

Course Title: *Clinical Trials: Design and Analysis of Medical Experiments*

Course Number: *BIST 0660*

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

Course Location: Public Health; Piscataway 2A

Course Date & Time: *Thursday 6:00 – 8:00 pm*

Course Instructor: *Joel Waksman, PhD, Adjunct Instructor, Rutgers-School of Public Health*
e-mail: jaw473@rutgers.edu

Office Hours: After class; by appointment

Course Assistant: *None*

Course Website: canvas.rutgers.edu

Required Course Text: *Shih and Aisner: Statistical Design, Monitoring, and Analysis of Clinical Trials - Principles and Methods; 2nd edition Chapman & Hall/ CRC Press, 2022 (ISBN# 978-0367772444)* An online version of the book is available from the Rutgers library; direct link to it is <https://bit.ly/3fjVMk3> (and then click on ProQuest Ebook Central)

Additional/Supplemental Readings/Resources:

(Optional References):

- *Cook and DeMets: Introduction to Statistical Methods for Clinical Trials Chapman & Hall/CRC Press; (ISBN: 978-1-58488-027-1)*
- *Meinert: Clinical Trials: Design, Conduct and Analysis Oxford University press, NY (ISBN 0-19-503568-2)*
- *Altman: Practical Statistics For Medical Research Chapman & Hall/CRC 1997 (ISBN # 0-412-27630-5)*
- *Fleiss: The Design and Analysis of Clinical Experiments Wiley & Sons 1986 (ISBN # 0-471-82047-4)*
- *Piantadosi: Clinical Trials: A Methodologic Perspective Wiley & Sons 1997 (ISBN # 0-471-16393-7)*
- *Green, Benedetti and Crowley (SWOG Statistical Center): Clinical Trials in Oncology Chapman & Hall/CRC, 1977 (ISBN 0-412-99631-6)*
- *Journals: Clinical Trials; Statistics in Medicine; BMJ; Biometrics; Statistical Methods in Medical Research; DIA Journal; Pharmaceutical Statistics*

- Useful Web Sites:

<https://research.rutgers.edu/search/site?q=training%20and%20education>

<https://www.fda.gov/cder/>

<https://www.ema.europa.eu/ema/>

ClinicalTrials.gov <https://clinicaltrials.gov/>

ICMJE guidelines <https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>

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 BIST 0625J (Fundamentals of Biostatistics), BIST 0535J (Biostatistical Computing), BIST 0551J (Applied Regression Analysis for Public Health Studies), or their equivalents. Students are expected to participate in group discussions during the class.

Selected Concentration Competencies Addressed:

The competencies addressed in this course for the MS, MPH, DrPH, and PhD in Biostatistics include:

1. *Apply basic probability theory and standard statistical methods to problems relevant to biomedical, clinical and public health research;*
2. *Conduct complex statistical analyses for a broad range of applications;*
3. *Use statistical computer packages to simulate, organize, analyze or report data;*
4. *Design experimental and observational studies in biomedical, clinical and public health research;*
5. *Critically analyze statistical methodology in scientific literature;*
6. *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. 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*

- a. *Participate in a clinical trial team in either an academic or an industrial setting,*
- b. *Function as a team member and contribute in the understanding and development of a trial protocol,*
- c. *Follow the design and conduct of a clinical trial, as well as assist in basic statistical analyses of efficacy and safety data,*
- d. *Read published clinical trial papers critically.*

Course Requirements and Grading:

- *GRADING basis:*
 1. *Attendance and participation: 10 pts*
 2. *Homework assignment: 20 pts*
 3. *Midterm: 35 pts*
 4. *Final: 35 pts*

Total: 100 pts.

Competency	Course Objectives(s)	Classes	Assessment(s)
1	a, b, c	1 - 15	Almost all homeworks
2	a, b	8, 9, 12-15	HWK 5.1, 5.3, 8.1; Class 12-14 homework; Final exam
3	a, b, c	1, 7-14	HWK 0, 2.2, 2.3, 3.2, Class 5-14 homework, Midterm exam; Final exam
4	a, b, d	1-7, 10-15	Classes 1-7, 10-15 homework, Midterm exam, final exam
5	d	2, 3, 4, 10, 11	HWK 2.1, 6.3
6	a, b	13	HWK 7.1

- *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

Course Schedule:

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

1. **Overview (1/19) [Class 1]**
 - 1.1 “Housekeeping”
 - 1.2 Basic clinical trial concepts
 - 1.3 Ethics of clinical research

2. **Concepts and Methods of Statistical Designs (1/26, 2/2) [Class 2-3]**
 - 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 (2/2, 2/9) [3-4]

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 (2/16, 2/23, 3/2) [5-7]

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 due March 9th

5. Analysis of Covariance and Stratified Analysis (3/2, 3/9) [7-8]

5.1 Principles of Data Analysis

5.2 Continuous Response – ANOVA & ANCOVA

5.3 Variance Reduction by Covariates

5.4 Stratified Analysis

5.5 Logistic Regression

■ 3/16 Spring Break

6. Regression Analysis of Survival Data (3/23) [9]

6.1 Kaplan-Meier Estimate and Log-Rank Test

6.2 Cox Regression and Proportional Hazards / Interpretation of Coefficients

6.3 Inference on Regression Coefficients Based on Partial Likelihood

6.4 Baseline Cumulative Hazard and Survival Function

6.5 Residuals for Model Diagnostics

7. Sequential Designs and Methods – Part I: Expected Sample Size and Two-Stage Phase II Trials in Oncology (3/30, 4/6) [10-11]

