**STA 545 – Statistical Design and Analysis of Clinical Trials**

**Fall Semester 2022**

**Professor**: James Godbold, Ph.D. **Phone**: via Zoom

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**Office Hours**: TBD

**Required Materials**:

Textbook: Shih WJ and Aisner J. *Statistical Design and Analysis of Clinical Trials, Principles and Methods.* CRC Press. New York. 2016.

Textbook: Chow S-C and Liu J-P. *Design and Analysis of Clinical Trials: Concepts and Methodologies (Third Edition).* Wiley. New York. 2014. (available online through Green Library at WCUPA).

**Course Description:** This course in the statistical design and analysis of clinical trials will focus on the scientific questions each phase of clinical trials (Phase I, Phase II, and Phase III) addresses. Vaccine trials will be explored. For oncology trials, various Phase I and Phase II designs will be explored, noting the strengths and weaknesses of each design. Students will use online software as well as SAS to calculate properties for the various designs studied. Group Sequential procedures that specify how interim analyses will be performed in Phase III trials will be explored, together will graphical methods associated with each procedure. Students will make oral presentations on examples of various topics studied in class and submit a written report as a companion paper to the oral presentation.

**Course Student Learning Outcomes:**

**Learning Objectives**

At the end of the course, the learner will be able to:

1. Specify the essential components of the biostatistics section of a clinical trials protocol.
2. State the broad goals for Phase I, Phase II and Phase III non-cancer clinical trials.
3. State the broad goals for Phase I, Phase II, and Phase III oncology trials.
4. Identify and state strengths and weaknesses of at least three Phase I designs for oncology trials.
5. Use statistical software (either R programs on websites, or SAS) to calculate properties of Phase I trials.
6. Describe three commonly used Group Sequential Procedures in broad terms of how they are distinguished from one another.
7. Interpret graphical output from a Group Sequential analysis as to whether the trial should, at an interim analysis, be stopped for futility, be stopped for demonstrated efficacy, or continue.
8. Define “efficacy” and “effectiveness” and distinguish between the two concepts.
9. Identify whether a clinical trial has been designed to address efficacy or effectiveness.
10. State and describe commonly employed statistical methods used to handle the problem of missing data in clinical trials.
11. Write a critique of a published journal article reporting on the design and results of a clinical trial.

**Competencies**

At the end of the course, the learner will demonstrate competency as someone who:

1. Selects an appropriate trial design for examining a specified clinical hypothesis.
2. Evaluates the adequacy of a protocol for a clinical trial.
3. Employs ethical principles in the design and conduct of clinical trials.
4. Interprets the results of data analysis from Phase II and Phase III clinical trials.
5. Interprets the results from interim data analysis in clinical trials.
6. Uses statistical software to obtain design parameters for clinical trials.
7. Uses statistical software to analyze data generated by clinical trials.
8. Utilizes information technology to collect, store, and retrieve data.
9. Communicates in writing and orally, in person, and through electronic means, with linguistic and cultural proficiency
10. Presents demographic, statistical, programmatic, and scientific information for use by professional and lay audiences
11. Determines the limitations of research findings

**Applicable Programmatic Student Learning Outcomes:**

Student Learning Outcomes for the Masters of Science in Applied Statistics:

1. Demonstrate an understanding of probability and statistical inference, including the fundamental laws of classical probability, discrete and continuous random variables, expectation theory, maximum likelihood methods, hypothesis testing, power, and bivariate and multivariate distribution theory.
2. Demonstrated the ability to apply the elementary methods of statistical analysis, namely those based on classical linear models, categorical methods, and non-parametric ideas to perform data analysis for the purposes of statistical inference.
3. Demonstrate proficiency in the effective use of computers for research data management and for analysis of data with standard statistical software packages, particularly SAS.
4. Learn to develop and critically assess design of experimental studies and the collection of data.
5. Apply one or more methods of statistical inference to a particular area of interest, particularly the program in the elective concentration.
6. Gain practical experience in statistical consulting and communicating with non- statisticians, culminating with interaction with research workers at a local company as part of the internship practicum.

**Meeting & Assessing Student Learning Outcomes:**

Assessment of Student Learning Outcomes will be made on the basis of:

1. Participation in class discussion
2. Participation in working on problem sets during class sessions.
3. Turned in homework assignments.
4. Oral presentations with accompanying written report on an example of a topic covered in class.
5. Mid-term exam,
6. In lieu of a final exam, each student will have the choice of either (a) writing a paper on an assigned topic, or (b) constructing a set of exam-type questions (with answers) on material covered after the mid-term exam.

