University of Florida
Colleges of Medicine and Public Health & Health Professions
Department of Biostatistics

GMS 6818 - Design and Conduct of Clinical Trials I
Spring 2013

Time: Wednesdays, 2–4pm

Location: McKnight Brain Institute (MBI) L3-101

Credits: 2 credits (one 2-hour session per week for 15 weeks)

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Office Hours: By appointment

COURSE DESCRIPTION
The sequence of courses, Design and Conduct of Clinical Trials I, and Design and Conduct of Clinical Trials II, is designed with the intent that the student takes both classes. In Design and Conduct of Clinical Trials I, the student will learn the ethics, principles and conduct of clinical trials for medical research. The protection of study participants and the need for equipoise will be covered, including regulatory restrictions and the latest patient privacy regulations for the dissemination and use of data associated with the participants in clinical trials. Various study designs will be discussed, including single-arm, crossover, factorial, sequential multi-stage, and dose-finding designs, plus the means to allocate study participants to appropriate treatment groups using randomization (blocked or stratified) and prognostic factors. The importance of equipoise, informed consent, and the use of intent-to-treat analysis will be emphasized. Data collection and management for the conduct of clinical trials will be briefly addressed. The roles of the Institutional Review Board (IRB), Data Monitoring Committee (DMC), and federal regulatory agencies in the approval and review of ongoing clinical trials will be discussed. Homework assignments will be extremely applied, and will make use of real clinical trials designs and data.

COURSE OBJECTIVES
By the end of this course, the student should be able to:
(1) Explain key concepts in the design of clinical trials.
(2) Describe the study designs commonly used.
(3) Identify key issues in data management for clinical trials.
(4) Describe the roles of Regulatory Affairs in clinical trials.

METHODS OF INSTRUCTION:
Class sessions will be a combination of presentation of major topics and class discussion of the presentations and additional readings. Attendance and active participation in all class discussions is required, and will be evaluated as part of the student's grade for the course. Students must read the

required readings prior to each class session. Students are expected to take an active role in initiating and leading discussions and debates.

TESTS AND QUIZZES: No midterm or final exam will be required in this course. Three short quizzes will occur at the beginning of Weeks 5, 11, and 13. (3x5%=15%)

ASSIGNMENTS
There are three requirements:

1. Homework: Based on material covered during Weeks 2, 3, 5-6, 7, and 13 and due via e-mail, E-Learning, or next class session. (5x7%=35%)

2. Class Participation: All students must attend class and participate in each class discussion. (10%)

3. Paper critique and Presentation: Each student will choose two published papers reporting results from clinical trials and
    a. Write a 3-5 (double-spaced) critique for one (20%)
    b. Present the other to class (20%)

EVALUATION AND GRADING
Grades will be based on the homework assignments (35%); attendance and class participation (10%); quizzes (15%); and paper critiques and presentations (40%). All deadlines must be met. Any assignment turned in after the deadline will receive one full letter grade below what it would have earned had it been submitted on time. The following grading system will be used: A (92.5% or higher), A- (89.5%-92.49%), B+ (86.5%-89. 49%), B (82.5%-86. 49%), B- (79.5%-82. 49%), C+ (76.5%-79. 49%), C (72.5%-76. 49%), C- (69.5%-72. 49%), D (59.5%-69. 49%), and F (<59. 49%).

CLASS ATTENDANCE
Class attendance is mandatory. Excused absences follow the criteria of the UF Graduate Catalogue (e.g., illness, serious family emergency, military obligations, religious holidays), and should be communicated to the instructor prior to the missed class day when possible. Missing three or more unexcused scheduled sessions will result in a failure. Regardless of attendance, students are responsible for all material presented in class and meeting the scheduled due dates for class assignments. Finally, students should read the assigned readings prior to the class meetings, and be prepared to discuss the material for each session.

E-LEARNING SUPPORT SERVICES
Course information, readings, and grades are available on the Sakai system at http://lss.at.ufl.edu/. You must have a Gatorlink account to log on.

STUDENTS WITH DISABILITIES
Students requiring accommodations must first register with the Dean of Students' Office. The Dean of Students' Office will provide documentation to the student who must then provide this documentation to the faculty member when requesting accommodation. The College is committed to providing reasonable accommodations to assist students in their coursework.

ACADEMIC INTEGRITY
Each student is bound by the academic honesty guidelines of the University and the student conduct code printed in the Student Guide and on the University website. The Honor Code states: "We, the members of the University of Florida community, pledge to hold ourselves and our peers to the highest standards of honesty and integrity." While topical discussion is encouraged, all writing and presentation assignments are to be solely the work of the individual student. Cheating or plagiarism in any form is unacceptable and inexcusable behavior.

Policy on Style for Citation and Plagiarism:

The two key purposes of citation are to (1) give appropriate credit to the authors of information, research findings, and/or ideas (and avoid plagiarism) and (2) facilitate access by your readers to the sources you use in your research.

