CLRES 2810  
Statistical Methods and Issues  
in Clinical Trials  
Dates: Spring Term  
Location: VALE 305A

**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**

| Class attendance | 5% |
| Written assignments and presentations | 55% |
| Final project | 40% |

**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:

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<thead>
<tr>
<th>Grade</th>
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<tbody>
<tr>
<td>A+</td>
<td>&gt;95%</td>
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<tr>
<td>A</td>
<td>92-95%</td>
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<td>A-</td>
<td>90-91%</td>
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<td>B+</td>
<td>88-89%</td>
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<td>B</td>
<td>82-87%</td>
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<td>B-</td>
<td>80-81%</td>
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<td>C</td>
<td>70-79%</td>
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<td>D</td>
<td>60-69%</td>
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<tr>
<td>F</td>
<td>&lt;60%</td>
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NOTE: Homework assignments, course information, and communication will be available at [http://courseweb.pitt.edu](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, 1986 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.

**Final Project for Modules 1 and 2:** Protocol development term paper guidelines (adapted from Pocock, 1996).

1. Title
2. Background and significance (1-2 pages)
3. Objectives: State hypotheses with respect to intervention and specific outcomes (efficacy and/or safety) to be addressed by the trial. State the primary question and response variable, secondary questions and response variables, and any subgroup hypotheses.
4. Participants and recruitment: disease state under investigation, and specific criteria for inclusion/exclusion of participants; source and recruitment plan.
5. Intervention: If you are proposing a drug therapy, describe the drug formulation, route of administration, amount of each dose, frequency of dose, duration of therapy, dose modification, monitoring participant compliance. If you are proposing a non-drug therapy intervention, describe similar information but for the specific type of intervention you are proposing. For example, if you are proposing an educational intervention, describe the content and format of the intervention (workshops, classes, mailouts), the frequency, the duration, etc.
6. Trial design: intervention allocation, randomization, blinding, placebo, etc.
7. Study measurements: baseline assessment, definition of primary and secondary study outcomes, side effects that will be monitored; specific adverse events; adherence to intervention
8. Assessment calendar: frequency of evaluations, tests, procedures (include any extended follow up period)
9. Sample size and statistical analysis: sample size justification, assumptions about drop-outs, withdrawals, losses to follow-up, and non-adherences, timeline for patient accrual, data and safety monitoring, interim analysis, final data analysis plan
10. Data and safety monitoring plan
11. References
# 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

### 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.

### 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.

## 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.

### Required reading:
1. FFD Ch 8 (Sample Size pg 133-155)

### Homework Assignment 2: 1) Sample size calculation 2) Baseline assessment analysis for homework trial.
Protocol Assignment 2: 1) Information for your study's sample size analysis 2) Create shell Table 1 for the clinical trial you are proposing.

<table>
<thead>
<tr>
<th>Session 3</th>
<th>Baseline assessment</th>
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<td>Consenting, enrollment, randomization, allocation, and flow chart discussions</td>
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At the conclusion of this lecture, the student will be able to:
1. Discuss 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

Required reading: Ch 9 (Baseline Assessment)

Due: Homework assignment 1
Due: Protocol assignment 1

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<tr>
<th>Session 4</th>
<th>Statistical analysis of Phase III trials</th>
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At the conclusion of this lecture, the student will be able to:
1. Understand concepts and basic methods of general linear models to continuous outcome data (change in score, etc.) from a parallel group clinical trial.
2. Understand concepts and basic methods of logistic regression to dichotomous outcome data from a parallel group clinical trial.
3. Understand 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.

Required reading: FFD Ch 15 (Survival Analysis)
FFD Ch 19 (Reporting and Interpreting of Results)
Supplemental reading: Pocock Ch 13 (Basic Principles of Statistical Analysis)

Homework Assignment 3: Conduct analyses on the primary and secondary outcomes of the homework trial.
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: Homework assignment 2
Due: Protocol assignment 2

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<th>Session 5</th>
<th>Finish statistical analysis of Phase III trials</th>
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<td>Issues in statistical analysis of Phase III trials</td>
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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. Understand the importance of specifying subgroup analyses prior to conduct of CT.
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. Analysis data set (who should be included/excluded) based on ineligibility, withdrawals, non-adherence, missing data, etc.
2. Covariate adjustment
3. Subgroup analyses
4. Key components in reporting and interpreting results of a clinical trial (tentative)

Required reading:
1. FFD Ch 17 (Issues in Data Analysis)
2. FFD Ch 19 (Reporting and Interpreting of Results)

Protocol Assignment 4: Presentation on proposed study (during class)

Session 6 Interim analyses

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. Understand 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

Required reading: FFD Ch 16 (Monitoring Response Variables)
Due: Homework assignment 3
Due: Protocol assignment 3

Session 7 Adaptive Designs
Multiplicity
Reporting Methods and Results for Clinical Trials

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)

Required reading:
2. FFD Ch 19 (Reporting and Interpreting of Results)

<table>
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<tr>
<th>Session 8</th>
<th>Protocol Presentations</th>
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<th>Special Session</th>
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