

PUBH 8482, SECTION 001

Sequential and Adaptive Methods for Clinical Trials
Fall 2019

COURSE & CONTACT INFORMATION

Credits: 3

Meeting Day(s): Monday and Wednesday

Meeting Time: 9:45a - 11:00a

Meeting Place: 2-120 Moos Health Science Tower

Instructor: Thomas Murray

Email: murra484@umn.edu

Office Phone: 612-626-6697

Office Hours: Wednesday 1p - 2p and Thursday 2:30p - 3:30p, or by appointment

Office Location: Mayo A459

COURSE DESCRIPTION

When done effectively, randomized controlled clinical trials are the gold standard for assessing the effect of an intervention in human subjects. Clinical trials are expensive, time-consuming and expose subjects to potentially harmful and ineffective treatments. Sequential and adaptive designs, as opposed to fixed-sample designs, can be more efficient and expose fewer subjects to harmful and ineffective treatments. These designs present many statistical challenges, however, such as controlling type I error. In this course, we will discuss sequential and adaptive designs for clinical trials; the statistical properties and challenges these designs engender; and their pros and cons relative to a fixed-sample design.

COURSE PREREQUISITES

Stat 8101-8102 or equivalent; students should be comfortable with the multivariate normal distribution and have some familiarity with Bayesian methods.

COURSE GOALS & OBJECTIVES

- Students will be familiar with standard group sequential methodology
- Students will be exposed to adaptive methods in clinical trials
- Students will understand the challenges of applying sequential and adaptive methods to clinical trials
- Students will understand the advantages and disadvantages of sequential and adaptive clinical trial designs

METHODS OF INSTRUCTION AND WORK EXPECTATIONS

Course Workload Expectations

PUBH 8482 is a 3 credit course. The University expects that for each credit, you will spend a minimum of three hours per week attending class or comparable online activity, reading, studying, completing assignments, etc. over the course of a 15-week term. Students are expected to attend class, participate in class discussions and complete homework assignments, the midterm exam, and final project. Working together on homework assignments is permitted but each student is expected to write-up solutions in their own words based on their own computing. The take-home midterm exam should be completed independently, however.

Learning Community

School of Public Health courses ask students to discuss frameworks, theory, policy, and more, often in the context of past and current events and policy debates. Many of our courses also ask students to work in teams or discussion groups. We do not come to our courses with identical backgrounds and experiences and building on what we already know about collaborating, listening, and engaging is critical to successful professional, academic, and scientific engagement with topics.

In this course, students are expected to engage with each other in respectful and thoughtful ways.

In group work, this can mean:

- Setting expectations with your groups about communication and response time during the first week of the semester (or as soon as groups are assigned) and contacting the TA or instructor if scheduling problems cannot be overcome.
- Setting clear deadlines and holding yourself and each other accountable.
- Determining the roles group members need to fulfill to successfully complete the project on time.

- Developing a rapport prior to beginning the project (what prior experience are you bringing to the project, what are your strengths as they apply to the project, what do you like to work on?)

In group discussion, this can mean:

- Respecting the identities and experiences of your classmates.
- Avoid broad statements and generalizations. Group discussions are another form of academic communication and responses to instructor questions in a group discussion are evaluated. Apply the same rigor to crafting discussion posts as you would for a paper.
- Consider your tone and language, especially when communicating in text format, as the lack of other cues can lead to misinterpretation.

Like other work in the course, all student to student communication is covered by the Student Conduct Code (<https://z.umn.edu/studentconduct>).

COURSE TEXT & READINGS

Although there is no required text, the lecture notes will draw from the following texts:

Jennison, C. and Turnbull, B. (1999) Group Sequential Methods with Applications to Clinical Trials, Boca Raton, FL: CRC Press. ISBN 0849303168 (Biostat Reading Room)

Proschan, M.A., Lan, K.K.G. and Wittes, J.T. (2006) Statistical Monitoring of Clinical Trials: A Unified Approach, New York, NY: Springer. ISBN 0387300597 (Biostat Reading Room)

Berry, S.M., Carlin, B.P., Lee, J.J. and Muller, P. (2010) Bayesian Adaptive Methods for Clinical Trials, Boca Raton, FL: CRC Press. ISBN 1439825483 (Biostat Reading Room)