**Class Rules:**

1. Active usage of cell phones and other similar devices is not allowed in class sessions. If you need to use these devices, please wait until a break. Violation of this policy will result in deductions from your ‘participation’ grade. If there are special circumstances that require cell phone usage, please let the professor know.

**Attendance Policy:** Attendance at the live class sessions is expected. Attendance will be recorded for each of these sessions. One unexcused absence is allowed with no penalty; every unexcused absence after the first will result in a deduction from the participation component of the course grade.

**Tentative Course Outline:**

Depending on how much material is actually covered in class each week, the schedule shown on the following pages may be revised from week to week. Please check D2L for changes. If/when changes are made to the course schedule, emails will be sent to each student with a statement regarding the change. The revised schedule will also be posted on D2L.

**Homework Policy and Grading**

Due dates/times for homework assignments are posted in the class schedule. Homework is to be submitted on D2L. Late homework will be accepted, but with reduced credit. Homework is assigned to provide an incentive for the student to engage with the material covered in class or with assigned outside readings. It will not be graded as to whether the answers are correct. Students are permitted to work with others in doing homework; although copying a classmate’s work will be of little value in mastering material which will reappear on examinations.

**Exams**

The **midterm exam** will be administered in class on October 13, 2022. A sample exam is posted on D2L with questions of similar format and similar content. All students in the course are expected to have professional integrity to complete the exam as a closed-book exam, without reference to materials in any form (hard-copy or digital) except for the websites specifically indicated as part of the exam (online sample size calculation apps). Students will be asked as part of the exam to indicate that they have abided by these rules. No proctoring software (e.g., Proctorio) will be employed.

Instead of a written **final exam** administered on D2L, each student can choose to do one of the following:

1.  Construct a final exam with an answer key covering material after the midterm using questions of any format(s), e.g., multiple choice, short answer, essay.

2.  In recent years safety profiles that emerged after some drugs had been approved and were being used in medical practice cast doubt on the original risk-benefit assessments.  In at least three high profile cases the pharmaceutical companies withdrew the drugs in question from the market (Rezulin, Vioxx, Avandia).  For each of these drugs, there are several articles available --- some in newspapers and the lay press, some in medical journals --- that give the time-line and a summary of events leading up to the withdrawal and an assessment of what went wrong along the way.  Students are to select one of these drugs and prepare a report in your own words (probably 5 - 7 pages) that tells what happened, what could have been done (if anything) to have detected the problem earlier (or prevented the problem), and what lessons have been learned as a result of the drug withdrawal that will improve the way future safety monitoring is done.

3. Whichever option above is chosen, the written exam or report is due no later than Saturday, Dec. 17, at 12:00 pm.

**Oral Presentation Guidelines**

Oral presentations should aim to be approximately 15 minutes in length with 5 minutes allowed for questions and discussion ( 15 + 5 = 20 min.). Students not presenting are expected to ask relevant questions about the material presented. PowerPoint or other slides are encouraged, but not required. Students can choose a topic from the list of possible topics provided below and should find a paper in the published medical literature reporting on a clinical trial with the feature listed as the topic of the presentation. **Students are required to get approval from the instructor for the paper**. For example, for the topic “Phase I oncology”, you would find a paper reporting on a Phase I dose-escalation trial for a cancer drug. You would report on which Phase I design was used (e.g., 3 + 3 design, Accelerated Titration design, etc.) and give the results of how the design played out in this real-world setting. Do not limit your comments to simply reporting information found in the paper. Include your own assessment of the trial and your assessment of the reporting on the trial: What are its strengths and weaknesses? Would you have done anything differently if you had been the statistician or investigator on the study? Are the conclusions justified by the data? Who funded the study? Do you think the funding source may have influenced the conclusions of the study?

The written report accompanying the oral presentation should be approximately 3 - 5 pages double spaced, font size = 12. It is due no later than Saturday, Dec. 17, at 12:00 pm. It should include reference not only for the main paper under review, but also references to any other material used.

A list of topics is shown below, and a schedule sheet is available for sign-up on One Drive for this activity. In addition to presenting, each student is expected to be an audience for five other students.

