HRM 732 • Adaptive Designs for Clinical Trials (Online)

Course Syllabus

Summer, 2019

1. Brief Description

Randomized clinical trials are the gold standard for testing the effect of a novel intervention. Clinical trials can be expensive, time consuming, and can expose subjects to interventions that are potentially harmful and/or ineffective. Standard trial designs generally do not allow for modifications to key design components during the trial, but adaptive designs, on the other hand, allow for modifications to be made based on accumulative data or new knowledge that becomes available during the trial. With this adaptive learning nature, adaptive designs can improve the efficiency of the trial and reduce the risk of patients being exposed to harmful and/or ineffective interventions; however, they can be more challenging to design and execute. There are several operational and statistical challenges that must be addressed in order to preserve the integrity of the trial. In this distance education course, we will discuss the principles and characteristics of adaptive designs, the advantages and disadvantages of conducting an adaptive clinical trial compared to a standard, fixed sample design, and potential operational and statistical challenges in adaptive designs.

2. Prerequisites

1. Students must meet McMaster School of Graduate Studies admission criteria (http://academiccalendars.romcmaster.ca/content.php?catoid=4&navoid=191)
2. **Students must meet at least one of the following criteria:**
    a. Have taken a HRM 702, HRM 721, and a graduate course in randomized clinical trials methods (HRM730 or 733) or equivalent
    b. Have prior experience performing randomized clinical trials
    c. Obtain permission from an instructor

3. Course Objectives

Students who successfully complete this course will:

- Have knowledge and skills to describe the principles, characteristics, advantages, and disadvantages of adaptive designs
- Be able to compare and contrast adaptive designs to standard trial designs
- Be able to critically appraise adaptive clinical trials for their strengths and limitations

Students will also gain familiarity with:

- Current concepts and controversies in adaptive design methods
- US and European Regulatory agencies' recommendations for planning and conducting adaptive trials

4. Unit Outline

Unit	Topic
1	Course introduction and history of adaptive trial designs and master protocols
2	Adaptive trial designs and master protocols: Characteristics, principles, and types
3	Adaptive designs for dose finding and efficacy
4	Case studies in seamless and sample-size re-assessment designs
5	Clinical trial simulations, decision rules, and statistical analyses
6	Precision oncology trials: Basket and umbrella trials
7	A case study on a platform trial: STAMPEDE trial
8	A case study on a platform trial: I-SPY2 trial
9	Standards for adaptive designs and master protocols
10	Practical considerations for funding and implementation of adaptive trial designs and master protocols
11	Writing week & Open office hour
12	Student presentations I
13	Student presentations II

5. Required Materials

Students are required to access readings online (as outlined weekly). Students are responsible for any costs incurred for other materials necessary for final projects. This may include library fees to obtain original full text publications of systematic reviews and studies to be reviewed.

Mailing of the materials to students: McMaster University Libraries do not have the ability to mail books obtained through inter-library loans directly to students (these materials are available to McMaster students only through library pick-up). Articles that are available in print only through McMaster Libraries may be mailed to students; however, the student is responsible for covering the cost of the reproduction, shipping and handling of these resources.

6. Course Format

This online course consists of 13 units. **For the first ten units (Unit 1 to Unit 10),** each unit is comprised of required readings, online discussion, and an online tutorial session. **Unit 11** will be a writing week with an option to have an open office hour. **The last two units (Unit 12 and Unit 13)** will be dedicated for student presentations.

All activities except for online tutorial sessions will be performed in the McMaster University online learning environment – Avenue to Learn (http://avenue.mcmaster.ca).

Students are required to attend at least eight of ten online tutorial sessions for the first ten units (Unit 1 to Unit 10). Tutorials will be held at the end of the week via web conferencing tool – WebEx at McMaster: http://mcmaster.webex.com. Links to the tutorials will be available on Avenue every week. You may also find the meeting by searching meetings at McMaster (http://mcmaster.webex.com). Participation in the live tutorial sessions is strongly encouraged as the most important opportunity to discuss and clarify conceptual issues related to each unit. The agenda for the individual tutorials will be tailored to the unresolved issues and questions raised in the discussion forums. Students will have the opportunity to post additional questions directly to the instructor in advance of each tutorial session.

There will be discussions each week about readings. Students are required to actively participate during the semester, and students will act as a discussion facilitator for one unit and submit their written summary of the discussion. There will be new facilitator for each unit. In the beginning of the semester, students can sign up for the unit in which they will act as a discussion facilitator. This will be done in first-come, first-served basis.

Student participation in the readings discussion board will be monitored and evaluated contributing to 20% to the final course evaluation (*12.5% for general participation and live tutorial; 7.5% for discussion facilitators*). For general participation and live tutorial, quality, quantity and timing of participation in course activities and during live tutorials will be considered in the final participation grade. Although participation in the *assignment* discussion board is not evaluated, students are strongly encouraged to take advantage of this additional opportunity to discuss issues with their peers. As discussion facilitators, students will be evaluated on their facilitation and their written summary of the discussion.

