THE UNIVERSITY OF MEMPHIS School of Public Health	**PUBH 7450/8450** **(PSYC 7315/8315)** **Randomized Clinical Trials** **Spring 2017** Wednesday, 2:00-5:00pm Robison 217

Instructor
Kenneth D. Ward, PhD
Professor and Director, Division of Social and Behavioral Sciences, School of Public Health
Office: 201 Robison Hall
Phone: 678.1702
E-mail: kdward@memphis.edu
Office Hours: by appointment

Course Description
This course provides students with a thorough grounding in the conduct of randomized clinical trials (RCTs) including design, management, evaluation, and resource acquisition.

Course Prerequisites
PUBH 7170/8170, PSYC 7301/8301 or a comparable graduate-level research methods class.

Learning Objectives
1. Demonstrate an understanding of the history, rationale, and appropriate applications of RCTs.
2. Critically evaluate published RCTs in terms of conformation to established reporting guidelines, internal and external validity issues, and ethical considerations.
3. Design a RCT and write a comprehensive protocol that would be suitable for submission to a health research funding agency.
4. Demonstrate an understanding of strategies and procedures for successful trial management.
5. Demonstrate an understanding of appropriate ethical considerations and requirements for the protection of human research subjects enrolled in RCTs.

Competencies
(MPH Competencies)
1. Describe steps and procedures for the planning, implementation, and evaluation of public health programs, policies, and interventions.
2. Describe the role of social and community factors in both the onset and solution of public health programs.
3. Describe the merits of social and behavioral science interventions and policies.
4. Apply evidence-based approaches in the development and evaluation of social and behavioral science principles.
5. Apply ethical principles to public health program planning, implementation, and evaluation.
6. Specify multiple targets and levels of intervention for social and behavioral science programs or policies.

(Doctoral Competencies)
1. Identify individual, organizational, community, and societal influences on health, health behaviors, disease, illness, injury, and disability.
2. Utilize social and behavioral science principles and applications to advance public health research and education.
3. Conduct and disseminate rigorous and innovative social and behavioral science research relevant to public health.

4. Develop, implement, and evaluate behavioral and structural interventions to promote health and health equity, prevent disease and injury, alleviate disability, and improve the quality of life.

Required Text(s)/Reading
Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. ISBN 978-1-4419-1585-6

Recommended But Not Required
Evans, I., Thornton, H., & Chalmers, I. (2006). Testing Treatments: Better Research For Better Healthcare. London: The British Library.

Each week, readings will be assigned in addition to the textbook, as detailed in this syllabus. Generally, these readings are divided into "Required readings for lecture" and "Required readings for discussion." Supplemental readings also are provided. Students are not expected to read supplemental materials to prepare for class. Rather, these are intended as a resource for students who wish to pursue a topic in greater depth.

Online Resource
Course materials are available at https://umdrive.memphis.edu/kdward/public/PUBH7450

Course Requirements and Grading Criteria
Grading will be based on attendance, participation, various homework assignments, and in-class assignments, as described below:

RCT grant proposal, including weekly section drafts and final full proposal	40%
Class attendance and participation	20%
Weekly quizzes	20%
Facilitation of RCT case study, including submission of CONSORT checklist	10%
Proposal presentation	10%

Details of each of these major evaluation components are as follows:

- RCT grant proposal (40%): Each student will design and submit a written proposal for a RCT. The topic of the RCT will be selected by the student in consultation with the instructor. The write-up of the proposal will follow the guidelines for grant submissions to the National Institutes of Health (NIH). Drafts of proposal sections will be submitted sequentially throughout the course, with the full final proposal due near the end of the semester. Students will be expected to modify the first draft of each section, based on written feedback from the instructor ,and knowledge gained from readings and class discussions, for submission of the final full proposal. Each writing assignment will contribute to the final grade as follows:
    - Week 3 writing assignment (One paragraph description of proposed RCT): not graded – *due February 1*
    - Week 4 writing assignment (Specific Aims): 2% -- *due February 8*
    - Week 5 writing assignment (Innovation): 1% -- due *February 15*
    - Week 6 writing assignment (Significance): 3% -- *due February 22*
    - Week 7 writing assignment (Approach: Preliminary Studies, Study Design, Target Population): 2% -- *due March 1*
    - Week 8 writing assignment (Approach: Subjects, Recruitment, Randomization, Blinding): 3% -- *due March 15*
    - Week 9 writing assignment (Approach: Interventions): 3% -- *due March 22*
    - Week 10 writing assignment (Approach: Retention, Adherence, Measures, and Data Quality Control and Management): 3% -- *due March 29*

- Week 11 writing assignment (Approach: Treatment Implementation, Sample size and power, Data analysis, Budget, Budget justification): 3% -- *due April 5*
- Week 12 writing assignment (Final complete proposal, including references): 20% -- *due April 12*

Note: You should submit all previously drafted sections with each assignment. For example, when you turn in your Innovation section on February 15th, you also should attach your draft of Specific Aims. This will help me to better understand the new section(s) I read. You are encouraged to revise previously submitted sections based on feedback you receive, but this is not required until the final submission of the full proposal.

A hard copy of each writing assignment should be turned in at the start of class on the due date, except as otherwise noted below. Additionally, each assignment should be submitted to me electronically (to kdward@memphis.edu) prior to the start of class on the due date. This will allow me to provide typed feedback directly on your submission (using "Track changes" in Microsoft Word), and I will e-mail my comments back to you.

Late Penalty: The penalty for late submission of writing assignments is an absolute reduction of 1% of the final course grade for each day or portion of a day that it is late (Weeks 3-11). However, students will be allowed to submit one assignment up to 24 hours late without penalty (note that this "get out of jail free" card may NOT be used for the full proposal). The penalty for late submission of the full proposal (Week 12) is an absolute reduction of 5% of the final course grade for each day or portion of a day that it is late.

