BIOST/STAT 524
Design of Medical Studies
Spring Quarter 2019
Dr. Fleming

SYLLABUS

I. INSTRUCTOR

Thomas R. Fleming, Ph.D.
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CO-INSTRUCTORS

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TA

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Office Hours: Monday (10a-11a) and Wednesday (10a-11a)
Location: Room H-657 (Biostatistics H-Wing Conference Room)

II. TEXTBOOK

Friedman LM, Furberg CD and DeMets DL: Fundamentals of Clinical Trials, Fifth Edition (2016), Mosby-Year Book, Inc., St. Louis, Missouri.

III. REFERENCES

Ellenberg S, Fleming TR and DeMets DL: Monitoring Clinical Trials: A Practical Perspective (Second Edition) (2019), Wiley & Sons

Pocock SJ, Clinical Trials: A Practical Approach (1983), New York: Wiley and Sons.

IV. Mondays and Wednesdays: 8:30 – 9:50 a.m., T-498

V. COURSE OBJECTIVES

This course will provide an introduction to the design, conduct and analysis of randomized clinical trials. Topics to be covered include: eliminating bias, need for randomization, intention-to-treat principles, reducing variation, phases of clinical research, computing power and sample sizes, choosing proper endpoints, role of surrogate biomarkers, interpreting confirmatory and exploratory analyses, identifying and addressing safety signals, when to use blinding, factorial designs, Phase 2b screening trial designs, conducting confirmatory studies, designing non-inferiority trials, data management, addressing missing data, group sequential guidelines, the importance of confidentiality of interim results, adaptive methods, addressing quality of trial conduct, role of data monitoring committees, and ethical issues in clinical research.

At the end of Biostat 524 a student should have made significant progress toward being able to:

1. Critique the design and plans for monitoring and analyzing a randomized clinical trial.

2. Design a clinical trial to address an important scientific problem, including:

    a. addressing the key ethical issues that must be considered,

    b. selecting an appropriate comparison group and specifying the scheme by which treatment assignment will occur,

    c. defining primary and secondary endpoints for measures of treatment outcome,

    d. justifying the sample size requirements for the study,

    e. reducing bias and variability in the design and conduct of the trial,

    f. specifying methods for monitoring the clinical trial,

    g. specifying methods for analysis of the results, and

    h. establishing to ability to identify and address safety signals

VI. COURSE PROJECT

There will be one major course project. After being grouped into research teams, students will respond to a selected Request for Proposal (RFP) by writing a grant which recommends and justifies a study design and includes the design of the management operation needed to run the study and analyze the data. The research teams will consist of 3 to 5 students and will be heterogeneous with respect to the area of specialization. By Wednesday, April 10, we plan to complete formation of these teams. By Monday, April 22, each team will submit a Letter of Intent (LOI) identifying the RFP to which they will respond. On Monday, May 20 a rough version of the proposal, providing approximately 75% of the final content, will be submitted. Some limited feedback on these submissions will be provided within one week by Dr. Fleming. At the end of the quarter, on June 5, the completed projects will be submitted to Dr. Fleming. These projects will be defended in a "mock" site visit during June 10 – 12. In addition to defending their proposal, each team will have the opportunity to serve as reviewers for another project. A final session will be held in the afternoon of June 12 in order to discuss the site review process.

VII. APPROXIMATE COURSE OUTLINE

(FFD = Friedman, Furberg, and DeMets book; Chapters correspond to 5th Edition)

(2 lec)	Introduction	
4/1, 4/3	Course Overview	
	Types of Clinical Studies	FFD Ch 1-5
	Steps in Clinical Experimentation	Pocock Ch 1, 3, 4
	The Study Protocol	Fleming & Ellenberg, *Cl Tr* 2016
	Observational Data Bases, Historical & Randomized Controls	
(1 lec)	Sample Size and Related Issues	FFD Ch 7
4/8	Point Estimates, Confidence Intervals	Pocock Ch 9
	Over/Underpowered Trials	
	False Positive and False Negative errors	
	Statistical vs. Clinical Significance	
(1 lec)	Endpoint Selection	FFD Ch 2, 12
4/10	Choosing Endpoints:	Fleming & DeMets, *Annals*
	Biologic Activity vs. Clinical Efficacy	*of Int Med,* 1996
	Role of Surrogate Endpoints	IOM (Biomarkers) 2010
	Patient Reported Outcomes	Fleming&Powers, *Stat Med* 2012
(1 lec)	Adjusted and Exploratory Analyses	FFD Ch 5, 8, 16
4/15	Confirmatory vs. Exploratory Analyses	Pocock Ch 5, 14, 15
	Prognostic Factors/Confounders	Fleming, *Ann Int Med*, 2010
	Effect Modifiers: Subset Analyses	
(1 lec)	Selected Design Issues	FFD Ch 2, 4, 6
4/17	When to use Blinding	Pocock Ch 8
	Factorial and Crossover Designs	(Lecture by Chloe Krakauer)
(1 lec)	Selected Design Issues	FFD Ch 2, 4, 6
4/22	Phase 2b Screening Trial Designs	Pocock Ch 8
	Confirmatory Trials	Fleming & Richardson, *JID* 2004
(1 lec)	Identifying and Addressing Safety Signals	Fleming, *4th Seattle Symp, 2013*
4/24	Pre- vs. Post-Marketing Safety Evaluations	Fleming, *NEJM* 2008
	Addressing Safety Signals	FFD Ch 11
(2 lec)	Non-Inferiority Designs	Pocock Ch 12
4/29, 5/1	Design, Conduct & Analysis	Fleming, *Stat in Med* 2008
	Setting the NI Margin	Fleming & Powers, *CID* 2008
	Illustrations	Fleming et al, *Clin Trials* 2011