Students are expected to:

- Review and complete the weekly lectures, readings, and assignments
- Participate in discussion boards with the instructor and fellow students about key issues related to each unit
- Participate in a live tutorial session each week

7. Student Evaluation

Students are given many opportunities to demonstrate their mastery of the course material. Final course marks will be calculated as follows:

- 20% = Online discussion participation
    - 12.5% for general participation and live tutorial
    - 7.5% for discussion facilitator
- 15% = Critical appraisal 1
- 15% = Critical appraisal 2
- 25% = Critical appraisal 3 (Final)
    - 5% for draft synopsis of final critical appraisal
    - 20% for final submission
- 25% = Final student presentation
    - 5% for participation
    - 20% for presentation

Grades in graduate courses at McMaster University are reported as letter grades using the following breakdown:

- A+ = 90 to 100 (consistently outstanding)
- A = 85 to 89 (overall superior quality)
- A– = 80 to 84 (high achievement)
- B+ = 77 to 79 (competent, but not consistently high quality)
- B = 73 to 76 (satisfactory quality)
- B– = 70 to 72 (only marginally acceptable)
- F = failure (inadequate work)

Weekly assignments will be posted each week together with other materials for each unit. These assignments are designed to guide students in the process of developing their guideline section with a recommendation. **Assignments will be due at the end of each week on Saturday, 12:00 am EDT (midnight).**

Weekly assignments are submitted online using the drop-box in Avenue to Learn.

To avoid confusion of submitted documents, students should appropriately name all their submissions with the following format.

"HRM732 – [semester year] – Critical appraisal [#]– [First Name LastName].docx"

For instance, if John Smith, who is taking the course in Summer 2019 session, was submitting his first assignment, the title of his document would read as "HRM732 – Summer 2019 – Critical appraisal 1 – John Smith.docx".

Online discussion: 20% in total

General participation and live tutorials (12.5%): Discussion with fellow students and instructors is critical to developing a successful and effective learning environment. Each week students are expected to participate in the online discussion forums and during the live tutorial sessions about readings and assignments. At a bare minimum, students are expected to post at least one original post on the weekly readings discussion board (i.e. not only a comment in the discussion). Students are also expected to respond to at least one thread initiated by others. Messages should generally introduce accurate and relevant information, which teaches others something new. Purely gratuitous or assertive posts (e.g. "Thank you!" or "I agree") will not be considered and will not contribute to student's evaluation. To allow significant time for discussion each week, the timing of a student's post will also be considered in evaluations. Quality, quantity and timing of participation in course activities will be considered in the final participation grade. Although participation in the *assignment* discussion board is not evaluated, students are strongly encouraged to take advantage of this additional opportunity to discuss issues with their peers.

Live tutorials will be held for the first ten units (Unit 1 to Unit 10). Students are required to attend at minimum eight live tutorials for this course.

Discussion facilitation (7.5%):

Each week, one student can sign up to facilitate discussion about the readings. Responsibilities of the discussion facilitator include:

- Posting a summary of the readings (as early in the week as possible, preferably the first day) on their *readings* discussion board. The summary should not be prepared article by article but an overall synthesis of the readings and preferably no longer than 250 words (including questions for the discussion).
- Facilitating discussion related to the readings (e.g. posting additional resources, posting thought provoking questions early in the week to start discussion and later to stimulate discussion, responding constructively to fellow students' posts, and working to direct discussion to the important issues of the session)
- Updating reading summaries as appropriate

- Preparing and posting a summary of the discussion (at the end of the week) that includes any outstanding issues or questions in order to help fellow students' understanding in the reading materials

Critical appraisal 1: 15% in total

For this exercise, students will perform a critical appraisal of the child sepsis trial conducted in India by Panigrahi et al. 2017 published in Nature. Students are responsible for finding any relevant additional resources (e.g. registered protocol) related to this trial.

1. Panigrahi P, Parida S, Nanda NC, Satpathy R, Pradhan L, Chandel DS, Baccaglini L, Mohapatra A, Mohapatra SS, Misra PR, Chaudhry R. A randomized synbiotic trial to prevent sepsis among infants in rural India. Nature. 2017 Aug;548(7668):407.

This critical appraisal, maximum two-page (double lined), will include:

- Assessment of appropriateness of the key methodological features of the selected trial
    - Description of interim analyses and group sequential designs (GSD)
- Advantages and disadvantages of GSD over traditional methods and other adaptive trial design methods
- Strengths and limitations of the selected trial
- Proposal of alternative methods/adaptations

Critical appraisal 2: 15% in total

For this exercise, students will first identify a randomized clinical trial with published results and then perform a critical appraisal of the trial. Students can select any published clinical trial that is adaptive or non-adaptive (conventional). *If a conventional clinical trial is selected*, the student should discuss the appropriateness of such design and how different adaptive trial designs could have improved the efficiency of the clinical trial. *If an adaptive clinical trial is selected*, the student should discuss the appropriateness of such design and discuss advantages and disadvantages that the trial has over a conventional, non-adaptive trial design.

