2012

Randomized Controlled Trials - Course Syllabus 2011-2012

Washington University in St. Louis

M19-550 Randomized Controlled Trials

Fall 2011

Time Monday 1 to 4 PM

Location Kingshighway Building, 7th floor, Room 7326

Instructors Graham Colditz, MD, DrPH, Esther Liu, PhD and guest speakers

Office hours By appointment and after class

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Target audience

Clinicians interested in conducting research, clinical training program participants, students enrolled in Genetic Epidemiology Master of Science program, students in MPH addressing primary prevention trials. 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

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

Course format and requirements

Students are expected to attend all classes. Readings assigned for each class should be read ahead of the class and students should be prepared to discuss the material from readings.

Readings: Text (Fundamentals of Clinical Trials: Friedman, Furberg, and DeMets. Fourth edition) plus the listing that follows accessible through the library listing.

Grading and Assignments – 3 homework assignments and submission of a written protocol make up the grading.

Grading scale

A	95-100%
A-	90-94.9%
B+	85-89.9%
B	80-84.9%
B-	75-79.9%
C+	70-74.9%
C	60-69.9%

Randomized Controlled Trials

Week	Date	Topic
Class 1	August 29	Overview – the role of RCTs in evaluating medical and public health interventions Goals for the course Homework assignments
Class 2	Sept. 12	Phase III trials; Efficacy vs. Effusiveness (Population definitions)
Class 3	Sept. 19	Ethical considerations Consent & IRB Homework 1
Class 4	Sept. 26	Bias and Error Randomization
Class 5	Oct. 3	Study Protocol Sample size & stopping rules
Class 6	Oct. 10	Defining and enrolling patients Baseline data collection Homework 2
Class 7	Oct. 17	Adherence to intervention
Class 8	Oct. 24	Data quality
Class 9	Oct. 31	Follow-up, data monitoring, interim analysis, & SAEs
Class 10	Nov. 7	Analysis – main hypothesis, secondary and subgroup analysis
Class 11	Nov. 14	Per protocol analysis
Class 12	Nov. 21	Data safety and monitoring Homework 3
Class 13	Nov. 28	Managing multi-center trials RCTs for prevention
Class 14	Dec. 5	Reporting CONSORT & EXTENDED consort Applying results of RCTs to clinical practice
Class 15	Dec. 12	Protocol presentations/Mock IRB session

Topics and Readings

Week	Date	Topic
Class 1	August 29	Overview – the role of RCTs in evaluating medical and public health intervention • Chapter 1. • Doll R. Controlled trials: the 1948 watershed BMJ 1998; 317: 1217-20 • Sydes Potential pitfalls in the design and reporting of clinical trials. Lancet Oncology 2010;11:694-700 • Taylor RP, 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, Br J Cancer 1976 34: 585-612 and Peto R, et al. Br J cancer 1977 35:1-39
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. Effusiveness (Population definitions) • Chapter 4 • Tunnis et al. Practical Clinical Trial JAMA 2003:290:1624-32 • Glasgow RE-AIM AJPH 1999:89:1322-7 • Ware J. Pragmatic trials – guides to better patient care. NEJM 2011 364:1685-7
Class 3	Sept. 19	Ethical considerations Consent & IRB Homework 1

Class 4	Sept. 26	Bias and Error Randomization • Chapter 5
Class 5	Oct. 3	Study Protocol Sample size & stopping rules • Chapter 7 Class exercise on sample size estimation
Class 6	Oct. 10	Defining and enrolling patients Baseline data collection Homework 2 • Chapters 3 and 9
Class 7	Oct. 17	Adherence to intervention • Chapter 13 and 15
Class 8	Oct. 24	Data quality • Chapter 10
Class 9	Oct. 31	Follow-up, data monitoring, interim analysis, & SAEs • Chapter 11
Class 10	Nov. 7	Analysis – main hypothesis, secondary and subgroup analysis • Chapter 16 • Guyatt BMJ (http://bit.ly/9RvH8r) • 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. 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	Data safety and monitoring
Class 13	Nov. 28	Managing multi-center trials 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 14	Dec. 5	Reporting CONSORT & EXTENDED consort • 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 Taking interventions from trials to practice • Glasziou et al., BMJ 2010 341:c3852
Class 15	Dec. 12	Protocol presentations/Mock IRB session Student presentation 10 minutes per protocol.