Guidelines for the Written RCT Proposal: This exercise is meant to be meaningful and (hopefully) enjoyable. As such, students will have considerable leeway in choosing the health issue on which to intervene, the trial objective (e.g., prevention, diagnosis, individual treatment, community-level change), method of intervention delivery (e.g., individual- or group-based behavioral treatment, social marketing campaign, public policy change, pharmacological agent, surgical procedures), and study design (e.g., parallel arm, factorial, cross-over, group randomized). The only absolute design requirement is that allocation to intervention be randomized. Students are encouraged to write a proposal that advances a field of inquiry and has the potential to be funded. The U.S. National Institutes of Health (NIH), the major funder of biomedical research in the United States, hosts a *Resources for New Investigators* page on their website (http://grants.nih.gov/ grants/new_investigators/index.htm) that contains much helpful information.

The proposal will follow the NIH R01 format. A description of the R01 mechanism can be found on-line at http://grants.nih.gov/grants/guide/pa-files/PA-10-067.html. Students will generate a Specific Aims, Research Strategy, and a simplified Budget and Budget Justification for their proposal. NIH guidelines for writing each section of the proposal can be found at:
http://grants.nih.gov/grants/funding/424/index.htm#inst.
The written proposal should be word-processed using Arial font, 11 point, single-spaced, with one inch margins all around. The required sections for the written proposal, and approximate page lengths, are as follows:

1. Specific Aims – ½ -1 page
2. Research Strategy (10-12 pages total, not counting references)
   a. Significance (1-2 pages)
   b. Innovation (½ – 1 page)
   c. Approach (9-10 pages)
   d. References (1-2 pages)
3. Budget – ½ page
4. Budget Justification – ½ page

We will adhere to the R01 rule that the maximum page length for the Research Strategy can be no more than 12 pages, excluding references. The instructor will distribute grant examples and an "Evaluation Criteria for Final Grant Proposal Write-Up" guideline to assist students in writing the proposal.

- Quizzes (20%). During the first 10 minutes of most classes, students will be given a brief quiz (approximately 5 multi-choice questions) to assess mastery of the major concepts and results presented in that week's readings. There will be no make-ups in the event of tardiness or absence from class. However, the lowest grade (of 10) will be dropped.

- Facilitation of RCT case studies (10%): During several classes we will discuss and critically evaluate published RCTs (listed on the syllabus as "Required readings for discussion"). One student will take primary responsibility for each article and will present a brief summary and lead the class in a discussion of the strengths and weaknesses of the study. Student-led discussions will begin Week 3. During Week 2, the instructor will present a published RCT and lead the class in discussion as a model for students. During the first week of the course, students will be asked to indicate their preferences for articles on which they would like to take the lead.

  The facilitator is responsible for completing a CONSORT checklist and submitting this to the instructor at the start of the class. CONSORT stands for Consolidated Standards of Reporting Trials, and the checklist helps ensure that a minimum set of recommendations for reporting is included in published RCTs. The standard checklist contains 25 items, and to this we will add five additional items to assess treatment implementation in behavioral studies. The checklist is available in the dropbox (https://umdrive.memphis.edu/kdward/public/PUBH7450). On the checklist, students should indicate the page of the paper that contains the CONSORT item or that the item was not presented in the paper. In addition, comments should be included about any irregularities or unusual reporting of items.

  Guidelines for Critiquing and Leading Discussions of RCT Case Studies: One student will lead the discussion of each paper. The leader should have a solid grasp of the article and start the discussion by providing a brief (no more than 10 minutes) overview of the study, including background, objectives, hypotheses, study design, and major results. The leader should not read passages directly from the article, but rather should succinctly summarize the main points. After this brief overview, the leader will facilitate a critical discussion of the article, which may include 1) the significance of the problem investigated; 2) the article's conformation to CONSORT reporting guidelines; 3) internal validity issues (e.g., appropriateness of the hypotheses, sample selection, randomization and blinding procedures, measures, intervention, attrition, quality assurance procedures, and data analysis); 4) external validity issues (generalizability, assessed by such features as whether the treatment works for only certain individuals or under certain conditions, and components of Glasgow's RE-AIM framework: reach, efficacy, adoption, implementation, and maintenance), and 5) ethical issues. The objective is for the leader to facilitate a class discussion about these issues, and not merely to summarize the issues him/herself.

- Proposal presentation (10%): The final two classes will be dedicated to student presentations of their RCT proposals. Each student should plan to deliver an oral presentation to the class on the proposal, lasting 15 minutes with an additional 5 minutes for questions. Please prepare slides using Powerpoint™ and provide "notes pages" to your audience. You will be assessed by the instructor and fellow students according to the following criteria:
  - The significance of your research question
  - The appropriateness of your selected research design and plan to answer your question.
  - Strategies used to maximize internal and external validity.
  - Your ability to answer peer and instructor's questions on your proposal and to defend your research design choices.

- Class attendance and participation (20%): Active participation is a vital component of the course. Students are expected to attend class, arrive on time, stay for the entire class, and participate actively in discussions. The 20% grading is divided into 10% for attendance and 10% for the quality of participation during class sessions. To allow for illness, conference travel, etc., students may miss or be late for one class without penalty. Subsequently, the penalty for absence/tardiness/early departure is 5% of the final grade for each occurrence. In extraordinary circumstances that require extended absence, the instructor will work with the student to make alternate arrangements for participation. The following rubric describes how expectations for participation during class sessions are linked to course grade. An overall performance at the "A" level in attention, participation, and professional demeanor earns a full 10%; "B" level performance earns 8%, "C" level earns 6%, and performance below a "C" level earns 0%.

