CLRES 2800  
Fundamentals of Clinical Trials  
Dates: Spring Term

Overview and Objectives: By the end of this course, students should be able to explain the key issues in RCT design, and describe the methodological components necessary for a randomized controlled trial. The student will learn by taking the information provided in class and readings to design a trial in their area of research. 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.
- 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. Most of the homework for the course involves developing components of your protocol. 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.
- All homework assignments will be assigned with a due date. You can 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.
- 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

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<th>Component</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Class participation and attendance</td>
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<tr>
<td>Written assignments</td>
<td>50%</td>
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<tr>
<td>Draft protocol</td>
<td>30%</td>
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<td>Final Exam</td>
<td>15%</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:

<table>
<thead>
<tr>
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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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<tr>
<td>A-</td>
<td>90-91%</td>
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<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.


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

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). 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 session, the student will be able to:
1. Define the meaning of a clinical trial and describe different phases of intervention testing.
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.
5. Describe the main features of a study protocol.

Topics:
1. Course overview
2. Good Clinical Practice Guidelines
3. Study protocol features
4. Research questions/hypotheses (FINER criteria/PICO)
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)

In class discussion: ENRICHD trial
Homework Assignment: Protocol 1 Assignment (primary question and outcome), due Session 2
Find a Phase I and a Phase II clinical trial in your area (for discussion Session 2)

Competency learning objectives addressed:
Problem formulation: propose significant and novel empirical, testable, hypothesis-driven research questions using, where appropriate, different disciplines and community engagement.
Sampling: identify appropriate study populations, control and comparison groups.
Measurement: describe the characteristics underlying data quality and their ability to answer clinical or translational research problems.

Session 2: Introduction to Phase I & II Trials
Introduction to Phase III 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.

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

Required reading and viewing:
1. Slides on Phase I, Phase II, and Other Study Designs


**Supplemental reading:**

4. FFD Chapter 5 (Basic study design)

**In class discussion:** Phase I and Phase II studies found in your area (work through questions of assignment) and Protocol 1 Assignment discussion (research questions and outcomes).

**Homework Assignment:** Protocol 2 Assignment. (study population, interventions, secondary questions, secondary outcomes), due Session 3.

**Competency learning objectives addressed:**

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

*Sampling:* Identify appropriate study populations and sample size, control and comparison groups, and possible sources of bias for research problems.

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### Session 3: Important Procedures 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. Describe the components of a study evaluation/assessment table.

**Topics:**

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

**Required reading:**

1. FFD Ch 6-7 (randomization, blindness)
2. FFD Ch 2 (pg 30-33)

**In class discussion:** Primary outcomes for protocols, surrogates, and biomarkers

**Homework Assignment:** Protocol 3 Assignment (allocation, randomization, blinding, due Session 4)

**Competency learning objectives addressed:**

*Methodology:* compare strengths and weaknesses (feasibility, efficiency, generalizability, validity, and ability to derive unbiased inferences) of different methodologies.

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### Session 4: Adverse Events

**Data and Safety Monitoring**

**Introduction to Interim Analyses**

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

1. Discuss the types of adverse events in clinical trials and methods of monitoring them.
2. Describe appropriate procedures for study monitoring.
3. Discuss the importance and role of the DSMB.
4. Describe the aim and general approach of interim analysis.
5. List the four major reasons for terminating a trial earlier than scheduled.

Topics:
1. Adverse event reporting
2. Study monitoring
3. Understand the role of a data and safety monitoring board (DSMB)
4. Introduction to interim analysis
5. Early termination

Required reading:
1. FFD Ch 12 Assessing and Reporting Adverse Effects (pp. 255-266)
2. FFD Ch 16 Monitoring Committee Structure and Function

Homework Assignment: Protocol 4 Assignment (study measures, eval timeline, AEs), due Session 5 and start on consent form http://www.irb.pitt.edu/consent-form-suggested-wording (Session 6)
Review “Ethics in Clinical Trials” slides and lecture from 2014 prior to class 1/19

Competency learning objectives addressed:
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.
Ethics and Professional Norms: identify violations of professional integrity, safeguard procedures in all phases of the research process, and explain appropriate reporting procedures.

