

**Design and Analysis of Clinical Trials**  
**Design of Clinical Experiments**  
**Clinical Investigation 390.612 = Biostatistics 140.642**  
**Class Syllabus**  
**Johns Hopkins, September 2007**

Tue-Thu 3:00-4:30

Location: Hampton B-14B

Please note: these two course numbers are cross listings of the same course

This document is posted on the course web site

[cancerbiostats.onc.jhmi.edu/Syllabus.pdf](http://cancerbiostats.onc.jhmi.edu/Syllabus.pdf).

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**Who should take this course?**

This course is offered first quarter each year, because it follows Design and Conduct of Clinical Trials (Epi 340.613) from 4<sup>th</sup> quarter and other Biostatistics and Epidemiology prerequisites. This is not an introduction to the subject and the prerequisites are real (see below). This is intended to be a 2<sup>nd</sup> year (or later) course. If you are curious or interested but have no background in trials and have not satisfied the prerequisites, you should first take the basic biostatistics and epidemiology series and then 340.613 in the 4<sup>th</sup> quarter.

**Book/Outline**

The textbook used in this course is ***Clinical Trials: A Methodologic Perspective, Second Edition*** (New York: John Wiley & Sons, 2005). This book can be purchased for about \$110 at the Hopkins medical bookstore or found in various libraries. It is available in either paper or electronic form. You cannot take the course without access to this book. The course outline will follow the book with a few exceptions to be noted later. *Readings should be done before class because the discussion will center on the chapters.* There may be guest lecturers announced later.

**Prerequisites**

This is a Biostatistics/Clinical Investigation course that builds on a background of biostatistics, basic epidemiology, and introductory clinical trials. Students must have

had the basic biostatistics and epidemiology series and the Design and Conduct of Clinical Trials course. This course is quantitative and is *not* a general introduction to clinical trials. A familiarity with, if not formal course work in, survival analysis is helpful. The readings, discussion, and assignments do not accommodate students without the prerequisites. In past years, a few students without prerequisites have taken the course. Such students have mostly survived but have taken less from the course than they should have.

### Course Objectives

1. To understand clinical trial design principles including bias control, random error control, randomization, blocking, and masking;
2. To have a working knowledge of quantitative properties of clinical trials including precision of estimation, power, sample size, and accrual dynamics;
3. To have experience with specific types of designs of practical and historical interest including translational, dose-finding, safety and efficacy, and comparative trials;
4. To understand the importance of design and its relation to the analysis of clinical trials;
5. To demonstrate knowledge of clinical trial methods by discussing specific design and/or analysis problems expertly.

### Other Course Materials

This syllabus and any other course materials or announcements are on my website: [www.cancerbiostats.jhmi.edu/courses.cfm](http://www.cancerbiostats.jhmi.edu/courses.cfm). No additional materials are needed besides the course text and class handouts. However, there are a number of helpful books and papers. I can recommend Silverman: *Human Experimentation* (Oxford), which is difficult to get. Other readings from my book are fairly extensive and, in some cases, very technical. They are chosen with three goals in mind: 1) they are modern classics to trial methodologists, 2) they are instructional for the student of trials, or 3) they contain references of importance so that they are convenient entry points into the literature. I suggest that you read them in order of technical ease. Later in life, you may have occasion to re-visit them. Biostatistics students may want to investigate power and sample size software, particularly PASS by NCSS (Hintze).

## Requirements and Grading

Grading is based on: 1) Weekly discussion problems/memos (homework - there are 5 or 6 of these), 2) classroom discussion, 3) topic summaries to be assigned first day of class. The time required each week for this course is substantial. Reading is a minimum of 1-2 Chapters per week plus an occasional supplementary paper or other document. Writing is about 2 pages per week, which depending on your style and ability, may require several hours (e.g., I cannot write faster than 1 page per hour). Class is 3 hours per week.

Discussion problems will be based on additional materials handed out in class or referenced in the book. The discussions are due 1 week from date given and must take the form of a typed single spaced memo not to exceed 2 pages of text (no tricks with margins or type fonts - use 1 inch margins and 11 or 12 point proportional font). References, tables, or figures may be listed on additional pages. **Raw computer output is not acceptable as a table** and must be presented in a coherent distilled form. Any non-human sources may be consulted. *For all assignments, assume that you are a consulting clinical trials methodologist asked by other investigators to comment succinctly and expertly on the question at hand. Your memo will be used to resolve some practical issue.* You must demonstrate an ability to write, reason quantitatively, be neat and professional, be coherent, be expert, and be on time.

