**STA545 – Statistical Design and Analysis of Clinical Trials**

**Fall Semester 2018**

**Professor**: **Phone**:

**Email**: **Office**:

**Office Hours**:

**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.

**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. For oncology trials, various Phase I designs will be explored, noting the strengths and weaknesses of each design. 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.

**Prerequisites:** A C or better in STA 512.

**Programmatic Student Learning Outcomes:**

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.

**Course Student Learning Outcomes:**

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. (PSLO4)
2. Evaluates the adequacy of a protocol for a clinical trial. (PSLO5)
3. Employs ethical principles in the design and conduct of clinical trials. (PSLO5)
4. Interprets the results of data analysis from Phase II and Phase III clinical trials. (PSLO5)
5. Interprets the results from interim data analysis in clinical trials. (PSLO 5)
6. Uses statistical software to obtain design parameters for clinical trials. (PSLO3)
7. Uses statistical software to analyze data generated by clinical trials. (PSLO3)
8. Utilizes information technology to collect, store, and retrieve data. (PSLO3)
9. Communicates in writing and orally, in person, and through electronic means, with linguistic and cultural proficiency. (PSLO6)
10. Presents demographic, statistical, programmatic, and scientific information for use by professional and lay audiences. (PSLO6)
11. Determines the limitations of research findings. (PSLO6)

**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 small groups working on problem sets in class.
3. Turned in homework assignments.
4. Oral presentations with accompanying written report on an example of a topic covered in class.
5. Written in-class examinations (mid-term and final).

**Class Rules:**

1. Active usage of cell phones and other similar devices are not allowed in class. If you need to use these devices, please leave the classroom or wait until the 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 is class is expected. Attendance will be recorded each class session. 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 below 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.

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| **Date** | **Textbook reading** | **Main Topic(s)** | **Outside reading** | **Reference material** | **Homework (Due 1 week later)** |
| **8/29/2018** | **Chap. 1 (Shih); Chow & Liu, Sec. 1.4.2** | **Personal Introductions; Overview; Ethical aspects** | **Rabin (NYT)** | **ICH Good Clin Practice; ICH Stat Principles; CONSORT 2010 checklist; CONSORT 2010 flow diagram; CONSORT extension checklist; CONSORT extension flow diagram: PRMC checklist** | **HW 1.1, 1.2** |
| **9/5/2018** | **Chap. 2;** | **Basic concepts of RCTs** | **Umscheid; de Boer (baseline); Getz; Kolata (flawed)** | **Estruch (NEJM)** | **HW 2.1, 2.2 part 1, 2.3, 2.4** |
| **9/12/2018** | **Chap. 3 (Shih)** | **Crossover designs** |  |  | **HW 3.1, 3.2** |
| **9/19/2018** | **Chap. 4 (Shih)** | **Sample size and Power** | **Shuster (CTS, 2014)** |  | **HW 4.1 .**  **Use CONSORT checklist and flow diagram** |
| **9/26/2018** | **Sect. 4.6 (Shih)** | **Non-inferiority trials** |  | **Mauri & D’Agostino (NEJM)** |  |
| **10/3/2018** | **Chap. 5 (Shih)** | **ANCOVA change scores; Stratified analysis.**  **Review for Mid-term exam.** | **Vickers & Altman;**  **Kahan and Morris** |  | **HW 5.1** |
| **10/10/2018** |  | **Mid-term exam** |  |  |  |
| **10/17/2018** | **Chap. 6 (Chow & Liu)** | **Phase I trials in cancer** | **Le Tourneau et al.; Lin & Shih; Hansen, Graham, et al.; Wheeler et al.** | **Probabilities for 3+3 design.xls; Ivanova et al** | **Problems using AplusB online calculator** |
| **10/24/2018** | **Chap. 6 (Shih)** | **Phase II trials in cancer** | **Simon (1989); Ratain & Karrison (2007); Koyama & Chen (2008)** | [**https://brb.nci.nih.gov/**](https://brb.nci.nih.gov/) | **Problem Set using NCI website** |
| **10/31/2018** | **Chap. 7 (Shih)** | **Monitoring for Safety & Futility; conditional power; Bayesian method** | **Yao (2013) sect. 3** | **Fayers (1997)** |  |
| **11/7/2018** | **Chap. 8 (Shih)** | **Group sequential methods** | **Chow & Liu p. 424; Chow & Liu, sect. 10.6** | **SAS documentation PROC SEQDESIGN** | **HW 8.1** |
| **11/14/2018** | **Chap. 9 (Shih)** | **Adaptive designs; sample size re-estimation** | **Chow & Liu, sect 12.9; Marchenko (2014)** | **FDA Guidance on Adaptive Designs; Tsiatis & Mehta – Inefficiency of adaptive design** |  |
| **11/21/2018** | **NO CLASS** |  |  |  |  |
| **11/28/2018** | **Chap. 10 (Shih)** | **Missing data; Pragmatic trials; meta-analysis** | **Beunckens – Direct likelihood;**  **Carroll (NYT);** |  |  |
| **12/5/2018** |  | **Review** |  |  |  |
| **12/12/2018** | **Final Exam** |  |  |  |  |

**Homework Policy and Grading**

Homework assignments on material covered in one week’s class will be due at the beginning of class the following week. Late homework will not be accepted. NO EXCEPTIONS. Homework may be submitted either as hard-copy or digitally on D2L.

Each homework assignment will receive a grade of 0 or 1 or 2.

0 = no attempt was made to answer any problem

1 = responses for some, but not all, of the problems

2 = responses for all assigned problems

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.

**Oral Presentation Guidelines**

Oral presentations should aim to be approximately 20 minutes in length with 10 minutes allowed for questions and discussion ( 20 + 10 = 30 min.). Students not presenting are expected to ask relevant questions about the material presented. PowerPoint or other slides are encouraged, but not required. Students 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 1 week after the oral presentation. It should include reference not only for the main paper under review, but also references to any other material used.

A sign-up sheet is available on Sign-up Genius for this activity, and emails will be sent to the class when the sign up sheet is available.

**Oral Presentations Schedule**

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| --- | --- |
| **Date** | **Presentation Topics** |
| **10/31/2018** | 1. **Phase I oncology trial** 2. **Phase II oncology trial** |
| **11/7/2018** | 1. **Group sequential** 2. **Adaptive design, sample size re-estimation** |
| **11/14/2018** | 1. **Missing data** 2. **Pragmatic trial** |
| **11/28/2018** | 1. **Meta-analysis of RCTs** 2. **Prevention trial** |
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**Evaluation & Grading for Course:**

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

Homework 10%

Attendance and Class Participation 20%

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

Midterm Exam 25%

Final Exam 25%

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

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| --- | --- | --- | --- |
| **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.