Overview and Objectives: Fundamentals of Clinical Trials course will provide information on the first three phases (Phases I-III) of intervention 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.

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:

- **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](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

**Website resources:**
- National Institutes of Health: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- Food and Drug Administration: [www.fda.gov](http://www.fda.gov)
- The Cochrane Collaboration: [www.cochrane.org](http://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). 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: Introduction to Clinical Trials

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)

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) Identify a Phase I and a Phase II study in your area of interest and answer the assigned questions for the articles (see homework handout for specific details).

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.

Session 2: Introduction to Phase I & II Trials

At the conclusion of this lecture, the student will be able to:
1. Discuss the primary goal, general designs, and outcomes of Phase I studies.
2. Discuss the primary goal, general designs, and outcomes of Phase II studies.
3. Discuss the advantages and disadvantages of randomized design.
4. Describe the main features of a study protocol.

Topics:
1. Overview of Phase I studies
2. Overview of Phase II studies
3. Introduction to Phase III trials
4. Protocol development guidelines

Required reading:
2. FFD Chapter 5 (Basic study design)
Supplemental reading:

Protocol assignment 2: Describe the study population and intervention for your proposed project.

Session 3: Important Procedures in Clinical Trials
Ethics in Clinical Trials

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. Discuss ethical issues surrounding intervention studies.
5. Discuss the history of research ethics.
6. Describe important issues of a well-designed informed consent form.
7. Discuss important concepts in obtaining informed consent.

Topics:
1. Randomization
2. Intent-to-treat concept
3. Blinding/Masking
4. Placebo controls
5. Ethical issues in clinical trials
6. International Harmonization Conference & Good Clinical Practice
7. Informed consent guidelines
8. Regulatory environment; roles of IRB, OHRP, FDA
9. University of Pittsburgh, CTSI, Regulatory Knowledge and Support Core: [http://www.ctsi.pitt.edu/content.asp?id=1448](http://www.ctsi.pitt.edu/content.asp?id=1448)

Required reading:
1. FFD Ch 6-7 (randomization, blindness)
2. FFD Chapter 2 (Ethics)

Supplemental reading:

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

Protocol assignment 3: Draft a 1-2 page document of the Background and Significance section for your protocol.
Note: Make two copies for turning in one to instructors and one for peer review. Background and Significance will be critiqued by classmate.

Session 4 Data Management and Coordination
Review of protocols
Small group discussions
(research questions, interventions, outcomes, populations)
At the conclusion of this lecture, the student will be able to:

1. Describe the factors involved in developing a well-designed clinical research form.
2. Discuss the different types of data management systems used in clinical trials.
3. Describe methods to minimize poor data quality.

Topics:

1. Clinical research forms & data collection
2. Data management & quality assurance

Required reading:
1. Ch 11 (Data Collection and Quality Control),
2. FDA guidance for industry: Computerized systems used in clinical trials (http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdlo002.PDF)

Protocol assignment 4: For your draft protocol, describe the follow components: (1) Secondary research questions; (2) Secondary outcome(s) and brief description of each; (3) A table with study measurements (baseline, primary and secondary outcomes); (4) Intervention allocation; (5) Randomization scheme and justification; (6) Type of blinding to be used and justification.

### Session 5: Study Coordination & Recruitment

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

1. Describe the role of a research coordinator.
2. Understand the components of successful recruitment.
3. Discuss the types of adverse events in clinical trials and methods of monitoring them.
4. Discuss methods of measuring/monitoring adherence.
5. Describe the components of a study assessment calendar.

Topics:

1. Recruitment and retention
2. Barriers to participation in research
3. Adverse event reporting
4. Adherence

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

Addition to Protocol assignment 4: Add a recruitment plan to your protocol and a study assessment calendar.

Due today: Protocol Assignment 3 and Homework 2

### Session 6: Data and Safety Monitoring

At the conclusion of the 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)

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 today: Protocol assignment 4 and Background and Significance classmate critiques

Session 7: Multicenter Trials
Reporting and interpreting study results

At the conclusion of this lecture, the student will have learned about:
1. Types of protocol deviations and violations.
2. Processes for study closeout
3. The reasons for conducting multicenter trials.
4. Guidelines for reporting results of clinical trials
5. Examples of authorship guidelines in protocols

Topics:
1. Protocol deviations
2. Study closeout
3. Multicenter trials
4. 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](http://www.consort-statement.org) (Click on CONSORT Statement, then in box on the right click on the JAMA article)

Supplemental Reading

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.

Session 8: Final Exam
Protocol discussion
Review recruitment/allocation/blinding Class discussion

Due today: Homework assignment 3