Quotations: When directly quoting an outside source, the borrowed text, regardless of the amount, must be surrounded by quotation marks or block quoted. Quoted text over two lines in length should be single-spaced and indented beyond the normal margins. Every quote must include a source—the author, title, volume, page numbers, etc.—whether an internal reference, footnote, or endnote is used in conjunction with a bibliography page.

Paraphrasing or Citing an Idea: When summarizing an outside source in your own words or citing another person's ideas, quotation marks are not necessary, but the source must be included. This includes, but is not confined to, personal communications from other students, faculty members, experts in the field, summarized ideas from published or unpublished resource, and primary methods derived from published or unpublished sources. Use the general concept of "when in doubt – cite."

Plagiarism is a serious violation of the academic honesty policy of the College. If a student plagiarizes others' material or ideas, he or she may receive an "E" in the course. The faculty member may also recommend further sanctions to the Dean, per College disciplinary action policy. Generally speaking, the three keys of acceptable citation practice are: 1) thoroughness, 2) accuracy, and 3) consistency. In other words, be sure to fully cite all sources used (thoroughness), be accurate in the citation information provided, and be consistent in the citation style you adopt. All references should include the following elements: 1) last names along with first and middle initials; 2) full title of reference; 3) name of journal or book; 4) publication city, publisher, volume, and date; and 5) page numbers referenced. When citing information from the Internet, include the WWW address at the end, with the "access date" (i.e., when you obtained the information), just as you would list the document number and date for all public documents. When citing ideas or words from an individual that are not published, you can write "personal communication" along with the person's name and date of communication.

Required Text:
Friedman, Furberg, and DeMets. *Fundamentals of Clinical Trials (4th Edition)*. Springer, 2010. Free text available online at http://dx.doi.org/10.1007/978-1-4419-1586-3

Optional/Recommended Texts:
Machin and Fayers. *Randomized Clinical Trials: Design, Practice and Reporting*. Wiley-Blackwell, 2010

Piantadosi S. *Clinical Trials: A Methodologic Perspective (2nd Edition*). New Jersey: John Wiley & Sons, 2005.

TENTATIVE SCHEDULE OF TOPICS

Week 1 (1/9) Introduction, Motivation, and Ethics of Clinical Trials (TJ)

a. Historical examples
b. Introduction to study designs and clinical trials
c. Ethics and Historically derived principles
    i. Nuremberg Code
    ii. Declaration of Helsinki
    iii. Belmont Report
d. Equipoise
e. Informed consent

Week 2 (1/16) Phases, Contexts, Examples (AN)

a. Description of trial phases (Phase 0, Phase I, II, III, and IV)
b. Trial contexts (types of trials: pharma, devices, etc.)
c. Trial examples

Week 3 (1/23) Study Protocol (MD)

a. Introduction, background, Objectives
b. Eligibility, Design, Randomization
c. Intervention details, assessments and data collection, case report forms
d. Violations
e. Amendments

Week 4 (1/30) The Study Population and Cohort (TJ)

a. Study population
b. Study cohort
c. Recruitment (planning, strategies, and sources)
d. Accrual (problems and solutions)
e. Inclusiveness and Representation

Weeks 5-6 (2/6, 2/13) Study/Trial Design (TJ/AN)

a. Phase I designs
    i. Dose-finding designs
b. Phase II designs
    i. Pilot studies
    ii. Single arm
    iii. Historical control designs
c. Phase III designs
    i. Factorial designs
    ii. Crossover designs
    iii. Multicenter studies
d. Pilot studies
e. Phase IV designs

Week 7 (2/20) Treatment Allocation (TJ)

a. Randomization
    i. Simple
    ii. Blocked

iii. Stratified
b. Adaptive allocation
c. Masking

Week 8 (2/27) Statistical Perspective (TJ)
a. Philosophy
b. Bayesian vs. Frequentist

Week 9 (3/6) SPRING BREAK – NO CLASS

Week 10 (3/13) Research Question and Outcomes (MD)
a. Research Question
b. Surrogate Outcomes

Week 11 (3/20) Measurement and Data Capture (MD)
a. Measures and endpoints
b. Required observations
c. Types of measures
d. baseline measurements
e. Case report forms
f. Data collection
i. Paper or electronic
ii. Parsimony
g. Database and software
h. Staffing and resources

Week 12 (3/27) Data Monitoring, Trial Conduct (AN)
a. Data quality assurance
b. Data delinquency
c. Data Monitoring
d. Trial Conduct
e. Occurrence and control of variation and bias

Week 13 (4/3) Introduction to Power and Sample Size (AN)
a. Hypothesis testing
b. P-values, confidence intervals
c. General power/sample size, estimating effect size
d. Matching sample size calculations to endpoints

Guests Week 14 (4/10) Privacy and IRB
a. Guest Lecture 1: Privacy/HIPAA Everall Peele, UF Privacy Manager
b. Guest Lecture 2: IRB, Tiffany Pineda, Education Coordinator, UF IRB

Week 15 (4/17) Regulatory Affairs (MD) / Class Presentations
a. Misconduct and fraud
b. Conflict of interest

Week 16 (4/24) Class Presentations