Syllabus

EPID 733 - Clinical Trials (Spring 2016)

Class Sessions: Tuesday/Thursday, 9:30-10:45 am. Hooker 003

Course Instructors:
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Shrikant I. Bangdiwala, PhD (kant@unc.edu)
Invited faculty

Introduction to the Course

Randomized controlled trials are the strongest research design for identifying the effects of an intervention, whether in the public health or clinical context, and whether aimed at prevention, treatment, or palliation. Therefore, a sound grounding in clinical trial methods helps one understand the evidence base for clinical and public health practice. It can also provide a perspective in which to judge the validity of less robust studies of interventions, such as non-randomized trials and observational studies.

In this course we will examine clinical trials from several perspectives. The core sessions will be about the design, conduct, and analysis of trials; combining trial results (meta-analysis); and dissemination of results. We will also discuss the ethics of human experiments and the role of human subjects committees. We will describe how basic methods are adapted to special questions, such as studies intended to establish non-inferiority, trials that randomize groups rather than individuals, very small trials (where randomization is less reliable) and large simple trials (which may be more feasible and generalizable).

This course is intended for health professionals who want advanced training in clinical trial methods to help them conduct clinical trials themselves and to understand their strength and meaning. We assume a basic grounding in research design and statistical methods. (Introductory epidemiology and biostatistics courses are prerequisites.)

Course Objectives:

By the end of the course, students should be able to:

1. Decide whether a proposed trial is ethical and understand how sponsoring institutions participate in the protection of human subjects.

2. Describe the various ways in which clinical trials can be designed and the advantages and disadvantages of each approach

3. Estimate sample size, taking into account the various real-world determinants such as the magnitude of a clinical/policy important effect size, available resources and patients, and whether randomization is by patient or groups of patients.

4. Describe basic approaches to analysis of clinical trial data, including time-to-event and repeated measures analyses and stopping rules.

5. Know how oversight of clinical trials is accomplished including the roles and responsibilities of Data Safety and Monitoring Boards

6. Describe guidelines for reporting clinical trials and how trials are published and made accessible to all stakeholders.

7. Be familiar with the basic principles of systematic reviews and meta-analyses of clinical trials.

8. Understand the biases that can affect publication and what is being done to control and estimate these biases.

9. Understand the role of special forms of clinical trials such as non-inferiority trials, small trials, large simple trials, and practical trials.

10. Develop a research protocol for a clinical trial.

Teaching Methods:

Most classroom learning will be in interactive large-group sessions. We will present information and lead discussions with the class as a whole. Often we will use a specific clinical trial to illustrate the concepts being discussed in class that day. You should become familiar with required reading before class to be adequately prepared to participate. Optional reading is listed for those with special interest in a topic. For several sessions, reading of clinical trial reports will be required.

There will be ample opportunity for other kinds of learning including student presentations and participation of invited faculty.

Textbook:

We recommend Machin D. Fayers PM, Randomized Clinical Trials Design, Practice and Reporting. Wiley-Blackwell, 2010. This is available at the student bookstore. We will not make chapter assignments. Rather, we recommend students to read most of the book, matching chapters to classroom session on their own.

Other useful resources:

Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. 5th ed. Springer, New York 2015. A few copies are available at the bookstore. This is a widely used textbook covering all of the basic issues concerning clinical trials. (The 4th edition would also be acceptable. This may be available at lower cost at Amazon.com.)

Piantadosi S. Clinical trials: A Methodologic Perspective, John Wiley-Interscience; 2nd edition (August 1, 2005). (Available electronically at the Health Sciences Library)

We also recommend that you be familiar with other key resources (See "Key Readings and Websites") and refer to these throughout the course. One of these will be a draft monograph that students may find helpful.

Expectations of Students:

1. ***Class participation***. You are expected to attend class and to participate in class discussions. Participation does not mean talking a lot but rather being present, thoughtful and well prepared, and making helpful points or raising questions that move the discussion in useful and interesting ways.

2. ***Required Readings***. You are expected to have read the required readings before class. Part of class discussion will be based on these readings.

3. ***Recommended reading***. We encourage you to read some of the articles on the Recommended Readings, especially in areas of special interest to you or those that you did not adequately understand in class**.**

4. ***Final project***. All students will prepare a research protocol that will be presented to the class, and submitted in writing (see below). This project is expected to synthesize what you have learned in the course and apply it to a research question that especially interests you, perhaps one you may actually study later. Students will be expected to critique each other's presentations. One student will be assigned to be a lead critic for each protocol and submit a brief written outline of a critique.

Final Report: Protocol

The final report for this course will be an abbreviated research protocol for a randomized controlled trial. The intervention can be anything related to health.

We want you to select a topic and submit it in writing (email) with a brief rationale by **Monday, February 22.** This early date will allow you to have time to refine or change your question if we think it is not particularly promising for the purposes of this course. We encourage you to discuss your plans for the project with us beforehand.

