

Course Title: Clinical Trials
Course Number: Epidemiology 205
Winter 2020

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: Deborah Grady, M.D., M.P.H.
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Teaching Assistants: Katherine Brown, MD
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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 23, 2020; February 20, 2020; and March 19, 2020

Rooms: Avins: Mission Hall 1105
Brenowitz: Mission Hall 1106
Hue: Mission Hall 1107

Phillips: Mission Hall 2106
Pressman: Mission Hall
1109/2107/1109

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 20, 2020 is MLK Holiday and homework for that week is due on Tuesday, January 21, 2020 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. This year we have made significant reductions in the reading so please try to complete the readings prior to lectures. 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 10, 2020** and your cumulative protocol assignment to your section leader according to the following schedule:

- by **12pm (noon) on Tuesday, January 21** for Section 1 on Thursday, January 23
- by **12pm (noon) on Tuesday, February 18, 2020** for Section 2 on Thursday, February 20
- by **12pm (noon) on Monday, March 16** for Section 3 on Thursday, March 19

H. Final Exam

There will be a required take home final exam. The exam will be posted on the course website on March 12, 2020, and will be due to the Teaching Assistants by **10am on Friday, March 20, 2020**.

Summary of Written Assignments and Due Dates			
Due date	Time due	Assignment	Send to
Friday 1/10/2020	by 5pm	Research Question (s)	Section Leader
Monday 1/13/2020	by 5pm	HW Lecture 1	Teaching Assistants
Tuesday 1/21/2020	by 12pm (noon)	Protocol Section I	Section Leader
Tuesday 1/21/2020	by 5pm	HW Lecture 2	Teaching Assistants
Monday 2/3/2020	By 5pm	HW Lecture 3	Teaching Assistants
Monday 2/10/2020	by 5pm	HW Lecture 4	Teaching Assistants
Tuesday 2/18/2020	by 12pm (noon)	Protocol Section II	Section Leader
Tuesday 2/18/2020	by 5pm	HW Lecture 5	Teaching Assistants
Monday 3/9/2020	by 5pm	HW Lecture 7	Teaching Assistants
Monday 3/16/2020	by 12pm (noon)	Protocol Section III	Section Leader
Friday 3/20/2020	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 2020

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

Week	Date/Time	Faculty/ Room	Title/Content	Assignment
1	Thursday 1/9/2020 8:45-10:15am	D. Black MH 1400	Lecture 1 Design, Subjects and Randomization <i>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, cross-over designs, matched pairs, cluster or grouped randomization</i>	Required Reading: Designing Clinical Research (4 th Edition), Chapter 10, pages 142-147 and Chapter 11, pages 151-158. Abstracts: Read abstract and watch a 3 min video abstract of a cluster randomized, international study. A community-based comprehensive intervention to reduce cardiovascular risk in hypertension (HOPE 4): a cluster-randomised controlled trial (Schwalm et al, Lancet 10/19) https://www.sciencedirect.com/science/article/pii/S014067361931949X?via%3Dihub Optional Reading: Another cluster randomized study (in China): The Chirpy Dragon study (Li, et al. 2019 PLOS) Fundamentals of Clinical Trials (4th Edition), Chapters 4, 5, and 6. Homework: Exercises from Lecture 1 are due Monday, January 13, 2020 by 5pm: email to Teaching Assistants. Email your research question(s) to your Section Leader on <u>Friday, January 10, 2020 by 5pm.</u>
	Friday 1/10/2020, 5pm		Research Question Due	
2	Monday 1/13/2020, 5pm		Homework Due	Exercises from Lecture 1 are due Monday, January 13, 2020 by 5pm: email to Teaching Assistants.
	Thursday 1/16/2020 8:45-10:15am	D. Grady MH 1400	Lecture 2 Blinding, Intervention and Controls <i>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</i>	Required Reading: Designing Clinical Research (4 th Edition), Chapter 10, pages 147-149. 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. Optional Reading: Fundamentals of Clinical Trials (4th Edition), Chapter 7. Homework: Exercises from Lecture 2 are due Tuesday, January 21, 2020 by 5pm: email to Teaching Assistants.

Week	Date/Time	Faculty/ Room	Title/Content	Assignment
	Tuesday 1/21/2020, 12pm (noon)		Section I Assignment Due	Email your protocol to your Section Leader by 12pm (noon) on Tuesday, January 21, 2020; 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 <i>You may summarize, but do not copy from other protocols.</i>
	Tuesday 1/21/2020, 5pm		Homework Due	Homework: Exercises from Lecture 2 are due Tuesday, January 21, 2020 by 5pm: email to Teaching Assistants
	Thursday 1/23/2020 8:45-10:15am	A. Avins MH 1105 W.Brenowitz MH 1106 T. Hue MH 1107 P. Phillips MH 2106 A. Pressman MH 1109	Section I	Bring to Section I: -Email your protocol to your section leader by 12pm (noon) on Tuesday, January 21, 2020; bring a copy to section meeting. -Bring your Lecture 1 & 2 homework for review.
4	Thursday 1/30/2020 8:45-10:15am	D. Black MH 1400	Lecture 3 Statistical Issues in Randomized Trials, Review of data analysis for RCTs; Factorial RCT designs and analysis approaches; Subgroups and multiple comparisons: implications for inference from RCT	Required Reading: Designing Clinical Research (4 th 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. <i>Please read/review the abstracts from the following 2 papers. For this lecture, review how statistical issues for multiple treatments, multiple outcomes and subgroups were handled.</i> 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) 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) (abstract only) Manson JE, et al. Marine n-3 Fatty Acids and Prevention Cardiovascular Disease and Cancer. N Engl J Med. 2019 Jan 3;380(1):23-32. Manson JE, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med. 2019 Jan 3;380(1):33-44.