Other useful texts include:

Whitehead, J. (1997) The Design and Analysis of Sequential Clinical Trials, 2nd Ed., New York, NY: John Wiley & Sons. ISBN 0471975508 (Physical copy via U-MN Libraries)

Yin, G. (2012) Clinical Trial Design: Bayesian and Frequentist Adaptive Methods, Hoboken, NJ: John Wiley & Sons. ISBN 0470581719 (Online access via U-MN Libraries)

Chow, S. and Chang, M. (2012) Adaptive Design Methods in Clinical Trials, 2nd Ed., Boca Raton, FL: CRC Press. ISBN 1439839883 (Online access via U-MN libraries)

Bartroff, J., Lai, T. and Shih, M. (2013) Sequential Experimentation in Clinical Trials: Design and Analysis, New York, NY: Springer. ISBN 1461461146 (Online access via U-MN Libraries)

Yuan, Y., Nguyen, H.Q. and Thall, P.F. (2016) Bayesian Designs for Phase I–II Clinical Trials, Boca Raton, FL: CRC Press. ISBN 1498709552 (Purchase)

Shih, W.J. and Aisner J. (2016) Statistical Design and Analysis of Clinical Trials, Boca Raton, FL: CRC Press. ISBN 1482250510 (Purchase)

This course uses journal articles, which are available via the University Libraries' E-Reserves and will be linked from the course site. It is good practice to use a citation manager to keep track of your readings. More information about citation managers is available at <https://www.lib.umn.edu/pim/citation>.

COURSE OUTLINE/WEEKLY SCHEDULE

Week	Topic	Readings	Activities/Assignments
Week 1: 9/4	<ul style="list-style-type: none"> Introduction 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> None
Week 2: 9/9 & 9/12	<ul style="list-style-type: none"> Multivariate Normal Distribution as It Relates to Sequential Testing 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW1
Week 3: 9/16 & 9/18	<ul style="list-style-type: none"> Sequential Testing of Normal Random Variables 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW1
Week 4: 9/23 & 9/25	<ul style="list-style-type: none"> Sequential Testing of Normal Random Variables 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW2
Week 5: 9/30 & 10/2	<ul style="list-style-type: none"> Error Spending Functions 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW2
Week 6: 10/7 & 10/9	<ul style="list-style-type: none"> Brownian Motion and Asymptotically Normal Test Statistics 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW3
Week 7: 10/14 & 10/16	<ul style="list-style-type: none"> Inference following a Group Sequential Test 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW3
Week 8: 10/21 & 10/23	<ul style="list-style-type: none"> Inference following a Group Sequential Test 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Midterm
Week 9: 10/28 & 10/30	<ul style="list-style-type: none"> Phase 1 Designs 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW4
Week 10: 11/4 & 11/6	<ul style="list-style-type: none"> Phase 1 Designs 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW4
Week 11: 11/11 & 11/13	<ul style="list-style-type: none"> Outcome Adaptive Trials 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW5
Week 12: 11/18 & 11/20	<ul style="list-style-type: none"> Special Topics 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> HW5
Week 13: 11/25 & 11/27	<ul style="list-style-type: none"> Special Topics 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> None
Week 14: 12/2 & 12/4	<ul style="list-style-type: none"> Special Topics 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> None
Week 15: 12/9 & 12/11	<ul style="list-style-type: none"> Student Presentations 	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> None

SPH AND UNIVERSITY POLICIES & RESOURCES

The School of Public Health maintains up-to-date information about resources available to students, as well as formal course policies, on our website at www.sph.umn.edu/student-policies/. Students are expected to read and understand all policy information available at this link and are encouraged to make use of the resources available.

