
CLRES 2800
Fundamentals of Clinical Trials

Dates: 1/5/11-2/2/11
Meeting time: MW 10:00-12:00
(**note:** no class January 17th)
Location: VALE 305A
Phone contact: 412-246-6961

Course Instructors:
Charity G. Moore, PhD
Sunday Clark, ScD

Email addresses:
moorecg@upmc.edu
clarks2@upmc.edu

Overview and Objectives: Fundamentals of Clinical Trials course will provide information on the first three phases (Phases I-III) of intervention/drug development and fundamental components of randomized clinical trials. A majority of lectures will focus on aspects of Phase III parallel group designs with discussions on topics including developing research questions and defining endpoints, recruitment, randomization, blinding, data management & quality, monitoring, study closeout, and presentation/interpretation of results. The student will be introduced to the Good Clinical Practice guidelines and the principles of planning and implementing clinical research protocols including: ethical issues and regulatory imperatives designed to protect human subjects in clinical research, adverse event reporting, protocol/proposal development, and publications. We will use manuscripts of clinical trials and protocols of completed studies to facilitate learning of concepts discussed in class.

Responsibilities:

- There will be reading assignments in the textbook and selected articles and guidelines. Readings of book chapters assigned in the syllabus are expected to be completed before class.
- Students will be assigned three homework assignments that will be graded. All homework assignments will be assigned with a due date. 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. Homework assignments are to be turned in at the beginning of class on the due date. No assignments will be accepted via email.
- Throughout the first and second modules of this course, you will be responsible for preparing a protocol for a clinical trial that will be turned in as a final project for both modules. You will be evaluated on your progress on this draft at the end of the first module. There are four draft protocol assignments during CLRES 2800. Be sure to include the title of the study and primary research question on all protocol assignments. Draft protocol assignments should be turned in on separate documents from the regular homework assignment. We will be discussing some submitted protocol assignments in class.
- Attendance and participation in class are required.
- Evaluation criteria for this module will be based on completion of the written assignments, progress on your draft protocol, participation and attendance, and the final exam.

Course Requirements

Class participation and attendance	5%
Written assignments	50%
Draft protocol	30%
Final Exam	15%

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 - Fourth Edition, Friedman LM, Furberg CD, DeMets DL., Springer, New York 2010.

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

Website resources:

National Institutes of Health: www.clinicaltrials.gov

Food and Drug Administration: www.fda.gov

The Cochrane Collaboration: www.cochrane.org

Academic Integrity: Students in this course will be expected to comply with the [University of Pittsburgh's Policy on Academic Integrity \(http://www.provost.pitt.edu/info/ai1.html\)](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.

ADD ICRE SPECIFIC INFORMATION

Course Schedule

Date : January 5, 2011

Session 1 : Introduction to Clinical Trials

Moore/Clark

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

1. Define the meaning of a clinical trial and describe different phases of drug development.
2. Discuss the characteristics of well-formed research questions and hypotheses.
3. Discuss different types of endpoints used in clinical trials and issues surrounding surrogate endpoints.
4. Determine the study population for a clinical trial.

Topics:

1. **Course overview**
2. **Introduction to clinical trials and study protocols**
3. **Brief overview study protocol features**
4. **Research questions/hypotheses (FINER criteria)**
5. **Intervention and study endpoints (primary, secondary, & surrogate)**
6. **Study population**

Required reading:

1. Friedman, Furberg, DeMets (FFD) Ch. 1 (Introduction to Clinical Trials), Ch 3 (What is the Question), Ch 4 (Study Population)
2. Fleming TR, DeMets DL. (1996) Surrogate end points in clinical trials: are we being misled? *Annals of Internal Medicine* 125:605-613.

Homework assignment 1: (1) Read one of the two selected articles and answer the assigned questions for the article you selected (see homework handout for specific details). (2) Read the assigned Phase I study and answer the assigned questions for the article. Identify a Phase II study in your area of interest and answer the assigned questions for the article (see homework handout for specific details). **Due** Wednesday, January 12, 2011.

