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CLRES 2520

Course instructor:

Special Issues in Clinical Trials in Older  
Populations

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Stephanie Studenski MD MPH

Faculty:

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Guest Speakers-trials in older adults PI (experienced and novice) and staff (Reynolds, Newman, Rollman, Munin, Goodpaster, Mulsant, Resnick, Weiner, Lenze, Schulz, Silverman, Hanlon, Whyte, Morone

Course Assistant: E Hile

I. Course description:

This 1 credit course explores the special challenges inherent in the design, implementation and evaluation of intervention studies in older adults. Common challenges faced by investigators working with older adults include population heterogeneity, reduced tolerance to demand, family protectiveness, and competing events. Sessions will examine the theoretical and practical issues confronting the investigator who must tailor the study population, setting, intervention, comparison arm, duration of follow-up, and outcome measures to fit together to achieve internally valid results while maintaining feasibility and generalizability. Students are expected to demonstrate integration of information provided over the course of the semester by critiquing a set of published clinical trials on an aging related topic of their choice. This course is required for completion of the aging concentration in the Clinical Research Training Program

II. Course objectives:

Specific objectives are to:

1. Describe the aspects of standard clinical trials design that must be considered when developing intervention trials for older adults.
2. Be familiar with the types of interventions that are relevant to the health of older adults.
3. Describe tradeoffs in the design of trials for older adults related to eligibility and exclusions, settings, adherence, intervention protocols and reproducibility and outcome determination.
4. Become familiar with the modifications to operations of clinical trials for older adults including adaptations to the manual of procedures, treatment protocols, staff training, data tracking, and safety monitoring.

III. Course requirements:

Prerequisites: Introduction to Patient Oriented Research in Aging, a prior course in clinical trials design and implementation is preferred but maybe waived by application to the instructor

IV. Location:

Room XXX

V. Course credits and contact hours:

1 credit; 16 contact hours; 1 session/week for 6 weeks (2 hours per session, plus 240 minutes for site visit)

VI. Grading:

Letter grade, based on assignments:

Class participation	20%
Clinical trials critique	30%
Study Site Visit report	30%
Oral Presentation	20%

VII. Readings:

1. Familiarity with the fundamentals of clinical trials design and operations is assumed. The following are classic texts on clinical trials that may be used for reference in this course.

Friedman LM Furberg CD DeMets DL Fundamentals of Clinical Trials 3<sup>rd</sup> Ed 1998 Springer New York

or

Piantadosi S Clinical Trials A Methodological Perspective 1997 John Wiley and sons New York

2. The following are overviews of issues in clinical trials with older adults. We will refer to these papers throughout the course.

Ferrucci L, Guralnik JM, Studenski S, Fried LP, Cutler GB Jr, Walston JD; Interventions on Frailty Working Group. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. J Am Geriatr Soc. 2004 Apr;52(4):625-34.

Applegate WB, Curb JD. Designing and executing randomized clinical trials involving elderly persons. J Am Geriatr Soc 1990; 38:943-50.

3. The following is a standard reference regarding the reporting of clinical trials

Moher D, Schulz KF, Altman DG; CONSORT. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol. 2001;1(1):2. Epub 2001 Apr 20

VIII. Teaching methodology:

Lectures and classroom discussions will be supplemented with readings discussing special issues in clinical trials involving older adults. Researchers who are currently conducting clinical trials with older adults will present their work for discussion. Students will observe and report on at least one ongoing trial involving older adults and will review the design and operation of published clinical trials in a topic relevant to their own work.

## IX. Major Assignments

1. Written critique of 2 or more clinical trials on a topic of interest to you using the attached format. This review should be at least 5 double spaced typed pages. It is due for class 6.
2. Oral presentation describing your findings from the written critique. This is a 20 minute presentation and discussion of your findings and recommendations. Presentations will be made at class 6.
3. A Site Visit Report, based on the attached structured format will be due at any time prior to the last class. You will visit one of the listed ongoing trials (or an alternative approved by the instructor) where you will review study design and plans, operations, protocols, materials and participants. You will provide a 15 minute oral report of your site visit at class 5.

