOL OF MEDICINE

M19-550 Randomized Controlled Trials

Fall 2016

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

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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/Richard_Doll

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 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

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).

Randomized Controlled Trials
2016

Week	Date	Topic
Class 1	Aug 29	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 2	Sept 12	Phase III trials; Efficacy vs. Effectiveness (Population definitions) Trials in context of CER Discuss HW assignments and final project expectations
Class 3	Sept 19	Bias and Error Randomization
Class 4	Sept. 26	**Homework 1: Schema Presentations**
Class 5	Oct 3	Sample size & stopping rules *Guest Speaker: Michael Avidan, MBBCh, Professor of Anesthesiology*
Class 6	Oct 10	Defining and enrolling patients Ethical considerations, health literacy and participant recruitment issues. **DUE: Homework 2 Primary outcome and sample size calculation**
Class 7	Oct 17	Adherence to intervention RCTs for Prevention
Class 8	Oct 24	Data quality Intermediate endpoints/biomarker endpoints Issues in data collection and management – REDCap - J Tappenden

Class 9	Oct 31	Follow-up, data monitoring, interim analysis, & SAEs *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**
Class 10	Nov 7	Analysis – main hypothesis, secondary and subgroup analysis
Class 11	Nov 14	Per protocol analysis Budgets, timelines, and feasibility
Class 12	Nov 21	**Final presentations**
Class 13	Nov 28	**Final presentations**
Class 14	Dec 5	Reporting CONSORT & EXTENDED consort Applying results of RCTs to clinical practice
Class 15	Dec 12	Data safety and monitoring *Guest Speaker TBA* **Due: Final protocol**

Topics and Readings

Week	Date	Topic
Class 1	Aug 29	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 and • 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 12	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 19	Bias and Error Randomization *Chapter 6. The randomization process* 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 26	**PROJECT SCHEMA PRESENTATIONS**
Class 5	Oct 3	Sample size & stopping rules *Chapter 8 Sample size* Class exercise on sample size estimation Lessons from Comparative effectiveness RCT at Barnes – Michael Avidan, MB BCh, Professor of anesthesiology See Avidan MS, et al NEJM 2008 and 2011
Class 6	Oct 10	Ethical considerations • *Chapter 2 Ethical Issues* Health literacy and enrolment issues (read HIPAA forms, WUSTL) 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 17	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: there place in how we understand the value of prevention strategies. Ann Rev Public Health 2010
Class 8	Oct 24	Data quality *Chapter 11 Data collection and quality control* Intermediate endpoints Issues in data collection and management – REDCap – J Tappenden
Class 9	Oct 31	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**
Class 10	Nov 7	Analysis – main hypothesis, secondary and subgroup analysis • Chapter 17 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 11	Nov 14	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 21	**FINAL PROTOCOL PRESENTATIONS**
Class 13	Nov 28	**FINAL PROTOCOL PRESENTATIONS**
Class 14	Dec 5	Reporting CONSORT & EXTENDED consort *Chapter 19 Reporting and interpreting 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 15	Dec 12	Data safety and monitoring **FINAL WRITTEN PROTOCOL DUE**