Course Title: Clinical Trials: Design and Analysis of Medical Experiments-Concepts and Methods

Course Number: BIST 0660

Course Pre- and Co-requisite(s): Regression analysis; SAS and R

Course Location: Room 234, School of Public Health Building, Piscataway

Course Date & Time: Wednesday 6:00 – 8:00 pm

Course Instructor: Weichung Joe Shih, PhD, Professor of Biostatistics, Rutgers-School of Public Health
e-mail: shihwj@sph.rutgers.edu; 732-235-9745

Office Hours: By Appointment Only

Course Assistant: None (volunteer?)

Course Website: canvas.rutgers.edu

Required Course Text:
- Friedman, Furberg, DeMets, Reboussin, Granger, Fundamentals of Clinical Trials
  Springer-Verlag, New York, NY. (ISBN#0-8151-3356-1)


NOTE: Most homework will come from this textbook

Additional/Supplemental Readings/Resources:

(Optional References):
- Cook and DeMets: Introduction to Statistical Methods for Clinical Trials
- Meinert: Clinical Trials: Design, Conduct and Analysis
- Altman: Practical Statistics For Medical Research
Course Description:

This course will teach students essential concepts and application of a wide range of statistical methods used in design, conduct, monitoring, and analysis of medical experiments. Prerequisites are PHCO 0504 (Introduction to Biostatistics), BIST 0535 (Biometrics Computing) BIST 0610 (Advanced Regression Methods for Public Health Studies), or their equivalents. Students are expected to participate in group discussions during the class.

Selected Concentration: Biostatistics

Selected Concentration Competencies Addressed:

The competencies addressed in this course include: Each Concentration identifies competencies for each degree offered. The competencies addressed in this course for the MS, MPH, DrPH, and PhD in Biostatistics:

- Apply basic probability theory and standard statistical methods to problems relevant to biomedical, clinical and public health research;
- Conduct complex statistical analyses for a broad range of applications;
- Use statistical computer packages to simulate, organize, analyze or report data;
- Communicate the results of statistical studies both orally and in writing to senior statisticians and other investigators, and lay audiences;
- Design experimental and observational studies in biomedical, clinical and public health research;
Critically analyze statistical methodology in scientific literature;
Provide leadership for a cross-disciplinary team working on the design and/or analysis of a research study.

Please visit the Concentration webpages on the School of Public Health’s website at sph.rutgers.edu for additional competencies addressed by this course for other degrees and concentrations.

Course Objectives: After completing this course, the students should be able to

- participate in a clinical trial team in either an academic or an industrial setting,
- function as a team member and contribute in the understanding and development of a trial protocol,
- follow the design and conduct of a clinical trial, as well as assist in basic statistical analyses of efficacy and safety data,
- read published clinical trial papers critically.

Course Requirements and Grading:

- GRADING basis:
  1. Attendance and participation: 10%
  2. Home work assignment: 25%
  3. Quiz: 15%
  4. Mid-term: 20%
  5. Final: 30%

  Total: 100 pts.

- Note: the school-wide uniform grading scale:

  Grading Policy: 94 - 100  A
                  90 - <94  A-
                  87 - <90  B+
                  84 - <87  B
                  80 - <84  B-
                  77 - <80  C+
                  70 - <77  C
                  <70  F

- Rutgers and SPH students honor codes (see below; more detail available on the SPH website) are highlighted at the first class, and will be observed.

- Quiz will be given in the beginning of (almost) each class starting at 3:00 pm (i.e., late comers may miss the quiz) and no makeup quiz will be given (since the correct answer will be discussed immediately following the quiz as a brief review).

- Homework assignments are expected to complete on time. Typed homework are preferred than hand written ones. Computer programming work (SAS or R) should be e-mailed in addition to paper. Discussion among students regarding homework is ok, but actual work should be individual.
Use of Canvas for class material distribution (no copy from instructor per SPH policy).

Midterm exam will be during the week of March 17, final exam will be on May 8. Except for “extremely unexpected personal hazardous emergency”, no early or late makeup exam will be granted. (For example, “I will have a business trip” will NOT be considered.) Format of the exams is yet to be determined.

Course Schedule:

This is a planned week by week schedule, which may be adjusted as the class progresses:

1. **Overview (1/23, 30)**
   - Check on pre-requisites (hypothesis testing, confidence interval, linear regression and biometrics computing)
   - Need to complete the on-line Ethics in Human Research to obtain certificate

2. **Concepts and Methods of Statistical Designs (1/30, 2/6)**
   2.1 External Validity
   2.2 Internal Validity
   2.3 Repeatability
   2.4 Bias
   2.5 Random Sample and Randomization
   2.6 Methods for Randomization

3. **Efficiency with Trade-offs and Crossover Designs (2/6, 2/13)**
   3.1 Statistical Efficiency of a Design
   3.2 Cross-Over Designs
   3.3 Analysis of 2x2 Cross-Over Designs