Week	Date/Time	Faculty/ Room	Title/Content	Assignment
				Optional Reading: Fundamentals of Clinical Trials (4th Edition), Chapter 17 Homework: Exercises from Lecture 3 are due Monday, February 3, 2020 by 5pm: email to Teaching Assistants.
5	Monday 2/3/2020 5pm		Homework Due	Homework: Exercises from Lecture 3 are due Monday, February 3, 2020 by 5pm: email to Teaching Assistants.
	Thursday 2/6/2020 8:45-10:15am	D. Black MH 1400	Lecture 4 Measuring Outcomes and Adverse Effects <i>Clinical outcomes and alternatives. Defining adverse events; elicited vs. volunteered; nuisance adverse events; pitfalls of attribution of cause; FDA adverse events classifications</i>	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 10, 2020 by 5pm: email to Teaching Assistants.
6	Monday 2/10/2020, 5pm		Homework Due	Homework: Exercises from Lecture 4 are due Monday, February 10, 2020 by 5pm: email to Teaching Assistants.
	Thursday 2/13/2020 8:45-10:15am	D. Black MH 1400	Lecture 5 Follow up, Adherence to the Protocol, Post-Randomization, and Introduction to Sample Size Planning <i>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</i>	Required Reading: Designing Clinical Research (4th Edition), Chapter 6, pages 55-59 and Chapter 11, pages 160-162. 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 17, 2020 by 5pm; email to Teaching Assistants.
7	Tuesday 2/18/2020, 12pm (noon)		Section II Assignment Due	Email your cumulative protocol to your Section Leader by 12pm (noon) on Monday, February 17, 2020; 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. Adverse event and side effect measures

Week	Date/Time	Faculty/ Room	Title/Content	Assignment
	Tuesday 2/18/2020, 5pm		Homework Due	Homework: Exercises from Lecture 5 are due Monday, February 17, 2020 by 5pm: email to Teaching Assistants.
	Thursday 2/20/2020 8:45-10:15am	A. Avins MH 1105 W.Brenowitz MH 1106 T. Hue MH 1107 P. Phillips MH 2106 A. Pressman MH 2107	Section II	Bring to Section II: -Email your cumulative protocol to your section leader by 12pm (noon) on Monday, February 17, 2020; bring a copy to section. - Bring your Lecture 4 homework for review
8	Thursday 2/27/2020 8:45-10:15am	D. Black MH 1400	Lecture 6 Multicenter Studies and Industry-Sponsored Trials <i>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</i>	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 6.
9	Thursday, 3/5/2020 8:45-10:15am	A. Huang MH 1400	Lecture 7 Ethics in Clinical Trials and Interim Monitoring <i>Ethical issues in clinical trials, including choice of interventions in control and intervention groups, randomization, selection of subjects, and interim analyses</i> <i>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</i>	Required Reading: Designing Clinical Research (4 th 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 7 are due March 9, 2020 by 5pm; email to Teaching Assistants.
10	Monday, 3/9/2020, 5pm		Homework Due	Homework: Exercises from Lecture 7 are due March 9, 2020 by 5pm; email to Teaching Assistants.
	Thursday 3/12/2020 8:45-10:15am	D. Grady MH 1400	Lecture 8 Nuts and Bolts – Conducting a Trial	Required Reading: Designing Clinical Research (4 th Edition), Chapter 11, pages 158-159 and Chapter 17.

Week	Date/Time	Faculty/ Room	Title/Content	Assignment
			<i>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</i>	Homework: There is no homework assignment for Lecture 8.
			Final Exam Posted	Take Home Final Exam to be posted on course website on March 12, 2020; and is due by 10am on Friday, March 20, 2020. Email to Teaching Assistants.
11	Monday 3/16/2020, 12pm (noon)		Section III Assignment Due	Email your cumulative protocol to your section leader by 12pm (noon) on Monday, March 16, 2020; 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. Methods for maximizing adherence 2. Plans for interim monitoring 3. List one or two ethical issues related to your protocol and how you plan to manage them.
	Thursday 3/19/2020 8:45-10:15am	A. Avins MH 1105 W.Brenowitz MH 1106 T. Hue MH 1107 P. Phillips MH 2106 A. Pressman MH 1109	Section III	Bring to Section III: -Email your cumulative protocol to your section leader by 12pm (noon) on Monday, March 16, 2020; bring a copy to section. - Bring your Lecture 7 homework for review Take Home Final Exam due March 20, 2020 by <u>10am</u>, email to Teaching Assistants.
	Friday 3/20/2020, 10am		Final Exam Due	