Grading is partly subjective and you will not get a high grade by doing only the written homework! To grade papers, I start by sorting the papers into three groups based on overall content and the objective concepts needed to answer the question: strong, average, and weak. Within each group, I further rank/sort the papers based on details that typically come from reading and thinking quantitatively and carefully about the problem. After ranking, a score of 0-10 is assigned. At the end of the quarter, your scores are averaged (often after dropping the lowest one) and ranked against your classmates, before final letter grades are assigned. Thus, you are graded partly in comparison to your classmates. This is why the prerequisites are vital. Many students in the class have had biostatistics, epidemiology, and introductory clinical trials, and many have had practical experience with trials and treating patients. Lack of preparation shows, and puts inexperienced students at a strong disadvantage.

### Memo Do's and Don'ts

With regard to the assigned homework memos, the following are requirements:

1. Use a typed formal memo style - consult a manual of style if you do not know what this is (e.g., University of Chicago Press Staff (2003). **The Chicago Manual of Style**. 15th Edition.)

2. Name on each following page in a header or footer;
3. Staple pages; Number the pages if there is more than 1;
4. Use headings/subheadings to help organize your thoughts (optional);
5. Use Tables and Figures to illustrate and document (optional);
6. Consult and cite the literature (optional).

With regard to the assigned homework memos, you **MAY NOT** do any of the following:

1. Exceed 2 pages (except for Tables/Figures/References);
2. Include a cover page (i.e., do not include any cover pages);
3. Turn in a homework assignment late;
4. Collaborate with classmates, students, or faculty;
5. Use quotations of any type. If you quote sentences or paragraphs from my book or other sources, you will fail the assignment. If you plagiarize (quote without credit) you will fail the course. References may be cited.
6. Use raw computer output of any kind as a table. Properly constructed tables are welcome. Computer generated graphs might be acceptable provided they are expert, neat, and properly edited;
7. Use a previous student's work in any form.

### **Journals to Know About**

Clinical Trials (Society for Clinical Trials)  
Statistics in Medicine (ISCB)  
Biometrics  
Biostatistica  
Lifetime Data Analysis

## Scheduling Problems

I may have schedule conflicts this year. Affected classes will be rescheduled or a substitute will be arranged. Current problem dates are September 18 and October 4.

### Lecture Schedule for Design and Analysis of Clinical Trials / Design of Clinical Experiments

| <b>Session</b> | <b>Date</b> | <b>Speaker</b> | <b>Chapter / Discussion Topic</b>  |
|----------------|-------------|----------------|--|
| 1              | Aug 30      | Piantadosi     | Chapters 1/2: Preliminaries / Clinical trials as research  |
| 2              | Sept 4      | Piantadosi     | Chapter 3: Ethics considerations   |
| 3              | Sept 6      | Piantadosi     | Chapter 4: Contexts  |
| 4              | Sept 11     | Piantadosi     | Chapter 5: Statistical perspectives  |
| 5              | Sept 13     | Piantadosi     | Chapter 6: Design  |
| 6              | Sept 18     |                | Chapters 7/8: Bias and random error / Objectives and endpoints   |
| 7              | Sept 20     | Piantadosi     | Chapters 9/10: Translational trials / Dose finding   |
| 8              | Sept 25     | Piantadosi     | Chapter 11: Sample size and power (first half)   |
| 9              | Sept 27     | Piantadosi     | Chapter 11: Sample size and power (second half)  |
| 10             | Oct 2       | Piantadosi     | Chapters 12/13: Clinical trial cohorts / Treatment allocation  |
| 11             | Oct 4       |                | Chapter 14: Treatment effects monitoring   |
| 12             | Oct 9       | Piantadosi     | Chapter 15: Intention to treat and other issues of counting  |
| 13             | Oct 11      | Piantadosi     | Chapter 16: Estimating clinical effects  |
| 14             | Oct 16      | Piantadosi     | Note: topics from #14 on are selected and ordered depending on the interests of the class.<br>Chapter 17: Prognostic factor analyses and adjusted analyses of comparative trials |

|           |           |            |                                |
|-----------|-----------|------------|--------------------------------|
| <b>15</b> | Oct 18    | Piantadosi | Chapter 18: Reporting          |
| <b>16</b> | Oct 23    | Piantadosi | Chapter 19: Factorial designs  |
| <b>17</b> | Alternate | Piantadosi | Chapter 20: Cross-over designs |
| <b>18</b> | Alternate | Piantadosi | Chapter 21: Overviews          |
| <b>19</b> | Alternate | Piantadosi | Chapter 22: Misconduct         |