4. **Sample Size and Power calculations (2/13, 2/20, 2/27)**
   4.1 Fundamentals
   4.2 Comparing Means for Continuous Outcomes
   4.3 Comparing Proportions for Binary Outcomes
   4.4 Comparing Time-to-Event (Survival) Endpoints
   4.5 Clustered (or Correlated) Observations
   4.6 Sample Size for Testing a Non-Inferiority or an Equivalence Hypothesis
   4.7 Comparing Ordinal Endpoints by Wilcoxon-Mann-Whitney Test
   4.8 Sample Size Adjustments
   4.9 Sample Size by Simulation and Bootstrap

   - Midterm on March 6 (half of the classes)

5. **Analysis of Covariance and Stratified Analysis (3/6, 3/13)**
   5.1 Principles of Data Analysis
   5.2 Continuous Response – ANOVA & ANCOVA
   5.3 Variance Reduction by Covariates
   5.4 Stratified Analysis

   - 3/20 Spring Break
6.1 Maximum Sample Size and Expected Sample Size
6.2 One-Stage Versus Two-Stage Cancer Phase II Trials
6.3 Simon’s Two-Stage Designs

7. Sequential Designs and Methods -- Part II: Monitoring Safety and Futility (4/3, 4/10)
7.1 Monitoring Safety
7.2 Monitoring Futility with Conditional Probability

8.1 Regulatory Requirements and Logistical Considerations for Trial Monitoring
8.2 Statistical Methods
8.3 Power, Information, and Drift Parameter
8.4 P-value When Trial is Stopped
8.5 Estimation of Treatment Effect

9. Monitoring the Maximum Information (4/24, 5/1)
9.1 Sample Size Re-Estimation
9.2 Monitoring Trial Duration for Studies with Survival Endpoints
9.3 Modification of the Classical Group Sequential Alpha-Spending Function Procedure
9.4 Adaptive Group Sequential Procedure

10. Final exam 5/8

Learning Management System: Canvas will be used extensively throughout the semester for course syllabus, assignments, announcements, communication and/or other course-related activities. It is the student’s responsibility to familiarize themselves with Canvas and check it regularly. If you have difficulties accessing Canvas, please inform the instructor and Canvas Support (help@canvas.rutgers.edu). Canvas is accessible at canvas.rutgers.edu.

School of Public Health Honor Code: The School of Public Health Honor Code is found in the School Catalog (sp.h.rutgers.edu/academics/catalog.html). Each student bears a fundamental responsibility for maintaining academic integrity and intellectual honesty in his or her graduate work. For example, all students are expected to observe the generally accepted principles of scholarly work, to submit their own rather than another’s work, to refrain from falsifying data, and to refrain from receiving and/or giving aid on examinations or other assigned work requiring independent effort. In submitting written material, the writer takes full responsibility for the work as a whole and implies that, except as properly noted by use of quotation marks, footnotes, etc., both the ideas and the works used are his or her own. In addition to maintaining personal academic integrity, each student is expected to contribute to the academic integrity of the School community by not facilitating inappropriate use of her/his own work by others and by reporting acts of academic dishonesty by others to an appropriate school authority. It should be clearly understood that plagiarism, cheating, or other forms of academic dishonesty will not be tolerated and can lead to sanctions up to and including separation from the Rutgers School of Public Health.

Students with Disabilities: Rutgers University welcomes students with disabilities into all of the University’s educational programs. In order to receive consideration for reasonable accommodations, a student must Apply for Services by first completing a Registration Form with the Rutgers Office of Disability Services (ODS) at ods.rutgers.edu. The student will also be required to participate in an ODS intake interview and provide documentation. If reasonable accommodations are granted, ODS will provide
you with a Letter of Accommodations which should be shared with your instructors as early in your
courses as possible.

**Graduate Student Computer Policy:** Students are required to possess a personal laptop, no older than
approximately two years, that must meet minimum requirements which may be found online at:
sph.rutgers.edu/student-life/computer-support.html.

**Policy Concerning Use of Recording Devices and Other Electronic Communications Systems:**
When personally owned communication/recording devices are used by students to record lectures and/or
classroom lessons, such use must be authorized by the faculty member or instructor who must give either
oral or written permission prior to the start of the semester and identify restrictions, if any, on the use of
mobile communications or recording devices.

**Policy Concerning Use of Turnitin:** Students agree that by taking this course all required papers may
be subject to submission for textual similarity review to Turnitin.com (directly or via learning management
system, i.e. Canvas) for the detection of plagiarism. All submitted papers will be included as source
documents in the Turnitin.com reference database solely for the purpose of detecting plagiarism of such
papers. Use of the Turnitin.com service is subject to the Usage Policy posted on the Turnitin.com site.
Students who do not agree should contact the course instructor immediately.

**Withdrawal/Refund Schedule:** Students who stop attending their course(s) without submitting a
completed Add/Drop Course form will receive a failing grade. Furthermore, students dropping to zero
credits for the semester are considered withdrawn and must submit a completed Leave of Absence form
from the School of Public Health’s Office of Student Affairs. The School of Public Health refunds tuition
only. Administrative and technology fees are non-refundable. You may find the Withdrawal/Refund
Schedule on the School of Public Health website at:
sph.rutgers.edu/academics/school-calendar.html