This critical appraisal, maximum two-page (double lined), will include:

For a clinical trial with adaptive trial designs	For a clinical trial with non-adaptive trial designs
Assessment of appropriateness of the key methodological features of the selected trial	Assessment of appropriateness of the key methodological features of the selected trial
Advantages and disadvantages of adaptations over conventional methods	Advantages and disadvantages of conventional trial design over adaptive methods
Strengths and limitations of the selected trial	Strengths and limitations of the selected trial

Proposal of alternative methods/adaptations	Proposal of alternative methods/adaptations

Critical appraisal 3 (Final): 25% in total

As the final critical appraisal paper, students will discuss how adaptive trial designs and/or master protocols can be applied to a research area of the student's interest. For this, students can select ongoing and/or recently published clinical trials that are well-known in their own clinical field. While not limited to a specific research area, students are encouraged to choose a research question related to their thesis and/or to their clinical expertise. Students can pick one or more relevant examples of proposed or published clinical trials in order to illustrate how adaptive trial designs and/or master protocols can be applied to their field.

As the final project for this course, it will consist of two parts.

1. Submission of a research synopsis on the final paper (maximum two-page) (worth 5%)
2. Final submission of critical appraisal paper (worth 20%)

All students should ensure they choose a topic that can be feasibly completed given the time and resource-limited nature of this course. Course instructors can help to assess the feasibility of the final critical appraisal paper and help to assess the feasibility of the project, if needed. Sample guidelines and the criteria for evaluation of the final project will be made available to students.

Submission of a research synopsis (5%):

The research synopsis, maximum two-page (double-lined), will include the following:

- Title
- Description of the clinical area
- Identify published and/or ongoing clinical trial(s) in the area
- Discuss the importance and relevance of the selected clinical trial(s)

Final critical appraisal paper (20%):

The final critical appraisal paper (maximum 5-pages, double-lined) should be outlined with the following sections:

1. **Abstract**: A 150-word, unstructured summary
2. **Introduction:** Provide a brief overview of the clinical area

3. **Summary of current evidence base**: Discuss the importance and relevance of selected clinical trial(s)
4. **Strengths and limitations of trial design**: Critically analyze the selected trial(s)
5. **Rationale for adaptive design and/or master protocols**: Discuss how adaptive trial design and/or master protocol can address the existing limitations and improve the efficiency of the selected trial(s)
6. **Figures:** (Optional) illustrations to aid the reader
7. **Tables:** (Optional)
8. **References:** Vancouver style

Final student presentation: 25%

In the last two weeks of the course, students will prepare a PowerPoint presentation – 20 minutes presentation followed by a 10 minutes Q/A – on the trial(s) selected for the final critical appraisal (third one). The presentation, worth 20% of the total grade, should mimic a conference oral presentation.

There will be 5% student participation mark as an audience member to the peer student presentations. Students are expected to attend both of the student presentation weeks, provide comments, and/or ask questions, as needed. Comments and questions should be positive, constructive, and courteous.

8. Online Discussion Guidelines

Participation in discussions with fellow students and instructors is critical to developing a sound understanding of course material. Below are some guidelines for successful on-line participation in discussion boards:

- Contribute at least one original post each week
- Respond to at least 2 threads initiated by others each week
- Ensure any message you post is accurate and meaningful
- Post information that is relevant to the discussion thread and that teaches others something new
- Properly reference content when appropriate; if you refer to the information from any source (e.g. papers, websites), provide the citation – this will enable others to refer to it later. The most valuable messages, however, are written in your own words.
- Thank someone for their assistance or let them know that you agree with what they have said.
- Include a subject line that conveys the main point you make in the message. It may not be enough to use a keyword or phrase as your subject. The most beneficial is a short Twitter-like sentence that states the main point of your message and provides enough information to determine its essence.
- Consider addressing issues that may not be of interest to the other students with instructors privately (e.g. more complex or advanced issues that you are personally vested in).

9. Policy on Late Assignments

10% will be deducted from all late assignments, and only in extreme situations final papers will be accepted up to 7 days after the due date.

The timely submission is crucial to the smooth running of the weekly sessions; therefore, flexibility on this issue would be to the detriment of the whole class. If something unforeseen comes up in the week you are assigned to facilitate the discussion, it will be your responsibility to find another student who would be willing to switch weeks with you.

Exceptions to this policy are at the discretion of the online instructor. It is important that you contact the instructor as soon as possible in the case of an emergency and well before a deadline in the case of previous commitments or restrictions.

10. Course Instructors

Edward Mills, PhD

Associate Professor, Department of Health Research Methods, Evidence, and Impact (McMaster University)

Email: millsej@mcmaster.ca

Kristian Thorlund, PhD

Assistant Professor, Department of Health Research Methods, Evidence, and Impact (McMaster University)

Email: thorluk@mcmaster.ca

Jay Park

Email: jpark@mteksciences.com

Please contact Jay Park for all administrative or process related issues (e.g. registration, technology, scheduling, etc.).

11. Course and Instructor Evaluations

Similar to other HRM courses, at the end of the course students will be asked to complete a formal evaluation of the course and of their primary instructor.

12. Feedback about the Course

A *Feedback Forum* discussion area will also be available throughout the duration of the course where students can post and discuss suggestions for improving and augmenting the content, organization and running of the course. This forum gives students an opportunity to discuss with others the pros and cons of specific tasks as well as allowing, where necessary and possible, the instructor to make immediate modifications to the course (e.g. the addition of a discussion forum or a student-created resource library).

