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

PHC 6937 – Design and Conduct of Clinical Trials
Fall 2016

Time: Mondays, 1:55–3:50pm
Wednesdays, 1:55–2:45pm

Location: Clinical and Translation Research Building (CTRB) 5235

Credits: 3 credits

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Office Hours: By appointment

COURSE DESCRIPTION

This is a new 3 credit course being offered in Fall 2016. It replaces the two-part series GMS 6818 and GMS 6819 offered in Fall and Spring respectively, in the past years. The two courses were combined into a 3 credit course to be offered every Fall going forward.

In PHC 6937 students will learn about 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. Writing the study protocol, data collection, analyses methods and reporting of results of a trial will be discussed. 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 addressed. The course will also include discussions on the application of the appropriate analytic methods for each specific type of study endpoint, approaches to performing interim safety monitoring, and adaptive trial designs. Translational research plays an increasing role in clinical trials, and the identification and rationale for the use of prognostic factors will be covered. Other topics to be touched upon include health-related quality of life measures, longitudinal data analysis, and meta-analysis. The roles of the Institutional Review Board (IRB), Data Safety Monitoring Committee (DSMC) 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.
(5) Identify the appropriate data analytic technique to match the study endpoint.
(6) Describe safety monitoring issues in clinical trials and related data analysis methods.
(7) Describe the basics of longitudinal data analysis and meta-analysis.
(8) Understand alternative trial designs.

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
No midterm or final exam will be required in this course but there will be 4 quizzes.

ASSIGNMENTS
There are four requirements:

1. Homework. Based on material covered during Weeks 3-4, 5-6, 7-8, 8-9, and 9-10 and due via e-mail, E-Learning, or next class session. (5x8%=40%).

2. Quizzes. There will be a quiz covering material from Weeks 2, 6, 10-12, and 13-14. (4x5%=20%).

3. Class participation. All students must participate in each class discussion. (10%)

4. Written report and presentation at the end of the course. (30%)

EVALUATION AND GRADING
Grades will be based on homework assignments (40%); quizzes (20%); attendance and class participation (10%); written report (15%) and presentation (15%). All deadlines must be met. Any assignment turned in after the deadline will be penalized, including non-acceptance of the assignment, at the discretion of the instructors.

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 be called upon to discuss the material for each session.

E-LEARNING SUPPORT SERVICES
Course information, readings, and lecture slides are available on the Canvas system at http://elearning.ufl.edu/. Click on the "Login to E-Learning" button and enter your GatorLink username and password into the boxes.

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.

INCLUSIVE LEARNING ENVIRONMENT
Public health and health professions are based on the belief in human dignity and on respect for the individual. As we share our personal beliefs inside or outside of the classroom, it is always with the understanding that we value and respect diversity of background, experience, and opinion, where every individual feels valued. We believe in, and promote, openness and tolerance of differences in ethnicity and culture, and we respect differing personal, spiritual, religious and political values. We further believe that celebrating such diversity enriches the quality of the educational experiences we provide our students and enhances our own personal and professional relationships. We embrace The University of Florida's Non-Discrimination Policy, which reads, "The University shall actively promote equal opportunity policies and practices conforming to laws against discrimination. The University is committed to non-discrimination with respect to race, creed, color, religion, age, disability, sex, sexual orientation, gender identity and expression, marital status, national origin, political opinions or affiliations, genetic information and veteran status as protected under the Vietnam Era Veterans' Readjustment Assistance Act." If you have questions or concerns about your rights and responsibilities for inclusive learning environment, please see your instructor or refer to the Office of Multicultural & Diversity Affairs website: http://www.multicultural.ufl.edu.

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 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.

Meinert CL. *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, 1986.

Pocock SJ. *Clinical Trials: A Practical Approach*. John Wiley & Sons, 1996.

TENTATIVE SCHEDULE OF TOPICS

Introduction, Motivation, and Ethics of Clinical Trials
a. Historical examples
b. Introduction to study designs and clinical trials
c. Ethics and historically derived principles (Nuremberg Code, Declaration of Helsinki, Belmont Report)
d. Equipoise
e. Informed consent

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

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

Study Protocol
a. Introduction, background, objectives
b. Eligibility, design, randomization
c. Intervention details, assessments and data collection, case report forms
d. Violations
e. Amendments

Research Question and Outcomes
a. Research question
b. Surrogate outcomes
c. Subgroup analysis

Privacy
Guest Lecture: Privacy/HIPAA, UF Privacy Office

Study/Trial Design
a. Phase I designs (Dose-finding designs)
b. Phase II designs (Single arm, historical control designs)
c. Phase III designs (Factorial designs, crossover designs, multicenter studies)
d. Pilot studies
e. Phase IV designs

Treatment Allocation
a. Randomization (Simple, blocked, stratified)
b. Adaptive allocation
c. Masking

Measurement and Data Capture
a. Measures and endpoints
b. Required observations
c. Types of measures
d. Baseline measurements
e. Case report forms
f. Data collection (Paper or electronic, parsimony)
g. Database and software
h. Staffing and resources
i. Data quality assurance
j. Data delinquency
k. Data Monitoring

Hypothesis Testing
a. Introduction, procedures, and examples
b. P-values and confidence intervals

Analytic Methods for Specified Endpoints, Assumptions and Diagnostics
a. Matching the method to the endpoint, diagnostics
   i. Binary (e.g., logistic regression)
   ii. Categorical (e.g., Fisher's exact test)
   iii. Ordinal (e.g., Kruskal-Wallis test)
   iv. Continuous (e.g., ANOVA)
   v. Linear models (e.g., ANCOVA)
   vi. Time to event (e.g., Kaplan-Meier curves, log-rank test, Cox PH model)

Trial Conduct
a. Random error and bias

Introduction to Power and Sample Size
a. General power/sample size, estimating effect size
b. Matching sample size calculations to endpoints

Design and Analysis Methods for Translational Research

Alternative Trial Designs
a. Equivalence and non-inferiority trials
b. Alternatives to RCTs

Issues in Data Analysis
a. Missing data
b. Intent-to-treat analysis (evaluability and exclusions)
c. Prognostic factors
   i. Identification (multivariable models, parsimonious model selection, interactions)
   ii. Application for risk/treatment group assignment
   iii. Adjusted analyses of comparative trials
   iv. Power and sample size in PFAs

Longitudinal Data Analysis
Guest Lecture

IRB
Guest Lecture: UF IRB

Adaptive, Enrichment, and Seamless Designs
a. Adaptive designs for exploratory development
b. Seamless phase II/phase III clinical trials
c. Adaptive designs for phase III clinical trials
   i. Group sequential methods
   ii. Sample size re-estimation/internal pilots
   iii. Combination methods (IPIA)
d. Barriers to using adaptive designs in clinical trials

Health-Related Quality of Life

a. Design considerations
b. Types of assessments
c. Selecting a QOL instrument
d. Data collection and analysis

Safety Monitoring

a. Toxicity
b. Data Safety Monitoring Committee
c. Statistical methods
    i. Early stopping rules
    ii. Multi-stage sequential designs
    iii. Monitoring boundaries
    iv. Conditional power

Meta-Analysis

Guest lecture

Regulatory Affairs

a. Misconduct and fraud
b. Conflict of interest

Reporting of Results

a. Timing of report
b. Analyses
c. Interpretation of results
d. Secondary analyses

Student Presentations