Overview and Objectives: Statistical Methods and Issues in Clinical Trials course will provide in depth information for conducting randomization, sample size planning, analysis of Phase III clinical trials, and reporting/interpreting results of studies. We will use manuscripts on clinical trials to facilitate learning of concepts discussed in class.

Responsibilities: There will be reading assignments in the textbook and selected articles. Readings of book chapters assigned in the syllabus are expected to have been read when you come to class. Students will be assigned written exercises that will be graded. All homework assignments will be assigned with a due date. There will be a final project, which will involve writing a study protocol. You are encouraged to work together on class projects and homework assignments, but you should write up your results individually, i.e. very similar papers will be assigned a zero grade. Late homework assignments will be penalized 10% per day over the due date unless prior arrangements have been made with the instructors. No homeworks will be accepted by email. Attendance and participation in class are required. Evaluation criteria will be based on completion of the writing assignments and presentations, completion of the final project, participation and attendance.

Course Requirements

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Class attendance</td>
<td>5%</td>
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<tr>
<td>Written assignments and presentations</td>
<td>55%</td>
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<tr>
<td>Final project</td>
<td>40%</td>
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Course Grading Scale: For the computation of the final course grade as well as for the course assignments, the following grading scale will be used:

- A+ >95%
- A 92-95%
- A- 90-91%
- B+ 88-89%
- B 82-87%
- B- 80-81%
- C 70-79%
- D 60-69%
- F <60%

NOTE: Homework assignments, course information, and communication will be available at http://courseweb.pitt.edu.


Other highly recommended textbooks to be used as references:

- Clinical Trials: A Practical Approach, 1996, Stuart J. Pocock, John Wiley & Sons
- Clinical Trials: Design, Conduct, and Analysis (2nd Ed), 2012, Curtis L. Meinert, Oxford
- Clinical Trials: A Methodologic Perspective, 2005, Steven Piantadosi, John Wiley & Sons

Academic Integrity: Students in this course will be expected to comply with the University of Pittsburgh’s Policy on Academic Integrity (http://www.provost.pitt.edu/info/ai1.html). Any student suspected of violating this obligation for any reason during the semester will be required to participate in the procedural process, initiated at the instructor level, as outlined in the University Guidelines on Academic Integrity. This may include, but is not
limited to, the confiscation of the examination of any individual suspected of violating University Policy. Furthermore, no student may bring any unauthorized materials to an exam, including dictionaries and programmable calculators.

Disability Resources and Services: If you have a disability for which you are or may be requesting an accommodation, you are encouraged to contact both your instructor and Disability Resources and Services (DRS), 140 William Pitt Union, (412) 648-7890/(412) 383-7355 (TTY), as early as possible in the term. DRS will verify your disability and determine reasonable accommodations for this course.

Course Schedule

| Session 1 | Randomization, Introduction to sample size |

At the conclusion of this lecture, the student will be able to:
1. Understand and conduct the most common types of randomization schemes.
2. Describe the factors needed to conduct sample size and power analyses.

Topics:
1. Advantages/disadvantages of simple randomization
2. Restricted randomization
3. Random permuted blocks
4. Stratified randomization
5. Adaptive randomization
6. Review of factors that determine sample size calculations

Competencies
Sampling: Identify appropriate study populations and sample size, control and comparison groups, and possible sources of bias for research problems.
Written Communication: Prepare written presentations of research at a variety of stages to a range of audiences, technical and non-technical, and respond to constructive criticism and questions.

Required reading:
1. FFD Ch 6 (The Randomization Process)

Supplemental reading:
1. Pocock Chapter 9
2. Meinert Chapters 9 & 10

Homework Assignment 1: Complete randomization problem. Due Session 2.
Protocol Assignment 1: Draft randomization description for protocol, include details about how randomization will occur and when randomization will occur. Create screening and randomization schema. Due Session 2
Session 2  Sample size and power analysis
   Class discussion sample size for protocols

At the conclusion of this lecture, the student will be able to:
1. Use statistical software to conduct sample size and power analyses for studies with binary, continuous, and time-to-event endpoints.

Topics:
1. Sample size calculations for dichotomous, continuous, and time to event outcomes in Phase III parallel group design.
2. Briefly discuss repeated measures designs.
3. Adjusting sample size for non-adherence and drop-out rate.
4. Software to conduct sample size calculations.

Competencies
Sampling: Identify appropriate study populations and sample size, control and comparison groups, and possible sources of bias for research problems.
Written Communication: Prepare written presentations of research at a variety of stages to a range of audiences, technical and non-technical, and respond to constructive criticism and questions.

Required reading:
1. FFD Ch 8 (Sample Size pg 165-188)

Homework Assignment 2: 1) Baseline assessment analysis for homework trial. Due Session 4.
Protocol Assignment 2: 1) Information for your study’s sample size analysis and initial attempt of sample size analyses for several scenarios 2) Create shell Table 1 for the clinical trial you are proposing. Due Session 4.

Due: Homework assignment 1
Due: Protocol assignment 1

Session 3  Baseline assessment
   Consenting, enrollment, randomization, allocation,
   and flow chart discussions

At the conclusion of this lecture, the student will be able to:
1. List important baseline data that should be collected on participants before the start of the intervention.
2. Effectively present baseline data on participants enrolled in a clinical trial.

Topics:
1. Baseline data collection
2. Baseline data presentation

Competencies
Methodology: Design basic features of research protocols based on specific research questions, appropriately addressing bias.

