Course Title: Clinical Trials
Course Number: Epidemiology 205
Winter 2015

A. Objectives

The objectives of this course are to provide a detailed understanding of experimental design options; methods of randomization; blinding; developing interventions and controls; measuring outcomes and adverse effects; follow-up; compliance and post-randomization problems.

B. Prerequisites

Designing Clinical Research (Epi 180.04) and possession of a M.D., Ph.D., D.D.S. or Pharm.D. or equivalent doctoral degree. Exceptions to these prerequisites may be made with the consent of the Course Director, space permitting.

C. Faculty

Course Director:
Dennis Black, Ph.D.
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Lecturers:
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Teaching Assistants
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D. Format

Lectures: eight (8) Thursdays: 8:45 to 10:15am *(you will be notified via email if lecture times change)*
Room: Mission Hall (lecture room 1400)

Sections: three (3) Thursdays: 8:45 to 10:15am on January 22, 2015; February 12, 2015; and March 5, 2015

Rooms:

Beattie:	Mission Hall 1105	Schafer:	Mission Hall 1108
Fukuoka:	Mission Hall 1106	Shepherd:	Mission Hall 1109
Hue:	Mission Hall 1107		

E. Textbooks

Designing Clinical Research, Fourth Edition, by Stephen B Hulley, et al (Philadelphia, PA: Lippincott Williams & Wilkins, 2013), ISBN-13: 978-1608318049
Book Purchase***:***

- Amazon, Textbooks.com or other vendor of your choice
- 5 copies are on 2 hour reserve at Parnassus – UCSF library call number *R853. C55 D47 2013*
- 1 copy is on 2 hour reserve at Mission Bay – UCSF library call number *R853. C55 D47 2013*

DO NOT PURCHASE *(*Available for download online via UCSF library call number *R853.C55 F75 2010eb*)
Fundamentals of Clinical Trials, **Fourth Edition** by Lawrence M. Friedman, Curt D. Furberg and David L. DeMets (New York, NY: Springer, 2010)

F. Homework

Lecture homework is due by **5pm PST on the Monday** *(Note: Monday, January 19, 2015 is MLK Holiday and homework for that week is due on Tuesday, January 20, 2015 by 5pm PST)* following the lecture where the homework is assigned. Homework must be emailed to the Teaching Assistants. No late homework will be accepted. Homework will be graded and returned. Questions on homework assignments will be addressed in the sections.

Reading Assignments: It is expected that all required reading assignments will be completed prior to the lecture or section. Please note that most reading assignments specify certain PAGES, or SECTIONS of journal articles to read, not the entire article. Refer to the reading assignment with each lecture and section to determine what parts of a chapter or journal article are required.

G. Protocol Assignment

A major focus of the sections is to develop a protocol for a randomized trial. The protocol will be based on your own research question. Contact your mentor, section leader or Dr. Black if you cannot come up with an idea for a research question for a clinical trial, or consult with your mentor about refining a protocol that is currently in development.

Email your research question(s) to **your Section Leader** by **5pm on Friday, January 9**, and your cumulative protocol assignment to your section leader according to the following schedule:

by **12pm (noon) on Tuesday, January 20** for Section 1 on Thursday, January 22
by **12pm (noon) on Monday, February 9** for Section 2 on Thursday, February 12
by **12pm (noon) on Monday, March 2** for Section 3 on Thursday, March 5

H. Final Exam

There will be a required take home final exam. The exam will be posted on the course website on March 5, 2015, and will be due to the Teaching Assistants by **10am** on **Friday, March 13, 2015.**

Summary of Written Assignments and Due Dates				
Due date		**Time due**	**Assignment**	**Send to**
Friday	1/9/2015	by 5pm	Research Question (s)	Section Leader
Monday	1/12/2015	by 5pm	HW Lecture 1	Teaching Assistants
Tuesday	1/20/2015	by 12pm (noon)	Protocol Section I	Section Leader
Tuesday	1/20/2015	by 5pm	HW Lecture 2	Teaching Assistants
Monday	2/9/2015	by 12pm (noon)	Protocol Section II	Section Leader
Monday	2/9/2015	by 5pm	HW Lecture 4	Teaching Assistants
Monday	2/23/2015	by 5pm	HW Lecture 5	Teaching Assistants
Monday	3/2/2015	by 12pm (noon)	Protocol Section III	Section Leader
Monday	3/2/2015	by 5pm	HW Lecture 6	Teaching Assistants
Friday	3/13/2015	by 10am	Final Exam	Teaching Assistants