**Topics for Student Presentations**

Crossover trial

Non-inferiority trial

Equivalence trial

Phase 1 cancer trial

Phase 2 randomized 2-arm cancer trial

Phase 2 randomized multiple-arm cancer trial

Combined Phase 2/3 trial

Phase 3 randomized trial

Vaccine trial (any phase)

Adaptive trial

Group Sequential Trial

Meta-analysis of randomized clinical trials

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| --- | --- | --- | --- | --- | --- |
| **Date** | **Textbook reading** | **Main Topic(s)** | **Outside reading** | **Reference material** | **Homework (Due 1 week later)** |
| 9/1/2022 | Shih: Chap. 1, 2; Chow & Liu: Sec. 1.4.2;  | Personal introductions; Requirements for course; Overview; Ethical aspects; Basic concepts of RCTs | Umscheid |  Getz; de Boer; ASA Ethical Guidelines; ICH Good Clin Practice; ICH Stat Principles; CONSORT 2010 checklist; CONSORT 2010 flow diagram | Shih: Problems 1.1; 1.2; 2.1; 2.2; Part 1, 2.3; 2.4 |
| 9/8/2022 | Shih: Chap. 3; Chap. 4 | Crossover designs; Sample Size & Power; Non-inferiority and Equivalence trials; Sample size calculation | Mauri & D'Agostino; Sample size calculation in-class worksheet | Ahn, Park, & Lee | Shih: Problems 3.1; 3.2; 4.1;  |
| 9/15/2022 |  | Phase I vaccine trial;  | Folegatti: Phase I trial paper; Folegatti: supplementary material (protocol);  | Hudgens  | Questions for Folegatti Phase 1 trial (read paper and protocol before class; we will work on questions and discuss in class on 9/15) |
| 9/22/2022 | Shih: Chap. 5 | ANCOVA change scores; Stratified analysis | Vickers & Altman | Fu & Holmer | Shih: Problem 5.1 (begin work in class) |
| 9/29/2022 | Chap. 6 (Chow & Liu) | Phase I trials in cancer | Le Tourneau et al.; Lin & Shih; Hansen; Wheeler | Probabilities for 3+3 design.xls; Ivanova et al | Problems using AplusB online calculator (will be done in class) |
| 10/6/2022 | Chap. 6 (Shih) | Phase II trials in cancer | Simon (1989); Ratain & Karrison (2007); Koyama & Chen (2008) | <https://brb.nci.nih.gov/> | Problem Set using NCI website (will be done in class) |
| **10/13/2022** |  | **Mid-term exam**  |  |  |  |
| **Date** | **Textbook reading** | **Main Topic(s)** | **Outside reading** | **Reference material** | **Homework (Due 1 week later)** |
| 10/20/2022 | Chap. 7 (Shih) | Monitoring for Safety and Futility; conditional power; Bayesian method | Yao (2013) Sect. 3; | Fayers (1997) |  |
| 10/27/2022 |  | Phase III randomized, placebo-controlled trial for treatment of obesity | Jastreboff et al. (2022) NEJM; Jastreboff protocol; Obesity supplemental appendix; |  | Questions for obesity trial |
| 11/3/2022 | Chap. 8 (Shih) | Group Sequential Methods | Chow & Liu p.424; Chow & Liu, Sect. 10.6 | SAS Documentation for PROC SEQDESIGN | HW 8.1 |
| 11/10/2022 |  | Phase III randomized, placebo-controlled trial for treatment of ALS | Belluck (March 2022); FDA briefing document; Finkelstein & Schoenfeld (1999) | AMX0035 Statistical Analysis Plan; Belluck (June 2022) | Questions for AMX0035 trial  |
| 11/17/2022 | Chap. 9 (Shih) | Adaptive Designs; Sample size re-estimation | Chow & Liu, Sect. 12.9; Marchenko (2014) | FDA Guidance on Adaptive Designs; Tisatis & Mehta - Inefficiency of adaptive design |  |
| 11/24/2022 | **NO CLASS** |  |  |  |  |
| 12/1/2022 | Chap. 10 (Shih) | Missing data; Pragmatic trials; Meta-analysis of RCTs; Prevention trials | da Costa & Juni; Lippman (SELECT) |  |  |
| 12/8/2022 |  | Student Presentations |  |  |  |
| 12/15/2022 | **No class --- Final Exam paper due 12/17/2022 12:00 pm** |  |  |  |  |

**Evaluation & Grading for Course:**

The final grade for the course will be determined from the following components, weighted as shown:

Homework 15%

Attendance and Class Participation 15%

Oral Presentation (10%) and Accompanying written report (10%) 20%

Midterm Exam 25%

Final Paper 25%

A letter grade will be assigned based on performance in the course, according to the following scale:

|  |  |  |  |
| --- | --- | --- | --- |
| **Grade** | **Quality Points** | **Percentage Equivalents** | **Interpretation** |
| A | 4 | 93 - 100 | Superior graduate attainment |
| A- | 3.67 | 90 - 92 |  |
| B+ | 3.33 | 87 - 89 | Satisfactory graduate attainment |
| B | 3 | 83 - 86 |  |
| B- | 2.67 | 80 - 82 |  |
| C+ | 2.33 | 77 - 79 | Attainment below graduate expectations |
| C | 2 | 73 - 76 |  |
| C- | 1.67 | 70 - 72 |  |
| F | 0 | < 70% | Failure |

D grades are not used. Refer to the Graduate Catalog for description of NG (No Grade), W, & other grades.

**ACADEMIC & PERSONAL INTEGRITY**

It is the responsibility of each student to adhere to the university’s standards for academic integrity. Violations of academic integrity include any act that violates the rights of another student in academic work, that involves misrepresentation of your own work, or that disrupts the instruction of the course. Other violations include (but are not limited to): cheating on assignments or examinations; plagiarizing, which means copying any part of another’s work and/or using ideas of another and presenting them as one’s own without giving proper credit to the source; selling, purchasing, or exchanging of term papers; falsifying of information; and using your own work from one class to fulfill the assignment for another class without significant modification. Proof of academic misconduct can result in the automatic failure and removal from this course. For questions regarding Academic Integrity, the No-Grade Policy, Sexual Harassment, or the Student Code of Conduct, students are encouraged to refer to the Department Graduate Handbook, the Graduate Catalog, the *Ram’s Eye View*, and the University website at www.wcupa.edu.

**STUDENTS WITH DISABILITIES**

If you have a disability that requires accommodations under the Americans with Disabilities Act (ADA), please present your letter of accommodations and meet with me as soon as possible so that I can support your success in an informed manner. Accommodations cannot be granted retroactively. If you would like to know more about West Chester University’s Services for Students with Disabilities (OSSD), please visit them at 223 Lawrence Center. The OSSD hours of Operation are Monday – Friday, 8:30 a.m. – 4:30 p.m. Their phone number is 610-436-2564, their fax number is 610-436-2600, their email address is ossd@wcupa.edu, and their website is at www.wcupa.edu/ussss/ossd.

**REPORTING INCIDENTS OF SEXUAL VIOLENCE**

West Chester University and its faculty are committed to assuring a safe and productive educational environment for all students. In order to meet this commitment and to comply with Title IX of the Education Amendments of 1972 and guidance from the Office for Civil Rights, the University requires faculty members to report incidents of sexual violence shared by students to the University's Title IX Coordinator, Ms. Lynn Klingensmith. The only exceptions to the faculty member's reporting obligation are when incidents of sexual violence are communicated by a student during a classroom discussion, in a writing assignment for a class, or as part of a University-approved research project. Faculty members are obligated to report sexual violence or any other abuse of a student who was, or is, a child (a person under 18 years of age) when the abuse allegedly occurred to the person designated in the University protection of minors policy.  Information regarding the reporting of sexual violence and the resources that are available to victims of sexual violence is set forth at the webpage for the Office of Social Equity at <http://www.wcupa.edu/_admin/social.equity/>.

**EXCUSED ABSENCES POLICY**

Students are advised to carefully read and comply with the excused absences policy, including absences for university-sanctioned events, contained in the WCU Graduate Catalog. In particular, please note that the “responsibility for meeting academic requirements rests with the student,” that this policy does not excuse students from completing required academic work, and that professors can require a “fair alternative” to attendance on those days that students must be absent from class in order to participate in a University-Sanctioned Event.

**EMERGENCY PREPAREDNESS**

All students are encouraged to sign up for the University’s free WCU ALERT service, which delivers official WCU emergency text messages directly to your cell phone. For more information, visit www.wcupa.edu/wcualert. To report an emergency, call the Department of Public Safety at 610-436-3311.

**ELECTRONIC MAIL POLICY**

It is expected that faculty, staff, and students activate and maintain regular access to University provided e-mail accounts. Official university communications, including those from your instructor, will be sent through your university e-mail account. You are responsible for accessing that mail to be sure to obtain official University communications. Failure to access will not exempt individuals from the responsibilities associated with this course.