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### Session 1 Introduction, orientation to assignments, overview of trials in the older adult, ethical issues in trials for older adults

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Date xxx

#### Topics:

1. What is different about trials in older adults-overview
2. Types of interventions that are relevant to aging
3. Consent to participate and influential others
4. Clinical equipoise

#### Session Objectives:

1. Identify the effects of age related clinical heterogeneity, low tolerance to burden and intervening events on clinical trials design and execution.
2. Describe types of interventions used in older adults (medications, exercise, counseling, surgery, medical procedures, organization of care, behavior change, education)
3. Discuss who influences the decision to participate in a trial for older adults
4. Consider the effect of the goal of clinical equipoise on trial design for older adults

#### Class Discussion:

1. Discuss ways in which the characteristics and needs of older adults conflict with classical RCT concepts
2. Consider patient, family and provider perspectives on trials participation for older adults

#### Readings:

Required

Tolmie EP, Mungall MM, Loudon G, Lindsay GM, Gaw A. Understanding why older people participate in clinical trials: the experience of the Scottish PROSPER participants. *Age Ageing*. 2004 Jul;33(4):374-8.

Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, Lam M, Seguin R. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodol*. 2003 Dec 22;3(1):28

## Optional

Marsden J, Bradburn J; Consumers' Advisory Group for Clinical Trials; Lynda Jackson Macmillan Patient and clinician collaboration in the design of a national randomized breast cancer trial. *Health Expect*. 2004 Mar;7(1):6-17

Barron JS, Duffey PL, Byrd LJ, Campbell R, Ferrucci L. Informed consent for research participation in frail older persons. *Aging Clin Exp Res*. 2004 Feb;16(1):79-85.

Hamajima N, Yuasa H, Nakamura M, Tajima K, Tominaga S. Nested consent design for clinical trials. *Jpn J Clin Oncol*. 1998 May;28(5):329-32

Scott D Halpern MSCE Prospective preference assessment: a method of enhancing the ethics and efficiency of randomized controlled trials *Controlled Clinical Trials* 2002 23:274-288

## Assignment

1. Precourse Survey
2. Consider topics you would like to explore through your analysis of RCT report due class 6. Identify at least two trials on your topic and submit a single page with your name, preferred topic and a minimum of two references to published trials to the instructor by class 2
3. Review options for site visit to an ongoing clinical trial involving older adults using attached list.

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## Session 2 participants, preparation for a clinical trial

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Date

### Topics:

1. Defining the target population: effect of responsiveness, expected event rate and heterogeneity
2. Tracking the source, target, recruited, randomized and completing sample
3. Study materials: manual of procedure, intervention protocols, data collection protocols, equipment and materials, staff training
4. Plan for site visit to ongoing clinical trial involving older adults

### Session Objectives:

1. Identify tradeoffs and challenges in obtaining an appropriate sample of older adults for a clinical trial
2. Be familiar with reporting expectations and study procedures related to recruitment
3. Understand the use and design of study materials for clinical trials

### Panel members: single site clinical trials

Debra Weiner- PENS for back pain in older adults

? Bruce Rollman- depression in primary care?

Benoit Mulsant or other from LLMD

### Class discussion for panel members:

1. What is your study design?

2. How did you define and find your target population?
3. How did you protocolize your intervention?
4. What is your comparison group?
5. What have you learned from your experience with RCTs in older adults? What is working well and what would you do differently?

### **Readings:**

#### Required

Gross CP, Mallory R, Heiat A, Krumholz HM. Reporting the recruitment process in clinical trials: who are these patients and how did they get there? *Ann Intern Med* 2002;137:10-16

Cohen-Mansfield J. Recruitment rates in gerontological research: the situation for drug trials in dementia may be worse than previously. *Alz Dis and Assoc Dis* 2002;16:279-282

#### Optional

Boult C, Boult L, Pirie P. Soliciting defined populations to recruit samples of high-risk older adults. *J Gerontol Med Sci* 1998;53:M379-M384

Levkoff SE, Chen H, Coakley E, et al. Design and sample characteristics of the PRISM-E multisite randomized trial to improve behavioral health care for the elderly. *J Aging Health* 2004;16:3-27

Whelton PK, Babnson J, Appel LJ, Charleston J, Cosgrove N, Espeland MA, Folmar S, Hoagland D, Krieger S, Lacy C, Lichtermann L, Oates-Williams F, Tayback M, Wilson AC. Recruitment in the Trial of Nonpharmacologic Intervention in the Elderly (TONE). *J Am Geriatr Soc*. 1997 Feb;45(2):185-93.