13. Communication Expectations & Netiquette

What you can expect from us

- We will respect you and take your questions and concerns seriously
- We will respond to your requests for assistance in a timely fashion

For important personal matters please email your instructor directly (using the contact information above) and we will respond within 24 hours during the week or 48 hours over the weekend.

Discussion boards

Interaction among students is important to building a learning community and the success of the course. Consequently, we will not respond to every post in a discussion board. We will monitor the discussion forums at least every 72 hours and will intervene when issues arise. If an issue arises that needs immediate attention of the instructor please follow-up with a personal email.

Feedback on assignments

You will receive feedback on your assignments within 1 week of submission. If this is not possible, we will let you know within this time when you can expect your mark and feedback.

What we expect from you

We expect everyone to communicate in a pleasant and efficient manner that respects all involved. You may want to review the core rules of netiquette: http://www.albion.com/netiquette/corerules.html

Netiquette – etiquette in technology – social conventions that facilitate communication in a polite and respectful manner in electronic networks (https://en.wikipedia.org/wiki/Etiquette_in_technology)

14. Academic Integrity

The Office of Academic Integrity at McMaster University supports students and faculty deal with issues of academic integrity. They have an excellent website (http://mcmaster.ca/academicintegrity/index.html) that includes:

- McMaster's policy on 'Academic Integrity'
- Services to assist students in avoiding dishonesty (including definitions, quizzes, and online services to check your work for plagiarism)
- The consequences of violating the University policies on academic integrity

15. Inclusivity, Accessibility, and Accommodations

McMaster University and your instructors are committed to creating an equitable and accessible environment and to encouraging openness to multiple perspectives and points of view. If you have a dis/ability or heath consideration that may require accommodations, please feel free to approach one of the instructors and/or Student Accessibility Services (https://sas.mcmaster.ca/) as soon as possible to discuss accommodations.

For further information, consult McMaster University's Policy for Academic Accommodation of Students with Disabilities: http://www.mcmaster.ca/policy/Students-AcademicStudies/AcademicAccommodation-StudentsWithDisabilities.pdf

HRM 732 Course Calendar:

This is a tentative calendar. You will be notified as soon as possible if any changes need to be made.

Units will start at 12:01AM on Sunday mornings and end at 11:59PM on Saturday night (All times refer to **Eastern Time** (USA and Canada).

Week	Unit and Topic	Dates	Tutorial time	Assignments
1	Course introduction and history of adaptive trial designs and master protocols	May 6 – 12, 2019	May 10, 3-5pm (EST)	--
2	Adaptive trial designs and master protocols: Characteristics, principles, and types	May 13 – 19, 2019	May 17, 3-5pm (EST)	--
3	Adaptive designs for dose finding and efficacy	May 20 – 26, 2019	May 24, 3-5pm (EST)	--
4	Case studies in seamless and sample-size re-assessment designs	May 27 – June 2, 2019	May 31, 3-5pm (EST)	--
5	Clinical trial simulations, decision rules, and statistical analyses	June 3 – 9, 2019	June 7, 3-5pm (EST)	Critical appraisal assignment 1
6	Precision oncology trials: Basket and umbrella trials	June 10 – 16, 2019	June 14, 3-5pm (EST)	--
7	A case study on a platform trial: STAMPEDE trial	June 17 – 23, 2019	June 21, 3-5pm (EST)	Critical appraisal assignment 2
8	A case study on a platform trial: I-SPY2 trial	June 24 – 30, 2019	June 28, 3-5pm (EST)	Synopsis on critical appraisal assignment 3
9	Standards for adaptive designs and master protocols	July 1 – 7, 2019	July 5, 3-5pm (EST)	--
10	Practical considerations for funding and implementation of adaptive trial designs and master protocols	July 8 – 14, 2019	July 12, 3-5pm (EST)	--
11	Writing week & Open office hour	July 15 – 21, 2019	July 19, 3-5pm (EST)	Critical appraisal assignment 3 (Final)
12	Student presentations I	July 22 – 28, 2019	July 26, 3-5pm (EST)	Presentations
13	Student presentations II	July 29 – Aug 4, 2019	August 2, 3-5pm (EST)	Presentations

Each assignment is due at the end of the week, Saturday at 11:59PM. The third peer review on final review paper is due the week (7 days) after the final submission deadline.

Important Dates (McMaster University Holidays)

- Victoria Day Monday, May 20th, 2019
- Canada Day Monday, July 1st, 2019

Unit 0: Orientation

Unit Introduction:

Some of you may be new to the online learning environment or to McMaster University's learning management system – Avenue to Learn, thus, there is no learning module for this week. Instead, we want you to use this time to meet each other and ensure that everyone is comfortable navigating around the course.