Criteria considered in grading:	**Not Passing**	**"C" Level**	**"B" Level**	**"A" Level**
Class attendance	Substantially late to or absent from class; no advance explanation provided.	Arrives to class later than the the scheduled start time. (Note: absence from class means no participation credit is earned for that session.)	Arrives on time, is seated and ready to begin at class start time.	Arrives on time, is seated and ready to begin at class start time, immediately ceases other activities at the time the class actually starts
Attention	Noticeably off-task during a portion of the class and/or distractive to others. Examples include, but are not limited to: attending to non-class matters (checking e-mails, PDAs and/or using a laptop for any task not directly relevant to what's going on in the class at the moment), cellphone /pager noise, off-topic conversations / passing notes / texts	Occasionally inattentive, such as engaging in side conversations or other off-task activities. Cellphone / pager noise is occasionally heard during class.	Generally attentive with most conversations focused on the in-class discussion. Rarely introduces peripheral noises or distractions (cellphones, pagers, and other devices).	Conversations are focused on the in-class discussion. No peripheral noises or distractions (cellphones, pagers, and other devices).
Participation	Does not ask / answer any questions; does not make comments (or relevant comments) during the session; or significantly derails the agenda of the class	Does not contribute to class discussion, or participates but comments are off-topic and/or reflective of a lack of preparation (e.g. asking questions that the readings already clearly addressed.)	Contributes at a good level (but without dominating); contributions add to (do not derail) the class discussion	Contributions augment / add to comments from peers; synthesizes / incorporates readings and assignments into the class discussion
Professional demeanor	Professionalism is lacking in one or more major ways (e.g. uses derogatory and/or other highly unprofessional language)	Professionalism is lacking in one or more minor ways (e.g. use of slang and/or minorly disrespectful or arrogant language)	Class participation reflects a good level of professionalism	Class participation reflects a noticeably high level of professionalism

This course is open to both master- and doctoral-level students. Doctoral students are required to demonstrate a more in-depth and comprehensive synthesis of knowledge of RCT methodology, in both oral and written

assignments, in accordance with the doctoral competencies listed in this syllabus. Doctoral students will take on greater responsibility for leading case study discussions and will be expected to generate a professional quality research grant proposal that could be submitted to NIH or an equivalent funder.

Grading Scale

The letter grades for each requirement are assigned using the following grading scale:

Percentage Grade	*Letter Grade*	*GPA*	*Percentage Grade*	*Letter Grade*	*GPA*
≥96%	A+	4.00	76%	C+	2.33
93%	A	4.00	73%	C	2.00
90%	A–	3.84	70%	C–	1.67
86%	B+	3.33	66%	D+	1.33
83%	B	3.00	60%	D	1.00
80%	B–	2.67	<60%	F	0.00

Promoting a Positive Learning Environment

The School of Public Health recognizes its responsibility to promote a safe and diversity-sensitive learning environment that respects the rights, dignity, and well-being of all students, faculty, and staff. Diversity means the fair representation of all groups of individuals, the inclusion of contrasting perspectives and voices, together with the appreciation and valuing of different cultural and socioeconomic group practices. Moreover, we aspire to foster a climate of mutual respect and empathy, among and between students, faculty, and staff, by nurturing an atmosphere that is free from discrimination, harassment, exploitation, or intimidation. Courses will strive to provide an opportunity for all students to openly discuss issues of diversity including, but not limited to, age, disability, ethnicity, gender, race, religious beliefs, and sexual orientation.

Personal Conduct

As a community of scholars, it is expected that the instructor and students will work together at all times to create an atmosphere that fosters shared discovery and mutual respect. The instructor will be prepared for each class meeting, and likewise, students are expected to arrive prepared to ask questions, discuss, and learn. Students are expected to handle feedback from the instructor in a constructive manner. Students are expected to complete all assigned readings and writing assignments, and to participate in class discussions. The grading rubric for class participation is presented above.

As noted above, class attendance is an important component of the course. In the event of an unavoidable absence, please notify the instructor beforehand if at all possible. Certain behaviors are disruptive and disrespectful to the instructor and other students and are not acceptable. These include tardiness, use of laptop computers, smart phones, or engaging in side conversations while others are talking. If arriving late is unavoidable, notify the instructor in advance, if possible. Set your cell phone to silent if it must be available for an emergency. In addition, students will not be allowed to use any electronic devices during the quizzes. Use of such devices during quizzes may result in a failing grade. Students who engage in these behaviors may be asked to leave and not allowed to return until a meeting with the instructor has occurred during which a plan to avoid future classroom disruptions has been worked out.

Make-Up and Absentee Policy

Students missing class are responsible for the content presented and are not excused from assignment due dates. You may be asked to make up for the missed class in the form of written critical commentaries on the readings or additional assignments. Please let the instructor know in advance if you will be absent on a given class day.

Writing Standards

Effective managers, leaders, and teachers are also effective communicators. Written communication is an important element of the communication process. The School of Public Health graduate program recognizes and expects exemplary writing to be the norm for course work.

Academic Conduct

All written work submitted must be the student's original work and conform to the guidelines of the *American Medical Association (AMA) or American Psychological Association (APA)* which are available online and via their publications. This means that any substantive ideas, phrases, sentences, and/or any published ideas must be properly referenced to avoid even the appearance of plagiarism. Plagiarism includes, but is not limited to, the use, by paraphrase or direct quotation, of the published or unpublished work of another person without full or clear acknowledgment. It also includes the unacknowledged use of materials prepared by another person or agency in the selling of term papers or other academic materials. It is the student's responsibility to know all relevant university policies concerning plagiarism. Any documented cases of plagiarism can and will result in dismissal from the course with a failing grade, and may result in other more serious sanctions by the School of Public Health and The University of Memphis.

Cheating is unacceptable at the University of Memphis. Cheating includes but is not limited to the following: using any unauthorized assistance in taking quizzes or tests; acquiring tests or other academic material before such material is revealed or distributed by the instructor; failing to abide by the instructions of the proctor concerning test taking procedures; influencing, or attempting to influence, any university employee in order to affect a student's grade or evaluations; any forgery, alteration, unauthorized possession, or misuse of University documents.

