BST 465: DESIGN OF CLINICAL TRIALS

SPRING 2018

Instructor	Chris Beck, Ph.D. Department of Biostatistics and Computational Biology christopher_beck@urmc.rochester.edu / 275-6781 Saunders Research Building (SRB), Room 4.146 Office Hours: by appointment
Lectures	Tuesday / Thursday, 9:00-10:30 AM – SRB, Room 1.416
Credit Hours	4.0
Dates	January 18 – May 1
Registration	The course reference number (CRN) is 71629. Please make sure that you are properly registered.
Prerequisites	BST 463 or equivalent
Textbooks	Friedman LM, Furberg CD, DeMets DL, Reboussin DM, Granger CB. *Fundamentals of Clinical Trials*, Fifth Edition. New York: Springer-Verlag, 2015. Piantadosi S. *Clinical Trials: A Methodologic Perspective*, Third Edition. New York: John Wiley and Sons, 2017. These are the primary texts (suggested, not required) for the course. They may be purchased from the College Town Bookstore. The following book, in addition to the primary texts, has been placed on reserve in Miner Library: Cook TD, DeMets DL. *Introduction to Statistical Methods for Clinical Trials*. Boca Raton: Chapman and Hall/CRC, 2008. The lectures will draw primarily from the texts mentioned above, but will also draw from other sources. Numerous examples from the medical literature will be used to illustrate the concepts presented in the lectures.
Assignments	There will be seven homework assignments of varying length. These will be due one week after being distributed. Graded assignments will be returned within one week. The final assignment will be to write a two-page critique of a published randomized clinical trial.

You are welcome to discuss the homework assignments with classmates, but you should write up the final solutions yourself. The exception to this is the final assignment, for which you are expected to do all of the work yourself, i.e., collaboration is not permitted.

Students will also be expected to keep up with assigned readings from the text and from selected journal articles.

Examinations

There will be two in-class examinations on March 8 and May 1. The second examination will not be cumulative. Review sessions will be held in class the week preceding each examination.

Grading

The final grade for the course will be based on the homework assignments (50%), the first examination (25%), and the second examination (25%).

Academic Integrity

Academic integrity is a core value of the University of Rochester. Students who violate the University of Rochester University Policy on Academic Honesty are subject to disciplinary penalties, including the possibility of failure in the course and/or dismissal from the University. Since academic dishonesty harms the individual, other students, and the integrity of the University, policies on academic dishonesty are strictly enforced. For further information on the University of Rochester Policy on Academic Honesty, please see the *Jurisdiction and Responsibility for Academic and Nonacademic Misconduct* section in the **Regulations and University Polices Concerning Graduate Studies** *http://www.rochester.edu/GradBulletin/PDFbulletin/Regulations.pdf*

Accommodations for Students with Disabilities

Students needing academic adjustments or accommodations because of a documented disability must contact the Access Services Coordinator. For information regarding access services and support at SMD, please refer to our webpage: https://www.urmc.rochester.edu/education/graduate/current-students/disability-supports-services.aspx

Web Site

You can access course material (syllabus, handouts, journal articles, homework assignments, lecture notes) using Blackboard (http://learn.rochester.edu). Please inform the instructor immediately if you have any trouble accessing course material or using Blackboard.

Objectives

The course has seven major objectives:

1. To provide a thorough understanding of the rationale for, and implications of, basic aspects of clinical trial design, including: specification of hypotheses and objectives, outcome variables, and

inclusion/exclusion criteria; randomization; blinding; and choice of an appropriate control group.

2. To provide practical knowledge of techniques for randomly assigning clinical trial participants to different treatment groups.

3. To provide an overview and understanding of the major issues regarding the ethical conduct of clinical trials, including the use of placebos, the concept of equipoise, the necessity of trial monitoring, the content of the Declaration of Helsinki, the concepts of autonomy, beneficence, and justice, and the role of the Institutional Review Board.

4. To provide a detailed understanding of more advanced aspects of clinical trial designs such as factorial designs, cross-over designs, equivalence or non-inferiority trials, group sequential designs (interim monitoring and analyses), and fully sequential designs.

5. To provide practical knowledge of methods for determining the sample size for a clinical trial.

6. To provide an overview and understanding of the major issues regarding the statistical analysis of clinical trial data, including the problem of protocol deviations (e.g., subject withdrawal, noncompliance, missing data), prioritizing analyses, hypothesis testing vs. interval estimation, subgroup analyses, multiple testing, interaction, and covariate adjustment.