Learning Objectives:

At the conclusion of this session you should:

- Understand the course format, assignments and evaluation methods.
- Know the expected format of final project results (guideline recommendations and packages)
- Know a bit about your peers and your instructor
- Know where to find help

Assignments:

1. Carefully read over the entire course syllabus and post any questions in the *General Discussion & Help* forum (see the link in the tree in the left-hand column under *The Essentials*).
2. Prepare a bio-blurb (1-3 short paragraphs), including:
    a. A brief description of your background and explanation of your area of study/work (Have you successfully explained what you study or do to any of your family members yet? Try to explain it to your fellow students and instructors as if they were uninitiated family members.)
    b. Reason(s) for taking this course, what you hope to gain by completing this course
    c. Some interesting information about you – e.g. how would you like others to address you (by your name, nickname etc.), how far from McMaster you currently live (pictures and short video clips are welcome), etc.
3. Post your bio-blurb on the *Introductions* discussion board and comment on some of your peers' posts – start a meaningful discussion.
4. Sign-up for facilitation of a discussion on the *Readings* discussion board (choose one week).
5. Confirm that you can access online readings through McMaster University library. For more information please refer to: http://library.mcmaster.ca/libaccess (Note: your login and password are your MAC ID and your MAC ID password).

Where to go for help:

- Anything concerning this HRM 732 course content – look in the course materials, ask your peers, search the Web. If all fails contact your instructor.
- Avenue to Learn technical help: use the *Help* section, if you cannot find an appropriate information please use a support ticket to contact the McMaster Institute for Innovation and Excellence in Teaching and Learning (MIIETL) directly: http://miietl.mcmaster.ca/site/avenue-to-learn/
- HRM Program or general inquiries – please contact Sheri Burns (HRM Program Assistant – hrmasst@mcmaster.ca) or (Course Instructor – Jay Park, jpark@mteksciences.com)

Unit 1: Introduction and history of adaptive trial designs and master protocols

Unit Introduction:

As (most) students will either have taken HRM 730 or 733 or will have experiences in randomized clinical trials, we assume the enrolled students are familiar with the classical trial designs. In this unit, we will provide a quick overview of classical randomized clinical trial designs and will introduce history of adaptive designs including group sequential designs.

It is highly recommended that students read documents related to the final critical appraisal assignment and corresponding presentation.

Learning Objectives:

1. To understand what constitutes adaptive trial designs trial and master protocols and their strengths and limitations

Required Readings:

1. Bauer P, Bretz F, Dragalin V, Konig F, Wassmer G. Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls. Stat Med. 2016;35(3):325-47.
2. Bhatt DL, Mehta C. Adaptive Designs for Clinical Trials. N Engl J Med. 2016;375(1):65-74.
3. Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB. Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study. Pediatrics. 1985;76(4):479-87.
4. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med. 2017;377(1):62-70.

Additional Recommended Readings and Resources:

1. Biswas S, Liu DD, Lee JJ, Berry DA. Bayesian clinical trials at the University of Texas MD Anderson cancer center. Clinical Trials. 2009;6(3):205-16.
2. Chow SC, Chang M. Adaptive design methods in clinical trials - a review. *Orphanet J Rare Dis* 2008; **3**: 11.
3. Sebille V, Bellissant E. Sequential methods and group sequential designs for comparative clinical trials. *Fundam Clin Pharmacol* 2003; **17**(5): 505-16.
4. Chapter 1. Introduction. In: Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. CRC Press; 1999.
5. Berry Consultants. What Clinicians Should Know About Adaptive Clinical Trials. https://www.youtube.com/watch?v=eFmpHxOvk1A

6. Berry Consultants. How to Design an Adaptive Trial – Lessons Learned…So Far. https://www.youtube.com/watch?v=S9iUOqtLAII

Assignments:

1. Read over the documents related to the final course project and post any questions in the *General Discussion & Help* forum (see the link in the tree in the left-hand column under *The Essentials*).
2. Sign-up for facilitation of a discussion on the *Readings* discussion board (choose one week).
3. Participate in online discussion forums about readings and assignments

Unit 2: Adaptive trial designs and master protocols: Characteristics, principles and types

Unit Introduction:

In this unit, we will introduce principles of clinical designs in the context of adaptive trial designs and master protocols, their characteristics, and different types.

Learning Objectives:

- To understand the characteristics, principles, and different types of adaptive designs
- To understand the characteristics, principles, and different types of master protocols (basket trials, umbrella trials, and platform trials)

Required Readings:

1. Thorlund K, Haggstrom J, Park JJ, Mills EJ. Key design considerations for adaptive clinical trials: a primer for clinicians. *BMJ* 2018; **360**: k698.
2. Park JJ, Thorlund K, Mills EJ. Critical concepts in adaptive clinical trials. *Clin Epidemiol* 2018; **10**: 343-51.
3. U.S. Food and Drug Administration. Adaptive Designs for Medical Device Clinical Studies Guidance for Industry and Food and Drug Administration Staff (2016)
4. U.S. Department of Health and Human Services Food and Drug Administration. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry (Draft Guidance) 2018 [Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621817.pdf.