Awarding an Incomplete Grade

A grade of "I" (Incomplete) may be assigned by the Instructor of any course in which the student is unable to complete the work due to EXTRAORDINARY events beyond the individual's control. The "I" may not be used to extend the term for students who complete the course with an unsatisfactory grade. Unless the student completes the requirements for removal of the "I" within 45 days (for undergraduate courses, or 90 days for graduate courses) from the end of the semester or Summer term in which it was received, the "I" will be changed to an "F," regardless of whether or not the student is enrolled.

Withdrawal Policy

The School of Public Health adheres to Graduate School policies and procedures regarding withdrawal from courses. Consult the Graduate School Dates & Deadlines Calendar for specific information. A late withdrawal is withdrawal from a course after the final date to drop classes, which falls around the middle of each semester. The drop is called a retroactive withdrawal if it takes place after grades have been issued. Before the drop deadline, students can process a drop on the web or over the phone without seeking anyone else's approval. The instructor, however, will appreciate the courtesy of being notified if you decide to drop the course. After the final drop date, the student must obtain approval for late drops or retroactive withdrawal from the Director of Graduate Studies of the School of Public Health. Instructors are not authorized to approve late drops or retroactive withdrawals.

Americans with Disabilities Act

The University of Memphis does not discriminate on the basis of disability in the recruitment and admission of students, the recruitment and employment of faculty and staff, and the operation of any of its programs and activities, as specified by federal laws and regulations. *The student has the responsibility of informing the course instructor (at the beginning of the course) of any disabling condition, which will require modification to avoid discrimination*. Faculty are required to provide "reasonable accommodation" to students with disabilities, so as not to discriminate on the basis of that disability. Student responsibility primarily rests with informing faculty at the beginning of the semester and in providing authorized documentation through designated administrative channels.

Special Needs
Any student who has special needs for assistance and/or accommodation, and who is registered with the Office of Student Disability Services should meet with the instructor during the first week of classes.

Inclement Weather Policy
In the event that inclement weather requires the cancellation of classes at the University of Memphis, local radio and television media will be notified. In addition, Tiger Text is The University of Memphis' emergency alert text messaging service that is offered to students, faculty and staff. This optional service will only be used in the event of an on-campus emergency, an unscheduled university closing, or a delay or cancellation of classes due to, for instance, inclement weather. For detailed information, visit https://umwa.memphis.edu/tigertext/index.php

Some On-line Resources for RCTs and Grantsmanship

http://www.ClinicalTrials.gov -- ClinicalTrials.gov provides regularly updated information about federally and privately supported clinical research in human volunteers, including a trial's purpose, who may participate, locations, and phone numbers for more details.

http://www.consort-statement.org/ -- The official webpage of the CONSORT statement, "an important research tool that takes an evidence-based approach to improve the quality of reports of randomized trials."

http://grants.nih.gov/grants/new_investigators/index.htm -- *Resources for New Investigators*, on the NIH website.

https://projectreporter.nih.gov/reporter.cfm -- NIH Reporter (Research Portfolio Online Reporting Tool) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions.

http://www.quackwatch.com – Website of Quackwatch, Inc., a nonprofit corporation whose purpose is to combat health-related frauds, myths, fads, fallacies, and misconduct.

Schedule of Topics

Week 1 – January 18	**- Course overview** **- Fair testing, causal inference, and the counterfactual approach** **- Basic RCT types, phases, and designs** **- Hypothesis specification**

Required Readings for Lecture

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 1 – Introduction to Clinical Trials)

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 3 – What is the Question?)

Rosen, L., Manor, O., Engelhard, D., & Zucker, D. (2006). In defense of the randomized controlled trial for health promotion research. American Journal of Public Health, 96, 1181-1186.

Supplemental Readings

Diabetes Prevention Program (DPP) Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New England Journal of Medicine, 346, 393-403.

Glass, T.A., Goodman, S.N., Hernan, M.A., & Samet, J.M. (2013). Causal inference in public health. Annual Review of Public Health, 34, 61-75.

Hill, A.B. (1965). The environment and disease: association or causation? Proceedings of the Royal Society of Medicine, 58, 295–300.

Maldonado, G., & Greenland, S. (2002). Estimating causal effects. International Journal of Epidemiology, 31, 422-429.

Week 2 – January 25	**- Standard and some alternative designs used in clinical trials** **- Reporting guidelines for RCTs** **- Guest presentation: Fawaz Mzayek, MD, PhD, MPH – *Phase I clinical trials: evaluating treatment safety***

Required Readings for Lecture

Davidson, K.W., Goldstein, M., Kaplan, R.M., Kaufmann, P.G., Knatterud, G.L., Orleans, C.T., Spring, B., Trudeau, K.J., & Whitlock, E.P. (2003). Evidence-based behavioral medicine: what is it and how do we achieve it? Annals of Behavioral Medicine, 26, 161-171.

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 5 – Basic Study Design)

Mzayek, F., Deng, H, Mather, F.J., et al. (2007). Randomized dose-ranging controlled trial of AQ-13, a candidate antimalarial, and chloroquine in healthy volunteers. PLOS Clinical Trials, Jan 5;2(1):e6 -- *Dr. Mzayek will lecture on this study tonight: you don't need to read the study in its entirety, but please at least skim it and carefully read the "Editorial Commentary" on p. 2.*

Trudeau, K.J., & Davidson, K. (Winter 2001-2002). A CONSORT Primer. Outlook (newsletter of The Society of Behavioral Medicine). pp. 5-8. *(this paper is to accompany Gidron et al., 1999)*

Required Reading for Discussion

Gidron, Y., Davidson, K., & Bata, I. (1999). The short-term effects of a hostility-reduction intervention on male coronary heart disease patients. Health Psychology, 18, 416-420.