Protocol assignment 1: Begin drafting your research question for the draft protocol that is due at the end of the module. For this homework assignment, turn in the title of your proposed project, the primary research question and a clear definition *and justification* of the primary response variable. In addition, consider the study population and intervention, which will be part of the second homework assignment. **Due** Monday, January 10, 2011.

Date : January 10, 2011

**Session 2: Drug Development,
Pharmacokinetics/Pharmacodynamics
Introduction to Phase I & II Trials**

**Poloyac
Moore**

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

1. Describe the stages of drug development from pre-clinical to clinical.
2. Describe important characteristics of PK/PD studies.
 1. Discuss the primary goal, general designs, and outcomes of Phase I studies.
 3. Discuss the primary goal, general designs, and outcomes of Phase II studies.

Topics:

1. **Overview of drug development, pharmacokinetics, pharmacodynamics**
2. **Overview of Phase I studies**
3. **Overview of Phase II studies**

Required reading:

1. Zhou Y (2004) Choice of designs and doses for early phase trials. *Fundamental & Clinical Pharmacology* 18:373-378.
2. Stallard N, Whitehead J, Todd S, Whitehead A (2001) Stopping rules for Phase II studies. *British Journal of Clinical Pharmacology* 51:523-529
3. Geller NL (1984). Design of phase I and II clinical trials in cancer: A statistician's view. *Cancer Investigation* 2(6) 483-491.

Protocol assignment 2: Describe the study population and intervention for your proposed project.
Due Wednesday, January 12, 2011.

Due today: Protocol Assignment 1

Date: January 12, 2011	
Session 3: Review of research questions (protocols)	Class discussion
Introduction to Phase III Trials	
Ethics in Clinical Trials	Clark

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

1. Discuss the advantages and disadvantages of randomized design.
2. Describe the main features of a study protocol.
3. Discuss ethical issues surrounding intervention studies.
4. Discuss the history of research ethics.
5. Describe important components of a well-designed informed consent form.
6. Discuss important concepts in obtaining informed consent.

Topics:

1. **Introduction to Phase III trials**
2. **Protocol development guidelines**
3. **Ethical issues in clinical trials**
4. **International Harmonization Conference & Good Clinical Practice**
5. **Informed consent guidelines**
6. **Regulatory environment; roles of IRB, OHRP, FDA**
7. **University of Pittsburgh, CTSI, Regulatory Knowledge and Support Core:**
<http://www.ctsi.pitt.edu/content.asp?id=1448>

Required reading:

1. FFD Chapter 2 (Ethics) and Chapter 5 (Basic study design)
2. Nuremberg Code <http://ohsr.od.nih.gov/nuremberg.php3>,
3. Belmont Report <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>
4. ICH/GCP <http://www.fda.gov/cder/guidance/iche6.htm> (Sections 1-4, and Section 6)

Homework assignment 2: (1) Read the assigned Bradford Hill article and answer the assigned questions for the article (see homework handout for specific details) (2) Informed consent

Due Wednesday, January 19, 2011.

Protocol assignment 3: Draft a 1-2 page document of the Background and Significance section for your protocol. **Due** Wednesday, January 19, 2011. Note: Make two copies for turning in one to instructors and one for peer review. Background and Significance will be critiqued by classmate. Critiques will be due Monday, January 24, 2011.

Due today: Homework assignment 1 & Protocol assignment 2

Date: January 19, 2011	
Session 4 Review of population and intervention (protocols)	Class discussion
Important Procedures in Clinical Trials	Moore

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

1. Compare the different types of randomization in clinical trials.
2. Discuss importance of blinding and issues pertaining to blinding.

3. Understand appropriate situations for using a placebo-controlled trial.
4. Describe the components of a study assessment calendar.

