
CLRES 2810**Statistical Methods and Issues
in Clinical Trials**

Dates: 2/3/10-3/1/10

Meeting time: MW 10:00-12:00

Location: VALE 305A

Phone contact: 412-246-6961

Course Instructors:
Charity G. Moore, PhD
Sunday Clark, ScDEmail addresses:
moorecg@upmc.edu
clarks2@upmc.edu

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 not be accepted. Late homework assignments will be penalized 10% per day over the due date unless prior arrangements have been made with the instructors.
- 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	65%
Final project	30%

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:

90 - 100 = A 80 - 85 = B 70 - 75 = C 60 - 65 = D
86 - 89 = B+ 76 - 79 = C+ 66 - 69 = D+ < 60 = F

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

Required Textbook: Fundamentals of Clinical Trials - Third Edition, Friedman LM, Furberg CD, DeMets DL., John Wright, PSH Inc. Boston, MA, 1998.

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

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, any subgroup hypotheses, and list any adverse effects that will be monitored.
4. Patient selection: source of participant recruitment, disease state under investigation, and specific criteria for inclusion/exclusion of participants
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. Study measurements: baseline assessment, definition of primary and secondary study endpoints, criteria of participant response, side effects that will be monitored
7. Trial design: intervention allocation, randomization, blinding, placebo, etc.
8. Study calendar: frequency of evaluations, tests, procedures (include any extended follow up period)
9. Sample size and statistical analysis: sample size justification, timeline for patient accrual, data and safety monitoring, interim analysis, final data analysis plan
10. Assumptions about drop-outs, withdrawals, losses to follow-up, and non-adherences.
11. References

Course Schedule

Date: February 3, 2010

Session 1	Randomization, Introduction to sample size
------------------	---

Clark/Moore

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. **Review of factors that determine sample size calculations**

Required reading:

1. FFD Ch 5 (The Randomization Process)
2. Schulz KF, Grimes DA (2005) Sample size calculations in randomised trials: mandatory and mystical. Lancet 365:1348-1353.

Supplemental reading:

1. Pocock Chapter 9
2. Meinert Chapters 9 & 10

Homework Assignment 1: (1) Work with your partner to find examples (one each) of Phase I and Phase II trials. Write one page summary for each study outlining the background/introduction, research question, intervention, study population, study design, primary endpoints (efficacy and safety), stopping rules (if any), statistical procedures (if applicable), number of participants, results for primary endpoint, and conclusion. (2) Complete randomization problem. **Due** Wednesday, February 10, 2010.

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** Wednesday, February 10, 2010.

Date: February 8, 2010

**Session 2 Sample size and power analysis
 Baseline assessment**

**Moore
Clark**

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.
2. Discuss important baseline data that should be collected on participants before the start of the intervention.
3. Effectively present baseline data on participants enrolled in a clinical trial.

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.**
5. **Baseline data collection and presentation.**

Required reading:

1. FFD Ch 7 (Sample Size pg 94-118 and 122-125) and Ch 8 (Baseline Assessment)
2. Altman, Dore (1990) Randomisation and baseline comparisons in clinical trials. Lancet 335:149-53.

Homework Assignment 2: 1) Sample size calculation 2) Baseline assessment analysis for Aspirin trial . **Due** Wednesday, February 15, 2010.

Protocol Assignment 2: 1) Information for your study's sample size analysis 2) Create shell Table 1 for the clinical trial you are proposing. **Due** Wednesday, February 15, 2010.

Date: February 10, 2010		
Session 3	Finish baseline assessment Consenting, enrollment, randomization, allocation, and flow chart discussions	Clark Class discussion

Presentation of assignments from 2/3/10.

Due: Homework assignment 1

Due: Protocol assignment 1

Date: February 15, 2010		
Session 4	Statistical analysis of Phase III trials	Moore/Clark

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 14 (Survival Analysis)

FFD Ch 18 (Reporting and Interpreting of Results)

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

Homework Assignment 3: Aspirin study: conduct analyses on the primary and secondary outcomes of the aspirin trial. **Due** Wednesday, February 24, 2010.

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** Wednesday, February 24, 2010.

Due: Homework assignment 2

Due: Protocol assignment 2

Date: February 17, 2010		
Session 5	Finish statistical analysis of Phase III trials Issues in statistical analysis of Phase III trials	Moore/Clark Clark

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. **Key components in reporting and interpreting results of a clinical trial**
2. **Analysis data set (who should be included/excluded) based on ineligibility, withdrawals, non-adherence, missing data, etc.**
3. **Covariate adjustment**
4. **Subgroup analyses**

Required reading:

1. FFD Ch 16 (Issues in Data Analysis)
2. FFD Ch 18 (Reporting and Interpreting of Results)
3. <http://www.consort-statement.org/>
4. Bailar JC, Mosteller F (1988) Guidelines for statistical reporting in articles for medical journals: Amplifications and explanations. *Annals of Internal Medicine* 108:266-273.
5. Durbin CG. (2004) Effective use of tables and figures in abstracts, presentations, and papers. *Respiratory Care* 49:1233-1237.

Protocol Assignment 4: Presentation on proposed study on March 1, 2010 (during class) and March 5, 2010 from 8-11 a.m.(breakfast provided). Final written protocol is due Friday, March 12, 2010.

Date: February 22, 2010		
Session 6	Interim analyses	Moore/Clark

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 15 (Monitoring Response Variables)

Date: February 24, 2010		
Session 7	Adaptive Designs Multiplicity	Wahed Moore

At the conclusion of this lecture, the student will be able to :

1. Describe the different situations in which multiplicity occurs.
2. Describe some solutions to multiplicity issues.

Topics :

1. **Different situations of multiplicity**
2. **What to do when multiplicity occurs**

Due: Homework assignment 3

Due: Protocol assignment 3

Date: March 1, 2010

Session 8

Protocol Presentations

Due: Protocol assignment 4

Date: March 5, 2010 8:00 -11:00 a.m.

Special Session

Protocol Presentations

Due: Protocol assignment 4