### **Assignment**

Turn in 1 page with your name, your choice of topic and at least two references to published clinical trials on your topic that you will use for your written critique and oral presentation.

Contact PI of your chosen trial to arrange at least one site visit. You may need to visit the trial more than once to acquire the information you need for your site visit report.

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### Session 3 Interventions

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Date

#### **Topics:**

1. single and combined interventions
2. design, comparison groups, number of arms
3. intervention and outcome target alignment
4. randomization
5. intervention reproducibility
6. staffing
7. respondent burden

## **Objectives**

1. Describe targets of interventions used for older adults (patient, provider, caregiver)
2. Identify the pros and cons of single versus multiple interventions
3. Describe the tradeoffs in randomization by individual versus cluster
4. Describe options for the comparison arm- placebo, usual care, delayed care, alternative trial intervention

## **Panel members: multisite trials**

LIFE-Newman or me

GEMS/Ginkgo – Dekosky or designee

Depression screening in primary care-

## **Class discussion for panel members:**

1. What is your study design?
2. How did you define and find your target population?
3. How did you protocolize your intervention?
4. What is your comparison group?
5. What have you learned from your experience with RCTs in older adults? What is working well and what would you do differently?

## **Readings:**

Miller FG, Brody H. What makes placebo-controlled trials unethical? *Am J Bioeth.* 2002 Spring;2(2):3-9.

McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: a systematic review. *JAMA.* 2003 May 21;289(19):2545-53

Gomberg-Maitland M, Frison L, Halperin JL. Active-control clinical trials to establish equivalence or noninferiority. *AM Heart J* 2003 146:398-403

## **Optional**

Reynolds CF 3rd, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, Mazumdar S, Houck PR, Dew MA, Stack JA, Pollock BG, Kupfer DJ. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. *JAMA.* 1999 Jan 6;281(1):39-45

Ouslander JG, Schnelle JF, Uman G, Fingold S, Nigam JG, Tuico E, Jensen BB. Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo-controlled trial. *J Am Geriatr Soc.* 1995 Jun;43(6):610-7.

Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. *Ann Intern Med.* 2000 Nov 7;133(9):687-95

## **Assignment:**

Continue work on critiques and site visit

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## Session 4 Outcomes

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Date

### Topics:

1. Primary and secondary outcomes, composite outcomes
2. Estimating event rates for power
3. Alternative methods for collecting data on primary outcome
4. Blinding
5. Methods of outcome monitoring and attribution
6. Design and implementation of the analysis plan: intention to treat, missing data, change effects

### Session Objectives:

#### Panel members: pilot studies, initial small trials

Morone, Munin, Whyte.

#### Class Discussion with panel:

1. What is your study design?
2. How did you define and find your target population?
3. How did you protocolize your intervention?
4. What is your comparison group?
5. What have you learned from your experience with RCTs in older adults? What is working well and what would you differently

#### Readings:

Required

DeMets DL. Statistical issues in interpreting clinical trials J Intern Med. 2004 May;255(5):529-37.

Shih W Problems in dealing with missing data and informative censoring in clinical trials. Curr Control Trials Cardiovasc Med. 2002 Jan 8;3(1):4.

Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA. 2003 May 21;289(19):2554-9

#### Assignment:

Continue work on critiques and site visit

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## Session 5 Safety monitoring, adverse events

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Date

**Topics:**

1. Safety monitoring plan and team members
2. Adverse event monitoring, tracking and reporting
3. Stopping rules
4. Staff training for safety

**Session Objectives:**

1. Describe methods for monitoring trial safety
2. Describe options for managing intervention protocols throughout intercurrent illnesses and events

**Panel members:**

RCT staff eg Nancy Glynn from LIFE re safety, me as head of the Safety Cmte for LIFE, Maryland Pepper DSMB, others...

