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**CLRES 2800****Fundamentals in Clinical Trials**

Dates: 1/5/09-2/2/09

Meeting time: MW 10:00-12:00

**(note:** no class January 19<sup>th</sup>)

Location: VALE 305A

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Course Instructors:

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**Overview and Objectives:** Fundamentals in Clinical Trials course will provide information on the first three phases (Phases I-III) of 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 on 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 have been read when you come to class.
- Students will be assigned four written exercises 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.
- 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.
- 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, and participation in class meetings with instructors.

**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 - 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

**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)

**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. References

## Course Schedule

**Date : January 5, 2009**

**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. **Adjudication**
7. **Study population**

### Required reading:

1. Friedman, Furberg, DeMets (FFD) Ch. 1 (Introduction to Clinical Trials), Ch 2 (What is the Question), Ch 3 (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.

### Supplemental reading:

1. Meinert Ch. 1, Pocock Ch 3 (protocol)
2. Mahaffey KW, Harrington RA, Akkerhuis M, Kleiman NS, Berdan LG, Crenshaw BS, Tardiff BE, Granger CB, DeJong I, Bhapkar M, Widimsky P, Corbalon R, Lee KL, Deckers JW, Simoons ML, Topol EJ, Califf RM for the PURSUIT Investigators. (2001) Systematic adjudication of myocardial infarction end-points in an international clinical trial. *Current Controlled Trials in Cardiovascular Medicine* 2; 180-186.

**Homework assignment:** (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) Begin drafting your research question for the draft protocol that is due at the end of the module. For this homework assignment, beginning thinking about a title of your proposed project, the primary research question and response variable. In addition, consider the study population and intervention, which will be part of the second homework assignment. **Due** Monday, January 12, 2009.

**Date : January 7, 2009**

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

**Moore  
Clark**

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
5. Discuss ethical issues surrounding intervention studies

### 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:

1. Stallard N, Whitehead J, Todd S, Whitehead A (2001) Stopping rules for Phase II studies. *British Journal of Clinical Pharmacology* 51:523-529.
2. FFD Ch. 4

##### Supplemental reading:

1. Zhou Y (2004) Choice of designs and doses for early phase trials. *Fundamental & Clinical Pharmacology* 18:373-378.
2. Geller NL (1984). Design of phase I and II clinical trials in cancer: A statistician's view. *Cancer Investigation* 2(6) 483-491.
3. Storer BE and DeMets D (1987). Current Phase I/II Designs: Are they adequate? *Journal of Clinical Research and Drug Development* 1:121-130.
4. Fleming, T.R. (1982) One-sample multiple testing procedure for Phase II clinical trials. *Biometrics* 38:143-151.
5. Gehan, E.A. (1961) The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *Journal of Chronic Disease* 13:346-53.
6. Simon R (1989) Optimal two-stage designs for Phase II clinical trials. *Controlled Clinical Trials* 10:1-10.
7. Pocock Ch 3 (protocol) & Ch 4 (Justification for RCT)

**Homework assignment:** (1) 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). (2) Describe the study population and intervention or your proposed project. **Due** Wednesday, January 14, 2009.

**Date: January 12, 2009**

**Session 3: Drug Development,  
Pharmacokinetics/Pharmacodynamics  
Ethics in Clinical Trials**

**Poloyac  
Clark**

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.
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. Drug development
2. Pharmacokinetics and Pharmacodynamics
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. Whitehead J, Zhou Y, Stallard N, Todd S, Whitehead A (2001). Learning from previous responses in phase I dose-escalation studies. *British Journal of Pharmacology* 52:1-7.
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)

### Supplemental reading:

1. Zhou Y (2004) Choice of designs and doses for early phase trials. *Fundamental & Clinical Pharmacology* 18:373-378.
2. Pocock Ch 7 (Ethics)

**Homework assignment:** (1) Read the assigned Bradford Hill article and answer the assigned questions for the article (see homework handout for specific details). (2) Begin drafting the Background and Significance section for the draft protocol that is due at the end of the module. **Due** Wednesday, January 21, 2009.

**Date: January 14, 2009**

**Session 4      Important Procedures in Clinical Trials:  
Recruiting, Randomization, Blinding**

**Moore  
Bonk**

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

1. Understand the components of successful recruitment.
2. Compare the different types of randomization in clinical trials.
3. Discuss importance of blinding and issues pertaining to blinding.
4. Understand appropriate situations for using a placebo-controlled trial.