7.1 Maximum Sample Size and Expected Sample Size

7.2 One-Stage Versus Two-Stage Cancer Phase II Trials

7.3 Simon's Two-Stage Designs

8. **Sequential Designs and Methods -- Part II: Monitoring Safety and Futility (4/6, 4/13, 4/20) [11-13]**

8.1 Monitoring Safety

8.2 Monitoring Futility with Conditional Probability

9. **Sequential Designs and Methods -- Part III: Classical Group-Sequential Trials (4/20, 4/27) [13-14]**

9.1 Regulatory Requirements and Logistical Considerations for Trial Monitoring

9.2 Statistical Methods

9.3 Power, Information, and Drift Parameter

9.4 P-value When Trial is Stopped

9.5 Estimation of Treatment Effect

■ *Final Exam due May 4th*

10. **Monitoring the Maximum Information (5/4) [15]**

10.1 Sample Size Re-Estimation

10.2 Monitoring Trial Duration for Studies with Survival Endpoints

10.3 Modification of the Classical Group Sequential Alpha-Spending Function Procedure

10.4 Adaptive Group Sequential Procedure

Assignment Standards:

- *Rutgers SPH students honor code (see below) will be observed.*
- *Homework assignments are expected to complete on time, and the grading will be based on their completion. Typed homework is preferred over handwritten ones. Computer programming work (SAS) should be posted (or e-mailed) in addition to paper. Discussion among students regarding homework is ok, but recommend that actual work should be by the individual. If help is needed on the homework, then request a Zoom meeting with me.*
- *Use of Canvas for class material distribution.*
- *Midterm exam will be due **March 9** (Spring Break 3/11-19), final exam will be due **May 4** (Note: Last day to submit grades 5/10).*

School Policies:

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@oit.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 (sph.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.

Commitment to Safe Learning Environment: The Rutgers School of Public Health is committed to helping create a safe learning environment for all students and for the School as a whole. Free expression in an academic community is essential to the mission of providing the highest caliber of education possible. The School encourages civil discourse, reasoned thought, sustained discussion, and constructive engagement. Provocative ideas respectfully presented are an expected result. An enlightened academic community, however, connects freedom with responsibility. The School encourages all students to disclose any situations where you may feel unsafe, discriminated against, or harassed. Harassment or discrimination of any kind will be not tolerated and violations may lead to disciplinary actions.

Student Well-Being: The School of Public Health recognizes that students may experience stressors or challenges that can impact both their academic experience and their personal well-being. If the source of your stressors or challenges is academic, students are encouraged to discuss these challenges and circumstances with their instructor, if they feel they may need additional support or temporary accommodations at the beginning or during this course. The course instructor may consider making reasonable temporary adjustments depending on the student's situation. For personal concerns or if additional support is needed, students may reach

out to the [Office of Student Affairs \(studentaffairs@sph.rutgers.edu\)](mailto:studentaffairs@sph.rutgers.edu) or any of the appropriate referral resources listed on the [SPH Student Connect Canvas page](#).

Reporting Discrimination or Harassment: If you experience any form of gender or sex-based discrimination or harassment, including sexual assault, sexual harassment, relationship violence, or stalking, know that help and support are available. You may report such incidents to the [RBHS Title IX Office](#) or to the School of Public Health's [Office of Student Affairs Office of Student Affairs](#). Rutgers University has staff members trained to support survivors in navigating campus life, accessing health and counseling services, providing academic and housing accommodations, and more. If you experience any other form of discrimination or harassment, including racial, ethnic, religious, political, or academic, please report any such incidents to the School's . The School strongly encourages all students to report any incidents of discrimination or harassment to the School. Please be aware that all Rutgers employees (other than those designated as confidential resources such as advocates, counselors, clergy and healthcare providers as listed in Appendix A to [Policy 10.3.12](#)) are required to report information about such discrimination and harassment to the School and potentially the University. For example, if you tell a faculty or staff member about a situation of sexual harassment or sexual violence, or other related misconduct, the faculty or staff member must share that information with the [RBHS Title IX Coordinator](#). If you wish to speak to a confidential employee who does not have this reporting responsibility, you can find a list of resources in Appendix A to University [Policy 10.3.12](#). For more information about your options at Rutgers, please visit [Rutgers Violence Prevention and Victim Assistance](#).

Overview of School Policies: Academic and non-academic policies and procedures, such Auditing a Course, Retaking Courses, Grade Grievance and others that cover registration, courses and grading, academic standing and progress, student rights and responsibilities, graduation and more may be found under [Policies](#) on the School of Public Health website. Below are select specific policies; however, students are responsible for keeping informed about academic and non-academic policies and procedures beyond those noted on this syllabus.

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 Leave of Absence](#) form will receive a failing grade. Furthermore, students dropping to zero credits for the semester are considered withdrawn and must submit a completed 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/academic-calendar.html