The University of Minnesota has official policies, including but not limited to the following:

- Grade definitions
- Scholastic dishonesty
- Makeup work for legitimate absences
- Student conduct code
- Sexual harassment, sexual assault, stalking and relationship violence
- Equity, diversity, equal employment opportunity, and affirmative action
- Disability services
- Academic freedom and responsibility

Resources available for students include:

- Confidential mental health services
- Disability accommodations
- Housing and financial instability resources
- Technology help
- Academic support

EVALUATION & GRADING

There will be approximately 4 homework assignments. Students will have two weeks to complete each assignment. There will be a take-home midterm exam towards the middle of the semester with the specific date to be determined. In addition, each student will complete a final project that will consist of a paper and a 15 minute presentation. For the final project, students are expected to complete a literature review of a sub-area of sequential and adaptive designs, providing a summary of current and past research and identifying open research questions in the area.

Final grades will be a weighted average of performance on homework (40%), the midterm (30%), and the final project (30%).

Grading Scale

The University uses plus and minus grading on a 4.000 cumulative grade point scale in accordance with the following, and you can expect the grade lines to be drawn *at least as generously* as follows:

% In Class	Grade	GPA
93 - 100%	A	4.000
90 - 92%	A-	3.667
87 - 89%	B+	3.333
83 - 86%	B	3.000
80 - 82%	B-	2.667
77 - 79%	C+	2.333
73 - 76%	C	2.000
70 - 72%	C-	1.667
67 - 69%	D+	1.333
63 - 66%	D	1.000
< 62%	F	

- A = achievement that is outstanding relative to the level necessary to meet course requirements.
- B = achievement that is significantly above the level necessary to meet course requirements.
- C = achievement that meets the course requirements in every respect.
- D = achievement that is worthy of credit even though it fails to meet fully the course requirements.
- F = failure because work was either (1) completed but at a level of achievement that is not worthy of credit or (2) was not completed and there was no agreement between the instructor and the student that the student would be awarded an I (Incomplete).
- S = achievement that is satisfactory, which is equivalent to a C- or better
- N = achievement that is not satisfactory and signifies that the work was either 1) completed but at a level that is not worthy of credit, or 2) not completed and there was no agreement between the instructor and student that the student would receive an I (Incomplete).

Evaluation/Grading Policy	Evaluation/Grading Policy Description
<p>Scholastic Dishonesty, Plagiarism, Cheating, etc.</p>	<p>You are expected to do your own academic work and cite sources as necessary. Failing to do so is scholastic dishonesty. Scholastic dishonesty means plagiarizing; cheating on assignments or examinations; engaging in unauthorized collaboration on academic work; taking, acquiring, or using test materials without faculty permission; submitting false or incomplete records of academic achievement; acting alone or in cooperation with another to falsify records or to obtain dishonestly grades, honors, awards, or professional endorsement; altering, forging, or misusing a University academic record; or fabricating or falsifying data, research procedures, or data analysis (As defined in the Student Conduct Code). For additional information, please see https://z.umn.edu/dishonesty</p> <p>The Office for Student Conduct and Academic Integrity has compiled a useful list of Frequently Asked Questions pertaining to scholastic dishonesty: https://z.umn.edu/integrity.</p> <p>If you have additional questions, please clarify with your instructor. Your instructor can respond to your specific questions regarding what would constitute scholastic dishonesty in the context of a particular class-e.g., whether collaboration on assignments is permitted, requirements and methods for citing sources, if electronic aids are permitted or prohibited during an exam.</p> <p>Indiana University offers a clear description of plagiarism and an online quiz to check your understanding (http://z.umn.edu/iuplagiarism).</p>
<p>Late Assignments</p>	<p>I will generously grant deadline extensions with adequate warning. If you need more time, please ask. If you do not ask, I reserve the right to deduct points.</p>
<p>Attendance Requirements</p>	<p>Students are expected to attend and participate in lectures.</p>
<p>Extra Credit</p>	<p>None available.</p>

CEPH COMPETENCIES

Competency	Learning Objectives	Assessment Strategies
<p>1. Apply epidemiological methods to the breadth of settings and situations in public health practice</p>		
<p>2. Select quantitative and qualitative data collection methods appropriate for a given health context</p>		
<p>3. Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software as appropriate</p>		
<p>4. Interpret results of data analysis for public health research, policy or practice</p>		
<p>12. Discuss multiple dimensions of the policy- making process, including the role of ethics and evidence</p>		
<p>16. Apply principles of leadership, governance and management, which include creating a vision, empowering others, fostering collaboration and , guiding decision making</p>		