(1 lec)	Monitoring Guidelines	FFD Ch 15; Pocock Ch 10
5/6	Motivation	Ellenberg, Fleming & DeMets
	Group Sequential Methods	Ch 5, 8
	Importance of Confidentiality	Fleming et al, *Clin Trials* 2008
(1 lec)	Adaptive Methods	Emerson & Fleming, *JBS* 2010
5/8	Controversial Issues	
(2 lec)	Data Monitoring Committees	Ellenberg, Fleming & DeMets
5/13, 5/15	Mission & Structure	Ch 1-4, 6-7, 9
	Illustrations	Fleming, *Clinical Trials* 2014
	Issues impacting DMC independence	Fleming et al, *Clinical Trials* 2017
(1 lec)	Recruitment/Retention/Adherence	FFD Ch 9, 13
5/20	Ineligible Patients	Pocock Ch 12
	Effects of Non-adherence	Probstfield & Frye, *JAMA* 2011
	Incomplete Evaluation	Butler et al, *JACC* 2013
	Inclusion of Withdrawals in Analysis	(Lecture by Prof. J. Probstfield)
(1 lec)	Subgroup Analyses/Site Visit Prep	(Lecture by Prof J. Probstfield)
5/22	Issues and Illustrations	
(1 lec)	Variability and Bias	FFD Ch 16
5/29	Addressing Missing Data	IOM (Missing Data), 2010
	Censoring Post-Randomization Events	Fleming, *Annals of Int Med* 2011
(1 lec)	Ethical Issues	Pocock Ch 7
6/3	Background	
	Principles	
	Informed Consent	
(1 lec)	Quality Control/Data Management	(Lecture by Prof. Kelley Branch)
6/5	Issues and Illustrations	
6/10 – 6/12	Grant Review Process	Room **TBD**
	Site Visits	
	Defending Grant Proposals	
	Serving as Site Visitor	
	Final summary	

Disability Statement

Access and Accommodations: Your experience in this class is important to me. If you have already established accommodations with Disability Resources for Students (DRS), please communicate your approved accommodations to me at your earliest convenience so we can discuss your needs in this course.

If you have not yet established services through DRS, but have a temporary health condition or permanent disability that requires accommodations (conditions include but not limited to; mental health, attention-related, learning, vision, hearing, physical or health impacts), you are welcome to contact DRS at 206-543-8924 or uwdrs@uw.edu or disability.uw.edu. DRS offers resources and coordinates reasonable accommodations for students with disabilities and/or temporary health conditions. Reasonable accommodations are established through an interactive process between you, your instructor(s) and DRS. It is the policy and practice of the University of Washington to create inclusive and accessible learning environments consistent with federal and state law.

Academic Integrity

Students at the University of Washington (UW) are expected to maintain the highest standards of academic conduct, professional honesty, and personal integrity.

The UW School of Public Health (SPH) is committed to upholding standards of academic integrity consistent with the academic and professional communities of which it is a part. Plagiarism, cheating, and other misconduct are serious violations of the University of Washington Student Conduct Code (WAC 478-120). We expect you to know and follow the university's policies on cheating and plagiarism, and the SPH Academic Integrity Policy. Any suspected cases of academic misconduct will be handled according to University of Washington regulations. For more information, see the University of Washington Community Standards and Student Conduct website.

(For printed syllabi, below are the URLs for the text that is hyperlinked above:

UW Student Conduct Code (WAC 478-120)
http://www.washington.edu/cssc/student-conduct-overview/student-code-of-conduct/
SPH Academic Integrity Policy
http://sph.washington.edu/students/academicintegrity/
Community Standards and Student Conduct
http://www.washington.edu/cssc/)

TAs

If you have any concerns about the class or your TA, please see the TA about these concerns as soon as possible. If you are not comfortable talking with the TA or not satisfied with the response that you receive, you may contact the Department of Biostatistics Associate Director of Academic Affairs (biostgp@uw.edu). If you are still not satisfied with the response that you receive, you may contact the Department of Biostatistics Chair (bchair@uw.edu). You may also contact the Graduate School at G-1 Communications Building, by phone at 206-543-5139 or by email at raan@uw.edu.