7. To enable the critical evaluation of published clinical trial reports.

Course Content

This course is designed for individuals interested in both the scientific and organizational aspects of clinical trials. An approximate timeline with specific topics to be covered is as follows (note that it is not necessary to read the material from <u>both</u> Piantadosi and Friedman, Furberg, DeMets, Reboussin, and Granger [FFDRG] – one is sufficient in most cases – but the journal articles are required reading):

1/18 Introduction; historical overview of clinical trials

1/23-1/30 Clinical trials in drug development; study protocol

<u>Read:</u> Piantadosi, Chapter 1, Chapter 2 (2.1-2.3), Chapter 4 (4.1-4.4, 4.7), Chapter 8 (8.7), Chapter12 (12.1-12.2), Chapter 13 (13.1-13.3), Chapter 14 (14.1-14.2); FFDRG, Chapter 1; The Parkinson Study Group (1989) [DATATOP]; The Multicenter Diltiazem Postinfarction Trial Research Group (1988) [MDPIT]

2/1-2/8	Aspects of study design (primary/secondary hypotheses and objectives; specification of response variables; surrogate outcomes; defining the study population; inclusion/exclusion criteria; generalizability of results) Read: Piantadosi, Chapter 5, Chapter 9, Chapter 15; FFDRG, Chapter 3, Chapter 4, Chapter 10; Fleming and DeMets (1996)
2/13-2/15	Randomized vs. non-randomized studies Read: Piantadosi, Chapter 2 (2.4), Chapter 6 (6.1-6.2), Chapter 8 (8.1-8.3), Chapter 17 (17.1-17.2); FFDRG, Chapter 5 (pp. 89-101); Hulley et al. (1998) [HERS]
2/20	Mechanics of randomization; techniques for randomization Read: Piantadosi, Chapter 17 (17.3-17.6); FFDRG, Chapter 6
2/22-2/27	Randomized consent design; blinding and placebos; ethical issues in clinical trials Read: Piantadosi, Chapter 3 (3.1-3.2), Chapter 8 (8.6.1), Chapter 17 (17.7); FFDRG, Chapter 7; O'Rourke et al. (1989) [ECMO] and accompanying editorial and letters.
3/1-3/6	Ethical issues in clinical trials (randomization/equipoise; informed consent; trial monitoring; use of placebo controls; surgical trials; Declaration of Helsinki; Belmont Report; institutional review boards) Read: Piantadosi, Chapter 3 (3.3-3.7), Chapter 4 (4.6), Chapter 8 (8.6.2); FFDRG, Chapter 2, Chapter 5 (pp. 109-115); Declaration of Helsinki; Freedman (1987); Temple and Ellenberg (2000)
3/8	**First Examination**
3/13-3/15	Spring Break
3/20	Factorial designs Read: Piantadosi, Chapter 22; FFDRG, Chapter 5 (pp. 104-106)
3/22-3/27	Design and analysis of cross-over trials Read: Piantadosi, Chapter 23; FFDRG, Chapter 5 (pp. 102-103)
3/29-4/3	Clinical trial monitoring; interim analyses; sequential and group sequential designs Read: Piantadosi, Chapter 18; FFDRG, Chapter 10 (pp. 225-230), Chapter 11 (pp. 244-250), Chapter 14 (pp. 311-314), Chapter 16, Chapter 17; Moss et al. (1996)

4/5-4/10	Determination of sample size and power Read: Piantadosi, Chapter 16 (omit Sections 16.2.3, 16.4.5-16.4.7, 16.5, 16.6, 16.7.3, 16.7.5-16.7.6, 16.7.8, 16.8, 16.9.4-16.9.5); FFDRG, Chapter 8
4/12-4/19	Issues in data analysis (intention-to-treat principle; missing data; dropouts; noncompliance; protocol deviations; hypothesis testing [p-values] vs. interval estimation; primary vs. secondary vs. post-hoc analyses; subgroup analyses; multiple testing; interactions; covariate adjustment; adverse event data) Read: Piantadosi, Chapter 19, Chapter 20 (20.1, 20.3-20.5, 20.7-20.9), Chapter 21 (21.3); FFDRG, Chapter 12, Chapter 18
4/24-4/26	Reporting of clinical trial results; evaluating clinical trial reports Read: Piantadosi, Chapter 25; FFDRG, Chapter 20; Moher et al. (2001), Schulz et al. (2010) [CONSORT]
5/1	**Second Examination**
5/8	**Final Assignment Due**