Required reading: Ch 9 (Baseline Assessment)
Session 4 Statistical analysis of Phase III trials

At the conclusion of this lecture, the student will be able to:
1. Explain concepts and basic methods of general linear models to continuous outcome data (change in score, etc.) from a parallel group clinical trial.
2. Explain concepts and basic methods of logistic regression to dichotomous outcome data from a parallel group clinical trial.
3. Explain concepts and basic methods of survival analysis to time to event data from a parallel group clinical trial.

Topics:
1. Order of analyses in a clinical trial
2. Analyses of parallel group design: continuous outcome, dichotomous outcome, time to event outcome.

Competencies:
*Applied Analytic Techniques:* Determine and apply a range of appropriate statistical techniques to answer research questions and explain the implications of missing data on conclusions drawn from statistical results.

*Supplemental reading:* Pocock Ch 13 (Basic Principles of Statistical Analysis)

Required reading: FFD Ch 15 (Survival Analysis)

Homework Assignment 3: Conduct analyses on the primary and secondary outcomes of the homework trial. Due Session 6.

Protocol Assignment 3: 1) Draft brief analysis plan for your primary and secondary outcomes 2) Create shell table(s) for the primary outcome(s) and secondary outcome(s) of your proposed project. Due Session 6.

Due: Homework assignment 2
Due: Protocol assignment 2

Session 5 Finish statistical analysis of Phase III trials
Issues in statistical analysis of Phase III trials

At the conclusion of this lecture, the student will be able to:
1. Determine which participants should be included in analyses.
2. Identify appropriate covariates that should be controlled for in analyses of a CT.
3. Describe the importance of specifying subgroup analyses prior to conduct of CT.

Topics:
1. Analysis data set (who should be included/excluded) based on ineligibility, withdrawals, non-adherence, missing data, etc.
2. Covariate adjustment
3. Subgroup analyses

Competencies:
*Applied Analytic Techniques:* Determine and apply a range of appropriate statistical techniques to answer research questions and explain the implications of missing data on conclusions drawn from statistical results.
**Applied Analytic Techniques:** Describe appropriate data analysis plans for addressing specific research questions.

**Required reading:**
1. FFD Ch 18 (Issues in Data Analysis)

**Protocol Assignment 4:** Presentation on proposed study on Session 8 (during class). Must use presentation template—presentations with added slides will receive a 0 grade. Final written protocol is due Session 8.

<table>
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<th>Session 6</th>
<th>Interim analyses</th>
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At the conclusion of this lecture, the student will be able to:
1. Discuss the advantages and disadvantages of interim analyses.
2. Discuss the different types of interim analyses plans.
3. Summarize a selection from the literature on clinical trials that have been terminated early due to interim analyses.

**Topics:**
1. Overview of study monitoring
2. Overview of inflating Type I errors with multiple testing
3. Group sequential methods (Pocock, O'Brien & Fleming)
4. Alpha-spending functions
5. Popular trials that have been terminated early

**Competencies:**

**Applied Analytic Techniques:** Describe appropriate data analysis plans for addressing specific research questions.

**Methodology:** Understand and explain Federal regulations regarding human subject research, and prepare an IRB application.

**Data Management and Biomedical Informatics:** Identify pertinent issues in the construction of effective data and safety monitoring plans and provide examples of best practices for protecting privacy throughout a study.

**Required reading:** FFD Ch 17 (Statistical Methods Used in Interim Monitoring)

**Due:** Homework assignment 3
**Due:** Protocol assignment 3

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<thead>
<tr>
<th>Session 7</th>
<th>Adaptive Designs</th>
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<tr>
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<td>Multiplicity</td>
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<td></td>
<td>Reporting Methods and Results for Clinical Trials</td>
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At the conclusion of this lecture, the student will be able to:
1. Describe different types of adaptations in clinical trials
2. Describe the different situations in which multiplicity occurs.
3. Describe some solutions to multiplicity issues.
4. Discuss key components for a methods section of a clinical trials manuscript.
5. Discuss key tables and statistics in reporting results of a clinical trial.
6. Evaluate the quality of a clinical trial based on the information reported.

**Topics:**
1. Adaptive trials
2. Different situations of multiplicity
3. What to do when multiplicity occurs
4. Key components in reporting and interpreting results of a clinical trial (tentative)

Competencies:

**Methodology:** Design basic features of research protocols based on specific research questions, appropriately addressing bias.

**Ethics and Professional Norms** Identify violations of professional integrity, safeguard procedures in all phases of the research process, and explain appropriate reporting procedures.

**Written Communication:** Prepare written presentations of research at a variety of stages to a range of audiences, technical and non-technical, and respond to constructive criticism and questions.

**Written Communication:** Organize and report statistical results.

**Required reading:**
2. FFD Ch 20 (Reporting and Interpreting of Results)

**Supplemental reading:**

<table>
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<tr>
<th>Session 8</th>
<th>Protocol Presentations from 8:00 am – 1:00 pm</th>
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**Due:** Protocol assignment 4

**Competencies:**

**Written Communication:** Prepare written presentations of research at a variety of stages to a range of audiences, technical and non-technical, and respond to constructive criticism and questions.

**Oral Communication:** Prepare and deliver oral presentations of research at a variety of stages to a range of audiences, and respond to constructive criticism and questions.

**FINAL PROTOCOLS DUE BEFORE CLRES 2820—NO EMAILS.**