

**M19-550 Randomized Controlled Trials**

**Fall 2017**

**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 Lu, PhD,

and guest speakers

Carrie Stoll MPH, MSW, Teaching Assistant

**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 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/Richard_Doll)

[**https://en.wikipedia.org/wiki/Austin\_Bradford\_Hill**](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

1. 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

1. 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

1. 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 blackboard*

* **HW 1: Schema**

Due September 24 by 11:59 pm. Submit via Schoology.

Presented in class on September 25.

* **HW 2: Primary outcome and sample size calculation**

Due Oct 9 by 11:59 pm. Submit via Schoology.

* **HW 3: Data collection and analysis plan**

Due Nov 5 by 11:59 pm. Submit via Schoology.

* **Final Presentation**

In class on Nov 20 and Nov 27. Students will sign up for a date in early October.

Presentation slides are due the night before your assigned presentation date. Submit via Schoology.

* **Final Protocol**

Due Dec 11 by 11:59 pm. Submit via Schoology.

**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**

**2017**

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| **Week** | **Date** | **Topic** |
| **Class 1** | Aug 28 | Overview – the role of RCTs in evaluating medical and public health interventions  Goals for the course  Homework assignments |
| **Class 2** | Sept 11 | Phase III trials;  Efficacy vs. Effectiveness (Population definitions)  Trials in context of CER  *Guest Speaker: Shane LaRue, MD, MPHS*  Discuss HW assignments and final project expectations |
| **Class 3** | Sept 18 | Bias and Error  Randomization  (Biostatistics issues 1) |
| **Class 4** | Sept. 25 | **Homework 1: Schema Presentations** |
| **Class 5** | Oct 2 | Sample size & stopping rules  *Guest Speaker: Methodius Tuuli, MD, MPHS* |
| **Class 6** | Oct 9 | Defining and enrolling patients  Ethical considerations, health literacy and participant recruitment issues. Dr. Drake.  **DUE: Homework 2 Primary outcome and sample size calculation** |
| **Class 7** | Oct 16 | Adherence to intervention  RCTs for Prevention |
| **Class 8** | Oct 23 | Data quality  Intermediate endpoints/biomarker endpoints  Issues in data collection and management – REDCap - J Tappenden |
| **Class 9** | Oct 30 | Analysis – main hypothesis, secondary and subgroup analysis |
| **Class 10** | Nov 6 | Follow-up, data monitoring, interim analysis, Adverse Events (AEs) & SAEs  **Due: Homework 3 data collection and analysis plan** |
| **Class 11** | Nov 13 | Per protocol analysis  Budgets, timelines, and feasibility |
| **Class 12** | Nov 20 | **Final presentations** |
| **Class 13** | Nov 27 | **Final presentations** |
| **Class 14** | Dec 4 | Reporting CONSORT & EXTENDED consort  Applying results of RCTs to clinical practice |
| **Class 15** | Dec 11 | Data safety and monitoring  *Guest Speaker TBA*  **Due: Final protocol** |

**Topics and Readings**

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| |  |  |  | | --- | --- | --- | | **Week** | **Date** | **Topic** | | **Class 1** | Aug 28 | 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](http://www.bmj.com/content/317/7167/1217.long) BMJ 1998; 317: 1217-20 * Sydes MR. [Potential pitfalls in the design and reporting of clinical trials](http://www.sciencedirect.com/science/article/pii/S1470204510700413). 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](http://cancerres.aacrjournals.org/content/54/7_Supplement/2029s.long). 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.](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1335942/?tool=pubmed) 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](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2025229/?tool=pubmed) 1976 34: 585-612 and   * Peto R, et al. [II. analysis and examples.](http://www.ncbi.nlm.nih.gov/pubmed/831755) Br J cancer 1977 35:1-39 * A. Bradford Hill. The Clinical Trial. NEJM 1952 | | **Class 2** | Sept 11 | Phase III trials;   * [COBALT investigators](http://www.nejm.org/doi/full/10.1056/NEJM199710163371604), NEJM 1997:337:1124-30 * Ware and Antman. [Equivalence trials](http://www.nejm.org/doi/full/10.1056/NEJM199710163371610) NEJM 1997; 337:1159-61   Efficacy vs. Effectiveness (Population definitions)   * *Chapter 5 Basic study design* * Tunis S, et al. [Practical Clinical Trial](http://jama.ama-assn.org/content/290/12/1624.long) JAMA 2003:290:1624-32 * Ware J. [Pragmatic trials – guides to better patient care](http://www.nejm.org/doi/full/10.1056/NEJMp1103502). NEJM 2011 364:1685-7 * Glasgow R, et al [RE-AIM](http://ajph.aphapublications.org/cgi/reprint/89/9/1322?view=long&pmid=10474547) 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 18 | 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](http://archinte.jamanetwork.com/article.aspx?articleid=1134848) | | **Class 4** | Sept 25 | **PROJECT SCHEMA PRESENTATIONS** | | **Class 5** | Oct 2 | Sample size & stopping rules  *Chapter 8 Sample size*  Class exercise on sample size estimation  Lessons from Comparative effectiveness RCT at Barnes –  Methodius Tuuli, MD MPH  See: N Engl J Med. 2016 Feb 18;374(7):647-55 | | **Class 6** | Oct 9 | 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 16 | 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](http://jnci.oxfordjournals.org/content/80/18/1442.long): 80;1442-4 * Colditz and Taylor. [Prevention trials: there place in how we understand the value of prevention strategies](http://www.annualreviews.org/doi/full/10.1146/annurev.publhealth.121208.131051?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed). Ann Rev Public Health 2010 | | **Class 8** | Oct 23 | Data quality  *Chapter 11 Data collection and quality control*  Intermediate endpoints  Issues in data collection and management – REDCap – J Tappenden | | **Class 9** | Oct 30 | 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](http://www.bmj.com/content/340/bmj.c117.long)… BMJ 2010, 340-   Wang et al., [Statistics in Medicine – Reporting of subgroup analyses in clinical trials](http://www.nejm.org/doi/full/10.1056/NEJMsr077003). NEJM 2007; 357:2189-94 | | **Class 10** | Nov 6 | 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** | | **Class 11** | Nov 13 | Per protocol analysis   * Ware J. [Interpreting incomplete data in studies of diet and weight loss](http://www.nejm.org/doi/full/10.1056/NEJMe030054) NEJM 2003; 348 : 2136-7 * Williamson et al., [Adherence is a multi-dimensional construct in the POUNDS LOST trial](http://www.springerlink.com/content/1q8t517024676w22/). J Behav Med 2010; 33:35-46 | | **Class 12** | Nov 20 | **FINAL PROTOCOL PRESENTATIONS** | | **Class 13** | Nov 27 | **FINAL PROTOCOL PRESENTATIONS** | | **Class 14** | Dec 4 | Reporting CONSORT & EXTENDED consort  *Chapter 20 Reporting and interpreting of results*   * Schulz et al [CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials](http://www.bmj.com/content/340/bmj.c332.long) BMJ 2010;340:c332 * Moher et al., [CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomized trials](http://www.sciencedirect.com/science/article/pii/S0895435610001034) BMJ 2010;340:c869 * Zwarenstein et al., [Improving reporting of pragmatic trials: an extension of the CONSORT statement](http://www.bmj.com/content/337/bmj.a2390.long). BMJ 2008;337:a2390 * Glasziou et al., [Taking interventions from trials to practice](http://www.bmj.com/content/341/bmj.c3852.long) 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 11 | Data safety and monitoring  **FINAL WRITTEN PROTOCOL DUE** | |