Session 5: Ethics in Clinical Trials
Data Management and Coordination

At the conclusion of this session, 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.
4. Discuss ethical issues surrounding intervention studies.
5. Discuss the history of research ethics.
6. Describe important components of a well-designed informed consent form.
7. Discuss important concepts in obtaining informed consent.

Topics:
1. Clinical research forms & data collection
2. Data management & quality assurance
3. Ethical issues in clinical trials
4. Informed consent guidelines
5. Regulatory environment; roles of IRB, OHRP, FDA

Required reading:
1. FFD Chapter 2 (Ethics)
2. Review slides from 2014 prior to class

Supplemental reading textbook
1. Ch 11 (Data Collection and Quality Control)

In class discussion: Data management and human subjects issues for your protocol.

Supplemental reading for data management, ethics and regulatory:
1. FDA guidance for industry: Computerized systems used in clinical trials (http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.PDF)
4. ICH/GCP Consolidated Guidance (Section 3)

**Homework Assignment:** Protocol 5 Assignment (background and significance) due by email on Session 6 @ 9am.

**Competency learning objectives addressed:**

*Data Management and Biomedical Informatics:* identify pertinent issues in the construction of effective data security and management plans for various research designs.

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

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**Session 6:**

**Protocol violations**

**Multicenter Trials**

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

1. Complicated reasons trials are stopped early
2. Types of protocol deviations and violations.
3. The reasons for conducting multicenter trials.

**Topics:**

1. Protocol deviations
2. Multicenter trials

**Required Reading**

1. FFD Ch 21 (Multicenter Trials)

**In class discussion:** DSMB simulation

**Homework Assignment:** Protocol Assignment 6 Protocol violation form for your study and develop a flow diagram for your protocol to include in the draft protocol.

**Competency learning objectives addressed:**

*Ethics and Professional Norms:* provide examples of the norms of professional integrity with regard to designing and conducting research including: data collection, sharing, and protection; and reporting of findings.

*Teamwork and Leadership:* describe the functions and roles of multiple disciplines with which they interact.

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**Session 7:**

**Publications and Reporting Adherence**

**Review of protocols (research questions, interventions, outcomes, populations, data management, measuring adherence)**

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

1. Guidelines for reporting results of clinical trials
2. Examples of authorship guidelines in protocols
3. Discuss methods of measuring/monitoring adherence.

**Topics:**

1. Reporting study results & Authorship guidelines in protocols
2. Adherence
**Required Reading**
1. FFD Ch 20 (Reporting and Interpreting of Results)
2. [http://www.consort-statement.org](http://www.consort-statement.org) (click on CONSORT statement, review checklist)
3. FFD Ch 14 (Participant Adherence)

**Supplemental Reading**

**Homework Assignment:** Protocol Assignment 7 (add recruitment plan, measure adherence, and study team)

**Competency learning objectives addressed:**
- **Ethics and Professional Norms:** provide examples of the norms of professional integrity with regard to designing and conducting research including: data collection, sharing, and protection; and reporting of findings.
- **Written Communication:** organize and report statistical results.

| Session 8: Final Exam | Discussion on Study Coordination & Recruitment |

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.

**Topics:**
1. Recruitment and retention
2. Barriers to participation in research

**Required Reading:**
1. FFD Ch 10 (Recruitment)

**Supplemental Reading:**
2. ICH/GCP Consolidated Guidance (Section 4)

**Competency learning objectives addressed:**
- **Management:** demonstrate behaviors needed to be an effective project manager including: oversight of fiscal regulations; recruitment; human resource management; and quality assurance activities.

**DON’T FORGET:** First day of CLRES 2810  
Draft Protocol and Draft Consent are due before CLRES 2810