I. Grading

Grades will be based on total points achieved on homework (25%), protocol development and critiquing of protocols (50%), and the final exam (25%). ***Late assignments are not accepted.***

Clinical Trials Course

Winter 2015

Syllabus (for updates, http://www.epibiostat.ucsf.edu/courses/schedule/clin_trials.html)

Week	Date/Time	Faculty/ Room	Title/Content	Assignment
1	Thursday 1/8/2015 8:45-10:15am	D. Black MH 1400	**Lecture 1** Design, Subjects and Randomization *Definition and importance of randomized controlled trials (RCT); examples of RCTs; disadvantages; alternatives; reasons for doing RCTs; randomization; inclusion/exclusion criteria; study designs including classical RCT, factorial designs, cross-over designs, matched pairs, cluster or grouped randomization*	**Required Reading:** Designing Clinical Research (4th Edition), Chapter 10, pages 142-147 and Chapter 11, pages 151-158. Lippman S, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers. JAMA. 2009;301(1) (doi:10.1001/jama.2008.864) *[Note: read abstract and comment sections, review the tables and figures and skim the rest]* Gaziano J, et al. Vitamins E and C in the prevention of prostate and total cancer in men: The Physicians' Health Study II randomized controlled trial. JAMA 2009;301(1) (doi:10.1001/jama.2008.862) *[Note: read abstract; skim the rest]* Black DM, et al. PaTH Study Investigators. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med. 2003;349:1207-15. *[Note: read abstract]* Section from PaTH Protocol **Optional Reading:** Fundamentals of Clinical Trials (4th Edition), Chapters 4, 5, and 6. **Homework:** Exercises from Lecture 1 are due Monday, January 12, 2015 by 5pm: email to Teaching Assistants.
	Friday 1/9/2015, 5pm		**Research Question Due**	Email your research question(s) to your Section Leader on Friday, January 9, 2015 by 5pm.
2	Monday 1/12/2015, 5pm		**Homework Due**	Exercises from Lecture 1 are due Monday, January 12, 2015 by 5pm: email to Teaching Assistants.
	Thursday 1/15/2015 8:45-10:15am	D. Grady MH 1400	**Lecture 2** Blinding, Intervention and Controls *Definition and importance of blinding; strategies if the study can't be blinded; strategies to evaluate blinding; considerations when choosing the intervention; multiple interventions; importance of the control or placebo; advantages and disadvantages of equivalence trials*	**Required Reading:** Designing Clinical Research (4th Edition), Chapter 10, pages 147-149. Fundamentals of Clinical Trials (4th Edition), Chapter 7. Noseworthy H, et al. The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial. Neurology 1994;44: 16-20. *[Note: PDF doc is poor quality.]* Kirkley A, et al. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2008 Sep 11;359(11):1097-107. **Homework:** Exercises from Lecture 2 are due Tuesday, January 20, 2015 by 5pm: email to Teaching Assistants.

3	Tuesday 1/20/2015, 12pm (noon) and 5pm		**Section I Assignment Due**	Email your protocol to your Section Leader by 12pm (noon) on Tuesday, January 20, 2015; bring a copy to Section I. **Protocol assignment due for Section I:** Draft the following sections of a protocol for a randomized trial to address your own research question (2 pages max). 1. Research question(s) 2. Type of randomized trial design 3. Subjects (target and accessible populations) and inclusion/exclusion criteria. 4. Outcome measures *You may summarize, but do not copy from other protocols.*
			Homework Due	**Homework:** Exercises from Lecture 2 are due Tuesday, January 20, 2015 by 5pm: email to Teaching Assistants
	Thursday 1/22/2015 8:45-10:15am	M. Beattie MH 1105 Y. Fukuoka MH 1106 T. Hue MH 1107 A. Schafer MH 1108 J. Shepherd MH 1109	**Section I**	**Required Reading:** *The following studies are examples of various clinical trial designs. Focus only on the <u>methods</u> described in each paper:* Dobscha SK, et al.,Collaborative care for chronic pain in primary care: a cluster randomized trial. JAMA. 2009 Mar 25;301(12):1242-52. Stearns V, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. J Clin Oncol. 2005 Oct 1;23(28):6919-30. **Bring to Section I:** -Email your protocol to your section leader by 12pm (noon) on Tuesday January 20, 2015; bring a copy to section meeting. -Bring your Lecture 1 & 2 homework for review.
4	Thursday 1/29/2015 8:45-10:15am	D. Black MH 1400	**Lecture 3** Statistical Issues in Randomized Trials *Pervasiveness of multiple comparisons in randomized trials; the general problem of multiple comparisons and statistical adjustments; multiple endpoints; statistical concerns about subgroup analyses; what to do with an unexpected subgroup finding; adverse experience categorization; multivariate adjustment*	**Required Reading:** Designing Clinical Research (4th Edition), Chapter 11, pages 164-166 Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med. 2007 Nov 22;357(21):2189-94. *The following 2 articles were read for Lecture 1. For this lecture, review how statistical issues for multiple treatments, multiple outcomes and subgroups were handled.* Lippman S, et al. Effect of selenium and vitamin E of risk on prostate cancer and other cancers. JAMA. 2009;301(1):(doi:10.1001/jama.2008.864) Gaziano J, et al. Vitamins E and C in the prevention of prostate and total cancer in men: The Physicians' Health Study II randomized controlled trial. JAMA 2009;301(1):(doi:10.1001/jama.2008.862) **Optional Reading:** Fundamentals of Clinical Trials (4th Edition), Chapter 17 **There is no homework assignment for Lecture 3**.