Supplemental Readings

Altman, D.G., Schulz, K.F., Moher, D., Egger, M., Davidoff, F., Elbourne, D., Gotzsche, P.C., Lang, T., for the CONSORT Group. (2001). The Revised CONSORT Statement for reporting randomized trials: explanation and elaboration. Annals of Internal Medicine, 134, 663-694.

Berger, M.L., Dreyer, N., Anderson, F., Towse, A., Sedrakyan, A., & Normand, S-L. (2012). Prospective observational studies to assess comparative effectiveness: the ISPOR Good Research Practices Task Force Report. Value in Health, 15, 217-230.

Bhatt, D.L., & Mehta, C. (2016). Adaptive designs for clinical trials. New England Journal of Medicine, 375, 65-74.

Bowen, D.J.,. Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., Bakken, S., Kaplan, C.P., Squiers, L., Fabrizio, C., & Fernandez, M. (2009). How we design feasibility studies. American Journal of Preventive Medicine, 36, 452-457.

Brown, A.W. (2015). Best (but often forgotten) practices: designing, analyzing, and reporting cluster randomized controlled trials. American Journal of Clinical Nutrition, 102, 241-248.

Ford, I., & Norrie, J. (2016). Pragmatic trials. New England Journal of Medicine, 375, 454-463.

Guyatt, G.H., Keller, J.L., Jaeschke, R., Rosenbloom, D., Adachi, J.D., & Newhouse, M.T. (1990). The n-of-1 randomized controlled trial: clinical usefulness: our three-year experience. Annals of Internal Medicine, 112, 293-299.

Hawe, P., Shiell, A., & Riley, T. (2004). Complex interventions: how "out of control" can a randomised controlled trial be? BMJ, 328, 1561-1563.

Hawkins, N.G., Sanson-Fisher, R.W., Shakeshaft, A., D'Este, C., & Green, L.W. (2007). The multiple baseline design for evaluating population-based research. American Journal of Preventive Medicine, 33, 162-168.

Hotopf, M. (2002). The pragmatic randomised controlled trial. Advances in Psychiatric Treatment, 8, 326-333.

Sanson-Fisher, R.W., Bonevski, B., Green, L.W., & D'Este, C. (2007). Limitations of the randomized controlled trial in evaluating population-based health interventions. American Journal of Preventive Medicine, 33, 155-161.

Schumi, J., & Wittes, J.T. (2011). Through the looking blass: understanding non-inferiority. Trials, 12:106

Shadish, W.R., Clark, M.H., & Steiner, P.M. (2008). Can nonrandomized experiments yield accurate answers? A randomized experiment comparing random and nonrandom assignments. Journal of the American Statistical Association, 103, 1334-1356.

Victora, C.G., Habicht, J-P., & Bryce, J. (2004). Evidence-based public health: moving beyond randomized trials. American Journal of Public Health, 94, 400-405.

West, S.G., Duan, N., Pequegnat, W., Gaist, P., Des Jarlais, D.C., Holtgrave, D., Szapocznik, J., Fishbein, M., Rapkin, B., Clatts, M., & Mullen, P.D. (2008). Alternatives to the randomized controlled trial. American Journal of Public Health, 98, 1359-1366.

Week 3 – February 1 - Writing a RCT proposal for NIH

Required Readings for Lecture

Moxley, J.M. (1992). Publish, Don't Perish: The Scholar's Guide to Academic Writing and Publishing. CT: Praeger. (Chapter 14: How to write proposals for grants, pp. 121-126).

National Institutes of Health: please browse through this page and its links: http://grants.nih.gov/grants/about_grants.htm

Required Reading for Discussion

Dilorio, C., McCarty, F., Resnicow, K., Lehr, S., & Denzmore, P. (2007). REAL men: a group-randomized trial of an HIV prevention intervention for adolescent boys. American Journal of Public Health, 97, 1084-1089

→ **Week 3 Assignment due:** 1-2 paragraph description of proposed RCT design project. The paragraph should include your research question or hypothesis, a brief background describing why your question/hypothesis is important, and your proposed design, intervention, and outcome measures (realizing, of course, that your design, intervention, and measures are early ideas and likely to change). Please bring a hard copy to class and also email it to kdward@memphis.edu prior to the start of class.

Week 4 – February 8	**- Internal and external validity** **- Guest presentation: Jim Murphy, PhD, Department of Psychology –** ***Improving brief alcohol interventions with a behavioral economic supplement***

Required Readings for Lecture

Delgado-Rodriguez, M., & Llorca, J. (2004). Bias. Journal of Epidemiology and Community Health, 58, 635-641. *(please read entire article but focus on Section 4: "Specific Biases in Trials" p. 640).*

Glasgow, R.E., Vogt, T.M., & Boles, S.M. (1999). Evaluating the public health impact of health promotion interventions: the RE-AIM framework. American Journal of Public Health, 89, 1322-1327.

Shadish, W.R., Cook, T.D., & Campbell, D.T. (2002). Chapter 2: Statistical Conclusion Validity and Internal Validity. In: Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Boston: Houghton Mifflin Company. *(you are responsible only for the section on Internal Validity, pp. 53-61)*

Required Reading for Discussion

Ransdell, L.B., Easte, E., Taylor, A., Oakland, D., Schmidt, J., Moyer-Mileur, L. & Shultz, B. (2003). Daughters and mothers exercising together (DAMET): effects of home- and university-based interventions on physical activity behavior and family relations. American Journal of Health Education, 34, 19-29.

Supplemental Readings

Dzewaltowski, D., Estabrooks, P.A., Klesges, L.M., Bull, S., & Glasgow, R.E. (2004). Behavior change intervention research in community settings: how generalizable are the results? Health Promotion International, 19, 235-245.