### Topics:

1. Recruitment and retention
2. Barriers to participation in research
3. Randomization
4. Intent-to-treat concept
5. Blinding
6. Placebo controls

### Required reading:

1. FFD Ch 5-6 & 9
2. El-Sadr W, Capps L (1992) The challenge of minority recruitment in clinical trials for AIDS. *JAMA* 267: 954-957.
3. Reporting the Recruitment Process in Clinical Trials: Who are these patients and how did they get there? *Annals of Internal Medicine* 2002;137: 10-16.
4. Inclusion of Women and Minorities in Clinical Trials and the NIH Revitalization Act of 1993—The perspective of NIH Clinical Trialists. *Controlled Clinical Trials* 16: 277-285.

### Supplemental reading:

1. Byington RP, Curb JD, Mattson ME for the  $\beta$ -Blocker Heart Attack Trial Research Group (1985) Assessment of double-blindness at the conclusion of the  $\beta$ -Blocker Heart Attack Trial. *JAMA* 253(12):1733-1736.
2. Moscucci M, Byrne L, Weintraub M, Cox C. (1987) Blinding, unblinding, and the placebo effect: An analysis of patients' guesses of treatment assignment in a double-blind clinical trial. *Clinical Pharmacology & Therapeutics* 41(3):259-265.

**Homework assignment:** For your draft protocol, describe the following components: (1) Secondary research questions and response variables; (2) Recruitment plan; (3) A table with study measurements (baseline, primary outcome; (4) secondary outcome(s)) and brief description of each; (4) Intervention allocation; (5) Randomization scheme and justification; (6) Type of blinding to be used and justification.. **Due** Monday, January 26, 2009.

**Date: January 21, 2009**

**Session 5: Study Coordination  
Data!! All these data!!**

**Koerbel  
Rubio**

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.
4. Discuss the types of adverse events in clinical trials and methods of monitoring them.
5. Discuss methods of measuring/monitoring adherence

**Topics:**

1. **Clinical research forms**
2. **Data collection**
3. **Data management**
4. **Quality assurance**
5. **Adverse event reporting**
6. **Adherence**

**Required reading:** FFD Ch 10 (Data Collection and Quality Control), Ch 11 (Assessing and Reporting Adverse Effects), & Ch 13 (Participant Adherence)

**Date: January 26, 2009**

**Session 6: Introduction to Interim Analyses  
Study Monitoring, DSMB**

**Moore/Clark  
Yasko/Alexander**

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

**Required reading:**

1. FFD Ch 15 Monitoring Response Variables (pp. 246-259)
2. FFD Ch 17 Closeout
3. Pressel SL, Davis BR, Wright JT, Geraci TS et al (Operational aspects of terminating the doxazosin arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Peart Attack Trial (ALLHAT). Controlled Clinical Trials 22:29-41.
4. 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)

**Supplemental reading:**

1. Todd S, Whitehead A, Stallard N, Whitehead J (2001) Interim analyses and sequential designs in Phase III studies. British Journal of Clinical Pharmacology 51:394-399.

2. Bell RL, Curb JD, Friedman LM, Payne GH (1985). Termination of clinical trials: The Beta-Blocker Heart Attack Trial and the Hypertension Detection and Follow-up Program experience. *Controlled Clinical Trials* 6:102-111.
3. Krol WF (1983) Closing down the study. *Controlled Clinical Trials* 4:505-512.
4. Muth K, Yu E, Alston B, Ellenberg JH (2001) The closeout process for a clinical trial terminated early for lagging enrollment and inadequate follow-up. *Controlled Clinical Trials* 22:49-55.
5. McBride R, Singer SW (1995) Interim reports, participant closeout, and study archives. *Controlled Clinical Trials* 16:137S-167S.

**Homework assignment:** (1) Read the assigned article and answer the assigned questions for the article. Identify a published clinical trial in your area of interest and answer the assigned questions for the article (see homework handout for specific details). (2) Combine each of the components of your draft protocol that have been included in your homework 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 2, 2009.

<b>Date: January 28, 2009</b>		
<b>Session 7:</b>	<b>Multicenter Trials</b>	
	<b>Reporting and interpreting study results</b>	<b>Moore/Clark</b>

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

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

**Required Reading**

1. FFD Ch 18 (Reporting and Interpreting of Results) & 19 (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.

**Supplemental Reading**

1. Pocock Ch 12 (Protocol deviations)
2. Meinert Ch 4 (Single-center versus multicenter trials) and Ch 5 (Coordinating and other resource centers in multicenter trials)
3. Egger M, Jüni P, Bartlett C for the CONSORT Group (2001) Value of flow diagrams in reports of randomized controlled trials. *JAMA* 285 :1996-1999.

<b>Date: February 2, 2009</b>		
<b>Session 8:</b>	<b>Final Exam</b>	
	<b>PI, study coordinator, CR nurse</b>	<b>Rollman</b>

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

1. Experiences of a study investigator, study coordinator, and clinical research nurse involved in a clinical trial.