5	Thursday 2/5/2015 8:45-10:15am	S. Cummings MH 1400	**Lecture 4** Measuring Outcomes and Adverse Effects *Defining adverse events; elicited vs. volunteered; nuisance adverse events; pitfalls of attribution of cause; FDA adverse events classifications*	**Required Reading:** Designing Clinical Research (4th Edition), Chapter 10, pages 140-142, Chapter 11 page 162. Psaty BM, Lumley T. Surrogate end points and FDA approval: a tale of 2 lipid-altering drugs. JAMA. 2008 Mar 26;299(12):1474-6. Bent S, et al. Brief communication: Better ways to question patients about adverse medical events: a randomized, controlled trial. Ann Intern Med. 2006 Feb 21;144(4):257-61. **Homework:** Exercises from Lecture 4 are due Monday, February 9, 2015 by 5pm: email to Teaching Assistants.
6	Monday 2/9/2015, 12pm (noon) and 5pm		**Section II Assignment Due**	Email your cumulative protocol to your Section Leader by 12pm (noon) on Monday, February 9, 2015; bring a copy to Section II. **Protocol Assignment due for Section II:** Continue to revise the protocol sections developed for Section I. Add the following sections (4 pages total max): 1. Control group(s) 2. Intervention(s) 3. Methods for randomization and blinding 4. Methods for maximizing adherence
			Homework Due	**Homework:** Exercises from Lecture 4 are due Monday, February 9, 2015 by 5pm: email to Teaching Assistants.
	Thursday 2/12/2015 8:45-10:15am	M. Beattie MH 1105 Y. Fukuoka MH 1106 T. Hue MH 1107 A. Schafer MH 1108 J. Shepherd / S. Kalkhoran MH 1109	**Section II**	**Required Reading:** Sackett DL. Superiority trials, noninferiority trials, and prisoners of the 2-sided null hypothesis. ACP Journal Club. March/April 2004; A-11. Granger CB, et al; Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92. *[Note: focus non-inferiority methods]* **Optional Reading:** *[Note: This study provides a very interesting example regarding choosing a proper control for an invasive intervention.]* Olanow CW, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol. 2003 Sep;54(3):403-14. Freeman TB, et al. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. NEJM. 1999;341:988-91. Macklin, R. The ethical problems with sham surgery in clinical research. NEJM. 1999; 341:992-6. **Bring to Section II:** -Email your cumulative protocol to your section leader by 12pm (noon) on Monday, February 9, 2015; bring a copy to section. - Bring your Lecture 4 homework for review.