Additional Recommended Readings and Resources:

1. U.S. Food Drug Administration. Guidance for the use of Bayesian statistics in medical device clinical trials. Maryland: US Food and Drug Administration. 2010.
2. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Reflection Paper On Methodological Issues In Confirmatory Clinical Trials With Flexible Design and Analysis Plan (2006)
3. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. JAMA. 2015;313(16):1619-20.
4. CHEOSNews. Bayesian Adaptive Trial Design—Dr. Roger Lewis, April 26, 2013. https://www.youtube.com/watch?v=SZUaiXreflU&index=1

5. Berry Consultants. Data and Safety Monitoring Boards (DSMBs) for Adaptive Trials. https://www.youtube.com/watch?v=bs8DMVJKb9c

Assignment:

1. Participate in online discussion forums about readings and assignments
2. Perform relevant research related to assignment on critical appraisal assignment 1 (due end of week 4)

Unit 3: Adaptive designs for dose finding and efficacy

Unit Introduction:

In this unit, we will review differences between exploratory and confirmatory trials and discuss commonly used adaptive designs for dose finding (exploratory) and confirmatory clinical studies.

Learning Objectives:

- To review the differences between exploratory and confirmatory clinical trials
- To understand different adaptive trial designs used for exploratory and confirmatory investigations.

Required Readings:

1. Harrington JA, Wheeler GM, Sweeting MJ, Mander AP, Jodrell DI. Adaptive designs for dual-agent phase I dose-escalation studies. Nat Rev Clin Oncol. 2013;10(5):277-88.
2. Emerson SS, Fleming TR. Adaptive methods: telling "the rest of the story". Journal of biopharmaceutical statistics. 2010;20(6):1150-65.
3. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, Holmes J, Mander AP, Sydes MR, Villar SS, Wason JM. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC medicine. 2018 Dec;16(1):2
4. Bothwell LE, Avorn J, Khan NF, Kesselheim AS. Adaptive design clinical trials: a review of the literature and ClinicalTrials. gov. BMJ open. 2018 Feb 1;8(2):e018320.

Additional Recommended Readings and Resources:

1. HARC HARC. Adaptive Trials and Master Protocols. Dr. Don Berry. https://www.youtube.com/watch?v=GXSLOBghnqc
2. CHEOSNews. Bayesian Adaptive Trial Design—Dr. Roger Lewis, April 26, 2013. https://www.youtube.com/watch?v=SZUaiXreflU&index=1
3. CytelVideos. Case Studies of Phase 2 Adaptive Dose-Finding Trials – Jim Bolognese. https://www.youtube.com/watch?v=xvEDsg_Fdic
4. CytelVideos. Alternative Methods to Designing Clinical Trials in Phase 1 Oncology. https://www.youtube.com/watch?v=Wy31PWtLzpo
5. CytelVideos. Model-based Designs in Oncology Dose-finding Studies. https://www.youtube.com/watch?v=oOb4LGQu92k

Assignment:

1. Participate in online discussion forums about readings and assignments

2. Perform relevant research related to assignment on critical appraisal assignment 1 (due end of week 4)

Unit 4: Case studies in seamless and sample size re-assessment designs

Unit Introduction:

In this unit, we will discuss build on the topics discussed in the previous units with case studies of seamless phase II/III and sample size reassessment designs.

Learning Objectives:

- To review key methodological concepts in seamless phase II/III and sample size reassessment designs
- To discuss case studies of seamless phase II/III and sample size reassessment designs

Required Readings:

1. Bauer P, Bretz F, Dragalin V, Konig F, Wassmer G. Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls. Stat Med. 2016;35(3):325-47.
2. Chow SC, Chang M. Adaptive design methods in clinical trials - a review. *Orphanet J Rare Dis* 2008; **3**: 11.
3. Cuffe RL, Lawrence D, Stone A, Vandemeulebroecke M. When is a seamless study desirable? Case studies from different pharmaceutical sponsors. Pharmaceutical statistics. 2014 Jul;13(4):229-37.

Additional Recommended Readings and Resources:

1. Berry DA. Adaptive clinical trials in oncology. Nat Rev Clin Oncol. 2011;9(4):199-207.

Assignment:

1. Participate in online discussion forums about readings and assignments
2. Critical appraisal assignment (due by the end of this week; worth 15% of overall grade)

Unit 5: Clinical trial simulations, decision rules, and statistical analyses

Unit Introduction:

In this unit, we will discuss the principles of clinical trial simulations and the benefits of performing clinical trial simulations for planning any clinical trials. We will also introduce decision rules that are commonly used in adaptive trial designs, as well as discuss the statistical analyses that can help the efficiency and interpretation of clinical trials research.

Learning Objectives:

- To understand the principles of clinical trial simulations and how they can be useful for trial planning
- To understand different decision rules that are commonly used in adaptive trial designs
- To understand the statistical analyses that can be used to improve the efficiency of clinical trial research

Required Readings:

1. Thorlund K, Golchi S, Haggstrom J, Mills E. Highly Efficient Clinical Trials Simulator (HECT): Software application for planning and simulating platform adaptive trials. Gates Open Research. 2019 Mar 18;3.
2. HECT – Highly Efficient Clinical Trial Simulator. https://mtek.shinyapps.io/hect/
3. Hummel J, Wang S, Kirkpatrick J. Using simulation to optimize adaptive trial designs: applications in learning and confirmatory phase trials. Clinical Investigation. 2015;5(4):401-13.
4. Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov* 2006; **5**(1): 27-36.
5. Saville BR, Connor JT, Ayers GD, Alvarez J. The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. Clin Trials. 2014;11(4):485-93.

