ST520 (Fall 2019)

Statistical Principles of Clinical Trials

Syllabus

Time: 1:30pm-2:45pm
Days: Tuesday and Thursday
Location: 2106 SAS Hall
Instructor: Shu Yang
4266 SAS Hall
(919) 515-1935
Email: syang24@ncsu.edu
Office hours for Instructor: Thursdays 3:00-4:00pm, also by appointment

Teaching Assistant: Rui Zhu
Email: rzhu4@ncsu.edu
Office hours for TA: 10:00–12:00 am on Wednesday, 1101 SAS Hall

Reference Textbooks
Fundamentals of Clinical Trials
By Friedman, L.M., Furberg, C.D. and DeMets, D.L.
Group Sequential Methods with Applications to Clinical Trials
By Jennison, C. and Turnbull B.W.

These texts are useful in describing principles of clinical trials from an applied perspective. The intended audience is clinicians and others interested in learning what clinical trials are. These are not intended as books to develop statistical methodology and consequently are not necessary for this course. The course will be based primarily on lecture notes that will be available at Moodle: http://wolfware.ncsu.edu. Your assignment grades will be posted at Moodle as well. While care is taken to enter the grades, it is your responsibility to alert the instructional team immediately if a mistake has been made during grade entry.

Prerequisties/Co-rerequisites:
ST501, ST701 or equivalent.

Student Conduct: The University's Code of Student Conduct will be strictly enforced in this course and misconduct will not be tolerated. All exams are to be completed individually. Although working together on out-of-class assignments to overcome obstacles is encouraged, each student must compose and write his/her/their own responses. All cases of misconduct will be handled as set out in university policies. For additional information, see: http://policies.ncsu.edu/policy/pol-11-35-01. If you are unclear or have any questions about the nature of an assignment, please ask me up front.

Requirements for Credit-Only (S/U) Grading: In order to receive a grade of S, students are required to take all exams, complete all assignments, and earn a grade of C- or better. Conversion from letter grading to credit only (S/U) grading is subject to university deadlines. Refer to the Registration and Records calendar for deadlines related to grading. For more details refer to http://policies.ncsu.edu/regulation/reg-02-20-15.

Requirements for Auditors (AU): Need at least a 50% grade on homework to get an official audit.

Attendance Policy: For complete attendance and excused absence policies, please see http://policies.ncsu.edu/regulation/reg-02-20-03.

Late Homework: Homework is due in class on the due date. Late homework with an excuse will be penalized.

Makeup Work Policy: Missing exams and late homework can only be made up or accounted for fairly if there is sufficient documentation of reasons for the absence or lateness. (See attendance policy above.)

Midterm Exam: There will be one midterm exam during the semester. The exam is closed book and closed notes; however a one page 8.5in by 11in cheat sheet (both sides) will be allowed. The exact exam date will be announced via Moodle.

Final Exam: The final is comprehensive and closed book and closed notes but again two pages of 8.5in by 11in cheat sheet (both sides) will be allowed.

Disability Reg: Reasonable accommodations will be made for students with verifiable disabilities. In order to take advantage of available accommodations, students must register with Disability Services for Students at 1900 Student Health Center, Campus Box 7509, 515-7653. For more information on NC State's policy on working with students with disabilities, please see the Academic Accommodations for Students with Disabilities Regulation (REG02.20.01)

Grades:

25% Homework (approximately every two weeks)

30% Closed book midterm (1.5–2 hours during class TBA)

40% Closed book final (Thursday December 12, 1:00–4:00 pm)

5% Class activity and instructor discretion

Conversion of these scores into letter grades will be made according to the following: A, 93–100; A-, 90–92; B+, 85–89; B, 80–84; B-, 75–79, C, 65–74. Scores below 65 will be handled on a case-by-case basis. The grade of A+ will be given at the discretion of the instructor for truly stellar individual performance. Depending on overall class performance, these ranges may be adjusted.

Course Outline

- Introduction to Epidemiology and Clinical Trials
- The different phases of clinical trials research
- Phase I dosing trials, Clinical pharmacology
- Phase II clinical trials (screening and feasibility)
  - review of confidence intervals
  - Gehan's two-stage design
  - Simon's two-stage sequential design
  - Discussion of surrogate markers
- Phase III clinical trials – fundamentals
  - What is the question? primary, secondary
  - study population
    - whom to target
    - likelihood of seeing event
    - identifying compliant population
    - generalizability
    - control group
  - Randomization
    - Role of randomization to control bias
    - competing designs (historical and literature controls)
    - types; simple, blocked, permuted block
    - stratification; pros and cons, how many strata?
    - dynamic balancing
    - response adaptive designs
  - Blinding
    - reasons, single blind, double blind
    - use of placebo controlled trials

  - Implementation
    * Administrative Issues
    * Institutional review boards (IRB's)
    * Ethical Issues
    * Protocol Documents/Forms
    * Quality Control-data management

Statistical Methods

- Endpoints
  - Continuous
    * t-test for two-sample comparison
    * ANOVA- F-tests for K-sample comparisons
    * Linear regression to adjust for covariates
  - Categorical
    * proportions test for two-sample comparisons
    * Chi-square test for K-sample comparisons
    * arc-sin square root transformation to stabilize variance
  - Time to event
    * staggered entry and censoring
    * Life-table methods and Kaplan-Meier estimator
    * Logrank tests for two and K-sample comparisons
  - For all endpoints
    * power and sample size considerations
    * multiple comparisons
  - Equivalency and Non-superiority trials
  - Intention to treat analysis
    * compliance
    * drop-outs

    - missing data
    - causal inference
- Monitoring Clinical Trials
    - group-sequential designs
    - Data safety monitoring boards