



Training and Student Information

Biostatistics Courses

Statistics 542: Introduction to Clinical Trials 1

[printable pdf page](#)

This course is intended for medical researchers interested in the design, conduct, and analysis of clinical trials. The course will develop skills in being a more critical reader of the medical literature and provide the tools to design your own protocol. Examples of clinical trials from the literature throughout the course.

The course is based on the text *Fundamentals of Clinical Trials* by Friedman, Furberg and DeMets.

Downloading Instructions for Slides and Articles

Download the files by RIGHT clicking on the link(s) associated with the title of each lecture, select "Save Link As" or "Save Target As", select the location where they want to pdf file stored, and save it.

To open the file, use My Computer on the desktop. You will need Acrobat Reader to view the documents. If you don't have Acrobat Reader, [click here](#) to download

Another way to do it is to simply click on the link, however, depending on the machine, if the file is too large, or the browser isn't configured to "spawn" Acrobat reader, the machine may get bogged down and confused. So the best way to do it is that right click method described.

[Programs for Computing Group Sequential Boundaries Using the Lan-DeMets Method, Version 2.1,](#)
[Last Update: 11/17/03](#)

Syllabus:

Class	Date	Topic (See download instructions --download may be slow!)	Chapter	Read Articles (See download instructions)
1	1/23	Introduction	1-3	1 Epi Limits 2 Hormone Rx 3 Grady/Hulley Editorial

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2	1/25	Defining the Question	1-3	4 Guyatt 5 IONDT 6 Levin Editorial
3	1/30	Design	4,6	7 CDP 8 4S
4	2/1	Design	4,6	9 PRAISE-I 10 VEST
5	2/6	Randomization	5	11 DCCT 12 CAST
6	2/8	Sample Size	7	13 PHS - Aspirin 14 FIT
7	2/13	Sample Size	7	15 ATBC 16 PHS - Beta Carotene 17 Greenberg/Sporn Editorial
8	2/15	Informed Consent / IRB Baseline, Recruitment, and Data Collection	8, 9, 10	18 Consent 19 NSABP-06 20 NSABP-06 Audit
9	2/20	Quality Control, Adverse Events, Quality of Life	11, 12, 13	21 NOTT 22 IPPB
10	2/22	Survival Analysis		23 ECOG (Tamoxifen) 24 Tamoxifen Prevention
11	2/27	Survival Analysis	14	25 A HEFT 26 NETT
12	3/1	Guest Lecture		
13	3/6	Data Monitoring	15	27 BHAT 28 ME RIT
14	3/8	Data Monitoring	15	29 WHI E + P 30 WHI E alone
15	3/13	Analysis Issues	16	31 ART '78 32 ART '80 33 Companion
16	3/15	Meta Analysis	16	34 Held et al. 35 PROSTATE
17	3/20	Follow Up/ Reporting/Close Out	17, 18, 19	36 APC 37 Approve
18	3/22	Class Discussion		38 Sample Protocol Project
	4/3	Critique Due		
	4/17	Protocol Due		

[Program for Computing Sample Size, Version 1.0,](#)

[Last Update: 2/25/04](#)

Link to Dr. DeMet's technical report "drop the loser designs." Download by right clicking and "save as." [Download.](#)

Schedule:

Tuesday and Thursday, 4:45 - 7:00 pm for 8 weeks: January 23 - March 22, 2007

Location:

1345 Health Science Learning Center, 750 Highland Ave.

Materials:

- Required - *Fundamentals of Clinical Trials* by Friedman, Furberg and DeMets, Springer-Verlag, New York, NY, 3rd edition, 1998
- Required - Randomized Clinical Trials (RCT) papers. See links under "Read Articles" column above
- Optional - Lecture notes (available online above)

Classes:

Classes are given in an 8 week block of two per week. Each class is divided into two parts:

- a. Lecture on basic fundamentals
- b. Discussion of published RCTs

Projects:

1. RCT Critique: A published RCT will be given near the end of the eight weeks of lectures. You are to critique this article, evaluating the strengths and weaknesses, using the fundamentals presented in the lectures. The critique should not be longer than 5 typed pages.
2. Protocol: You are to write a protocol with all of the components presented in some detail. (An example is provided.) You may select the disease or question that is of most interest to you. You may also form a partnership with one other classmate. Get my approval of your topic before you start. Caution: Do not wait until week 8 to start.