7	Thursday 2/19/2015 8:45-10:15am	D. Black MH 1400	**Lecture 5** Follow up, Adherence to the Protocol, Post-Randomization, and Introduction to Sample Size Planning *Follow-up in RCTs; what happens after randomization; patient compliance or adherence; effect of incomplete follow-up; strategies to enhance compliance; intention-to- treat and per-protocol analyses; analysis based on post-randomization; subgroup analysis*	**Required Reading:** Designing Clinical Research (4th Edition), Chapter 6, pages 55-59 and Chapter 11, pages 160-162. Fundamentals of Clinical Trials (4th Edition), Chapter 14. Hollis and Campbell. What is meant by intention to treat analysis? Survey of published randomized controlled trials. BMJ. 1999;319;670-4. **Homework:** Exercises from Lecture 5 are due February 23, 2015 by 5pm; email to Teaching Assistants.
8	Monday 2/23/2015, 5pm		**Homework Due**	**Homework:** Exercises from Lecture 5 are due Monday, February 23, 2015 by 5pm: email to Teaching Assistants.
	Thursday 2/26/2015 8:45-10:15am	D. Grady MH 1400	**Lecture 6** Ethics in Clinical Trials and Interim Monitoring *Ethical issues in clinical trials, including choice of interventions in control and intervention groups, randomization, selection of subjects, and interim analyses* *Why alter/stop a clinical trial early; who should decide to stop the trial; what parameters should be monitored and how often; what statistical methods should be used; statistical approaches*	**Required Reading:** Designing Clinical Research (4th Edition), Chapter 11, pages 163-164 and 168-169. Lo B. Ethical issues in clinical trials, pages 1-7. Dixon D, Freedman R et al. Guidelines for data and safety monitoring for clinical trials not requiring traditional data monitoring committees. Clinical Trials. 2006 Nov 3; 314-19. Bryant J and Wolmark N. Letrozole after tamoxifen for breast cancer--what is the price of success? N Engl J Med. 2003 Nov 6;349(19):1855-7. **Optional Reading:** DeMets DL, Pocock SJ, Julian DG. The agonizing negative trend in monitoring of clinical trials. Lancet. 1999;354:1983-88. **Homework:** Exercises from Lecture 6 are due March 2, 2015 by 5pm; email to Teaching Assistants.
9	Monday 3/2/2015, 12pm (noon) and 5pm		**Section III Assignment Due** **Homework Due**	Email your cumulative protocol to your section leader by 12pm (noon) on Monday, March 2, 2015; bring a copy to section. **Assignment due for Section III:** Continue to develop and finalize sections of your protocol started in prior sections. Draft the following sections (6-7 pages total max): 1. Adverse event and side effect measures 2. Plans for interim monitoring 3. List one or two ethical issues related to your protocol and how you plan to manage them. **Homework:** Exercises from Lecture 6 are due Monday, March 2, 2015 by 5pm; email to Teaching Assistants.

	Thursday 3/5/2015 8:45-10:15am	M. Beattie MH 1105 Y. Fukuoka MH 1106 T. Hue MH 1107 A. Schafer / S. Meffert MH 1108 J. Shepherd MH 1109	**Section III**	**Required Reading:** Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized trials stopped early for benefit: a systematic review .JAMA. 2005 Nov 2;294(17):2203-9. *Note: read abstract only.* Pocock SJ. When (not) to stop a clinical trial for benefit. JAMA. 2005 Nov 2;294(17):2228-30. **Bring to Section III:** -Email your cumulative protocol to your section leader by 12pm (noon) on Monday, March 2, 2015; bring a copy to section. - Bring your Lecture 5 & 6 homework for review.
			Final Exam Posted	***Take Home Final Exam to be posted on course website on March 5, 2015; and is due by 10am on Friday, March 13, 2015. Email to Teaching Assistants.***
10	Thursday 3/12/2015 8:45-10:15am	D. Grady MH 1400	**Lecture 7** Nuts and Bolts – Conducting a Trial *Should one do a trial; pilot studies; funding sources; contracts; budgets; the study team; team management; space; recruitment of study subjects; starting the protocol; forms; compliance and follow-up; final visit and post-trial*	**Required Reading:** Designing Clinical Research (4th Edition), Chapter 11, pages 158-159 and Chapter 17. **Homework: There is no homework assignment for Lecture 7.**
	Friday 3/13/2015, 10am		**Final Exam Due**	***Take Home Final Exam due March 13, 2015 by 10am, email to Teaching Assistants.***
11	Thursday 3/19/2015 8:45-10:15am	S. Cummings MH 1400	**Lecture 8** Multicenter Studies and Industry-Sponsored Trials *The anatomy and physiology of multicenter trials; how to work effectively and make use of data from such trials; how industry trials operate; pros and cons of participation in industry sponsored trials and principles that may minimize bias*	**Required Reading:** Fundamentals of Clinical Trials (4th Edition), Chapter 8, pages 159-161. (*Other readings may be distributed before the lecture.*) **Homework: There is no homework assignment for Lecture 8.**