The protocol itself will be in abbreviated form, relative to a full proposal such as one might submit to the National Institutes of Health. The maximum length is 5 pages of double-spaced text, including references, formatted in no less than 12 point font and 1 inch margins. Most protocols should consider the issues summarized during the Feb 23 session regarding trial protocols. Protocols should be specific to the topic rather than generic statements of clinical trial principles in general, and should reflect the reasons for the choices in design and analyses. We understand that shorter protocols are more difficult than long ones, because you cannot include everything and must decide which issues are more and less important. The protocol should be submitted by email as an MS Word document by April 26th (April 28th for presenters on April 26). Please title your word document as follows: Your Last name, Abbreviated Project Title (Example: Baron Aspirin for Prevention of Colorectal Cancer)

The last several class sessions are reserved for student presentations. We ask that each of you summarize your protocol, pointing out special challenges and opportunities and how you dealt with them. We estimate that there will be 20 minutes per student (10 for presentation, 5 minutes for formal critique (see below) and 5 minutes for class discussion). The oral presentation should be prepared with Powerpoint images with paper hand-outs if needed.

Protocol Critique

Each student will be responsible for critiquing the strengths and weaknesses of a protocol prepared by one other student. The critique should be prepared in written bullet form, systematically considering the protocol's weaknesses in no more than 2 pages of double spaced text. The protocol presenter will provide the discussant with a pdf file of the protocol presentation 2 days before his/her class discussion. The written critique will be due at the time of the protocol presentation and will be presented to the class with Powerpoint slides in no more than 5 minutes.

Grading:

1. ***Attendance and Classroom Participation***. Thirty four percent of the final grade will be based on classroom participation, particularly in exercises that will be discussed in class. As stated above, this is not about sheer volume of comments but how thoughtful, penetrating, and stimulating they are. However, it is fair to say that one cannot display any of these qualities without participating at all. Do not be reticent to comment or question; other students may well share your interest in the issue.

2. ***Protocol Exercise***. Fifty percent of the final grade will be based on the presentation of the protocol and the subsequent written submission. We will grade the protocols on completeness, sound reasons for the approaches taken,

appropriateness of design to the research question, understanding of the concepts of randomized trials and the verbal response to the critique.

3. Critique of Final Protocol. Sixteen percent of the final grade will be based on the written critique of another student's protocol and the presentation of the critique.

4. There is no final examination.

Clinical Trials Epidemiology
Epidemiology 733
Spring 2016

John Baron, MD, MS, MSc. Course leader
Shrikant Bangdiwala, PhD, Co-instructor

Course Schedule

Jan 12	Introduction	Monograph, pages 1-9	Baron
Jan 14	Randomization	Monograph, pages 30-38	Bangdiwala
Jan 19	Preliminaries	Monograph, pages 10-16	Baron
Jan 21	Ethics of Clinical Trials	Monograph, pages 20-21	Baron
Jan 26	Design I: Questions, subjects, outcomes	Monograph, pages 22-8, 39-40	Baron
Jan 28	Analysis I: ITT, Per protocol, etc.	Monograph, pages 55-60, 64-5	Baron
Feb 02	Sample Size	Monograph, pages 23-25	Schwartz
Feb 04	Design II: Basic Designs	Monograph, pages 68-72	Bangdiwala
Feb 09	Some Ethical Issues in Clinical Trials: Placebos, Sham Surgery and Response-Adaptive Randomization		~~Ivanova~~ Baron
Feb 11	Conduct I: Blinding, Trial Components	Monograph, pages 32-3, 41-44	Baron
Feb 16	Pragmatic Trials		Baron
Feb 18	Analysis II: Primary analysis, Survival		Bangdiwala
Feb 23	Conduct II: DSMBs, Protocols, etc.	Machin & Fayers Ch. 7	Bangdiwala
Feb 25	Analysis III: Residual Confounding	Monograph, pages 64-65	Bangdiwala
Mar 01	Analysis IV: Interim analyses, early stopping	Monograph, pages 50-54	Bangdiwala
Mar 03	Analysis V: Subgroup analysis Debate	Monograph, pages 60-64	Bangdiwala/Baron
Mar 08	Equivalence/non-inferiority trials	Monograph, pages 72-74	Bangdiwala
Mar 10	Journal Club		Baron/Bangdiwala
Mar 15 Mar 17	No class – Spring Break		
Mar 22	Group Randomized Trials		Bangdiwala
Mar 24	Small and Large Trials		Fletcher
Mar 29	Drug Approval Exercise		Baron/Bangdiwala
Mar 31	Systematic Reviews, Meta-analysis		Weber
Apr 5	Special Topics in Randomized Trials		Baron/Bangdiwala
Apr 7	Presentations		
Apr 12	Presentations		
Apr 14	Presentations		
Apr 19	Presentations		
Apr 21	Presentations		
Apr 26	Presentations		