Glasgow, R.E., Lichtenstein, E., & Marcus, A.C. (2003). Why don't we see more translation of health promotion research to practice? Rethinking the efficacy-to-effectiveness transition. American Journal of Public Health, 93, 1261-1267.

Slack, M.K. & Drugalis, J.R. (2001). Establishing the internal and external validity of experimental studies. American Journal of Health-Systems Pharm, 58, 2173-2184.

Sussman, J.B., & Hayward, R.A. (2010). Using instrumental variables to adjust for treatment contamination in randomised controlled trials. BMJ, 340, 1181-1184.

→ **Week 4 Assignment due:** first draft of Specific Aims. Please bring a hard copy to class and email a copy to kdward@memphis.edu prior to the start of class. Follow NIH guidelines for writing your Specific Aims and all other sections https://**grants.nih**.gov/**grants/funding/424**/sf**424**_rr_**guide**_general_adobe_verc.docx). According to these guidelines, in your Specific Aims you should "State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved. List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology."

Week 5 – February 15	**- Selection of the study population** **- Inclusion and exclusion criteria** **- Recruitment**

Required Readings for Lecture

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 4 – Study Population)

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 10 – Recruitment of Study Participants)

Watson, J.M., & Torgerson, D.J. (2006). Increasing recruitment to randomised trials: a review of randomised controlled trials. BMC Medical Research Methodology, 6:34, doi:10.1186/1471-2288-6-34

Required Reading for Discussion

Ward, K.D., Asfar, T., Al-Ali, R., Vander Weg, M.W., Eissenberg, T., & Maziak, W. (2013). Randomized trial of the effectiveness of combined behavioral/pharmacological smoking cessation treatment in Syrian primary care clinics. Addiction, 108, 394-403. [*Please also read the accompanying commentary, which is attached to the end of the paper:* Lando, H. (2013). Commentary on Ward *et al*. (2013): Failure to find a treatment effect for NRT in a low-income country – implications.]

→ **Week 5 Assignment due:** First draft of Innovation section. Please bring a hard copy to class and email your draft (including your Specific Aims) to kdward@memphis.edu prior to the start of class.

Week 6 – February 22	**- Randomization** **- Control groups, blinding, and placebos**

Required Readings for Lecture

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 6 – The Randomization Process)

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 7 – Blindness)

Required Reading for Discussion

Mehlenbeck, R., Ward, K.D., Klesges, R.C., & Vukadinovich C.M. (2004). A pilot intervention to increase calcium intake in female collegiate athletes. International Journal of Sport Nutrition and Exercise Metabolism, 14, 18-29.

Moseley, J.B., O'Malley, K., Petersen, N.J., Menke, T.J., Brody B.A., Kuykendall, D.H. et al. (2002). A controlled trial of arthroscopic surgery for osteoarthritis of the knee. New England Journal of Medicine, 347, 81-88.

Supplemental Readings

Beecher, H.K. (1955). The powerful placebo, JAMA, 27, 1602-1606.

Featherstone, K., & Donovan, J.L. (2002). "Why don't they just tell me straight, why allocate it? The struggle to make sense of participating in a randomised controlled trial. Social Science & Medicine, 55, 709-719.

Hrobjartsson, A. and Gotzsche, P.C. (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. New England Journal of Medicine, 344, 1594-1602.

Kaptchuk, T.J., Stason, W.B., Davis, R.B., Legedz, A.T.R., Schnyer, R.N., et al. (2006). Sham device v. inert pill: randomised controlled trial of two placebo treatments. BMJ, doi:10.1136/bmj.38726.603310.55.

Onder, R.F. (2005). The ethics of placebo-controlled trials: the case of asthma. Journal of Asthma and Clinical Immunology, 115, 1228-1234.

Schulz, K.F., & Grimes, D.A. (2002). Allocation concealment in randomised trials: defending against deciphering. The Lancet, 359, 614-618.

Schulz, K.F., & Grimes, D.A. (2002). Blinding in randomised trials: hiding who got what. The Lancet, 359, 696-700.

Schulz, K.F., & Grimes, D.A. (2002). Generation of allocation sequences in randomised trials: chance, not choice. The Lancet, 359, 515-519.

Schulz, K.F., & Grimes, D.A. (2002). Unequal group sizes in randomised trials: guarding against guessing. The Lancet, 359, 966-970.

Stang, A., Hense, H-W., Jockel, K-H, et al. (2005). Is it always unethical to use a placebo in a clinical trial? PLOS Medicine, 2, e72.

Student. (1931). The Lanarkshire Milk Experiment. Biometrika, 23, 398-406.

Wood, L., Egger, M., Glud, L.L. et al. (2008). Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ, doi:10.1136/bmj.39465.451748.AD

→ **Week 6 Assignment due:** First draft of Significance section. Please bring a hard copy to class and email your draft (including previously submitted sections) to kdward@memphis.edu prior to the start of class.

Week 7 – March 1	**- Selection of measures and instruments** **- Mediators, moderators, and confounders**

Required Readings for Lecture

Kraemer, H.C., Wilson, G.T., Fairburn, C.G., & Agras, W.S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. Archives of General Psychiatry, 59, 877-883.

Windsor, R. et al. (1994). Measurement issues in data collection. In: R. Windsor et al., Evaluation of Health Promotion, Health Education, and Disease Prevention Programs. Mountain View: Mayfield Publishing Company.

Required Reading for Discussion

Harris, W.S., Gowda, M., Kolb, J.W., Strychacz, C.P., Vacek, J.L., Jones, P.G., Forker, A., O'Keefe, J.H., & McCallister, B.D. (1999). A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. Archives of Internal Medicine, 159, 2273-2278.

Supplemental Readings

Baron, R.M., & Kenny, D.A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. Journal of Personality and Social Psychology, 51, 1173-1182.