Topics:

1. **Randomization**
2. **Intent-to-treat concept**
3. **Blinding/Masking**
4. **Placebo controls**
5. **Study calendar**

Required reading:

1. FFD Ch 6-7 (randomization, blindness)

Protocol assignment 4: For your draft protocol, describe the follow components: (1) Secondary research questions and response variables; (2) Recruitment plan; (3) A table with study measurements (baseline, primary and secondary outcomes); (4) Secondary outcome(s) and brief description of each; (5) Intervention allocation; (6) Randomization scheme and justification; (7) Type of blinding to be used and justification; (8) Study assessment calendar. **Due** Wednesday, January 26, 2011.

Due today: Homework assignment 2 &: Protocol Assignment 3.

Date: January 24, 2011

**Session 5: Study Coordination & Recruitment
Data Management and Coordination**

**Belnap
Rubio**

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

1. Describe the role of a research coordinator.
2. Understand the components of successful recruitment.
3. Describe the factors involved in developing a well designed clinical research form.
4. Discuss the different types of data management systems used in clinical trials.
5. Describe methods to minimize poor data quality.
6. Discuss the types of adverse events in clinical trials and methods of monitoring them.
7. Discuss methods of measuring/monitoring adherence

Topics:

1. **Recruitment and retention**
2. **Barriers to participation in research**
3. **Adverse event reporting**
4. **Adherence**
5. **Clinical research forms & data collection**
6. **Data management & quality assurance**

Required Reading: FFD Ch 10 (recruitment), Ch 11 (Data Collection and Quality Control), Ch 12 (Assessing and Reporting Adverse Effects), & Ch 14 (Participant Adherence)

Homework assignment 3: (1) Read the assigned article and answer the assigned questions for the article. (2) Identify a published clinical trial in your area of interest and answer the assigned questions for the article (see homework handout for specific details). **Due** Monday, January 31, 2011.

Due today: Background and Significance classmate critiques

Date: January 26, 2011

**Session 6: Data and Safety Monitoring
Introduction to Interim Analyses**

**Yasko/Alexander
Moore**

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

1. Describe appropriate procedures for study monitoring.
2. Discuss the importance and role of the DSMB.

3. Describe the aim and general approach of interim analysis.
4. List the four major reasons for terminating a trial earlier than scheduled.
5. Describe what is involved in closing out a study.

Topics:

1. **Study monitoring**
2. **Understand the role of a data and safety monitoring board (DSMB)**
3. **Introduction to interim analysis**
4. **Early termination**

Required reading:

1. FFD Ch 16 Monitoring Response Variables (pp. 246-259)
2. ICH/GCP: <http://www.fda.gov/cder/guidance/iche6.htm> (Sections 5: Sponsor, 7: Investigator's Brochure, and 8: Essential Documents for the Conduct of a Clinical Trial)

Draft Protocol: Combine each of the components of your draft protocol that have been included in your protocol assignments. Turn in a "draft" version of your complete protocol with all required sections except the sample size and statistical analysis section. **Due:** Monday, February 7, 2011.

Due today: Protocol assignment 4

Date: January 31, 2011	
Session 7:	Multicenter Trials
	Reporting and interpreting study results
	Boat Moore

At the conclusion of this lecture, the student will have learned about :

1. Discuss methods of handling protocol deviations.
2. The reasons for conducting of multicenter trials.
3. Guidelines for reporting results of clinical trials
4. Examples of authorship guidelines in protocols

Topics:

1. **Protocol deviations**
2. **Multicenter trials**
3. **Reporting study results & Authorship guidelines in protocols**

Required Reading

1. FFD Ch 19 (Reporting and Interpreting of Results) & 20 (Multicenter Trials)
2. <http://www.consort-statement.org> (Click on CONSORT Statement, then in box on the right click on the JAMA article)
3. Fontanarosa PB, DeAngelis CD. (2008) Publication of clinical trials in JAMA. JAMA 299 : 95-96.
4. Flanagan A, Fontanarosa PB, DeAngelis CD. Authorship for research groups. JAMA. 2002;288(24):3166-3168.

Due today: Homework assignment 3

Date: February 2, 2011	
Session 8:	Final Exam
	Protocol discussion
	Review recruitment/allocation/blinding
	Class discussion

DON'T FORGET: February 7, 2011 (first day of Module 2) Draft Protocol Is Due!!