Additional Recommended Readings and Resources:

1. Burton A, Altman DG, Royston P, Holder RL. The design of simulation studies in medical statistics. Stat Med. 2006;25(24):4279-92.
2. Ventz S, Alexander BM, Parmigiani G, Gelber RD, Trippa L. Designing Clinical Trials That Accept New Arms: An Example in Metastatic Breast Cancer. Journal of Clinical Oncology. 2017:JCO. 2016.70. 1169.
3. MD Anderson Cancer Center. CRM Simulator. https://biostatistics.mdanderson.org/softwaredownload/SingleSoftware.aspx?Software_Id=13
4. MD Anderson Cancer Center. One-Arm Time-to-Event Simulator. https://biostatistics.mdanderson.org/softwaredownload/SingleSoftware.aspx?Software_Id=98

5. LearnBayes package in R
6. Stata. Introduction to Bayesian Statistics, part 1: The basic concepts. https://www.youtube.com/watch?v=0F0QoMCSKJ4
7. Stata. Introduction to Bayesian Statistics, part 2: MCMC and the Metropolis Hastings algorithm. https://www.youtube.com/watch?v=OTO1DygELpY
8. Berry Consultants. Multiplicities, Big Data = Big Problems, Irreproducible Research, & The Umbrella Man. https://www.youtube.com/watch?v=ICOiKThwjoc

Assignment:

1. Participate in online discussion forums about readings and assignments
2. Perform relevant research related to critical appraisal 2 assignment (due end of week 7)

Unit 6: Precision oncology trials: Basket and umbrella trials

Unit Introduction:

In this unit of precision oncology trials, we will review new emerging designs in basket and umbrella trials. We will discuss motivations, strengths, and pitfalls of these biomarker-guided trials.

Learning Objectives:

- To understand the concept of basket trials and umbrella trials
- To understand the motivations, strengths, and limitations of biomarker-guided precision oncology trials

Required Readings:

1. Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. Annals of Oncology. 2016 Oct 11;28(1):34-43
2. Hirakawa A, Asano J, Sato H, Teramukai S. Master protocol trials in oncology: Review and new trial designs. Contemporary clinical trials communications. 2018 Dec 1;12:1-8.

Additional Recommended Readings and Resources:

1. Antoniou M, Jorgensen AL, Kolamunnage-Dona R. Biomarker-Guided Adaptive Trial Designs in Phase II and Phase III: A Methodological Review. PLoS One. 2016;11(2):e0149803.

It is highly recommended that students to start on the required reading of week 7 and week 8.

Assignment:

1. Participate in online discussion forums about readings and assignments
2. Perform relevant research related to critical appraisal 2 assignment (due end of week 7)

Unit 7: A case study on a platform trial: STAMPEDE trial

Unit Introduction:

In this unit, we will continue to apply the concepts from Unit 1 and 6 by critically appraising the first ever conducted platform trial called STAMPEDE. The STAMPEDE trial is a platform trial on prostate cancer; it is an interesting example of an open-form multi-arm and multistage trial that particularly terminated several treatments arms and added novel treatment arms over several years.

Learning Objectives:

- To identify the strengths and limitations of the STAMPEDE trial
- To assess the appropriateness of the key methodological features of the designs of the STAMPEDE trial

Required Readings:

1. James ND, Sydes MR, Mason MD, Clarke NW, Anderson J, Dearnaley DP, et al. Celecoxib plus hormone therapy versus hormone therapy alone for hormone-sensitive prostate cancer: first results from the STAMPEDE multiarm, multistage, randomised controlled trial. Lancet Oncol. 2012;13(5):549-58.
2. STAMPEDE Protocol Version 15.0 29-Mar-2016. http://www.stampedetrial.org/87548/87552/STAMPEDE_Protocol_v15.0_clean.pdf
3. STAMPEDE Appendices Version 14.0 29-Mar-2016. http://www.stampedetrial.org/87548/87552/STAMPEDE_Appendices_v14.0_clean
4. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N Engl J Med* 2017; **377**(4): 338-51.

Additional Recommended Readings and Resources:

1. Berry Consultants. I-SPY 2 and Other Platform Trials. https://www.youtube.com/watch?v=nwiVixhni8A
2. BATTLE trial, https://clinicaltrials.gov/ct2/show/NCT00409968
3. Sydes MR, Parmar MK, James ND, Clarke NW, Dearnaley DP, Mason MD, et al. Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial. Trials. 2009;10:39.
4. Sydes MR, Parmar MK, Mason MD, Clarke NW, Amos C, Anderson J, et al. Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. Trials. 2012;13:168.
5. STAMPEDE trial website, http://www.stampedetrial.org/

Assignment:

- Participate in online discussion forums about readings and assignments
- Critical appraisal 2 assignment (due by end of this week, worth 15% of the overall grade)
- Perform relevant research related to critical appraisal assignment 3 (synopsis due by end of week 8; worth 5% of the overall grade)

Unit 8: A case study on a platform trial: I-SPY2 trial

Unit Introduction:

I-SPY 2 trial is a platform trial, a biomarker-guided adaptive trial that evaluated 12 neoadjuvant therapies for breast cancer. This is one of the hallmark study for personalized medicine and adaptive design trials. In this unit, we will use the concepts from Unit 1 to 7 in order to review and critically appraise the I-SPY2 trial for its key methodological features and discuss its strengths and limitations.