Bauman, A.E., Sallis, J.F., Dzewaltowski, D.A., & Owen, N. (2002). Toward a better understanding of the influences on physical activity: the role of determinants, causal variables, mediators, moderators, and confounders. American Journal of Preventive Medicine, 23(2S), 5-14.

Dossey, L., et al. (1999). Prayer and medical science: a commentary on the prayer study by Harris et al., and a response to critics. JAMA, 160, 1735-1738.

Evans, S. (2007). When and how can endpoints be changed after initiation of a randomized clinical trial? PLOS Clinical Trials, 2, e18. Doi:10.1371/journal.pctr.0020018.

John, O.P., & Benet-Martinez, V. (2000). Measurement: reliability, construct validation, and scale construction. (pp. 339-360). In H.T. Reis, & Judd, C.M. (Eds.). Handbook of Methods in Social and Personality Psychology. Cambridge: Cambridge University Press.

Kraemer, H.C., Frank, E., & Kupfer, D.J. (2006). Moderators of treatment outcomes: clinical, research, and policy importance. JAMA, 296, 1286-1289.

Paul, G. (2008). The remote prayer delusion: clinical trials that attempt to detect supernatural intervention are as futile as they are unethical. Journal of Medical Ethics, 34, e18.

Pocock, S.J., & Stone, G.W. (2016). The primary outcome fails: what next? New England Journal of Medicine, 375, 861-870.

Pocock, S.J., & Stone, G.W. (2016). The primary outcome is positive: is that good enough? New England Journal of Medicine, 375, 971-979.

Schulz, K.F., & Grimes, D.A. (2005). Multiplicity in randomised trials I: endpoints and treatments. The Lancet, 365, 1591-1595.

→ **Week 7 Assignment due:** First draft of Approach sub-sections Preliminary Studies, Study Design, and Target Population. Please bring a hard copy to class and email your draft (including previously submitted sections) to kdward@memphis.edu prior to the start of class.

March 8 - No class (Spring Break)

Week 8 – March 15 - Data collection and quality control
- Missing data

Required Readings for Lecture

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 11 – Data Collection and Quality Control).

Nelson, D.B., Partin, M.R., Fu, S.S., Joseph, A.M., & An, L.C. (2009). Why assigning ongoing tobacco use is not necessarily a conservative approach to handling missing tobacco cessation outcomes. Nicotine & Tobacco Research, 11, 77-83.

Required Readings for Discussion

Katz, D.A., Holman, J.E., Nugent, A.S., Baker, L.J., Johnson, S.R., Hillis, S.L., Tinkelman, D.G., Titler, M.G. & Vander Weg, M.W. (2013). The Emergency Department Action in Smoking Cessation (EDASC) Trial: impact on cessation outcomes. Nicotine & Tobacco Research, 15, 1032-1043.

Ross, L., Thomsen, B.L., Boesen, E.H., & Johansen, C. (2004). In a randomized controlled trial, missing data led to biased results regarding anxiety. Journal of Clinical Epidemiology, 57, 1131-1137.

Supplemental Readings

Donders, A.R.T. van der Heijden, G.J.M.G., Stijnen, T., & Moons, K.G.M. (2006). Review: a gentle introduction to imputation of missing values. Journal of Clinical Epidemiology, 59, 1087-1091.

Schafer, J.L., & Graham, J.W. (2002). Missing data: our view of the state of the art. Psychological Methods, 7, 147-177.

Schultz, K.F., & Grimes, D.A. (2002). Sample size slippages in randomised trials: exclusions and the lost and wayward. The Lancet, 359, 781-785.

→ **Week 8 Assignment due:** First draft of Approach sub-sections Subjects, Recruitment, Randomization, and Blinding. Please bring a hard copy to class and email your draft (including previously submitted sections) to kdward@memphis.edu prior to the start of class.

Week 9 – March 22 (Dr. Ward out of town)	**- Statistical analysis in RCTs** **- Guest Presentation: George Relyea, MS, MA -- *Power Analysis*** **- Guest Presentation: Matt Smeltzer, PhD, MS -- *Outcomes Analysis***

Required Readings for Lecture

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 17 – Issues in Data Analysis)

Hall, S.M., Delucchi, K.L., Velicer, W.F., Kahler, C.W., Ranger-Moore, J., Hedeker, D., et al. (2001). Statistical analysis of randomized trials in tobacco treatment: longitudinal designs with dichotomous outcome. Nicotine & Tobacco Research, 3, 193-202.

Supplemental reading

Kraemer, H.C., Mintz, J., Noda, A., Tinklenberg, J., & Yesavage, J.A. (2006). Caution regarding the use of pilot studies to guide power calculations for study proposals. Archives of General Psychiatry, 63, 484-489.

→ **Week 9 Assignment due:** First draft of Approach sub-section Interventions. Please email your draft (including previously submitted sections) to kdward@memphis.edu prior to the start of class. Dr. Ward will not be in class, so you don't need to bring a hard copy with you.

Week 10 – March 29	**- Treatment implementation** **- Trial management** **- Adherence and retention**

Required Readings for Lecture

Borrelli, B. (2011). The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. Journal of Public Health Dentistry, 71, S52-S63.

Coday, M., Boutin-Foster, C., Sher, T.G., Tennant, J., Greaney, M.L., Saunders, S.D., & Somes, G.W. (2005). Strategies for retaining study participants in behavioral intervention trials: retention experiences of the NIH Behavior Change Consortium. Annals of Behavioral Medicine, 29 (Special Supplement), 55-65.

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 14 – Participant Adherence).

Margitic, S.E., & Miles, N.L. (1998). Ten commandments of successful trial management. Preventive Medicine, 27, 84-92.