**Class discussion:**

1. What are the challenges of managing safety in trials with older adults?
2. What protocols and training have you used to promote safety in these trials?

**Hour 2: reports from site visits**

Informal discussion of comparisons between studies, effectiveness of the site visit experience and report as a learning tool

**Readings:**

LIFE MOP safety chapter 22

Site visit reports due today

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Session 6 Student Presentations

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Date

**Student Presentations**

Post course survey

### Guidelines for Critique of a Topic based on Published Clinical Trials in Older Adults

1. Your goal is to summarize, compare and critique at least two clinical trials of one or more interventions on a single topic such as a condition or a geriatric problem.
2. Create a table summarizing each trial using the table format below. You may add columns if there are more than two trials in your critique.
3. Discuss methodological and pragmatic challenges faced in the trials and suggest alternative strategies for overcoming them. Consider issues such as representativeness of the sample, reproducibility of the intervention, blinding, choice of control or comparison intervention, management of censoring and choice of main analytic strategy.

Trial aspects	Study 1	Study 2
Participants: eligibility criteria		
Participants: sources		
Study setting		
Intervention description		
Comparison description		
Primary outcome (s)		
Secondary outcomes (s)		
Sample size (planned and achieved)		
Method of randomization		
Allocation concealment		
Randomization implementation		
Blinding (participants, interventionists, outcome assessors, analysts)		
Assessment of blinding		
Statistical methods for primary outcome		
Participant flow (create diagram as per CONSORT and attach)		
Baseline characteristics		
Numbers analyzed		
Summary of results for each group with effect size and precision		
Additional analyses		
Adverse events		

## Guidelines for a site visit to an ongoing clinical trial involving older adults

1. Your goal is to understand the original research proposal and to become familiar with the implementation of the study.
2. Summarize in 1-2 pages the original research trial plan in terms of hypothesis, sample, intervention and comparison group and main outcomes.
3. Address the following aspects of the study.
  - A. What is the setting for this study? Clinic, health care setting, home or other?
  - B. Is there a manual of procedures? What study processes are addressed?
  - C. Describe the recruitment plan and its success to date.
  - D. How is randomization managed? Who does it? When do they do it? Can they tell what the next assignment will be?
  - E. Review the protocol for the intervention. Who does it? How were they trained? Is there a written protocol? Are there guidelines for managing side effects, intercurrent illnesses or other potential modifications of the treatment plan? Is there a process for monitoring adherence?
  - F. Review the protocol for the comparison intervention. Is it a placebo, usual care or other? Is the degree of attention and interaction similar to the study intervention?
  - G. How is blinding managed? Who is blind and who is not? Do blinded persons have ways of detecting treatment arm?
  - H. How is data collected? Who does it? What variables are collected? What are the forms like and are they recorded on paper, laptop tablets or computers?
  - I. How is data stored? Who enters it?
  - J. How is data quality monitored?
  - K. How are adverse events monitored, tracked and reported?
3. Comment on the challenges and tradeoffs faced by this study. Consider aspects such as target versus recruited sample, adherence to the intervention, participant satisfaction with the comparison arm, losses to follow up, effectiveness of blinding plan, potential generalizability versus specificity of effect of the eventual findings. What might you do differently if this was your study?

## Ongoing Clinical Trials involving older adults at Pitt

1. the LIFE study, Newman PI: an exercise intervention for mobility limited older adults
2. GEM Gingko study: DeKosky PI trial of Gingko Biloba to prevent dementia
3. PENS study: Weiner PI Trial of PENs for back pain in older adults
4. C. Reynolds LLMD and AgeWise
5. Rollman depression after CABG
6. Intervention for detrusor instability Resnick PI
7. Caregivers of SCI patients Schulz PI: intervention to support caregivers of aging spinal cord injured veterans
8. Greenspan alendronate in prostate ca
9. VanSwearingen exercise for balance
- 10.