Grades:

The grades are 80% based on the critique and the protocol. Homework accounts for 20%.

Homework:

Homework will be assigned and graded. Some assignments are given on, for example - randomization, sample size, and survival analysis. Solutions are given on the homework as a handout.

Course Description

Over the past three decades, randomized clinical trials have become one of the basic research tools in

medicine to evaluate the benefits and risk of new therapeutic or prevention strategies. These may be pharmacologic, biologic, device, a procedure or behavioral modalities. Despite this wide range of modalities and disease processes, the basic fundamentals of clinical trial design are applicable. This course, based on the text by Friedman, Furberg, and DeMets, introduces the basic fundamental concepts of clinical trial design without requiring technical statistical training beyond an introductory course.

The course uses standard lecture material summarizing the fundamental concepts plus a series of published clinical trials to illustrate the concepts along the way. The course starts with an overview of clinical research, indicating the unique role that clinical trials play in the research spectrum which includes anecdotal observations, observational cohort studies and planned prospective experiments. The course focuses mostly on the comparative, also called Phase III, randomized clinical trial (RCT).

The fundamentals start with defining the question to be tested in the RCT. Many studies fail because the question is not well defined, either in concept or in the measurement of it. Since all of the design issues follow from the definition of the question, this is probably the most important step to be resolved. Once the question is carefully laid out, there are several standard RCT designs that can be selected. Central to most of these designs is the process of randomization in the assignment of the experimental or control strategy to individual participants. Several randomization techniques are outlined which achieve comparability of risk factors and other demographics between the experimental and control arms.

The size of the study is always a crucial component to the design of any study since cost and effort are a direct function of this sample size. Depending on the question, the nature of the primary outcome measurement for that question and the basic trial design, sample size concepts and calculations are outlined. For some situations, the answers can be presented simply in tables or graphs. Concepts such as significance level and power are conceptually described and their role in the sample size estimation as indicated.

Several operational issues are also covered including recruitment of participants, data collection and quality control. Many studies also fail because the amount of data collected exceeds what is necessary and what is affordable. The burden of collecting too much data that is not critical can consume resources and jeopardize the main goals of the study. Thus, this issue must be given careful consideration.

A brief presentation of survival analysis is included since this is such a common statistical technique in the analysis of many clinical trials, but not always taught in introductory statistical courses. One of the major activities during the conduct of any RCT is monitoring accumulating data for evidence of harm or early benefit, as well as timeliness and quality of data. While data must be monitored for ethical, scientific, and fiscal reasons, the process of repeated evaluation of data for evidence of harm or early benefit can lead to erroneous conclusions if special care is not taken. Statistical methods are presented which allow for early stopping if interim results are sufficiently convincing, but these methods control the false positive error rates to conventional levels; that is false positive error rates of 1% or 5%.

Once the trial is complete, the data must be analyzed and reported. Several common mistakes in analyzing the data are presented, such as not including all the participants in the analysis due to errors in verifying eligibility or due to patient non-compliance to therapy. While many of these reasons sound compelling at first, they can introduce substantial bias into the comparison of experimental and control arm outcomes and thus must be avoided. Finally, RCTs must be reported succinctly, but still be accurate and detailed to convey to the reader the essential components. Failures in proper reporting may damage the interpretation, or even worse, the credibility of the trial which may have been conducted and analyzed properly.

While the fundamentals described are very basic and straightforward, the challenge in the successful design, conduct, and analysis of an RCT is to implement all of these basic elements together.

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