Required Reading for Discussion

Ludwig, J., Sanbonmatsu, L., Gennetian, L., Adam, E., Duncan, G.J., Katz, L.F., Kessler, R.C. et al. (2011). Neighborhoods, obesity, and diabetes: a randomized social experiment. *New England Journal of Medicine, 365,* 1509-1519.

Supplemental Reading

Brueton, V.C., Tierney, J.F., Stenning, S., Meredith, S., Harding, S., Nazareth, I., & Rait, G. (2014). Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. BMJ Open, 4:e003821, 1-18.

Kelly, S.A., Oswalt, K., Melnyk, B.M., & Jacobson, D. (2015). Comparison of intervention fidelity between COPE TEEN and an attention-control program in a randomized controlled trial. Health Education Research, 30, 233-247.

Lichstein, K.L., Riedel, B.W., & Grieve, R. (1994). Fair tests of clinical trials: a treatment implementation model. Advances in Behaviour Research & Therapy, 16, 1-29.

→ **Week 10 Assignment due:** First draft of Approach sub-sections Retention, Adherence, Measures, and Data Quality Control and Management. Please bring a hard copy to class and email your draft (including previously submitted sections) to kdward@memphis.edu prior to the start of class.

Week 11 – April 5	**- Reporting adverse events** **- Stopping rules** - **Guest presentation: Leslie Robinson, PhD, Department of Psychology –** ***Recruitment, retention, and adherence in clinical trials***

Required Readings for Lecture

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 12 – Assessing and Reporting Adverse Events).

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 16 – Monitoring Response Variables).

Required Reading for Discussion

Walton, R.G., Hudak, R., & Green-Waite, R.J. (1993). Adverse reactions to aspartame: double-blind challenge in patients from a vulnerable population. Biological Psychiatry, 34, 13-17.

Supplemental readings

Delgado-Herrera, L., & Anbar, D. (2003). A model for the interim analysis process: a case study. Controlled Clinical Trials, 24, 51-65.

DeMets, D.L., & Ellenberg, S.S. (2016). Data monitoring committees: expect the unexpected. New England Journal of Medicine, 375, 1365-1371.

Schultz, K.F., & Grimes, D.A. (2005). Multiplicity in randomised trials II: subgroup and interim analyses. The Lancet, 365, 1657-1661.

Slutsky, A.S., & Lavery, J.V. (2004). Data safety and monitoring boards. New England Journal of Medicine, 350, 1143-1147.

→ **Week 11 Assignment due:** First draft of Approach sub-sections Treatment Implementation, Sample Size and power, Data Analysis, Budget, and Budget Justification. Please bring a hard copy to class and email your draft (including previously submitted sections) to kdward@memphis.edu prior to the start of class.

Week 12 – April 12	**- Ethics and protection of human research subjects** **- Guest presentation: Rebecca Krukowski, PhD, Department of Preventive Medicine, UTHSC – *Conducting weight management research in the real world: Design and implementation considerations and trade-offs***

Required Readings for Lecture

Freedman, B. (1987). Equipoise and the ethics of clinical research. New England Journal of Medicine, 317, 141-145.

Friedman, L.M., Furberg, C.D., & DeMets, D.L. (2010). Fundamentals of Clinical Trials, 4th Edition. NY: Springer-Verlag. (Chapter 2 – Ethics).

Krukowski, R.A., Hare, M.E., Talcott, G.W. Johnson, K.C., Richey, P.A., Kocak, M., Balderas, J., Colvin, L., Keller, P.L., Waters, T.M., & Klesges, R.C. (2015). Dissemination of the Look AHEAD intensive lifestyle intervention in the United States Air Force: study rationale, design and methods. Contemporary Clinical Trials, 40, 232-239.

Required Reading for Discussion

Nelson, C.A. III, Zeanah, C.H., Fox, N.A., Marshall, P.J., Smyke, A.T., & Guthrie, D. (2007). Cognitive recovery in socially deprived young children: The Bucharest Early Intervention Project. Science, 318, 1937-1940.

Supplemental readings

Angell, M. (1997). The ethics of clinical research in the third world (editorial). New England Journal of Medicine, 337, 847-849.

DeAngelis, C.D., Drazen, J.M., Frizelle, F.A., Haug, C., Hoey, J., Horton, R. et al. (2004). Clinical trial registration: a statement from the International Committee of Medical Journal Editors. JAMA, 292, 1363-1364.

Halpern, S.D., Karlawish, J.H.T., & Berlin, J.A. (2002). The continuing unethical conduct of underpowered clinical trials. JAMA, 288, 358-362.

Mathieu, S., Boutron, I., Moher, D., Altman, D.G., & Ravaud, P. (2009). Comparison of registered and published primary outcomes in randomized controlled trials. JAMA, 302, 977-984.

Mills, N., Donovan, J.L., Smith, M., et al. (2003). Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study. Controlled Clinical Trials, 24, 272-282.

Ness, R.B. For the Joint Policy Committee Societies of Epidemiology (2007). Influence of the HIPAA Private Rule on health research. JAMA, 298, 2164-2170.

Royall, R.M. (1991). Ethics and statistics in randomized clinical trials. Statistical Science, 6, 52-88. (*the comment by Bartlett & Cornell and others in the same issue are also worth reading)*

Weir, C., & Murray, G. (2011). Fraud in clinical trials: detecting it and preventing it. Significance. December issue, pp 164-168.

Whalen, C.C., Johnson, J.L., Okwera, A., Hom, D.L., Huebner, R., Mugyenyi, P., et al. (1997). A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. New England Journal of Medicine, 337, 801-808.

→ **Week 12 Assignment due:** The final, complete draft of your RCT proposal, including references, is due by the start of class (2:00pm) today. Please email your complete proposal to kdward@memphis.edu by 2:00pm.

Week 13 – April 19	**- Student presentation of proposals (Part 1)**

Week 14 – April 26	**- Student presentation of proposals (Part 2)**