Learning Objectives:

- To identify the strengths and limitations of the I-SPY2 trial
- To assess the appropriateness of the key methodological features of the I-SPY 2 trial

Required Readings:

1) Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. JAMA. 2015;313(16):1619-20.
2) Park JW, Liu MC, Yee D, Yau C, van 't Veer LJ, Symmans WF, et al. Adaptive Randomization of Neratinib in Early Breast Cancer. N Engl J Med. 2016;375(1):11-22.
3) Renfro LA, Mallick H, An MW, Sargent DJ, Mandrekar SJ. Clinical trial designs incorporating predictive biomarkers. Cancer Treat Rev. 2016;43:74-82.
4) Rugo HS, Olopade OI, DeMichele A, Yau C, van 't Veer LJ, Buxton MB, et al. Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer. N Engl J Med. 2016;375(1):23-34.

Additional Recommended Readings and Resources:

1. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009;86(1):97-100.
2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01042379
3. I-SPY trials website. http://www.ispytrials.org/home
4. Berry Consultants. I-SPY 2 and Other Platform Trials. https://www.youtube.com/watch?v=nwiVixhni8A

Assignment:

- Participate in online discussion forums about readings and assignments
- Synopsis of critical appraisal assignment 3 (due by the end of this week; worth 5% of overall grade)

Unit 9: Standards for adaptive designs and master protocols

Unit Introduction:

In this unit, we will discuss methodological standards that generally apply to adaptive clinical trials. We will specifically refer to the document by Detry and colleagues, "Standards for the Design, Conduct, and Evaluation of Adaptive Randomized Clinical Trials," and the CONSORT extension to adaptive trial designs (Dimariro et al 2018)

Learning Objectives:

- To understand general methodological standards for adaptive clinical trials proposed by Detry et al 2012 and Dimariro et al 2018
- To critically appraise Detry et al 2012 for its strength and limitations
- To critically appraise Dimariro et al 2018for its strength and limitations

Required Readings:

1. Detry 2012. Standards for the Design, Conduct, and Evaluation of Adaptive Randomized Clinical Trials. The Patient-Centered Outcomes Research Institute (PCORI)
2. Dimairo M, Coates E, Pallmann P, Todd S, Julious SA, Jaki T, et al. Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design. BMC Med. 2018;16(1):210.

Additional Recommended Readings and Resources:

1. AHRQ Primary Care. Adaptive Trial Design and Learning Evaluation: Methods for PCOR and Quality Improvement Assessment. https://www.youtube.com/watch?v=ZJrDsk01w2Y

It is highly recommended that students to start on the required reading of week 9 (see Antoniou 2016 and Berry 2015).

Assignment:

1. Participate in online discussion forums about readings and assignments
2. Perform relevant research for critical appraisal assignment 3 (due by the end of week 11)

Unit 10: Practical considerations for funding and implementation of adaptive trial designs and master protocols

Unit Introduction:

In this unit, we will summarize the lessons gained from previous units (Unit 1-9) and discuss practical considerations for funding and implementation of adaptive trial designs and master protocols. While there are no assigned readings this week, students are encouraged to review assigned and/or recommended readings from previous units.

Learning Objectives:

- Discuss practical considerations for funding and implementation of adaptive trial designs
- Discuss practical considerations for funding and implementation of master protocols

Required Readings:

There are no required readings.

Additional Recommended Readings and Resources:

There are no recommended readings and resources.

Assignment:

1. Participate in online discussion forums about readings and assignments
2. Perform relevant research for critical appraisal assignment 3 (due by the end of week 11)
3. Sign up for presentation time for either week 12 or 13

Unit 11: Writing week and open office hour

Unit Introduction:

There will be no required readings and online tutorials. Students will have an opportunity to spend this week as a writing week for the final critical appraisal. There will be an optional open office hour where the students will have an opportunity to ask questions and discuss regarding their final critical appraisal and presentations.

Learning Objectives:

There are no intended learning objectives for this unit.

Required and Additional Recommended Readings and Resources:

There are no required readings, recommended readings and resources.

Assignment:

- Final critical appraisal assignment 3 (due at the end of this week)
- Sign up for student presentation
- Student presentation during week 12 or 13

Unit 12 and 13: Student presentation weeks

Unit Introduction:

In these two units (the last two weeks of the course), students will present on their final critical appraisal assignment. The student presentation will mimic a conference presentation. Students will be responsible for providing summaries of the case studies for the presentation and the readings to their peers.

Required Readings:

There are no required readings.

Additional Recommended Readings and Resources:

There are no recommended readings and resources.

Assignment:

- Critical appraisal assignment 3 (Final) due at the end of this week (worth 25% of overall grade)
- Sign up for presentation time for either week 12 or 13 (worth 25% of overall grade)